STUDIES WITH THE BENZYLISOQUINOLINIUM MUSCLE RELAXANTS

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FOR THE DEGREE OF DOCTOR OF MEDICINE
University of Edinburgh
1990

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DECLARATION

This thesis has been composed by myself. The work presented is my own or that performed in co-operation with other members of a research group.

DEDICATION

I dedicate this thesis to my father and mother for their continual support and encouragement throughout my education.

ACKNOWLEDGEMENTS

I would like to acknowledge the following:-

The Department of Anaesthetics in Edinburgh for stimulating my interest in research at an early stage in my anaesthetic career.

Dr Valerie Goat, and subsequently Dr Colin Blogg, of the Nuffield Department of Anaesthetics, Oxford, for their help and encouragement in developing my interest in neuromuscular blockade.

Professor John Savarese, of Harvard Medical School and the Massachusetts General Hospital, for creating excellent opportunities for study in laboratory and clinical pharmacology, and for being an outstanding mentor.

Dr John Moss and colleagues, of Harvard Medical School, for performing the histamine assay.

Dr Fred de Bros, of Harvard Medical School and the Massachusetts General Hospital, for performing the atracurium assay and calculating the pharmacokinetic parameters.

Dr Hassan Ali, of Harvard Medical School and Massachusetts General Hospital, for his advice on neuromuscular monitoring.

Dr David Hoaglin, of Harvard Medical School, for his statistical advice.

Professor John Norman, of the University Department of Anaesthesia, Southampton, for his collaboration and encouragement.

Dr Alistair Chambers, of the Department of Anaesthetics at the Royal Infirmary of Edinburgh, for reading this thesis and providing so much constructive, helpful criticism.

Wellcome Research Laboratories, both at Research Triangle Park, North Carolina, and Beckenham, Kent, for funding some of the initial work on atracurium, BWB1090U, and BWA938U.

Finally, and most importantly, the hundreds of patients who consented to participate in the investigations.

Abstract of Thesis

The characteristics of the hypothetical ideal neuromuscular blocking drug are described and some of the unwanted effects of the older muscle relaxants are reviewed. The history behind the development of short acting rapid onset non-depolarising neuromuscular blockers is outlined. Attention is focused on the benzylisoquinolinium compounds. The development of atracurium, the animal pharmacology and the preliminary studies in man are discussed.

Patient studies are performed to investigate how closely the pharmacological characteristics of atracurium relate to those of the ideal drug. Some potential clinical uses for atracurium are investigated.

Atracurium is noted to have an onset time significantly slower than suxamethonium. Onset time and duration are found to vary with the mode of neuromuscular monitoring and anaesthetic depth. When 0.6 mg kg^{-1} atracurium is injected rapidly, there is a significant elevation in serum histamine concentration. The associated haemodynamic response may be attenuated by slowing the speed of injection or by pretreating with intravenous H1 and H2 antagonists. Onset time may be shortened by using 0.8 mg kg^{-1} but at the expense of a transient drop in blood pressure and increase in heart rate unless administration is slowed. Priming provides no improvement in onset time, nor in haemodynamic stability. Atracurium shows no tendency to cumulate when administered as an infusion. The pharmacodynamics and pharmacokinetics of atracurium in anephric patients are found to be very similar to those of healthy patients. Pretreatment with atracurium does not prevent postoperative

suxamethonium myalgia. When suxamethonium is administered during a recovering atracurium block, very high doses of suxamethonium are required to produce 100% blockade of the twitch. The response to atracurium by patients with myasthenia gravis is described.

Initial studies with two further benzylisoquinolinium compounds are reported.

BWB1090U is a benzylisoquinolinium non-depolarising muscle relaxant hydrolysed by plasma cholinesterase. The initial laboratory studies with Rhesus monkeys and the neuromuscular and cardiovascular effects on volunteers are reported. BWB1090U appears to be a potent drug with a short duration, minimal cumulative activity and reasonable cardiovascular stability. The transient changes observed in the haemodynamic parameters are thought to be due to histamine release.

BWA938U is discussed and the first pilot study is described. The first study in patients in Europe is also reported. BWA938U appears to be a very potent long acting non-depolarising blocking drug devoid of haemodynamic effects. It is well reversed with neostigmine but not by edrophonium.

Finally, current and future research in the development of new, rapid onset, short acting neuromuscular blocking agents is discussed.

ABBREVIATIONS

$t_{\frac{1}{2}}\ \alpha$	Alpha half-life
ASA	American Society of Anesthesiologists
$t_{\frac{1}{2}}\ ß$	Beta half-life
BWA938U	Doxacurium Chloride
BWB1090U	Mivacurium Chloride
°C	Degrees Centigrade
Cl	Clearance
CO2	Carbon dioxide
CPAP	Continuous positive airways pressure
ECG	Electrocardiograph
EMG	Electromyograph
H1, H2	Histamine receptor types
Hb	Haemoglobin
i.m.	Intra-muscular
IMV	Intermittent mandatory ventilation
IPPV	Intermittent positive pressure ventilation
i.v.	Intravenous
kg	Kilogram
kPa	Kilopascal
MAC	Minimal alveolar concentration
mg	Milligramme
min	Minute
ml	Millilitre
mm Hg	Millimetre of mercury
mmol	Millimole
n	Number in a group
N2O	Nitrous oxide
O2	Oxygen

P	Probability
PaCO2	Tension of carbon dioxide in arterial blood
PO	Per oral
post	After
pre	Before
pre-op	Before the operation
r	Regression coefficient
sec	Second
SD	Standard deviation
SEM	Standard error of the mean
SSIR	Steady state infusion rate
SV	Spontaneous ventilation
VDSS	Volume of distribution at steady state
yr	Year
μg	Microgramme
<	Less than
>	Greater than

INTRODUCTION

Ever since civilised man identified curare, the arrow tip poison, as a neuromuscular blocking agent with essentially no central nervous system effect, there has been increasing interest in this mechanism of achieving muscle relaxation in clinical situations. Over the years, curare has been used for a variety of muscle dystonias from acute sprains to a pharmacological substitute for the 'spasmolytic' warm packs in the treatment of acute poliomyelitis during the early 1950s. The introduction of curare to anaesthesia by Griffith and Johnson [1] in 1942 was to promote the most important use of this drug. The flaccid patient greatly facilitated abdominal surgery. However, it took over a decade before Beecher and Todd [2] were to point out that 'using curare for many trivial purposes is not justified' [2]. They remarked that 'despite artificial respiration of a generally effective type [bag squeezing], many curare patients die of circulatory collapse. It is not hertofore been recognised that a common cause of death from curare is circulatory failure'. Because some of the methodology in Beecher and Todd's report was flawed, the conclusions were invalid. Nevertheless, it took some years to recognise that spontaneous ventilation is unsafe when neuromuscular blocking agents are given. Additional years of practice and astute observations were required before ganglionic blockade and histamine release were recognised as sequelae to tubocurarine administration.

Suxamethonium was hailed as tubocurarine's successor and was thought to be devoid of ganglion blocking and histamine releasing properties.

The rapid onset of action and evanescent period of paralysis meant that suxamethonium quickly achieved universal acceptance. However, over the ensuing decade after its introduction, it became apparent that a number of undesirable side effects occurred, mostly as a consequence of its depolarising action.

Foldes and Churchill-Davidson first suggested that a short acting neuromuscular agent which did not have the agonist or depolarising properties of suxamethonium may well avoid these unwanted effects.

Many of the unwanted side effects of neuromuscular blocking drugs are produced by the interaction of quarternary molecules with cholinoceptors other than those at the myoneural junction. A number of promising experimental non-depolarising drugs which possessed the desired muscle relaxing properties in animals have not been suitable for clinical use because of this.

Histamine release is a non-cholinoceptive side effect which has also prevented the introduction of certain experimental compounds, in particular the benzylisoquinolinium agents.

A hypothetical ideal neuromuscular blocking drug has been described by Savarese and Kitz [3].

This drug should have the following clinical characteristics:-

1. <u>A rapid onset of action</u>.

   One hundred per cent blockade of the single twitch would

occur in 30-45 seconds permitting rapid intubation of the trachea. This would make it a suitable alternative to suxamethonium for a rapid sequence induction technique. None of the traditionally used non-depolarising agents have onset times as rapid as suxamethonium.

2. Rapid dissipation of neuromuscular blockade.

Muscle activity would recover to 90% of control levels within 10-20 minutes after intubation of the trachea.

Generally speaking, the shorter-acting a muscle relaxant is, the more flexible and forgiving its usage becomes.
In terms of duration, however, it may be argued that three types of muscle relaxants are required. In addition to the short acting muscle relaxant described above, an intermediate duration non-depolarising agent without cumulative effects would provide an action span shorter than the more traditional non-depolarising agents.
Savarese and Kitz [3] proposed that a drug with a rapid recovery (15-20 minutes) would decrease the need for reversal of neuromuscular blockade at the termination of anaesthesia, thereby decreasing the possibility or danger of postoperative residual curarisation.

Also, the anticholinesterase agents are not without morbidity in their own right and may on occasion deepen blockade. They went on to suggest that a drug metabolised by the body whose action was terminated by its own destruction would also be very appealing.

A third type of agent, a long acting non-depolarising agent devoid of cardiovascular side effects, might also be useful, particularly in cardiac surgical procedures.

3. Lack of cumulative effects

Neuromuscular activity would recover to 90% of control levels within 10-20 minutes of stopping an infusion or following multiple incremental doses.

4. Antagonism of blockade by suitable antidote.

This will usually be by an anticholinesterase agent. It is important that the muscle relaxant does not also significantly inhibit acetylcholinesterase otherwise the effectiveness of the anticholinesterase agent will be reduced. This problem arose with one experimental drug called benzoquinonium [4]. The powerful acetylcholinesterase inhibiting action of benzoquinonium which would otherwise have been a useful relaxant lead to its withdrawal as a neuromuscular blocking drug.

5. Absence of pharmacological action or toxicity of metabolites.

6. High potency.

Although not always true, generally speaking the more potent a muscle relaxant is, the less side effects it will have. The

therapeutic index or margin of safety will be greater. Furthermore, it avoids the cumulation of large quantities of metabolites.

7. Histamine release.

With muscle relaxants, histamine release by chemically mediated reactions happens much more frequently than by immunologically mediated reactions [5]. This occurs when the injected substance acts directly on the tissue mast cells or circulating basophil leucocytes leading to the release of histamine without antibody or complement involvement.

8. Absence of cardiovascular effects.

As well as releasing histamine and possibly other vaso-active mediators, muscle relaxants may also stimulate or inhibit peripheral autonomic sites [6]. (See Figure 1).

Tubocurarine blocks ganglionic nicotinic receptors and produces some ganglionic blockade in a dose range slightly greater than that required to produce neuromuscular blockade. It may have a slightly more powerful action on parasympathetic than on sympathetic ganglia [7]. Autonomic reflexes arising in the course of surgical operations may be impaired by this ganglion blocking action, and this action may contribute to hypotension [8,9]. However, there is evidence suggesting that the role of ganglionic blockade in the hypotensive action of

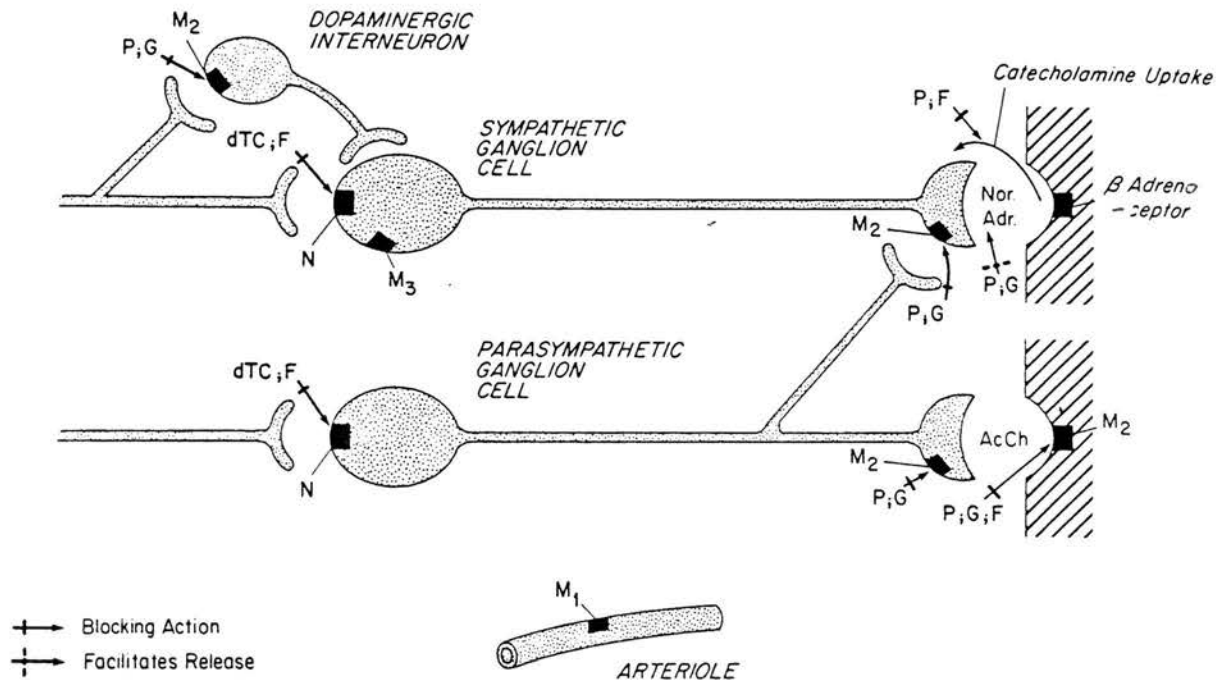


Figure 1

Diagrammatic representation of the automonic nervous system with respect to the heart and sites of action of some neuromuscular blocking agents on this system. The muscarinic receptors have been divided into three subclasses (M1, M2, M3).

N = nicotinic receptor P = pancuronium G = gallamine
F = fazadinium dTc = tubocurarine

tubocurarine is possibly less important than its ability to release histamine [10]. Metocurine and alcuronium are weaker ganglion blockers and other neuromuscular blocking drugs such as gallamine and pancuronium have no ganglion blocking activity in the doses used clinically. Suxamethonium has a weak ganglion stimulant action which may occasionally cause a rise in blood pressure [11].

By definition, all muscarinic receptors are stimulated by muscarine and blocked by atropine. However, evidence has accumulated in recent years that these receptors are probably not a homogeneous group. A lucid account by Bowman [12] describes how they may differ with respect to their interaction with other agonists and antagonists. Figure 1 is a diagrammatic representation of the main components of the autonomic nervous system with respect to the heart. For the purpose of this diagram, the muscarinic receptors have been labelled M1, M2 and M3 receptors, but this is not a strict classification and is probably an oversimplification [13].

9. Independence of renal function.

Most of the traditionally used muscle relaxants are dependent to a greater or lesser extent on the kidney for their elimination and hence their termination of action. In patients with impaired renal function, a prolongation of effect is usually observed.

THE DEVELOPMENT OF NEW MUSCLE RELAXANTS

All potent neuromuscular blocking agents are quarternary ammonium compounds. Less potent neuromuscular properties have been demonstrated with other positively charged organic molecules, such as tertiary sulphonium, quarternary phosphonium, quarternary arsonium, and quarternary stibonium groups [14].

The quarternary structure is analogous to the quarternary group of acetylcholine and is the principle chemical feature responsible for the interaction of quarternary molecules with receptor sites which bind acetylcholine and at which acetylcholine exerts its physiological actions. The interactions of quarternary molecules with cholinoceptors other than those at the myoneural junction produce the unwanted side effects present in most clinically used neuromuscular blocking drugs. These interactions are also responsible for the failure of a number of promising experimental non-depolarising agents, some of which possessed a brief duration of action in animals.

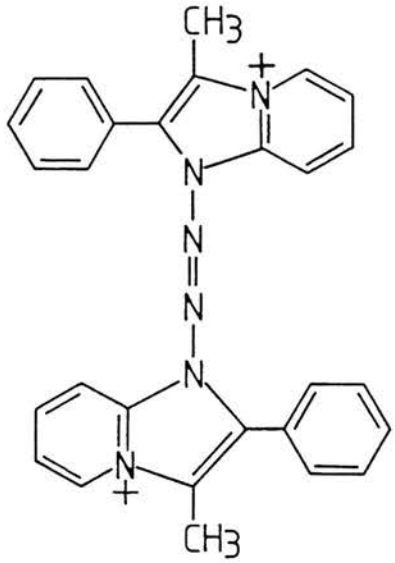
Many short acting drugs have been produced over the last three decades. All of these compounds when tested in the cat have demonstrated a spontaneous recovery from 95% blockade in less that 15 minutes.

The short acting non-depolarising neuromuscular blocking agents that have been studied may be classified on the basis of their chemical structure.

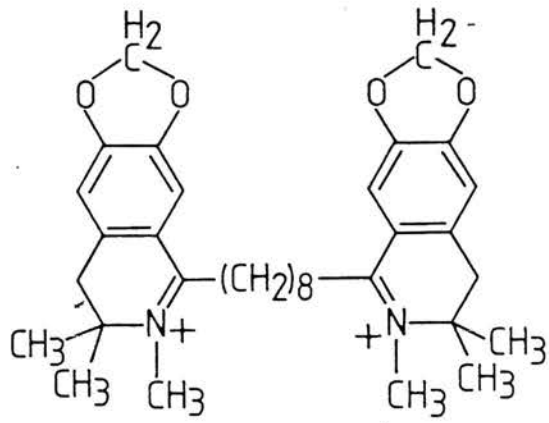
1. Arylimidazobispyridinium Compounds.
2. Bis-dihydroisoquinolinium Compounds.
3. Phenylammonium Ketothiosemicarbazones.
4. Quarternary Steroidal Compounds.
5. Non-depolarising Ester Neuromuscular Blocking Agents.
   (Figures 2 and 2A)

A series of arylimidazobispyridinium compounds studied by Bolger et al, 1972 [15], and Brittain and Tyers, 1972 [16], were shown to produce a non-depolarising type neuromuscular blockade of short duration in a wide variety of species. NADPH dependent azo reduction of one of the compounds AH8165 (fazadinium) [Figure 2] was shown to occur rapidly in liver microsomes [Bolger et al, 1972] and explained its brief action. Although a rapid onset of action was noted in man [17] recovery times were no faster than the traditionally used non-depolarising drugs [18]. Furthermore, blockade was always accompanied by a marked tachycardia and increased cardiac output. After a brief clinical exposure, fazadinium has been withdrawn from routine use.

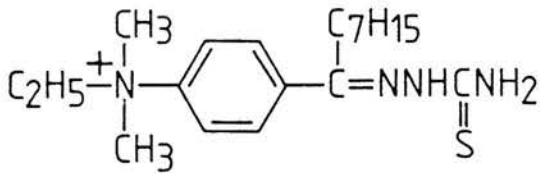
A series of bis-dihydroisoquinolinium compounds synthesised by Copp et al, 1972 [19] demonstrated a brief, potent, neuromuscular blocking action of the non-depolarising type, particularly in the dog and cat. The short action span in the cat was attributed to rapid hepatic and renal clearance of the agents from the blood stream. The duration of action of these drugs, however, was much longer in monkeys and man. In addition, considerable anticholinesterase activity was noted with 252C64 and excessive hypertension and tachycardia followed the administration of 403C65. [Figure 2].



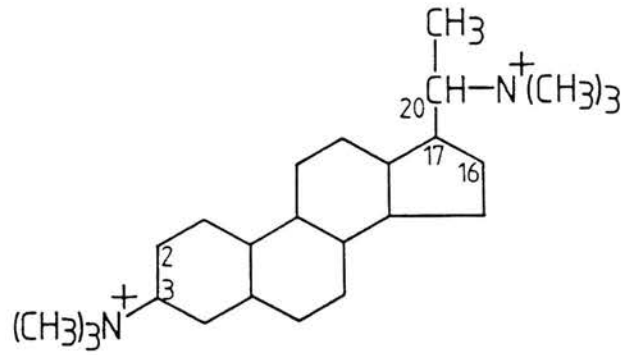
AH 8165



BW 403 C 65



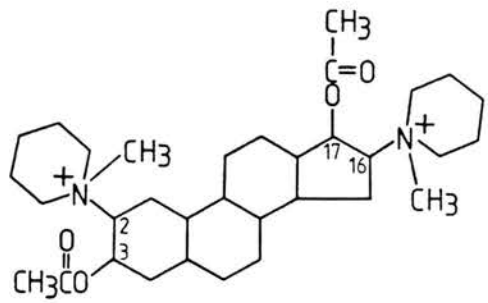
M + B 15,944 A



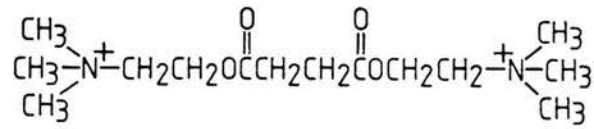
Malouétine

Figure 2

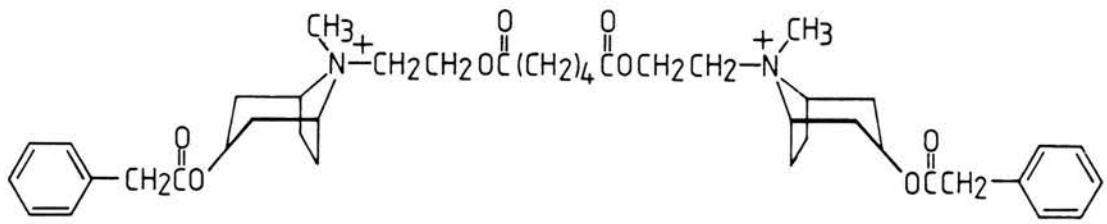
Chemical formulae for some non-depolarising neuromuscular blocking agents.



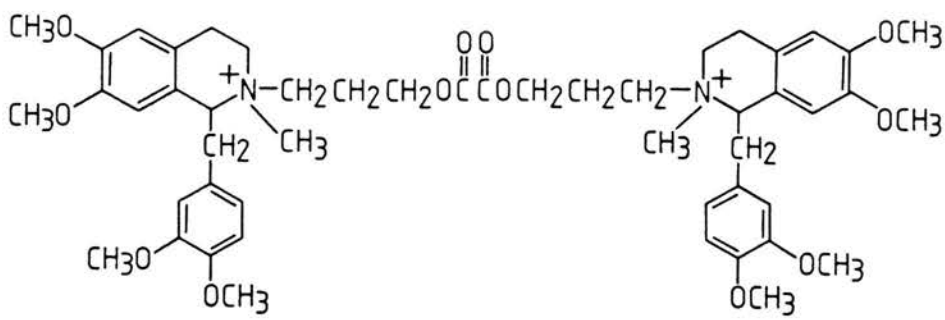
Pancuronium



Succinylcholine



DF 596



γ-oxalolaudonium

Figure 2A

Chemical formulae for some neuromuscular blocking agents.

The latter problems were attributed to a combination of blockade of the cardiac vagus and ß-adrenoceptor stimulation.

The clinical features of these dihydroisoquinolinium compounds illustrates three major undesirable actions encountered in the pharmacological evaluation of neuromuscular blocking agents.

1. Excessive Anticholinesterase Properties.
2. Blockade of Cardiac Muscarinic Receptors.
3. Poor Correlation of the Duration of Action of the Compounds in Experimental Animals with that Noted in man.

A series of mono quarternary compounds were studies by Bamford et al [20]. The phenylammonium kethothiosemicarbazones represented by M+B 15944A [Figure 2] demonstrated desirable properties in experimental animals. In all species, the neuromuscular blocking action of M+B 15944A was similar in duration to that of suxamethonium but had a non-depolarising character, reversible by anticholinesterase agents. Considerable autonomic ganglion blocking activity was noted in the cat and hypotension consistent with a ganglion blocking action also occurred in man [21].

Despite the interesting nature of the previous three groups of compounds, the most recent and by far the most productive research in the field of neuromuscular blockade today is with two groups of compounds, namely the quarternary steroids and the ester compounds.

In 1960, Quevauviller and Huu-Lainé [22] described non-depolarising neuromuscular blocking properties in a naturally occurring

bis-quarternary aminosteroid, malouétine [Figure 2]. The duration of action of this compound was similar to that of suxamethonium in the cat and chicken, but in contrast to suxamethonium the paralysis could be antagonised by anticholinesterase agents. The drug was not tested clinically because of its hypotensive effects [23], however, the fact that malouétine had a brief action stimulated the subsequent synthesis of many more mono and bis quarternary steroidal neuromuscular blocking agents.

Unfortunately, the duration of action of most of the earlier steroids was found to be considerably longer in the primates than in the cat. Also, clinical neuromuscular blockade was often accompanied by a tachycardia secondary to a vagal blocking effect.

Nevertheless, these experimental studies resulted in the introduction in 1967 of pancuronium [Figure 2A] following clinical studies by Baird and Reid [24], and more recently in the intermediate duration compound vecuronium. Vecuronium is not only shorter acting than the traditionally used agents, but following administration the patients remain haemodynamically stable.

The initial work with the ester neuromuscular blocking agents was carried out by Bovet et al, 1951 [25], the outcome of which was the development of suxamethonium [Figure 2A]. Until 1959 most of the investigations of quarternary ester compounds were concerned with esters of choline and resulted in the production of depolarising agents. In 1959, Haining et al [26] studied a series of tropanium esters. Compound DF596 [Figure 2A] produced a short duration of action when tried clinically, but as might have been expected from the tropanium quarternary grouping, the atropine like qualities of

compound DF596 resulted in excessive tachycardia.

Gamma-oxalolaudonium bromide [27] [Figure 2A] was a laudanosinium ester whose duration of action in the cat was half that of suxamethonium. Its neuromuscular blocking action could be antagonised by neostigmine. The low potency of gamma-oxalolaudonium and its tendency to cause hypotension precluded any clinical trial. The brief duration of action was thought to be due to the hydrolysis of the ester linkage; although actual hydrolysis by plasma cholinesterase was not demonstrated, the compound was noted to be unstable in solution.

The bulky ester concept (Kitz et al, 1969 [28], Ginsburg et al, 1971 [29]) states that substitution of groups larger than ethyl upon the quarternary nitrogen atom may improve the potency of non-depolarising ester neuromuscular blocking agents.

For over 15 years Savarese and colleagues at the Massachusetts General Hospital at Harvard Medical School have been designing, synthesising and evaluating a series of bisbenzylisoquinolinium diester compounds. These compounds are hydrolysed at varying rates by plasma cholinesterase.

More recently, the agents BWA785U, BWA444U, BWB1090U and BWA938U have been studied.

BWA785U [30] was an interesting compound with a short duration of action in animals and man, not dissimilar to suxamethonium. Unfortunately, it was even less potent than tubocurarine as a

muscle relaxant and had an even lower margin of safety for histamine release.

BWA444U [31] showed an intermediate duration of action and lack of cardiovascular effects in animals. However, BWA444U was also noted to release histamine in humans at the ED95 range (0.16 mg kg -1)

BWA444U and BW33A (atracurium) were produced more or less simultaneously by the same manufacturer, Burroughs-Wellcome. Clinical trials indicated the pharmacological superiority of atracurium over BWA444U in humans, a difference which would have been difficult to anticipate on the basis of animal studies. Consequently, the further development of atracurium was scheduled to continue while additional human studies with BWA444U were not planned.

The relative success of BWA444U in its own right, however, did suggest that further developmental research in the area of non-depolarising ester relaxants might yield clinically useful compounds.

During a two year spell at the Massachusetts General Hospital and Harvard Medical School, the author was engaged in research with two further benzylisoquinolinium esters, namely BWB1090U and BWA938U, which have since reached full scale clinical trials. This work will be reported in the latter part of this thesis.

Since 1980, however, the author has been involved with clinical studies of another benzylisoquinolinium compound, namely atracurium.

This thesis will describe clinical studies undertaken by the author in collaboration with colleagues at the Nuffield Department of Anaesthetics in Oxford; Harvard Medical School and the Massachusetts General Hospital in Boston, USA; and the University Department of Anaesthetics, Southampton.

PART I

CHAPTER 1

ATRACURIUM

Development

While Savarese and colleagues continued work on the benzylisoquinolinium esters, Stenlake and colleagues in the United Kingdom were working with a similar group of compounds. Their philosophy, however, was that quarternary esters wholly dependent on plasma pseudocholinesterase or liver acetylase metabolism for biodegradation were unlikely to provide the key for the much sought after short acting muscle relaxant.

In an entirely unrelated study they observed that a nitrogenous constituent of a plant leontice leontopetalum was a simple 1-benzyltetrahydroiso-quinoline quarternary salt which underwent unexpectedly fascile degradation in mild alkali by the well known Hofmann elimination pathway. This observation prompted Stenlake to the possibility of designing a novel class of short acting neuromuscular blocking agents capable of rapid biodegradation by this purely chemical pathway activated solely by the mild alkaline conditions which are obtained at physiological pH.

Four series of isoquinoline type structures were subsequently synthesised. All were designed to undergo the Hofmann elimination in which a quarternary nitrogen group degrades to a tertiary amine at relatively high temperature and alkaline pH.

The benzylisoquinolinium structure of the quarternary group of atracurium was chosen for a number of reasons. This group when quarternised provides good neuromuscular blocking potency when a chain of appropriate length is interposed between two of the structures. Laudexium, a now obsolete relaxant which achieved slight popularity during the mid 1950s, is an early example of such a structure. The quarternary group of laudexium is the quarternary form of laudanosine, which also appears in atracurium. The chain in atracurium is longer (n = 13 vs 10 atoms in laudexium) and includes two ester linkages. It is, however, the reversed ester groups in atracurium that enhances susceptibility to a Hofmann reaction [Figure 3].

The benzylisoquinoline structure (laudanosine) has long been known to confer neuromuscular blocking potency without vagolytic property, hence it was felt that synthesis of molecules of this type would avoid the vagolytic side effect responsible for the demise of BW403C65. In the atracurium series the ratio of neuromuscular blocking potency to vagolytic property was compared. The safety ratio was greatest in atracurium where n=5 in the central chain carbons. Neuromuscular blocking potency, however, was greatest when n=6. Thus a compound with lesser potency was chosen because of its greater safety regarding potential vagolytic side effects. The histamine releasing potencies of the two compounds, however, were not carefully compared. Since potential histamine release is the only prominent side effect inherent in benzylisoquinoline-type neuromuscular blocking agents this may have been an oversight in the pre-clinical evaluation of the series. (The n=6 compound could possibly have been the better of the two).

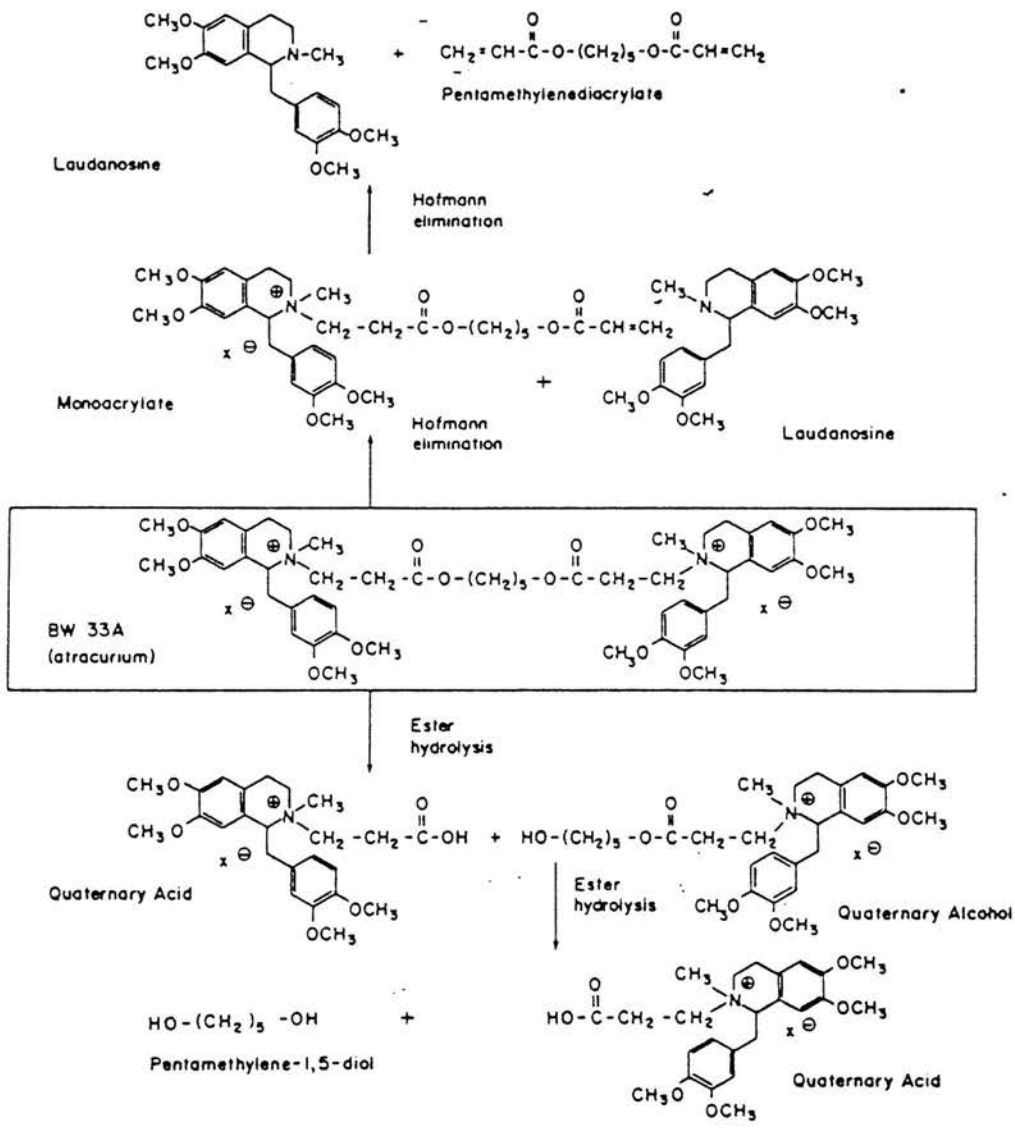


Figure 3

Proposed pathways of inactivation of atracurium by Hofmann elimination reaction and Ester hydrolysis.

Promotion of the Hofmann reaction was achieved by spacing the quarternary nitrogen two carbons away from the ester group. These two molecular features both withdraw electrons from the beta-carbon atom to allow the elimination of a proton to occur under physiological conditions. In the atracurium series the Hofmann reaction proceeds rapidly to completion resulting in the breakdown products pentamethylene diacrylate (the central chain) and laudanosine (the quarternary group).

In studies of the degradation of atracurium in-vitro it was observed that the process occurs more rapidly in plasma than in buffer suggesting that another route of degradation (ester hydrolysis), possibly enzyme catalysed, occurs in the plasma. Molecular fragmentation by these two routes is the unique feature of atracurium which distinguishes the drug from all other non-depolarising relaxants, and which is the underlying basis for much of its clinical and basic pharmacology.

Animal Pharmacology

The initial animal studies were reported by Hughes and Chapple [32]. In a chick biventer-cervicis preparation, atracurium produced a neuromuscular block typical of a non-depolarising drug.

In chloralose anaesthetised cats, intravenous doses of 0.25 or 0.5 mg kg -1 were sufficient to produce complete neuromuscular paralysis of the tetanic and single twitch responses of the gastrocnemius muscles within one to two minutes. Full recovery of both responses occurred within 37 minutes. Neuromuscular paralysis was also antagonised by neostigmine 0.05 mg kg -1 iv.

In the dog, cat and monkey, the potency and duration of atracurium was remarkably constant, a unique feature. Atracurium was slightly more potent that tubocurarine in the cat and approximately equipotent in the dog and monkey.

In the chloralose anaesthetised cat, vagal blockade only became apparent after doses of 2 mg kg -1 iv, that is, at eight times the full neuromuscular paralysing dose. Sympathetic blockade was only evident after supramaximal doses of 4 mg kg -1 when systemic arterial pressure was reduced by a mean of 34%. Rhesus monkey studies demonstrated similar results.

In all species, the only side effect of any note was histamine release. At a dose of 2 mg kg -1 atracurium, evidence of histamine release was obtained in two chloralose anaesthetised dogs. H1 and H2 receptor antagonists (mepyramine 10 mg kg -1 and burimamide 15 mg kg -1) reduced the hypotension caused by atracurium 2 mg kg -1 (eight times the full paralysing dose) from 52% to 16% and from 42% to 25% respectively in each dog.

Preliminary Studies in Man

Hunt, Hughes and Payne [33] were the first to report studies in anaesthetised man. They reported than an intravenous dose of atracurium 0.2 mg kg -1 was sufficient to cause complete paralysis of the tetanic responses of the adductor policis muscle. Blockade was of medium duration and readily antagonised by neostigmine. No cardiovascular changes were observed at this dose.

A dose of 0.6 mg kg -1 atracurium also produced minimal changes in blood pressure and heart rate. In two patients receiving this dose, tracheal intubation was performed within one minute of receiving the drug and full block was completely reversed after 10 and 20 minutes respectively by neostigmine.

A lack of cumulative effects in patients given multiple incremental doses was noted.

Atracurium - Clinical Studies

Payne and Hughes [34] reported the first formal evaluation of atracurium in anaesthetised man. A quantitative assessment of the time course of blockade showed that the onset of complete block was significantly shortened when the dose was increased from 0.3 to 0.6 mg kg -1 iv.

The tetanic contraction of the adductor policis muscle following supramaximal stimulation of the ulnar nerve at the wrist every 12 seconds with tetanic bursts of 50 Hz for one second was recorded. Onset (n=3) was reported to be 1.1 minute at 0.6 mg kg -1 using this mode of stimulation. In three patients good intubating conditions were provided in 50 to 55 seconds.

This report of a rapid onset of action stimulated the author to carry out the study in the next chapter.

CHAPTER 2A

ATRACURIUM: ITS SPEED OF ONSET - A COMPARISON WITH SUXAMETHONIUM

Many studies have evaluated the speed of onset of muscle relaxants. In some, judgement of paralysis has been largely subjective using clinical criteria such as jaw relaxation, ease of tracheal intubation and the absence of response to laryngoscopy and intubation (Harrison and Feldman, 1981 [35]; Hey, 1973 [36]). Despite all efforts to eliminate bias, ease of intubation depends not only upon the degree of neuromuscular blockade but also upon the depth of anaesthesia, the anatomical configuration of the patient and not least upon the skill of the anaesthetist. An objective comparison of the rate of onset of neuromuscular blocking drugs can best be obtained by recording the response of a muscle to stimulation of its motor nerve.

In this study the speed of action of atracurium was monitored using a repeated 2 Hz train-of-four stimulus and compared with suxamethonium. This comparison was chosen since the fast onset time reported in Payne and Hughes' [34] preliminary study had suggested to the investigators that this new non-depolarising muscle relaxant could well be used as an alternative to suxamethonium.

Methods

Forty healthy patients undergoing minor dental surgery requiring intubation were studied. Patients who gave informed consent to the trial were between 18 and 45 years of age. Any patient receiving

concurrent medication apart from the contraceptive pill or in whom pregnancy was suspected was excluded. Ethical consent for this study was obtained and the trial was conducted with the authority of a clinical trials certificate issued by the Committee on the Safety of Drugs.

After a premedication with papaveretum and hyoscine a modified Elcomatic transducer (Armstrong, Goat and Loach, 1977) [37] was attached to the patient's dominant hand and positioned to achieve maximal mechanical response to thumb adduction. Anaesthesia was induced with fentanyl 3 μg kg -1 and thiopentone 5 mg kg -1 and maintained with nitrous oxide and oxygen; ventilation of the lungs was assisted by a face mask. Stimulation of the ulnar nerve at the wrist was carried out by cutaneous electrodes using a Grass S48 nerve stimulator with an SIU5 isolation unit. The stimulus width was 0.2 milliseconds. Once it was certain that the stimulus was supramaximal, the stimulator was set to produce a 2 Hz train-of-four stimulus repeated once every 12 seconds. The mechanical response to nerve stimulation was measured by the transducer and displayed on an Elcomatic recorder.

The patients had been randomly selected to receive either atracurium 0.6 mg kg -1 or suxamethonium 1 mg kg -1 diluted to the same volume for injection. All drugs were administered via a peripheral indwelling needle and the relaxant injected at the time of nerve stimulation, the start of injection coinciding with the first stimulus of the train. The time from administration of the muscle relaxant to the first depression of any response in the train was noted. This was called the initial onset time. The time

at which 100% block of all four peripheral twitches occurred was also noted. At this time no recorded response was obtained from the stimulus. Tracheal intubation was attempted by the author at 100% block using the nasal route under direct vision.

During induction of anaesthesia the ECG was monitored continuously and changes in heart rate noted. After intubation 1% halothane was added to the anaesthetic; this concentration was reduced during surgery to allow a rapid return of consciousness at the end of the procedure. Neuromuscular monitoring was not continued during surgery and at the completion of the operation those patients who had received atracurium were given neostigmine 2.5 mg with atropine 1.2 mg. The time of administration of these drugs was noted and reversal of paralysis shown by the ability of the patient to maintain a head lift for five seconds (Dam and Guldmann, 1961) [38].

After surgery all patients received standard analgesic and anti-emetic drugs and were interviewed at 24 hours. They also received a questionnaire which they were asked to return after 72 hours in order to detect any major problems.

Results were analysed using the unpaired two tailed student T test. The results are summarised in Table 1. There were no significant differences between the groups with regard to age and weight. The initial onset of neuromuscular block was faster by almost 15 seconds in those patients receiving suxamethonium and this difference in initial onset time was significant ($p < 0.01$).

	No of patients	Mean age (yr)	Mean wt (kg)	Mean initial onset time	Mean time to 100% block of T1	Male
Suxamethonium	20	24.9 (SD 5.4)	64.9 (SD 11.9)	34.8 (SD 11.6)	69.9 (SD 18.5)	10
Atracurium	20	24.3 (SD 6.0)	63.8 (SD 11.1)	49.8* (SD 8.9)	129.0** (SD24.3)	7

Table 1

Patient characteristics and neuromuscular blockade data. Significance (Students T test).

* $P < 0.01$ ** $P < 0.001$

One hundred per cent block (absence of all four twtches) occurred in all patients in both groups. A highly significant difference was seen in the time to 100% block with atracurium taking nearly twice as long as suxamethonium.

Changes in heart rate were minimal in both groups and there was no significant difference between the two groups (Table 2). No specific problems were encountered after surgery in those patients receiving atracurium, although 11 patients in the suxamethonium group complained of moderate to severe muscle pains.

Discussion

While Payne and Hughes [34] reported the mean onset of maximal effect to be 1.2 minutes at a dose of 0.6 mg kg -1. This study found the time to maximal effect was just over two minutes (129 seconds). The discrepancy between these results could be explained by the mode of stimulation used. Although the response to tetanic stimulation is a more sensitive indication of receptor occlusion than either the single twitch response or the train-of-four, tetanic stimulation may distort subsequent neuromuscular transmission (Lee and Katz, 1980) [39] and increase the apparent degree of neuromuscular blockade. The train-of-four stimulus was chosen for this study since it is slightly more sensitive to receptor occlusion than is the single twitch. It also lacks the equivalent of post-tetanic distortion of a subsequent muscle response and is therefore suitable for repeated application up to once every 10 seconds.

	No Patients	No with heart rate change	
		>10 beats min -1	<10 beats min -1
Suxamethonium	20	2	2
Atracurium	20	2	2

Table 2

Heart rate change

The use of volatile anaesthetic agents was avoided until after monitoring had been discontinued because of the well documented interaction between volatile and neuromuscular blocking agents (Waud and Waud, 1979) [40}.

In conclusion, atracurium appeared to be a relatively potent competitive neuromuscular blocking agent. Although its onset of blockade seemed fast with 100% block of T1 occurring in just over two minutes, this was found to be significantly slower than the action of suxamethonium. No peri-operative problems were encountered.

CHAPTER 2B

SINGLE TWITCH AND TRAIN-OF-FOUR RESPONSES FOR ATRACURIUM AND VECURONIUM

It became apparent at the First International Symposium on Atracurium in 1982 that workers were reporting different onset times. It was obvious that the onset time of atracurium was not only dose dependent but that the results were affected by the nature of the anaesthetic and the mode of peripheral nerve stimulation used to monitor the block.

Two common methods of evaluating responses to muscle relaxant administration are evoked single twitch nerve stimulation and evoked train-of-four nerve stimulation. Single twitch stimulation at 0.15 Hz has been found to be clinically relevant for determining adequate neuromuscular blockade for tracheal intubation and abdominal surgical relaxation [41]. Train-of-four stimulation (2 Hz for two seconds once every 10 -12 seconds) offers the advantage of being able to monitor recovering neuromuscular blockade without the need to establish a control response. In addition, it has been shown for the older relaxants (tubocurarine, metocurine and pancuronium) that when the single twitch returns spontaneously to control height the mean train-of-four ratio is less than 50% [42]. This study was undertaken to define for the new relaxants atracurium and vecuronium which method of stimulation is clinically most useful.

Methods

ASA Class 1 and 2 patients aged between 18 and 59 years were studied. Each patient gave written institutionally approved informed consent to the study. All patients were premedicated one hour preoperatively with diazepam 0.15 mg kg -1 PO and morphine 0.1 mg kg -1 i.m.

Anaesthesia was induced with fentanyl (6 ug kg -1) and thiopentone (4-8 mg kg -1). The trachea was intubated without a relaxant following the use of topical anaesthesia to the vocal cords and trachea with a 4% lignocaine spray. Ventilation was controlled to maintain an end tidal CO2 in the range of 4-5 kilopascals. Anaesthesia was maintained with N2O/O2 at a ratio of 2:1. Once the mechanical response of the adductor pollicis muscle to ulnar nerve stimulation had been stable for 10 minutes, a bolus dose of relaxant was administered and onset time to maximum block and duration to 95% recovery were recorded. The dosage groups were as follows (mg kg -1): atracurium 0.1, 0.2, 0.4 and 0.5; vecuronium 0.02, 0.04, 0.06 and 0.1. For each drug half of the subjects were monitored using single twitch responses at 0.15 Hz and half using train-of-four responses at 2 Hz for two seconds repeated every 10 seconds. These responses were generated by stimulating the ulnar nerve at the wrist using square wave supramaximal pulses from a Grass S44 nerve stimulator and recording the mechanical response of the adductor pollicis muscle on a Grass polygraph. In the single twitch groups when the response had returned to control levels a train-of-four was performed and the ratio documented.

Dose response curves were generated for each group using the method of Litchfield and Wilcoxon [43]. Results were analysed using a students T test where appropriate. A p value <0.05 was considered statistically significant. Values expressed are means +/- standard error.

Results

Dose response curves for single twitch and train-of-four stimulation for atracurium showed a good fit and parallelism but ED95 values differed significantly.

The same was true for vecuronium. Single twitch ED95 for atracurium was 0.26 mg kg -1 and 0.20 mg kg -1 for train-of-four. Single twitch ED95 for vecuronium was 0.056 mg kg -1 while for train-of-four it was 0.037 mg kg -1.

The neuromuscular response data is displayed in Table 3 for atracurium and Table 4 for vecuronium.

Conclusion

In this study train-of-four stimulation was found to be more sensitive in detecting changes in neuromuscular function for both atracurium and vecuronium as shown by lower ED95 values, shorter onsets and longer durations of action. Clinically, when assessing potency and time to good intubating conditions, single twitch data yield more useful information. In assessing recovery, when the single twitch returned to control the train-of-four ratio for both drugs is greater than 75%. Thus for assessing recovery from neuromuscular blockade train-of-four nerve stimulation remains

Dose mg kg -1	no	Stimulation	% Block	Onset (min)	95% Recovery (min)
0.2	10	ST	73.2±11.1	6.6±0.4	33.5±2.9
	10	TO4	94.1±0.3*	3.9±0.5*	44.1±2.4*
0.4	10	ST	98.9±0.7	3.9±0.5	51.1±2.7
	10	TO4	99.8±0.1	1.7±0.2*	63.5±2.7*
0.5	10	ST	100	2.3±0.2	59.1±1.9
	10	TO4	100	1.7±0.1*	67.6±5.4**

* P at least <0.05 ** T4/T1 at 95% ST = 0.69±0.04

ST = single twitch TO4 = Train-of-four

Table 3

Atracurium - Pharmacodynamic data

Dose mg kg -1	no	Stimulation	% Block	Onset (min)	95% Recovery (min)
0.04	10	ST	72.6±14.1	5.3±0.5	26.7±3.7
	10	T4	97.6±1.4*	3.3±0.6*	31.4±1.8*
0.06	10	ST	99.1±0.7	4.0±0.5	42.5±3.2
	10	T4	99.9±0.1	2.7±0.2*	35.7±1.2*
0.10	10	ST	100	3.8±0.3	48.4±3.7
	10	T4	100	1.5±0.1*	63.3±7.6*

* P at least < 0.05 ** T4/T1 at 95% St = 0.60±0.06

Table 4

Vecuronium - Pharmacodynamic data

superior to single twitch.

In this thesis, both mechanomyographic and electromyographic approaches to neuromuscular monitoring are used. The technique selected was by necessity dictated by the availability of equipment in the particular department the author was working. It should be noted, however, that no attempt is made to compare pharmacodynamic parameters generated by these two different modes of neuromuscular monitoring.

The next chapter will focus attention on haemodynamic stability, another of Savarese and Kitz criteria for the ideal neuromuscular blocking agent. The inter-relationship between onset time and haemodynamic stability in the clinical use of atracurium will become apparent in subsequent studies.

CHAPTER 3

ATRACURIUM: CLINICAL STRATEGIES FOR PREVENTING HISTAMINE RELEASE AND ATTENUATING THE HAEMODYNAMIC RESPONSE

Pre-amble

Atracurium demonstrates a wide margin of safety for cardiovascular effects in animals. Dogs appear to be the most sensitive to the cardiovascular effects of atracurium, but even so, eight times the full paralysing dose (2 mg kg -1) was required to cause a significant fall in mean arterial blood pressure. This hypotensive effect was thought to be due to histamine release.

The original report by Payne and Hughes [34] in man was consistent with the haemodynamic stability found in animals. Other workers also noted little or no cardiovascular changes in dosages up to 0.5-0.6 mg kg -1 [44-46]. Indeed, in our initial study in Oxford we found no significant change in heart rate.

Basta [47] and colleagues using direct monitoring of arterial pressure also noted that at all doses up to and including two times the ED95 (0.4 mg kg -1) atracurium produced no statistically significant changes in arterial pressure or heart rate when paired T test comparisons were made between control values and maximum changes from control values within the first 10 minutes after the administration of atracurium. However, with very careful observation these workers noted that at 2.5 (0.5 mg kg -1) and three times (0.6 mg kg -1) the ED95 dose there were mild decreases in arterial pressure to 86.7% and 79.5% of control levels

respectively. There were also mild increases in heart rate to 105.5% and 108.3% of control levels respectively. Changes in arterial pressure were statistically significant only at the 0.6 mg kg -1 dose ($p < 0.05$). Heart rate changes were significant for both the 0.5 mg kg -1 and 0.6 mg kg -1 doses ($p < 0.05$). These changes were of short duration, the maximal effect occurring 1 - 1.5 minutes after drug injection with a total duration of less than five minutes. These cardiovascular changes were associated with slight facial flushing.

Previous studies with tubocurarine [48] and with the experimental neuromuscular blocking agents BWA785U [30] and BWA444U [31] showed: (1) that there was a dose dependent release of histamine, and (2) that the level of plasma histamine concentration correlated with heart rate and arterial blood pressure changes following administration of these drugs. It also appeared from these studies that the dose of neuromuscular blocking agent which increased plasma histamine to about 200% of control values resulted in clinically and statistically significant changes in heart rate and arterial pressure in healthy patients.

In another study, Basta [49] and colleagues observed a similar effect with atracurium.

Using a sensitive isotope radioenzymatic assay technique for histamine, they compared the histamine releasing potencies of atracurium, dimethyltubocurarine and tubocurarine. They found that the ability of atracurium to release histamine relative to its neuromuscular blocking potency was approximately one half that of

dimethyltubocurarine and less than one third that of tubocurarine.

Previously, the lack of a sensitive and reliable assay for plasma histamine had made it difficult to document the role of the histamine so released in drug induced cardiovascular changes. The development of the radioenzymatic technique used above (Snyder, Baldasserarini and Axelrod, 1966 [50]; Beavan, Jacobsen and Horakova, 1972 [51]; Beavan and Horakova, 1978 [52]; Iverson, Iverson and Snyder, 1979 [53]) and its improvement by the discovery of renal histamine methyltransferase (Shaff and Beavan, 1979 [54]) have greatly enhanced the ability to detect histamine clinically in important situations.

Using the above histamine assay the author elected to investigate clinical strategies for preventing the histamine release by atracurium and thereby attenuating the associated haemodynamic response.

A number of clinical strategies have been used to attenuate the adverse reactions to the histamine release by certain drugs. It has been shownthat even small time differences in the rate of administration of intravenous agents can lead to significant changes in the likelihood of generating clinically significant histamine release (Rosow et al, 1980 [30]; Basta et al, 1981 [55]). Furthermore, there is abundant evidence suggesting that this prophylactic use of H1 and H2 antagonists can also attenuate the haemodynamic responses to certain histamine releasing drugs including morphine (Philbin et al, 1981 [56]), BW785U (Rosow et al,

1980 [30]) haemaccel (Lorenz et al, 1980 [57]) and tubocurarine (Moss et al, 1982 [10]).

This study was designed to determine the effects of a rapid bolus dose of atracurium 0.6 mg kg -1 on arterial pressure, heart rate and plasma histamine concentration and to compare these values with those obtained by (a) giving the same dose of atracurium slowly over 75 seconds, and (b) pretreating with H1 and H2 antagonists.

Patients and Methods

Twenty seven (ASA Class 1 or 2) patients gave institutionally approved informed consent to the study and were assigned to one of three sub-groups at the discretion of the investigator. All the patients were aged between 18 and 60 years, weighed 45-110 kg and were undergoing elective surgical procedures. Any patient with recent exposure to antihistamines or antidepressants was excluded from the trial.

Premedication consisted of morphine 0.1 mg kg -1 i.m. and diazepam 0.2 mg kg -1 by mouth. Anaesthesia was induced with fentanyl 3-4 ug kg -1 and thiopentone 5 mg kg -1 intravenously and maintained with nitrous oxide in oxygen by a face mask. Heart rate (by tachograph), ECG and intra-arterial pressure were recorded continuously on a Grass model 7 polygraph. After a stable 10 minute baseline period a single bolus of atracurium 0.6 mg kg -1 was administered over five seconds to patients in group 1. Patients in group 2 received the same dose of atracurium slowly (over 75 seconds). The patients in group 3 were pre-treated with cimetidine 4 mg kg -1 and chlorpheniramine 0.1 mg kg -1

intravenously 15 minutes before induction. They were then given atracurium 0.6 mg kg -1 as a five second bolus. Maximum changes in heart rate and arterial pressure were noted. Intubation of the trachea was delayed for 10 minutes following the administration of atracurium to avoid a cardiovascular response to laryngoscopy.

Arterial blood samples were drawn immediately before the injection of atracurium and at two and five minutes after injection; these samples were analysed for histamine by an isotope radioenzymatic assay technique (Moss et al, 1981 [10]). End tidal carbon dioxide concentration was kept within the normal limits during the course of the study.

Results

The results are summarised in Tables 5 and 6: the data displayed are mean values. The changes in mean arterial pressure and heart rate are the maximum changes that occurred in the 10 minutes following the administration of atracurium calculated as a percentage of the base line values. The absolute values at base line, two minutes and five minutes for mean arterial pressure and heart rate are displayed in parenthesis in Table 5. Figure 4 illustrates the mean changes in plasma histamine concentration in the three groups, and figure 5 the changes in plasma histamine concentration in the individual patients. Patients in group 1 demonstrated a significant increase in plasma histamine concentration at two minutes ($p < 0.05$; analysis of variance). Seven patients (77%) in this group showed clinical signs of histamine release with the development of mild to moderate erythema over the trunk and face. The changes in heart rate and arterial

	no	Map* % of baseline	HR* % of baseline
Group I 5 sec bolus	9	82.1±6.4% (78.4/63.5/74.8)*	108.6±4.6% (65/70.1/64.1)*
Group II 75 sec dose	9	95.7±2.6% (75.1/71.8/73.5)*	97.7±2.3% (66/64.2/62.4)*
Group III H1 + H2 prophylaxis	9	96.2±2.2% (65.7/63.0/65.2)*	102.3±2.2% (60.2/62.1/60.4)*

MAP = mean arterial pressure
HR = heart rate

* Actual values at baseline, 2 and 5 minutes for mean arterial pressure and heart rate are shown below in brackets. The units are mm Hg and beats per minute respectively.

Table 5

Effect of 0.6 mg kg -1 atracurium on mean arterial pressure and heart rate

	PLASMA HISTAMINE pg ml -1		
	CONTROL	+2 MINS	+5 MINS
Group I 5 sec bolus	715.3±93.6	1415.1±203.5*	1086.3±237.9
Group II 75 sec slow injection	954.1±131.7	949.9±154.1	939.4±162.7
Group III H1 + H2 prophylaxis	751.1±113.3	1107.0±160.4	854.1±146.0

* $P < 0.05$ (one way analysis of variance)

Table 6

Effect of 0.6 mg kg -1 atracurium on plasma histamine levels

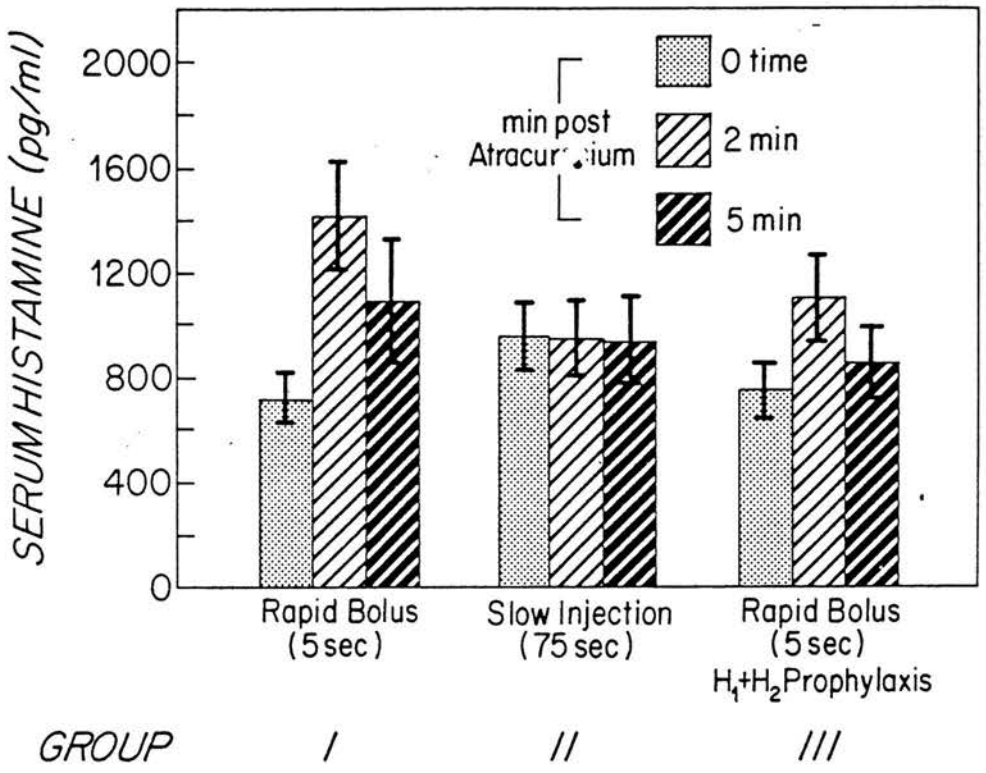


Figure 4

Mean plasma histamine concentrations in the three groups at control, two minutes and five minutes following administration of atracurium 0.6 mg kg -1 i.v.

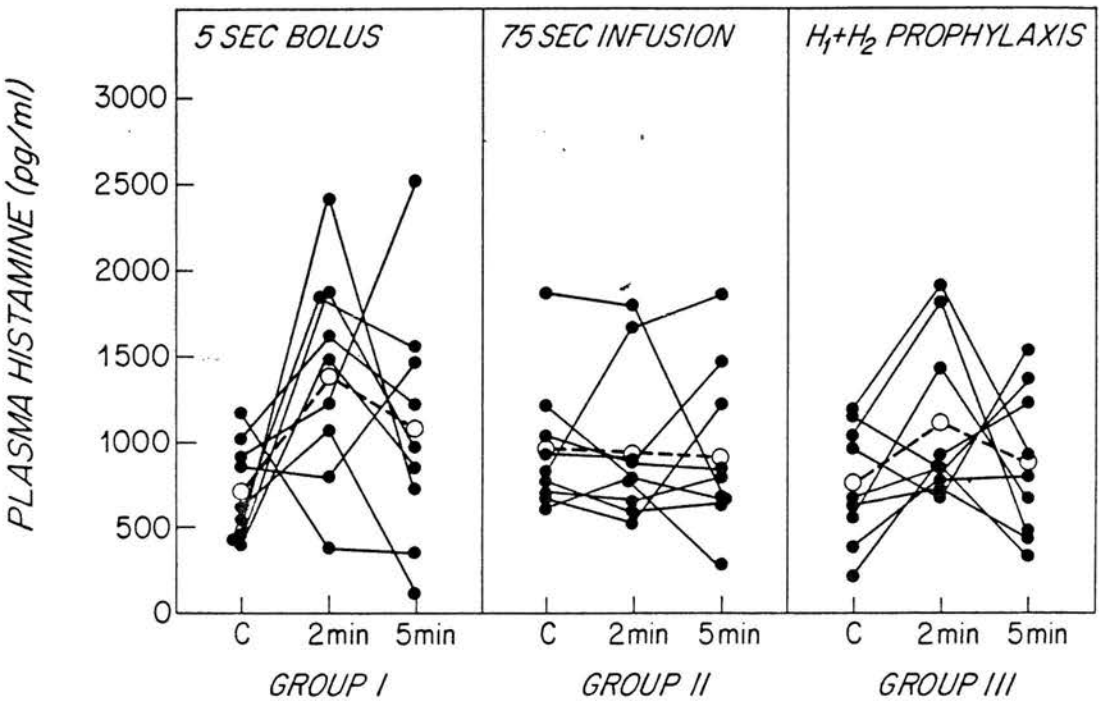


Figure 5

Plasma histamine concentrations in individual patients in the three groups at control, two minutes and five minutes following administration of atracurium 0.6 mg kg -1 i.v.

pressure in this group were all transient and had almost returned to base line values by five minutes. Figure 6 illustrates the transient haemodynamic response observed following a bolus of 0.6 mg kg -1 of atracurium.

A moderate increase in histamine concentration at the two minute sample in group 3 approached but did not reach a statistical significance $0.1 > p > 0.05$.

None of the patients in groups 2 or 3 showed clinical signs of histamine release nor any haemodynamic changes of statistical or clinical significance.

Discussion

All basic compounds may disrupt mast cells and cause release of histamine if the dose is large enough (Paton, 1957 [58]). Among the neuromuscular blocking drugs this effect appears to be most pronounced with d-tubocurarine, possibly because of its free hydroxyl groups which are thought to enhance histamine releasing potency (Buckett and Frisk-Holmberg, 1979 [59]).

Simple histamine release by many drugs including neuromuscular blocking agents does not involve immunological mechanisms, but rather a non-specific displacement of histamine and possibly other vaso-active substances from vascular mast cells. The transient nature of the changes in arterial pressure and heart rate following a bolus dose of atracurium 0.6 mg kg -1 i.v. and the significant increases in plasma histamine concentration would seem to confirm that this haemodynamic response results from release of endogenous

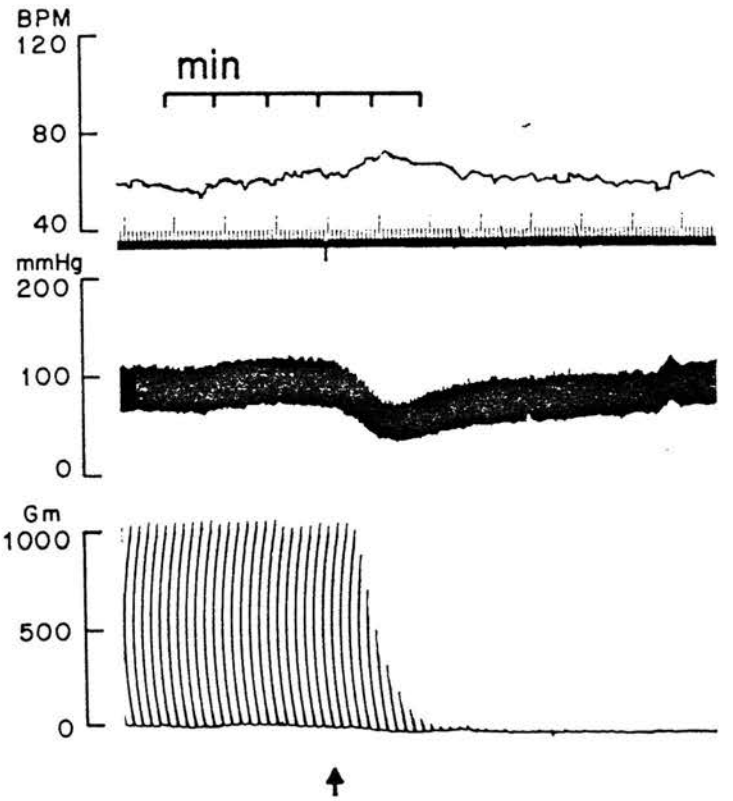


Figure 6

The transient haemodynamic response occasionally observed following a bolus of 0.6 mg kg -1 of atracurium. Illustrated are the heart rate (by tachograph), intra-arterial blood pressure, and the single twitch at 0.15 Hz. Atracurium 0.6 mg kg -1 was injected as a rapid bolus at the arrow mark to a patient under balanced anaesthesia.

histamine. Atracurium has a very high margin of safety for ganglionic blockade (Hughes and Chapple, 1981 [32]), the duration of which tends to parallel neuromuscular blockade (Savarese, 1976 [60]). Thus a hypotensive response to atracurium, mediated by a ganglionic blockade, would seem unlikely.

It appears that small differences in the plasma concentration of a histamine releasing drug can produce large changes in the amount of histamine liberated. In this study slowing the administration of atracurium appeared to prevent the increase in histamine concentration and subsequent change in haemodynamic variables.

The wide variety of agents with which combined histamine receptor blockade is effective demonstrates the clinical importance of histamine release as well as the effectiveness of combined blockade. In the present study the patients receiving a rapid bolus of atracurium intravenously who were pre-treated with H1 and H2 antagonists did show an increase in plasma histamine concentration. The haemodynamic response, however, was markedly attenuated.

It should be noted that not all patients will release histamine at high doses of atracurium as indicated by the large standard error. However, as the size of the bolus dose increases there is a greater likelihood of this response occurring (Basta et al, 1981, [55]). Although this transient haemodynamic response is probably of little clinical significance in healthy patients the effect may be more important in the haemodynamically unstable patient who is hypovolaemic or has cardiovascular disease.

In conclusion, it appears that the release of histamine by large bolus doses of atracurium (0.6 mg kg -1) and any associated haemodynamic response can be prevented by administering the dose slowly (over 75 seconds). In addition, the haemodynamic response to a rapid (5 second) bolus can be minimised by pre-treatment with H1 and H2 receptor antagonists such as chlorpheniramine and cimetidine given intravenously 15 minutes before atracurium.

Rapidity of onset and cardiovascular stability were two characteristics of the ideal muscle relaxant described by Savarese and Kitz. In the previous studies, the author has examined both of these aspects with regard to atracurium. The clinical inter-relationship between these two characteristics are studied in more detail in the subsequent paper.

CHAPTER 4

THE CLINICAL PHARMACOLOGY OF HIGH DOSE ATRACURIUM

While atracurium appears to have come closer to the ideal in terms of duration of action and cardiovascular stability than the earlier agents, the onset time is still significantly slower than that of suxamethonium in the clinical dose range [61]. For rapid sequence induction, suxamethonium remains the drug of choice.

Other workers have shown that the speed of onset of atracurium is dose dependent [34, 47]. Theoretically, its administration in very high dose should provide a more rapid onset of action without the excessively prolonged duration of action that may be observed following high doses of the longer acting agents. Indeed, Waldburger, Nielsen and Mulroy, 1984 [62] have suggested that atracurium 0.8 mg kg -1 will allow satisfactory intubating conditions in all patients within 90 seconds of injection without prolonged blockade or significant variation in haemodynamic indices. This, of course, is at variance with our previous study which showed that atracurium at 0.6 mg kg -1 causes a moderate reduction in mean arterial pressure as a result of histamine release [63], an effect which may be prevented by injecting the drug slowly over 75 seconds or by pre-treating with i.v. H1 and H2 antagonists.

More recently, it has been demonstrated that the speed of onset and degree of blockade of competitive neuromuscular blocking drugs may be enhanced if the agents are administered in divided doses

(Schwartz et al, 1985 [64]; Mehta et al, 1985 [65]). From these data it is postulated that an initial sub-paralysing dose (priming dose) may occupy 70-75% of cholinoceptors without causing unpleasant symptoms in awake patients. Tracheal intubation might then be performed more rapidly after a second larger dose that increases receptor occupancy quickly to the 90-95% level necessary for paralysis. Furthermore, priming may improve the haemodynamic profile by releasing less histamine as divided dosing may have the same effect as slow injection.

This study was designed to determine the safety and efficacy of administering atracurium 0.8 mg kg -1 to healthy patients. The speed of onset and the haemodynamic response were studied in an attempt to find modes of administration that would combine fast onset times with haemodynamic stability. Some of the data are compared with data obtained using the same investigative procedure but with the lower dose of 0.5 mg kg -1, the highest recommended dose in the United States.

Patients and Methods

Fifty six (ASA Class 1 or 2) patients gave informed consent for the study and were assigned to one of seven sub groups at the discretion of the investigator. The patient criteria were the same as for the previous study.

Premedication consisted of morphine 0.1 mg kg -1 i.m. and diazepam 0.2 mg kg -1 orally. In groups 1 to 5 anaesthesia was induced with fentanyl 5 ug kg -1 and thiopentone 5 mg kg -1 i.v. The trachea was intubated without the use of a neuromuscular blocking drug,

additional increments of thiopentone being administered when appropriate to facilitate this procedure. Ventilation of the lungs was controlled to produce normocapnoea and anaesthesia was maintained with nitrous oxide in oxygen. Volatile agents were not used. Heart rate, ECG, radial arterial pressure and the single twitch adductor response at the thumb were recorded continuously on a Grass polygraph. A Grass S44 stimulator with subcutaneous needle electrodes and a Statham strain gauge were used. The single twitch was produced at a frequency of 0.15 Hz with a stimulus duration of two milliseconds. After a stable base line period (10 minutes) a bolus dose of atracurium 0.8 mg kg -1 was administered over five seconds to patients in groups 1 and 4. This dose was given over 30 seconds to patients in group 2 and over 75 seconds to patients in group 3. Group 5 patients received a priming dose of 0.08 mg kg -1 followed six minutes later by a 0.72 mg kg -1 bolus. Patients in group 4 were pre-treated with cimetidine 4 mg kg -1 and chlorpheniramine 0.1 mg kg -1 i.v. 15 minutes before induction. Maximum changes in heart rate and arterial pressure were noted. Arterial blood samples were drawn immediately before administration of the atracurium and at two and five minutes after injection. These samples were analysed for histamine concentration by a radioenzymatic assay technique (Moss et al, 1981 [48]).

In groups 6 and 7 anaesthesia was induced with thiopentone 5 mg kg -1 only. Group 6 patients received a priming dose of atracurium 0.08 mg kg -1 five minutes before induction followed by a bolus of 0.72 mg kg -1 30 seconds after induction. Group 7 patients received a bolus of atracurium 0.8 mg kg -1 given in five seconds, 30 seconds after induction. In these two groups the trachea was

intubated 90 seconds following this last dose of atracurium and the intubating conditions were classified as 1 (excellent), 2 (satisfactory), 3 (fair), or 4 (poor) according to the criteria of Lund and Stovner, 1970 [66].

Blood samples were not analysed for histamine concentrations in these two groups as it would be difficult to correlate any changes in plasma histamine concentration with the inevitable haemodynamic response to intubation. Furthermore, the histamine response in these two dose regimes had already been analysed in groups 1 and 5 under stable haemodynamic conditions.

Results

The results are summarised in Tables 7, 8 and 9. The data displayed are mean values with standard errors of the mean (SEM). The changes in mean arterial pressure and heart rate are the maximum changes calculated as a percentage of the base line values that occurred in the 10 minutes after the administration of atracurium. The actual values at control, two minutes and five minutes for mean arterial pressure and heart rate are displayed in parenthesis in Table 7. The data on mean arterial pressure, heart rate and histamine concentration (Table 8) at base line and two minutes were analysed according to a three factor analysis of variance with group and time crossed and patient (a random factor) nested within group. In order to stabilise their variability and more closely satisfy the assumptions underlying the analysis of variance the histamine data were analysed on a logarithmic scale. Tests of significance for the change from base line to two minutes within each group then used T statistics setting the critical value

	no	MAP % of baseline	HR % of baseline
Group I 5 sec bolus	8	*74.6±5 (80.8/60/76.5) [52-97]	113.25±3.75 (64.25/72.1/65.8) [100-138]
Group II 30 sec dose	8	*77±7.5 (67.25/50.75/64.75) [49-104]	114.75±10.8 (60/67.5/58.8) [89-191]
Group III 75 sec dose	8	95.7±1.2 (71.1/68.5/70.1) [90-100]	102.6±1.17 (55.2/56/55.7) [96-107]
Group IV Anti-histamine	8	83.3±7.1 (77.3/65.6/75.1) [38-100]	109.9±3.65 (59.1/64.7/60) [96-125]
Group V Prime	8	*76±7.6 (68.5/52.5/64.6) [43-103]	109.3±2.83 (63.5/69.3/65) [100-126]

MAP = Mean Arterial Pressure
HR = Heart Rate

Actual values at baseline, 2 and 5 minutes for mean arterial pressure and heart rate are shown above in brackets. The units are mm Hg and beats per minute respectively.

The range of the maximum per cent, change in MAP and HR is shown above in square brackets.

t-test * = $P < 0.05$ (simultaneous)

Table 7

Cardiovascular Data.
Effect of 0.8 mg kg -1 atracurium on mean arterial pressure and heart rate.

	n	PLASMA HISTAMINE pg ml -1 Control	+2 mins	5 mins
Group I 5 sec bolus	8	557±232 [177-2110]	*1646±419 [710-4070]	721±167 [100-1552]
Group II 30 sec dose	8	453±81 [230-1023]	2137±984 [247-8999]	1030±268 [308-2127]
Group III 75 sec dose	8	669±171 [182-1347]	791±123 [466-1500]	541±86 [147-972]
Group IV Anti-hist	8	485±100 [192-922]	**6154±4063 [105-34064]	2251±1463 [59-12016]
Group V Prime	8	203±44 [94-470]	**1874±804 [95-6871]	558±158 [60-1259]

t-test * $P < 0.05$ (simultaneous) ** $P < 0.01$

Table 8

Effect of 0.8 mg kg -1 atracurium on plasma histamine concentration.

	ONSET (MINS) END INJECTION TO COMPLETE BLOCK	RECOVERY (MINS) 5-95%	DURATION (MINS) INJECTION TO 95% RECOVERY	INTUBATING CONDITIONS AT 90 SECONDS
Group I 5 sec bolus	1.82±0.25 (2.3±0.2)	20.8±1.22 (24)	70±1.49 (59±1.9)	
Group III 75 sec dose	1.71±0.21	24±2.1	69.7±5.4	
Group IV Anti-hist	2.0±0.17	30.75±3.6	83.1±6.6	
Group V Prime	1.9±0.21	29.8±1.2	81.25±6.6	
Group VI Prime Thiopentone only	3.0±0.5			1.62±0.26
Group VII 5 sec bolus Thiopentone only	3.48±0.54 (4.6±0.4)			1.9±0.26 (1.9±0.4 at 150 secs)

All data in brackets refers to 0.5 mg kg -1 atracurium (n=10)

Table 9

Pharmacodynamic data (Mean values with standard errors).

according to Bonferroni's inequality so that the simultaneous significance level would not exceed 0.05 (or 0.01 as appropriate).

There were significant decreases in mean arterial pressure in groups 1, 2 and 5 ($p < 0.05$) (Table 7). The moderate decrease in group 4 approached but did not reach statistical significance ($0.1 > p > 0.05$). In all patients the changes in arterial pressure and heart rate were transient and had returned to base line values by five minutes.

Patients in groups 1, 4 and 5 demonstrated significant increases in plasma histamine concentrations at the two minute sample (Table 8).

There were no significant differences in onset time (Table 9) between any of the techniques of administration when atracurium 0.8 mg kg -1 was administered during nitrous oxide and fentanyl anaesthesia. Nor was there a significant difference between groups 6 and 7 in which atracurium was administered following induction with thiopentone. Atracurium 0.8 mg kg -1 produced a significantly shorter onset time ($p > 0.05$) than 0.5 mg kg -1 under nitrous oxide-opiate anaesthesia. Atracurium 0.8 mg kg -1 also produced a significantly more rapid onset than 0.5 mg kg -1 following induction with thiopentone alone ($p < 0.05$).

The depth of anaesthesia appeared to have an effect on onset time and both the bolus (group 1) and prime (group 5) groups had significantly shorter onset times ($p < 0.05$) under nitrous oxide-fentanyl anaesthesia when compared with the bolus (group 7) and prime (group 6) groups respectively receiving thiopentone

alone.

There were no significant differences between the recovery times or the durations of action in the four groups in which these were recorded.

The intubation score was slightly better in the prime group (6) than in the bolus group (7) but this was not significant. The intubation score produced by the 0.8 mg kg -1 bolus group at 90 seconds was the same as that produced by 0.5 mg kg -1 at 150 seconds.

Discussion

We have shown previously that atracurium 0.6 mg kg -1 given over five seconds is associated with a doubling of plasma histamine concentration and a significant reduction in mean arterial pressure. These changes can be prevented by administering the drug over 75 seconds or by pre-treating with antihistamines (cimetidine 4 mg kg -1 and chlorpheniramine 0.1 mg kg -1 iv) 15 minutes before the injection of the neuromuscular blocker.

In this study decreasing the rate of injection of atracurium 0.8 mg kg -1 to 75 seconds also minimised the haemodynamic changes and prevented the increase in histamine concentration. However, in the antihistamine group the haemodynamic protection was incomplete and was associated with a highly significant increase in plasma histamine concentration. The patient with the most marked increase in plasma histamine concentration and the greatest decrease in mean arterial pressure was in this group. This large increase in plasma

histamine concentration may have been the result of the known inhibitory effect of cimetidine on histamine-n-methyltransferase, the enzyme responsible for one of the major catabolic pathways of histamine. The substantial increase in plasma histamine concentration in this group may have overcome the protection offered by the antihistamines by a simple dose response effect.

Although there was almost a five fold increase in plasma histamine concentration following the 30 second injection, this was not found to be statistically significant because of the large between patient variation and hence the large standard deviation in this group. Considerable variability for histamine release among subjects is well recognised. Not all patients will release histamine after high doses of atracurium but as the size of the bolus dose increases there is a greater likelihood of this occurring in most individuals. In animal studies mast cells from different species and even individual tissues within a single animal are shown to vary markedly in their response to a given inducer of histamine release (Pearce, 1982 [67]).

This histamine releasing response to the higher doses of atracurium must be kept in perspective. Basta and colleagues, 1983 [49] have shown that the ability of atracurium to release histamine relative to its neuromuscular blocking potency is only one half that of di-methyltubocurarine and less than one third that of tubocurarine. Nevertheless, this response could be of significance in the hypovolaemic patient or the patient with cardiovascular disease.

Several studies have demonstrated more rapid onset of blockade and superior intubating conditions when the priming principle was used (Hutton et al, 1983 [68]; Bevan et al, 1984 [69]; Nagashima et al, 1984 [70]; Mehta, 1985 [65]; Schwartz et al, 1985 [64]). However, there is little uniformity among these studies in terms of the drugs used, the priming dose, the intubating dose, the time between priming and intubating dose and the anaesthetic technique used. These variables may require proper adjustment for each competitive neuromuscular blocking agent. We can only conclude that with the dose regime and time interval used in this study priming does not improve onset times or intubating conditions; nor does it have any protective haemodynamic effect.

A wide variety of onset times at a number of different doses has been reported for atracurium (Payne and Hughes, 1981 [34]; Scott and Goat, 1982 [61]; Foldes et al, 1983 [71]; Gergis et al, 1983 [72]). However, standardisation of anaesthetic technique is very important before any effective comparison can be made. In particular, the starting point and end point in the measurement of onset time, the mode of peripheral nerve stimulaton and the anaesthetic agents used should all be defined clearly. This is emphasised in this study by the significantly shorter onset times under nitrous oxide-opiate anaesthesia compared with those associated with thiopentone alone. The different measurements recorded when using different modes of peripheral nerve stimulation have already been emphasised in a previous paper in this thesis.

It is concluded that atracurium 0.8 mg kg -1 will produce a significantly more rapid onset of blockade than 0.5 mg kg -1 with a

similar intubation score one minute earlier (at 90 seconds compared with 150 seconds). This may be associated with a transient but significant decrease in mean arterial pressure. This effect which is probably of little importance in the healthy patient can, however, be attenuated by injecting the drug more slowly - over 75 seconds.

CHAPTER 5

ADVERSE EFFECTS OF SUXAMETHONIUM - A STUDY OF PREVENTION BY ATRACURIUM OR FAZADINIUM

It is now apparent that while atracurium may have a speed of onset as fast as the other non-depolarising agents it is still not a substitute for suxamethonium. It does not, therefore, fulfil the first criteria of Savarese and Kitz for an ideal muscle relaxant and cannot be recommended for routine use in a rapid sequence induction technique.

Unfortunately, suxamethonium has many side effects. These include muscle fasciculations, post-operative myalgia [73,74] and a transient rise in serum potassium [75, 76]. Historically an alternative approach to this problem has been to advocate pre-treatment regimes to reduce the incidence and severity of these side effects. The most widely accepted approach is the use of a sub-paralysing amount of a non-depolarising drug given two to three minutes before suxamethonium [77, 78]. This technique, however, is not without side effects itself and may result in clinical neuromuscular blockade during the pre-treatment period with a decrease in the paralysing action of suxamethonium, as well as making intubation more difficult.

Atracurium was selected as a mode of pre-treatment in the prevention of these adverse effects of suxamethonium. Its action was compared with that of fazadinium, another non-depolarising relaxant, which has been used for pre-treatment [79] and was routinely used by one of the investigators (Blogg) for this

purpose.

Methods

One hundred healthy patients aged between 18 and 45 years participated in the study which was approved by the local Ethics Committee. Informed verbal consent was obtained from all participants. The patients were to undergo minor oral surgical procedures and required nasal intubation. They were receiving no concurrent medication apart from the contraceptive pill.

They were allocated randomly into four groups to receive pre-treatment as follows: GroupA - atracurium 2.5 mg; Group B - atracurium 5 mg; Group C - fazadinium 3.75 mg; Group D - normal saline 1 ml. In each case the volume administered was 1 ml.

Premedication of papaveretum and hyoscine was given by intramuscular injection approximately one hour before induction of anaesthesia. On arrival in the anaesthetic room the patient's arterial blood pressure was measured and electrocardiograph monitoring was established to record heart rate continuously. An 18 gauge cannula was inserted into a large vein in the antecubital fossa of the non-dominant arm and a blood sample taken without the use of a tourniquet and stored in a heparinised tube for the subsequent estimation of serum potassium. All samples were analysed within four hours of collection. The mean of three estimations was recorded. The cannula was used for all sampling and drug administration and was flushed with saline between each use.

Prior to induction of anaesthesia a modified Elcomatic [37] transducer was attached to the dominant hand and positioned to measure the optimal response to thumb adduction. Disposable pre-gelled ECG electrodes were positioned over the ulnar nerve at the wrist and connected via an isolation unit to a nerve stimulator (Grass S48).

Anaesthesia was induced with fentanyl 3 ug kg -1 and thiopentone 5 mg kg -1 and maintained with nitrous oxide 70% in oxygen. Ventilation was assisted mechanically using a face mask and ventilator connected via a Bain system. Immediately after induction of anaesthesia stimulation of the ulnar nerve was commenced (pulse width 0.2 milliseconds) and adjusted to produce the maximum mechanical response from contraction of the adductor pollicis muscle. When the stimulation was supramaximal the stimulator was set to repeat a 2 Hz train-of-four stimuli every 12 seconds. A control response to the stimuli was recorded before the pre-treatment drug was injected and the start of the injection was timed to coincide with the first response of the next train. Three minutes later suxamethonium 1 mg kg -1 was administered and the presence or absence of fasciculations was noted. As soon as there was no detectable response to nerve stimulation laryngoscopy was performed and intubation was attempted by the nasal route. All intubations were performed by one of the investigators, who also noted the intubating conditions and who was not aware of the nature of the pre-treatment drug.

Neuromuscular monitoring was continued until the first response of the train of four had returned to 80% of its control height.

Halothane was then added to the inhaled anaesthetic and surgery was begun. Further venous blood samples were taken two and 30 minutes after the administration of suxamethonium.

Neuromuscular blockade during the pre-treatment period was assessed by measuring the height of the most depressed first twitch of a train of four and expressing it as a percentage of the control first twitch response obtained before the pre-treatment drug was given. Fade within the train of four was also measured and was expressed as the ratio of the fourth twitch to the first. Onset of paralysis following suxamethonium was monitored and expressed as the time from injection of suxamethonium to maximum depression of the first twitch response.

The rate of recovery of neuromuscular function was measured and expressed as the time from maximum paralysis to 25% recovery of the first twitch response. The recovery index was also measured, namely the rate of recovery of the first twitch response from 25%-75% of its control value.

The patients were visited by one of the investigators approximately 24 hours following anaesthesia and helped to complete a simple questionnaire. A number of questions were asked, some relating to muscle pains and the site of the pain was noted. Because of the nature of the surgery head and neck pain was considered to be of surgical origin and was not included. The muscle pains were classified as follows: mild, not requiring analgesia or interfering with normal activity; moderate, requiring simple analgesia but not interfering with normal activity; severe, not controlled by simple

analgesics and interfering with normal activity.

A similar questionnaire was given to all patients to complete 72 hours after anaesthesia. These were completed at home and returned by post. Post-operatively oral analgesics were prescribed for pain relief as required.

Results

Table 10 shows that the four groups were comparable with regard to age, weight and sex.

Neuromuscular Blockade During the Pre-Treatment Periods

Small degrees of depression of the first twitch T1 and of the ratio T4/T1 were seen in a number of patients in all groups except those who received saline as pre-treatment. Three patients, all of whom received atracurium 5 mg, showed depression of the first twitch of the train to 70% or less of control.

Fasciculations

The incidence of fasciculations was significantly less ($p < 0.01$, chi-squared test) in patients who had received pre-treatment with one of the non-depolarising drugs than in those who received saline (Table 11). There was no relationship between the intensity of fasciculations and the severity of the post-operative muscle pains.

All patients in groups A, C and D achieved 100% block T1 of the adductor of the thumb. In group B, four patients failed to become fully paralysed. The mean onset time in this group was 79.7 seconds which was significantly longer than in the other groups.

GROUP	ATRACURIUM 2.5 MG	ATRACURIUM 5 MG	FAZADINIUM 3.75 MG	SALINE
Mean age (Years)	24.29 (5.93)	25.36 (6.9)	24.41 (6.8)	27.93 (7.7)
Mean weight (kg)	62.59 (8.7)	61.75 (10.1)	62.39 (10.2)	63.26 (9.5)
No of Patients	25	25	25	25
Male:Female	10:15	10:15	10:15	10:15

Table 10

Anthropomorphic Data (SD)

	YES	NO
GROUP A Atracurium 2.5 mgs	8	17
GROUP B Atracurium 5 mgs	4	21
GROUP C Fazadinium	8	17
GROUP D Control	24	1

Table 11

Incidence of fasciculation

There was no significant difference between the other three groups (Table 12).

Intubating Conditions

All patients were intubated without the need for additional muscle relaxants. Although not statistically significant, features likely to result in a difficult intubation were found more frequently in those patients receiving the larger dose of atracurium (Table 13).

Recovery from Neuromuscular Blockade

Recovery to 25% of control was faster in the atracurium 5 mg group than all others and was slowest in the saline group. These differences were significant ($p < 0.01$). There was no difference between atracurium 2.5 mg and fazadinium and no difference in the recovery index between any group (Table 12).

Incidence of Pain

There was no significant difference in the incidence of muscle pain between groups at either 24 or 72 hours. It was noted that in all groups the incidence of muscle pain was greater at 72 hours than at 24 hours (Table 14).

Potassium

The blood samples were analysed for potassium using a Nova 1 ion selective electrode. The results are shown in Table 15. Two way analysis of variance, Duncan's multiple range test and a one way analysis of variance were performed on these results. For all groups, the sample taken 30 minutes after induction differed from that taken at two minutes and from the pre-induction sample (p

PRETREATMENT	ONSET (secs)	0-25% (T1) (secs)	25-75% (T1) (secs)
Atracurium 2.5 mg	58.08 (11.32)	265.56 (65.65)	87.04 (33.37)
Atracurium 5 mg	79.68* (22.68)*	166.28* (87.54)*	81.14 (23.97)
Fazadinium 3.75 mg	57.5 (8.65)	264.57 (90.47)	98.18 (47.80)
Saline	55.2 (14.28)	430.33* (116.75)*	107 (40.02)

* P = 0.01

Table 12

Mean onset and recovery times of neuromuscular block following pre-treatment and suxamethonium 1 mg kg -1.

	Jaws		Cords		Reaction to Intubation	
	Relaxed	Not Relaxed	Not Moving	Moving	Absent	Present
Group A	24	1	21	4	15	10
Group B	22	3	18	7	13	12
Group C	25	0	25	0	12	13
Group D	24	1	25	0	20	5

Table 13

Intubation conditions following pre-treatment and suxamethonium.

		Incidence at 24 Hours		Incidence at 72 Hours	
Group	n	Mild	Moderate + Severe	Mild	Moderate + Severe
A	25	5	6	8	7
B	25	2	4	6	4
C	25	5	2	5	5
D	25	8	1	10	5

Table 14

Incidence of pain following pre-treatment and suxamethonium.

Pre-treatment Group		Potassium Levels (SD)		
		K1	K2	K3
A	Atracurium 2.5 mg	3.89 (0.26)	3.79 (0.19)	4.16 (0.25)
B	Atracurium 5 mg	3.83 (0.20)	3.79 (0.19)	4.03 (0.27)
C	Fazadinium 3.75 mg	3.88 (0.25)	3.86 (0.21)	4.15 (0.20)
D	Saline	3.89 (0.21)	3.86 (0.21)	4.11 (0.26)

Table 15

Potassium levels (mmol 1 -1) taken before suxamethonium (K1) and 2 mins (K2) and 30 mins (K3) after suxamethonium

<0.001 for both differences for all drugs) However, there was no difference between the groups and no value exceeded the normal range.

Discussion

Non-depolarising muscle relaxants used for the prevention of muscle fasciculation and post-operative myalgia following the use of suxamethonium delay the onset of paralysis and reduce its duration of action [80, 81]. The amount of non-depolarising drug required for this purpose remains unclear; some advocate a weight related dose of pre-treatment drug [82] while others prefer a fixed dose regime [78]. Because of the problem of administering variable small doses of drugs accurately, it was decided to use a fixed dose regime and to select the dose of fazadinium which appeared from preliminary studies to be the minimum effective in preventing muscle fasciculations. Two doses of atracurium were compared to determine which would be most effective.

In all cases, pre-treatment with a non-depolarising muscle relaxant delayed the onset of paralysis produced by suxamethonium and the duration of blockade was reduced compared to controls. These effects were maximal with the larger dose of atracurium. In addition, of the 100 patients studies during the pre-treatment phase, only three, all of whom received atracurium 5 mg, developed clinically significant neuromuscular blockade during the pre-treatment.

It is surprising that there was no initial increase in serum potassium following suxamethonium and curious that in all cases the

level of serum potassium fell to below the control value at two minutes, although this was not significant. The values at 30 minutes showed an increase to above control levels and it is possible that the sample at two minutes was taken before an increase in potassium would be detectable, although in all cases paralysis had occurred.

The incidence of muscle pains following suxamethonium varies widely and is thought to be influenced by the choice of anaesthetic, the patient's age and sex, and by time to ambulation. These patients would, by these criteria, be considered to be highly at risk for developing post-operative myalgia. However, the incidence of muscle pains was surprisingly low even in the control group (36% at 24 hours rising to 66% at 72 hours). The apparent failure of all the pre-treatment regimens may be explained by the use of an analgesic premedication and post-operative medication which had largely worn off by the time of the assessment at 72 hours.

In conclusion, in this small group of subjects atracurium and fazadinium failed to influence the incidence of muscle pains following suxamethonium when used as part of a pre-treatment regime. The larger dose of atracurium resulted in a shorter period of paralysis with a delay in onset and the quality of intubating conditions was impaired. Although there was a significant rise in plasma potassium at the 30 minute sample when compared to the pre-induction sample, there was no significant difference between the groups.

CHAPTER 6

THE EFFECT OF SUXAMETHONIUM GIVEN DURING RECOVERY FROM ATRACURIUM

While the previous study outlined the effect of a small pre-treatment dose of atracurium on a suxamethonium block, it occurred to the author that some anaesthetists occasionally give suxamethonium at the end of a non-depolarising block with the belief that they are creating a short period of increased blockade. This study looks at the effect of suxamethonium on a recovering atracurium block.

An alternative approach to neuromuscular monitoring, the electromyograph was used.

Introduction

At the end of an abdominal operation, muscle relaxation may be inadequate and a transient increase in block may be needed to facilitate closure. Suxamethonium is the only short duration agent currently available and has been used in these circumstances. Whilst its interactions with long acting competitive agents have been described [83-87], its effects on recovery from the block produced by atracurium have not. This study was designed to assess the effects of increasing doses of suxamethonium on the recovery of block produced by atracurium and on the subsequent interaction with neostigmine.

Methods

Thirty eight patients aged between 18 and 70 years and weighing

between 45 and 110 kg were studied after they had given informed consent. They were undergoing elective surgical procedures and were divided into 10 sub groups. The protocol included the same exclusion criteria as in previous studies.

Diazepam (0.1 - 0.2 mg kg -1) and metoclopramide (10 mg) were given orally one hour before anaesthesia was induced with thiopentone (4-6 mg kg -1) and fentanyl (2-4 ug kg -1). Anaesthesia was maintained with nitrous oxide (66%) and enflurane (0.5%), supplemented by additional doses of fentanyl and thiopentone as required. When paralysed following neuromuscular blockade, the lungs were artificially ventilated and the end-tidal carbon dioxide tension maintained between four and five kilopascals.

The integrated rectified and gated electromyographic response of the hypothenar muscles was recorded in response to supramaximal train-of-four stimuli delivered to the ulnar nerve at 20 second intervals using a Datex Relaxograph. Control values were obtained after induction of anaesthesia but before the administration of 0.4 mg kg -1 of atracurium. Once the first twitch response of the train-of-four (T1) had recovered to 50% of the initial value, a predetermined dose of suxamethonium of between 0.25 and 3 mg kg -1 was given. To mimic a possible clinical situation, in four patients neostigmine (35 ug kg -1) was given when T1 had returned to 25% following the initial atracurium dose and 3 mg kg -1 of suxamethonium. Neostigmine (35 ug kg -1) was also given to some patients in each combination group once T1 had returned to 100% following suxamethonium. Three groups of patients were studied to provide data for the spontaneous recovery following atracurium, for

recovery from atracurium accelerated by neostigmine, and for recovery from suxamethonium.

Results

Giving suxamethonium when T1 had returned to 50% after atracurium could produce either no response, a slight reversal of the block, and enhancement or a combination with a biphasic response. Figure 7 illustrates some of these responses. There was a wide between patient variability in response particularly at the lower doses. When 0.5 and 1 mg kg -1 of suxamethonium were used the mean net effect was one of slight reversal, whereas with doses of 1.5 mg kg -1 and more the block was increased. Only at 3 mg kg -1 was 100% block consistently produced: the full block then lasted on average some eight minutes. The results are summarised in Table 16.

Table 17 summarises the recovery indices in five groups of four patients for the final recovery phase. When atracurium was given alone the mean recovery index (25%-75% recovery T1) was 13.1 minutes, and when neostigmine was given at T1 of between 10-25% this time was shortened, on average to 4.5 minutes. Suxamethonium in a dose of 1.5 mg kg -1 given without any preceding atracurium produced a recovery index of 3.0 minutes. When 3 mg kg -1 of suxamethonium was given at the 50% T1 point of recovery from atracurium, after the 8.0 minute period of complete block, the index was 2.75 minutes. This recovery pattern resembled a spontaneous suxamethonium recovery except that fade always persisted following the combination block. The fade was, however, always reversed by neostigmine administered at 100% T1 recovery. Neostigmine also reversed fade when administered at 25% recovery T1

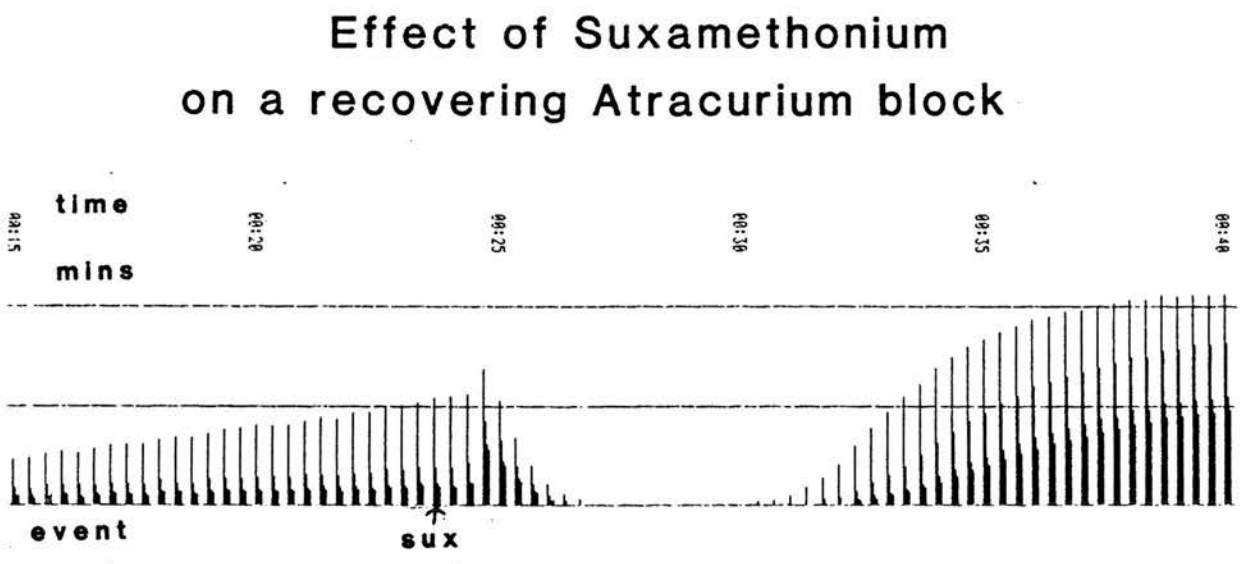


Figure 7

Suxamethonium (2 mg kg -1) is administered at 50% T1 recovery from an atracurium (0.4 mg kg -1) blockade. Illustrated is the subsequent biphasic response followed by a brief period of 100% block of T1 and a rapid recovery.

Sux. Dose mg kg -1	n	No with biphasic response	Mean % change in block (± SD)	T1 100% block time (min)
0.25	1	0	-10	
0.5	4	2	-1.25 (±10.3)	
1.0	4	2	-1 (±12.5)	
1.5	3	2	34 (±17.7)	
2.0	6	4	40.5 (±13.5)	
3.0	8	3	50*	8

* A 50% change in block represents 100% block of T1.

Table 16

The effect of suxamethonium on a recovering (50% T1) atracurium block.

Group	no	25-75% Recovery (± SD) (min)	5-95% Recovery (± SD) (min)
AS	4	2.75 (± 0.28)	8.25 (± 0.95)
AS + N	4	7.25 (± 3.6)	12.3 (± 5.9)
S	4	3 (± 0)	7.75 (± 0.5)
A	4	13.1 (± 1.8)	38.3 (± 7.6)
A + N	4	4.5 (± 0.57)	14.5 (± 1.73)

Key:

AS = Suxamethonium 3 mg kg -1 administered at a 50% T1 atracurium recovery

AS + N = Neostigmine administered at T1 25% recovery of a AS block

S = Suxamethonium 1.5 mg kg -1

A = Atracurium 0.4 mg kg -1

A + N = Neostigmine reversed (at 10-25% T1) atracurium blockade

Table 17

Reversal data.

of a combination block (3 mg kg -1 suxamethonium), but lengthened the mean recovery index to 7.25 minutes and in one case transiently increased block by 10% prolonging the 5-95% recovery time to 19 minutes. Thus, the recovery index was fastest after suxamethonium alone or when suxamethonium was used to potentiate the atracurium block. The addition of neostigmine as an extra reversal agent slowed recovery. Suxamethonium given after atracurium never produced muscle fasciculations.

Discussion

This study was designed to mimic a clinical problem The relaxation produced by atracurium was allowed to wear off to a point at which T1 had recovered to 50% and where all four responses to train-of-four stimulation were apparent. This level is usually too light to allow closure of the abdomen without deep general anaesthesia, and the clinician needs to intensify the block. One clinical approach is to use a small dose of suxamethonium for this rather than give an increment of a long acting competitive blocker.

Our results show that low doses of suxamethonium may antagonise the partial block seen during the recovery from atracurium, but that larger doses will usually enhance the block. The subsequent recovery pattern of a combination block is faster than that seen with atracurium alone or when antagonised by neostigmine. However, during the recovery of a combination block, fade of the train-of-four response is seen. Similar results have been reported with the interaction of suxamethonium with longer acting competitive blocking drugs [83-87]. Young [86] and Walts [83] demonstrated similar patterns of dose related effect with

tubocurarine as did Katz [85] for pancuronium. The biphasic pattern has been described by Walts [83] and in more detail by Buzello and his colleagues [87]. This last study demonstrated that with a constant dose of suxamethonium (0.5 mg kg -1) the proportional relationship between reversal and subsequent increase of blockade depends on the stage of recovery from non-depolarising neuromuscular blockade at the time of suxamethonium administration. Gray [84] and Young [86] have reported similar findings with other drugs.

What are the mechanisms which produce these interactions? The traditional view would be that atracurium produces mainly a competitive block of the post-synaptic receptors. Such a block can be overcome by increasing the concentration of agonist usually in clinical practice by the anticholinesterase action of neostigmine. However, suxamethonium also acts as an agonist and interacts with the post-synaptic receptors leading to the opening of ionic channels and a depolarisation of the membrane. This in turn may initiate the muscle action potential and the contraction. If the amount of suxamethonium is too great the depolarisation is maintained and the muscle membrane becomes unexcitable. Hence low doses could act as agonists, but larger ones as the depolarisation develops will produce a block. During recovery from the combination block we still need to explain why the recovery index is quicker, why neostigmine slows it and why fade of the train-of-four response persists. Again the traditional views of neuromuscular block can offer explanations. The enhanced recovery index by itself is somewhat of a red herring. It is likely that what we are observing is a simple competitive displacement by the

law of mass action at the post-junctional receptor. The dose response curve of suxamethonium is shifted to the right because of the presence of atracurium molecules on the receptor. It appears from Buzello's study that when suxamethonium is administered during a pancuronium recovery phase, 100% T1 recovery was not achieved at 30 minutes following suxamethonium when administered at 25% or 75% recovery of T1. In this study every patient had recovered to 100% T1 from a combination (3 mg kg -1 suxamethonium) block within 20 minutes of administration of suxamethonium. This observation supports the above hypothesis. As suxamethonium is catabolised and the local concentration declines at the end plate the post-junctional receptors could again be occupied by the longer acting pancuronium molecules, which are eliminated more slowly. This does not occur with the intermediate duration drug atracurium because elimination is occurring more rapidly than with pancuronium during the time suxamethonium is being hydrolysed. Thus, the fast recovery index reflects the fact that most of the block will be due to suxamethonium. The fact that neostigmine slowed recovery after suxamethonium may be due to its effect on plasma as well as acetyl cholinesterase delaying the breakdown of suxamethonium.

Fade is now believed to be due either to a block of pre-junctional acetylcholine receptors by competitive drugs or to a use-dependent post-junctional ion channel occlusion [45]. However, the latter hypothesis ignores the findings of Hutter [88] and Otsuka [89] and colleagues that tubocurarine induced fade is associated with a diminished acetylcholine release, and certainly the evidence from drugs used in clinical circumstances favours the first of these two mechanisms. The fade demonstrable during the recovery from

suxamethonium following atracurium is most probably accounted for by the residual pre-junctional action of atracurium. It could be due to the development of a phase 2 [90] block by suxamethonium but this would seem unlikely with the rapid recovery time. Furthermore, neostigmine did not shorten the recovery time and on one occasion actually increased block adding substance to the hypothesis that a depolarising block is present. In any case all these explanations are speculative, especially with the difficulties inherent in comparing the evoked electromyographic responses demonstrable in man with the precise studies now possible in the laboratory. A detailed study of the interactions would presumably need voltage [91] and patch clamp studies to ascertain which effects are due to interaction with the acetylcholine receptor on the muscle and which to effects on the nerve terminals.

Although we did not see a prolonged block when suxamethonium in a dose of 3 mg kg -1 was given after recovery from atracurium to a 50% T1 level, we would not recommend giving such a dose to enhance muscle relaxation in clinical practice unless a peripheral nerve stimulator was used to monitor the degree and duration of block. If such a technique was used then neostigmine appears not to accelerate the subsequent recovery and should not be used. It is important to remember that we gave the suxamethonium at the 50% T1 point at which time all four responses to train-of-four stimulation were present. An alternative clinical solution would be to increase the block with a small increment of atracurium. The intensity, duration and subsequent recovery of the block would then obviously depend on the size of dose used. A laboratory model may elucidate the events at the neuromuscular junction.

CHAPTER 7

CONTINUOUS INFUSION OF ATRACURIUM: DOSAGE TIMING AND ANTAGONISM OF RESIDUAL BLOCKADE

The speed of onset of atracurium and its cardiovascular effects in particular in relation to histamine release have been examined. The next study examines the cumulative potential of atracurium, its dissipation of action following single bolus doses and infusions, and its ability to be antagonised by an anticholinesterase. Since atracurium has a relatively short duration of action and in animal studies has been shown to have a low propensity for cumulation, this would seem to make it an ideal agent for administration by an infusion technique.

Initial studies by Basta et al [47] and Payne and Hughes [34] showed lack of cumulation, ie repetitive bolus injections of identical doses resulted in neuromuscular blockade of unvarying depth and duration. Bolus doses require to be given relatively frequently because atracurium has an intermediate duration of action and this might be considered an inconvenience during long operations.

In this study, in order to achieve a stable level of surgical relaxation without the inconvenience of frequent dosing atracurium was administered as a continuous infusion. The aims of this investigation were (1) to evaluate a large number of patients receiving atracurium by infusion in order to establish limits for infusion rates necessary to provide levels of neuromuscular

blockade which are usually consistent with good clinical relaxation (90-99% twitch depression); (2) to ascertain whether or not a cumulative property might be evident during infusion; and (3) to determine ease of antagonism of residual blockade by neostigmine after termination of the infusion. For the purpose of this study evidence of a lack of 'cumulative effect' was defined as (a) maintenance of a constant percentage twitch inhibition for a period of 30-60 minutes or more without alteration of atracurium infusion rate; and (b) 5-95 and 25-75% twitch recovery times after termination of infusion which were comparable to times recorded after single bolus doses of drug.

Methods

One hundred and twenty nine ASA Class 1 or 2 patients, 19-59 years of age undergoing elective surgery, gave institutionally approved written informed consent. All subjects were premedicated with morphine (0.1 - 0.15 mg kg -1) i.m. and diazepam (0.1 - 0.2 mg kg -1 PO) one hour before surgery. Neuromuscular function recording was begun under local anaesthesia at least five minutes prior to induction of general anaesthesia. Single twitch responses of the adductor pollicis stimulated through 23 gauge steel needle electrodes at 0.15 Hz were evoked via the ulnar nerve at the wrist using square wave pulses 0.2 milliseconds in duration, which were generated by a Grass S 88 stimulator through an isolation unit. Mechanical responses of the thumb were recorded on a Grass model 7 polygraph.

Anaesthesia was induced with thiopentone (5 mg kg -1) i.v. and the trachea was intubated after an intravenous bolus of atracurium

(0.3, 0.4 or 0.5 mg kg -1). Ventilation was controlled to keep end tidal CO2 within normal limits. Anaesthesia was maintained using nitrous oxide and oxygen (4 litres - 2 litres) in a semi-closed system with additional morphine, fentanyl and/or thiopentone given i.v. as needed to maintain stable cardiovascular responses. Automated oscillotonometric blood pressure (Dinamap) and the electrocardiogram were also monitored.

Forty four patients received a single dose of 0.3 (n=18), 0.4 (n=13) or 0.5 (n=13) mg kg -1 atracurium. The block was allowed to recover spontaneously.

Eighty five additional subjects received an initial bolus of 0.5 mg kg -1 atracurium followed by an infusion begun when twitch height had recovered to 5% of base line. Atracurium was diluted in 5% dextrose in water at a concentration of 0.5 mg ml -1, the infusion rate was always set initially at 10 μg kg -1 minute -1 and was then adjusted upward or downward to maintain 90-99% suppression of the twitch. The infusion rate was controlled by an Imed volumetric infusion pump. Duration of atracurium administration was measured from the initial 0.5 mg kg -1 bolus to the termination of the infusion.

Fifty-five of the 85 patients who received atracurium infusions were allowed to recover spontaneously from neuromuscular blockade after the infusion was discontinued. Measurements were made of: (a) recovery from 5-95% twitch height, and (b) recovery from 25-75% twitch height. This group was further subdivided into patients receiving long infusions (greater than 120 minutes: n=33) or short

infusions (less than 120 minutes: n=22). Recovery rates were compared in these two sub groups. In the 30 additional patients who received atracurium infusions, residual block was antagonised 5-15 minutes after termination of the infusion by administering neostigmine (60 ug kg -1) together with atropine (30 ug kg -1) as a slow (one minute) i.v. bolus.

In all patients a steady state infusion rate (SSIR) was calculated over the last 30-60 minutes of the atracurium infusion. During this period the infusion rate was not altered.

Results were compared with students T test by analysis of variance and by linear regression. Statistical comparisons were considered to show significant differences if $p < 0.05$.

Results

The results are summarised in tables 18 to 20. The duration of infusion of atracurium varied from 58 to 416 minutes (mean 142.3 minutes). The steady state infusion rate for all patients who received infusions was 7.9 ± 0.4 μg kg -1 minute -1. Neuromuscular blockade was maintained at 90-99% twitch suppression during this time interval.

The spontaneous recovery rates following discontinuation of the atracurium infusion were compared with those obtained following single bolus doses of 0.3, 0.4 and 0.5 mg kg -1 atracurium (Table 18). Both 5-95% and 25-75% recovery rates showed no statistically significant differences between patients who received infusions or single bolus doses. In those patients with greater than 5% twitch

Dosage Group	No	Recovery Rates (min ± SE) 5-95%*	25-75%*
Infusion	55	27.7 ± 0.9 (NS)	12.0 ± 0.5 (NS)
0.3 mg kg -1 bolus	18	27.1 ± 1.7 (NS)	11.1 ± 0.8 (NS)
0.4 mg kg -1 bolus	13	28.2 ± 2.2 (NS)	11.9 ± 1.0 (NS)
0.5 mg kg -1 bolus	13	28.8 ± 2.5 (NS)	11.5 ± 1.1 (NS)

* Twitch heights, expressed as percentage of control values
(NS) = Not significant

Table 18

Comparison of spontaneous recovery from atracurium given by repetitive bolus or by infusion

n	Duration of Infusion (min ± SE)	SSIR* (μg/kg/min) ± SE	Recovery Rate (min) ± SE 5-95%	25-75%
22	92.1 ± 4.4 (58.2 - 117.5)	8.4 ± 0.5	26.5 ± 1.2	11.3 ± 0.7
33	175.8 ± 8.0 (121.2 - 415.7)	7.7 ± 0.4	28.7 ± 1.3	12.6 ± 0.7
		($p > 0.2$)	($p > 0.2$)	($p > 0.2$)

*SSIR = Steady State Infusion Rate necessary to maintain 90-99% twitch inhibition

Table 19

Recovery rates following long and short atracurium infusions.

Group	no	Recovery Time (min ± SE) from 25 to 95% twitch height
Induced recovery*	13	7.0 ± 1.2
Spontaneous recovery	55	18.1 ± 1.2
		($p < 0.01$)

*Reversal with neostigmine (60 μg kg -1) and atropine (30 μg kg -1)

Table 20

Comparison of induced* versus spontaneous recovery from atracurium infusion

recovery at the end of infusion only 25-75% recovery rates were measured.

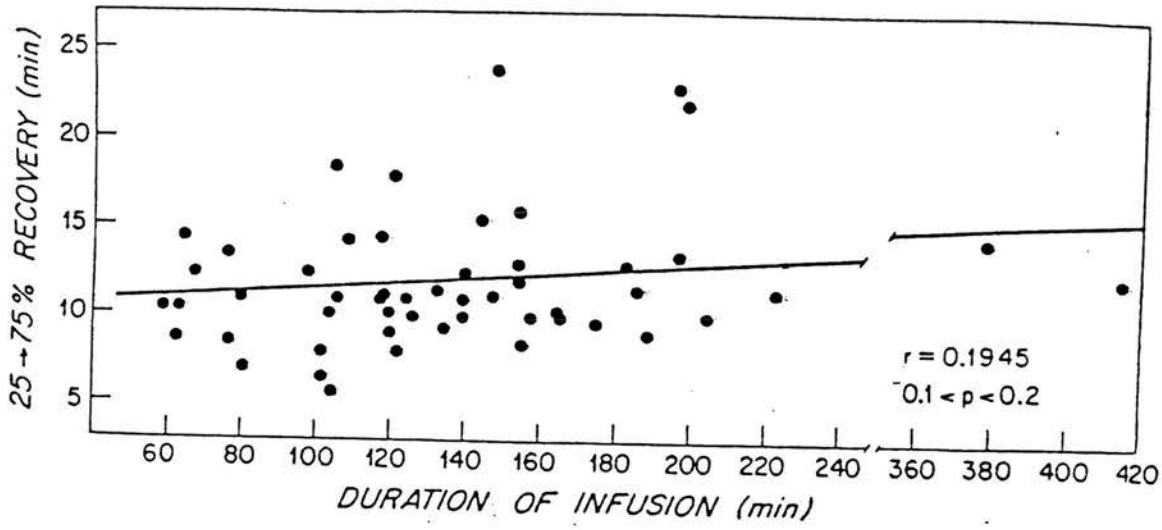
Using linear regression analysis no relationship could be found between the duration of atracurium infusion and the spontaneous recovery rates (Figure 8, $p > 0.1$ for both 5-95% and 25-75% recovery times).

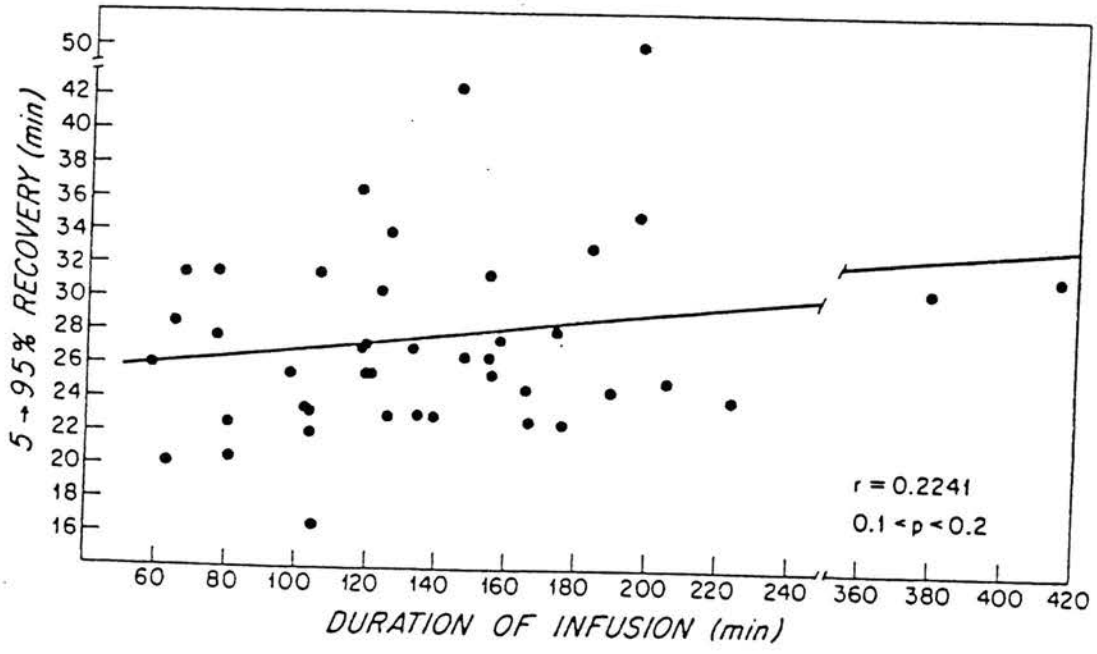
Comparisons were made of spontaneous recovery rates and steady state infusion rates (SSIR) after infusions lasting less than and more than two hours (Table 19). There were no statistically significant differences ($p > 0.2$).

In 30 patients residual atracurium blockade was readily antagonised (Figure 9) with neostigmine (60 ug kg -1) and atropine (30 μg kg -1). In eight of these subjects reversal took place at similar depths of block (mean 75.6% twitch suppression). In these patients the average time from neostigmine injection to recovery of twitch to 95% of control was 7.1 minutes. Comparative data for patients receiving repetitive bolus increments of atracurium in a study by Basta et al [47] showed a mean reversal time of 8.2 minutes, when the identical neostigmine dose (60 ug kg -1) was given at a similar block depth of 75.3% twitch suppression. The difference is not statistically significant.

Discussion

A lack of cumulative property during atracurium blockade is strongly supported by the following observations:





Figures 8A and 8B

Linear regression analysis comparing 25-75% recovery interval (A) and 5-95% interval (B) with duration of atracurium infusion. Speed of recovery was not related to duration of infusion in either case.

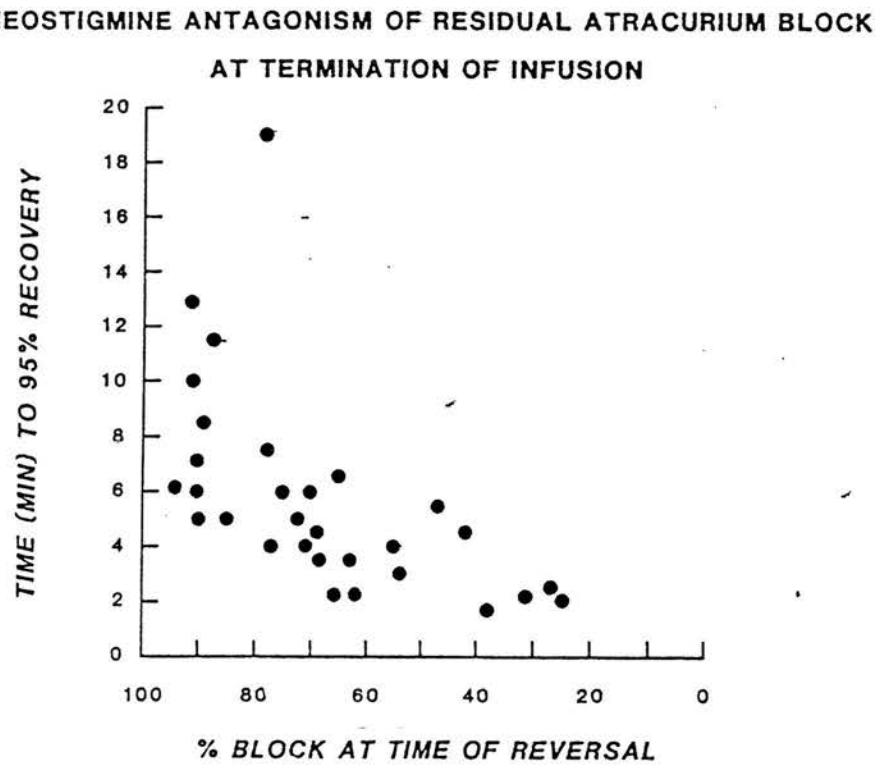


Figure 9

Scattergram relating speed of reversal to depth of block after atracurium infusion. Each dot is a single patient in whom atracurium infusion was stopped 2 - 15 minutes beforehand. At time 0, each patient received neostigmine (60 μg kg -1) and atropine (30 μg kg -1) together as one bolus i.v. The general pattern is similar to that seen after reversal of atracurium and other non-depolarising relaxants administered as repetitive boluses; speed of reversal is inversely related to depth of block at time of reversal.

1. Achievement of constant infusion rates of atracurium.
2. Maintenance of stable levels of neuromuscular blockade.
3. Demonstration that spontaneous recovery rates after termination of infusions are unrelated to duration of infusion.

Until the advent of the intermediate acting non-depolarising muscle relaxants, suxamethonium had been the only relaxant commonly used as an infusion during operations of relatively short to moderate duration. During infusion the characteristics of a suxamethonium induced neuromuscular blockade often change from an initial depolarising phase (phase 1) to a second phase which shows monitoring characteristics (fade of train-of-four response or of tetanus) which resemble a non-depolarising block. This is called phase 2 block. The simultaneous occurrence of tachyphylaxis with phase change was seen consistently in studies by Lee et al [92] and Donati and Bevan [93, 94] using suxamethonium under enflurane, isoflurane, and halothane, and by Ramsey [90] et al under balanced anaesthesia.

In 25% of the subjects studied by Ramsey et al phase 1 block persisted throughout the infusion even after some subjects received up to 17 mg kg -1. In the remaining 75% of the subjects phase 2 (train-of-four ratio less than 0.5%) developed in every individual. One half of these patients (12 out of 24) showed very slow recovery after the infusion was stopped with diminished twitch strength and train-of-four fade persisting for 30 minutes or more. Neostigmine antagonism of residual phase 2 block was uniformly successful in these individuals. Most importantly Ramsey et al found that (1)

speed of recovery from phase 2 block was unrelated to dose of drug or to duration of infusion and (2) tachyphylaxis was evident in 25% of all patients studied.

These observations of Ramsey et al demonstrate classical clinical difficulties with suxamethonium infusions: (1) change in character of the block, (2) tachyphylaxis, (3) unpredictably slow recovery in a high percentage of subjects (33%). In addition, the clinical management of slow recovery from suxamethonium during well established phase 2 block is still somewhat controversial. While antagonism of phase 2 block using anticholinesterase agents is often successful this type of block must be clearly identified before reversal is attempted. Furthermore, at least 10-20 minutes should have elapsed from termination of the suxamethonium infusion to injection of reversal agents. This waiting period allows plasma suxamethonium levels to diminish thus avoiding possible inhibition of suxamethonium hydrolysis by anticholinesterase drugs [93, 94, 95]. For these reasons, suxamethonium infusions are usually maintained for no more than one hour and total dosage is kept under 10 mg kg -1. These difficulties contrast markedly with the unchanging characteristics of an atracurium block and the ease of clinical management of an atracurium infusion.

Since atracurium is a non-depolarising substance neuromuscular blockade retains this mechanism throughout the infusion with the advantages of lack of tachyphylaxis or cumulative effect and an unvarying infusion rate once a steady state is achieved. In addition, the non-depolarising nature of the block ensures that antagonism of residual blockade with anticholinesterase agents may

be elected at any time after the infusion is terminated. Reversal then should proceed along a time course similar to reversal of atracurium block where intermittent bolus doses were given [47].

Some studies of vecuronium infusions [96] also suggest that relatively constant levels of neuromuscular blockade may be maintained without tachyphylaxis or cumulation. Mean 25-75% recovery times were longer following vecuronium infusion when compared to bolus administration and 25-75% recovery times which averaged 26 minutes after infusion seemed longer than after atracurium infusions. In a more recent study however by Gramstad and Lilleaasen [97], a prolonged 25-75% recovery index was not observed after vecuronium infusions in young healthy patients.

Vecuronium infusions may exhibit age dependent dose responses. D'Hollander et al [98] studied the pharmacodynamics of vecuronium infusions under balanced anaesthesia. Three groups of patients were studied: under 40 years of age, 40-60 years of age and over 60 years old. The infusions lasted at least 90 minutes and infusion rates were adjusted to maintain 10% of control twitch height. Significant decreases in steady state infusion rate and increases in 25-75% recovery time were observed in patients more than 60 years old. In a comparative study of atracurium [99] under similar conditions no age differences were noted.

D'Hollander's findings suggest that age related decreases in the function of the organs of elimination may lower the maintenance dose requirements and slow the speed of recovery from muscle relaxants such as vecuronium which are eliminated by the kidneys or

liver. These parameters seem less affected by age when atracurium, which undergoes extensive decomposition, is infused.

As with any other relaxant the wide individual variation in steady state infusion rate for atracurium emphasises the importance of objective monitoring of neuromuscular blockade during infusions. Monitoring should provide finer adjustment of depth of neuromuscular blockade and should also confirm return of normal function following spontaneous or induced recovery (reversal). Because of the relatively rapid spontaneous recovery rates after termination of atracurium infusions normal neuromuscular function may often be restored without the need for anticholinesterase drugs.

When reversal is necessary, however, the pattern of antagonism of residual block following an atracurium infusion seems similar to antagonism of atracurium following repetitive bolus administration.

The pattern also seems to be similar to neostigmine antagonism of the long acting agents metocurine, tubocurarine and pancuronium. Although Katz [100] administered less neostigmine (2.5 mg per subject or approximately 35 μg kg -1) than was given in the present study, time for reversal was directly related to the depth of block at the time of neostigmine injection, ie reversal at deeper levels of block occurred more slowly than at shallow levels. Patients showing 90% or more twitch inhibition required as long as 15-25 minutes for full reversal. Savarese, Ali and Antonio [101] found that when neostigmine 50 ug kg -1 was given to patients showing 79% twitch inhibition by metocurine, reversal took place within 7.6

minutes. This timing does not differ significantly from data for atracurium reversal presented in this study or previously by Basta et al [47].

In summary, atracurium produces 90-99% single twitch suppression under balanced anaesthesia at an average steady state infusion rate of 7.9 μg kg -1 minute -1. Spontaneous recovery intervals after infusion are comparable to intervals observed after single bolus doses of 0.3, 0.4 or 0.5 mg kg -1. Length of atracurium infusion does not seem to influence recovery time or steady state infusion rate. Reversal of residual block following termination of atracurium infusion requires similar neostigmine dosage and timing as reversal following bolus administration at a comparable depth of block. The administration of atracurium by infusion is readily accomplished and may be advantageous under certain clinical circumstances where steady depth of relaxation might be important for periods of one hour or more.

CHAPTER 8

PHARMACOKINETICS AND PHARMACODYNAMICS OF ATRACURIUM DURING ISOFLURANE ANAESTHESIA IN NORMAL AND ANEPHRIC PATIENTS

In this study, atracurium will be assessed in relation to the final characteristic of an ideal muscle relaxant outlined in the introduction to this thesis; that is the ability to be used without change in dosing technique in patients with renal disease.

While Hofmann elimination has been considered to be the main breakdown process for atracurium more recent work has suggested that enzymatic hydrolysis by nonspecific plasma esterases is also involved and may be of even greater importance [102, 103]. Studies in animals [104, 105] and humans [106-108] have confirmed that both pathways are responsible for deactivating pharmacologically atracurium in the systemic circulation. Consequently, normal kidney function may not be essential for elimination of atracurium.

This study evaluates the pharmacokinetics and pharmacodynamics of atracurium in normal and anephric patients under isoflurane anaesthesia.

Methods

Sixteen patients gave informed consent to the study which received prior approval from the local institutional Review Board. Eight patients (ASA Class 1 or 2) with normal renal function served as the control group. Eight patients (ASA Class 2 or 3) without renal function served as the anephric group. All patients in the

anephric group were scheduled for elective kidney transplant and were haemodialyzed within 24 hours prior to surgery. Premedication consisted of 5-10 mg diazepam orally one hour prior to surgery. Anaesthesia was induced with 4 mg kg -1 thiopentone and tracheal intubation was performed under 0.75 - 2.0% isoflurane and nitrous oxide/oxygen anaesthesia without the use of muscle relaxants. Ventilation was controlled and anaesthesia maintained with 0.8% isoflurane in 60% nitrous oxide and 40% oxygen. The PCO2 was maintained between 4-5 kPa as measured by end tidal capnometry, and oesophageal temperature was maintained within 35-37°C. Neuromuscular function was measured by recording the force of contraction of the adductor of the thumb with a Grass FT 10 force displacement transducer. Supramaximal single twitch stimuli of 0.15 Hz were used to indirectly stimulate the ulnar nerve at the wrist using subcutaneous electrodes.

After stabilisation of vital signs and the twitch response atracurium 0.5 mg kg -1 was injected over 20 seconds. Blood samples for determination of plasma levels of atracurium were drawn 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, 60, 75, 90 and 120 minutes later. Samples were handled and analysed according to a modification [109] of the method of Neil and Jones [110]. One of the difficulties in measuring atracurium concentration in the systemic circulation is the continuous decay of atracurium in plasma outside the body unless preventative steps such as acidification and freezing to -20°C are not performed rapidly. The plasma of each blood sample was immediately separated from the red cells by centrifugation in an Eppendorf 5414 bench model and transferred into glass vials pre-rinsed with 0.1 NlHCl. The plasma

samples were then embedded in dry ice to facilitate quick freezing. The sensitivity of the assay was 10 mg ml -1. The plasma atracurium concentration versus time data was fitted to a biexponential equation that describes a two compartment pharmacokinetic model with input into the central compartment and elimination from both compartments. The computer programme NONLIN was used in the curve fitting procedure yielding values for four pharmacokinetic parameters (A, α, B and ß). The α and ß half lives were calculated by the relationship of 1 n 2 divided by the macroscopic rate constants (α and ß) respectively. The clearance (CL) was calculated from the dose area relationship and the volume of distribution (Vd ß) was calculated by taking the ratio between CL and ß. Onset, duration and recovery times were measured from the twitch recordings. In the statistical analysis students T test was used and $p < 0.05$ was considered statistically significant.

Results

The mean plasma decay curves for atracurium in normal and anephric patients are shown in figures 10 and 11 respectively. There were no differences between the two groups in the major pharmacokinetic parameters as can be seen from Table 21. Similar results were obtained in the comparison of pharmacodynamic data in the two groups (Table 22). Onset, duration of action and recovery time were almost identical in the two groups and parallel the behaviour of the pharmacokinetic parameters. This observation is further supported by plotting the plasma levels of atracurium versus twitch suppression during the elimination phase of the injection. The similarity of the two families of curves in both normal and anephric patients (figure 12) shows that the potency of atracurium

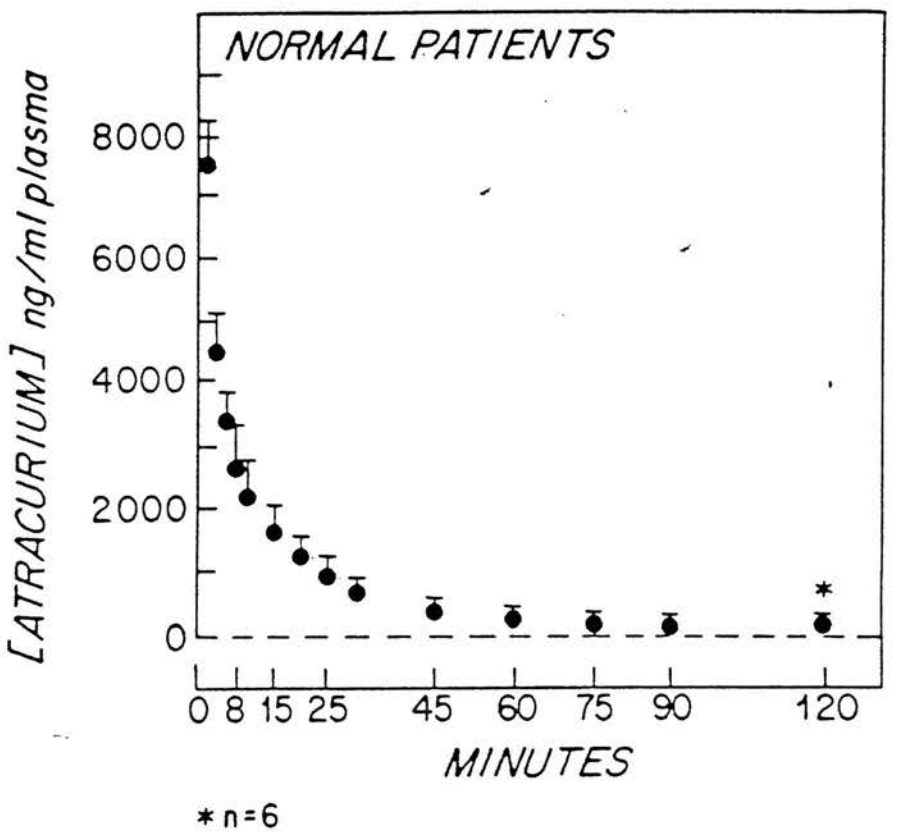


Figure 10

Plasma concentration of atracurium measured 2 - 120 mins after injection of 0.5 mg kg -1 at time zero N in eight normal patients

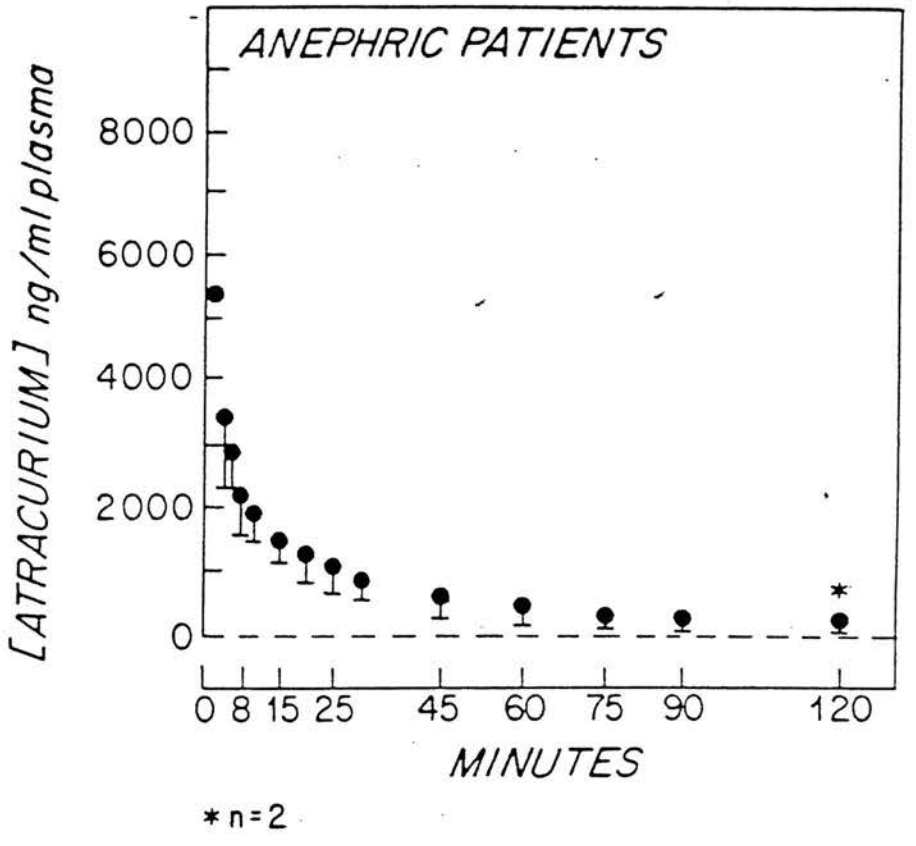


Figure 11

Plasma concentration of atracurium measured in anephric patients (n=8) 2 - 120 minutes after injection of 0.5 mgs at time zero. The exponential decay of the concentrations show that atracurium is virtually eliminated from plasma after 60 minutes.

		Normal		Anephric	
Parameter	Units	Mean	SEM	Mean	SEM
A	ng ml -1	8770	1620	7960	2190
α	min -1	0.30	0.03	0.30	0.07
B	ng ml -1	2500	210	2100	410
ß	min -1	0.04	0.002	0.04	0.004
$t_{½ß}$	min	16.9	0.8	21.1	2.5
Vl	L kg -1	0.05	0.007	0.10	0.028
Cl	ml min kg	5.93	0.64	6.89	0.71
VDß	L kg -1	141.9	12.3	211.8	31.0

A - zero time intercept
α - rate constant (distribution phase)
B - zero time intercept
ß - rate constant (elimination phase)
$t_{½ß}$ - half life
Vl - volume of distribution
Cl - clearance
VDß - volume of distribution (steady state)

Table 21

Pharmacokinetic parameters derived from a two compartment model. There are no statistically significant differences between the normal and anephric group.

Parameters	Normal (min ± SD)	Anephric (min ± SD)
Onset (inj → max block)	2.3 ± 0.9	2.7 ± 0.9
Duration (inj → start recovery)	38 ± 8	37 ± 9
Duration (inj → 25% twitch recovery)	52 ± 10	52 ± 9
Duration (inj → 75% twitch recovery)	72 ± 17	73 ± 14
Duration (inj → 95% twitch recovery)	80 ± 18	80 ± 10
Duration (25% → 75% twitch recovery)	21 ± 8	21 ± 10

Table 22

Pharmacodynamic parameters after a single bolus injection of 0.5 mg kg -1 atracurium i.v. to normal and anephric patients. (There are no statistically significant differences between the two groups).

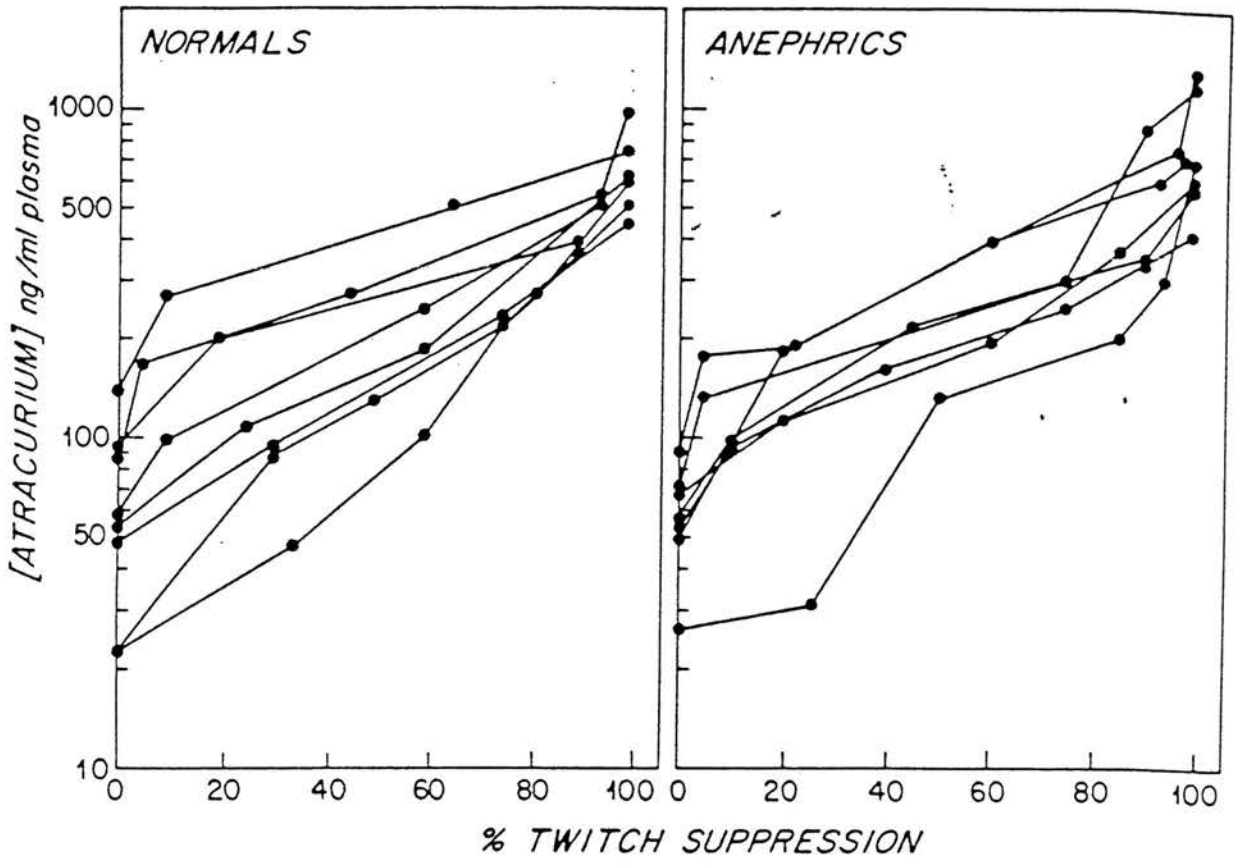


Figure 12

Recovery of twitch suppression during the elimination phase of atracurium from plasma in normal and anephric patients. Each curve represents the data points collected from individual patient. The similarity of the two families of curves show that the potency of atracurium is no different in normal and anephric patients.

is no different either in normal or in anephric patients.

Discussion

This study demonstrates that during isoflurane anaesthesia renal function has no specific effect on uptake, distribution and elimination of atracurium. The kidney plays no significant role in the rate of decline of plasma concentration of atracurium following a single injection. A two compartment pharmacokinetic model with elimination from both compartments was used to describe the pharmacokinetic behaviour of atracurium because the drug is eliminated by two processes (ester hydrolysis catalysed by nonspecific esterases and degradation via Hofmann elimination) that take place in the systemic circulation and the tissues simultaneously. Although it was feasible to determine the macroscopic rate constants (α and ß), the microscopic rate constants (k 12, k 21, k 10 and k 20) and the volume of distribution at steady state (VDSS) could not be determined because these latter parameters were interdependent on each other mathematically. The remaining pharmacokinetic parameters (eg, clearance, half life and volume of central compartment) so obtained are useful to clinicians for estimation of dosage scheduling and for the determination of infusion rates for use in surgical procedures. Attempts to fit simultaneously the twitch and plasma atracurium data to the Hill equation were unsuccessful because the best approach to such an analysis would require a constant rate infusion of the drug for 10-20 minutes with frequent collection of blood samples and twitch data during this period.

The pharmacokinetics of atracurium were first described by Ward et al [106] in healthy anaesthetised patients and subsequently in patients [107] with severe hepatic and renal disease. The results of our study in anaesthetised patients are similar. Our data obtained during isoflurane anaesthesia also confirmed the observation of Fahey et al [108] during halothane anaesthesia that the pharmacokinetics and pharmacodynamics of atracurium in anephric patients are no different from normal patients.

It is recognised that the pharmacodynamics of neuromuscular relaxants may be affected by volatile anaesthetic agents. Thus before the injection of atracurium the concentration of isoflurane to each patient was adjusted so that there was no somatic response to the incision. Thereafter during maintenance of anaesthesia the isoflurane concentration was kept constant at about MAC. This satisfied the clinical needs of the patients within the constraints of the study. Not surprisingly patients given slightly higher concentrations of isoflurane showed somewhat slower recovery of twitch suppression but the mean values for both groups were not significantly different.

This study demonstrated that anephric patients distribute and eliminate atracurium in a similar manner to normal patients. Pharmacodynamic measurements show almost identical times for duration and recovery from neuromuscular blockade in normal and anephric patients under isoflurane anaesthesia. This study confirms previous observations that atracurium appears to be a neuromuscular blocking agent well suited for administration to patients in renal failure.

CHAPTER 9

THE RESPONSE OF ATRACURIUM TO MYASTHENIA GRAVIS

Patients with myasthenia gravis are generally believed to have increased sensitivity to non-depolarising muscle relaxants. Some authors, however, do not agree with this conclusion. For example, two clinical reports describe the response of myasthenic patients receiving steroids and pyridostigmine therapy. In the first the author concluded that myasthenic patients are quite sensitive to tubocurarine and require greatly reduced doses [111], but in the second report the authors did not find an increased sensitivity to tubocurarine [112]. Other authors [113] reported on the use of very small doses of pancuronium 5.0 ug kg -1 which produced 90% twitch suppression with uneventful recovery. On the other hand resistance and early appearance of phase 2 block have been reported following the administration of suxamethonium [114]. More recently, the use of atracurium has been reported in six patients with myasthenia gravis [115-117]. The unique mode of elimination of atracurium may offer an advantage over the previously available long acting muscle relaxants.

This review presents two additional case reports of the anaesthetic management of myasthenic patients using atracurium. These findings are compared with previous reports.

Report of Two Cases

Case 1

A 64 year old woman weighing 76 kg was scheduled for an elective sigmoid colectomy for diverticulitis. She presented with a two year history of myasthenia gravis manifesting bulbar symptoms and progressive limb weakness. She was diagnosed in 1982 with electromyography and a positive edrophonium test. The patient also had a history of hypertension and insulin dependant adult onset diabetes mellitus. Initially, treatment with pyridostigmine led to an improvement. However, increasing gastrointestinal symptoms as well as dysphagia and a possible history of aspiration of gastric contents resulting in her physician prescribing a regime of steroids and reducing the dose of pyridostigmine which was stopped in January 1983. The patient underwent plasmapheresis in August 1983 and experienced a marked improvement of her symptoms. Upon admission her pulmonary function tests were 85% of normal with a vital capacity of 2.5 litres. Prior computerised axial tomography and chest X-rays showed no evidence of thymoma. Her prednisolone dosage had been increased to 12 mg per day. Pre-operatively she received 5 mg diazepam PO, 30 units of NPH insulin subcutaneously and 100 mg hydrocortisone i.v. Anaesthesia was induced using a total of 300 ug fentanyl, 10 mg diazepam and 200 mg thiopentone intravenously.

Force of thumb adduction was monitored in response to ulnar nerve stimulation (0.2 milliseconds at a frequency of 0.15 Hz) at the wrist via two percutaneous needle electrodes using a Grass FT10

force transducer and a Grass polygraph. Incremental doses of atracurium 0.065 mg kg -1 (5 mg) were given every four minutes until the twitch height was depressed to 5% of control. A total dose of 25 mg (0.33 mg kg -1) was required to achieve 95% depression of the control response (Figure 13). Two incremental doses of atracurium 5.0 mg each were given further as clinically indicated over the next hour. One hour after induction of anaesthesia halothane was added at an inspired concentration of 1.0% and up to 20 mg hydralazine was given to control hypertension. After the last 5 mg dose of atracurium the twitch was allowed to recover spontaneously to 95% of control. Arterial pH was maintained between 7.43 and 7.46 with a PaCO2 between 4-5 kPa. Serum sodium and potassium concentrations were normal and blood sugar was 233 mg dl -1. The 5-95% recovery time was estimated to be 83 minutes. The recovery index (25-75% recovery time) was 32 minutes (Figure 13). Four hours after induction of anaesthesia clinical relaxation was again required and further incremental doses of atracurium to a total of 20 mg were given over the next half hour without complete ablation of the first twitch of the train-of-four. The operation ended six hours after induction of anaesthesia and the patient was taken to the Intensive Care Unit. She was arousable and had a tidal volume of 300 ml. During the following hour she became more alert and her tidal volume increased to 400 ml with a vital capacity of 1600 ml and a negative inspiratory pressure of 40 cm H2O.

Decreasing rates of intermittent mandatory ventilation (IMV) were instituted followed by a trial of spontaneous ventilation with continuous positive airway pressure (CPAP). Four and a half hours

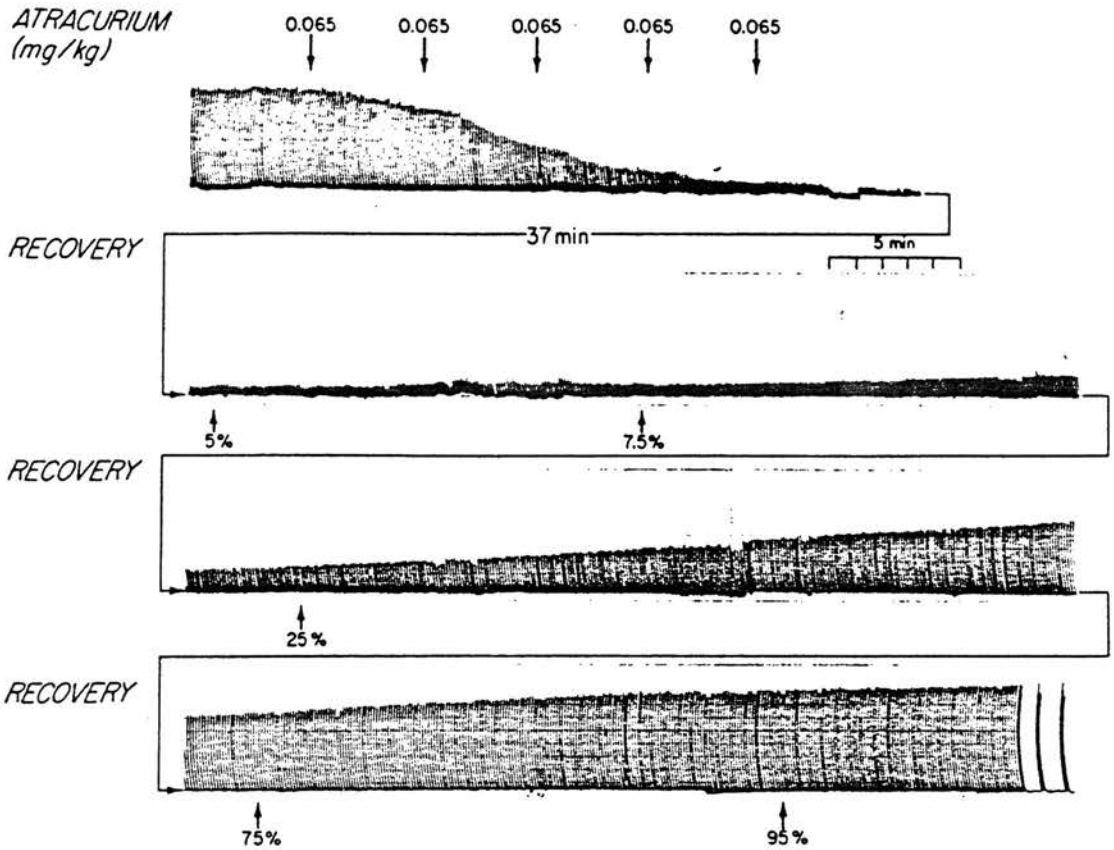


Figure 13

Evoked thumb adduction in response to ulnar nerve stimulation at 0.15 Hz. Upper panel de monstrates the response to five increments of atracurium of 0.065 mg kg -1 each. In the second panel, two further increments of 0.065 mg kg -1 were given 15 minutes after the arrow, (denoting 5%), with minimal effect. At the second arrow (7.5%) spontaneous recovery was allowed to occur. The following three arrows denote 25, 75 and 95% recovery of the single twitch compared with the control. Note at the end of the last panel (right side) train-of-four response showed almost complete recovery.

postoperatively her trachea was extubated without difficulty with a vital capacity of 1500 ml. Postoperatively she progressed well and was discharged on a daily dose of 12.5 mg prednisolone. Muscle function upon discharge was reported to be good.

Case 2

A 28 year old woman weighing 60 kg presented with a three year history of myasthenia gravis. She was admitted to undergo trans-sternal thymectomy for treatment of her disease. At the time of her admission the condition was well controlled with a daily dose of 480 mg pyridostigmine and steroid therapy. She had no bulbar symptoms or limb weakness. The night before surgery she was given a long acting spansule containing 180 mg of pyridostigmine. Anaesthesia was induced with 250 mg thiopentone intravenously and maintained with 60% nitrous oxide in oxygen and 1.5% inspired concentration of isoflurane. Her trachea was intubated without the use of muscle relaxants after spraying the vocal cords and trachea with 4% lignocaine. Anaesthesia was maintained thereafter with isoflurane 0.7% (end tidal concentration) and 60% nitrous oxide in oxygen and controlled ventilation. Thumb twitch was monitored visually in response to ulnar nerve stimulation at the wrist via percutaneous needle electrodes using train of four nerve stimulation. Initially 1 mg atracurium was administered intravenously with no visible effect. Five minutes later an additional 2 mg of atracurium was given (a total dose of 0.05 mg kg -1). This resulted in approximately 95% depression of the first twitch of the train-of-four response. Twenty five minutes later the train -of-four appeared to have

recovered completely. Upon completion of surgery 90 minutes after induction the patient received 10 mg pyridostigmine intravenously and her trachea was extubated shortly thereafter in the operating room. She was returned to the Intensive Care Unit in a stable condition. Postoperative course was uneventful.

Discussion

Previous reports [111-113] suggest that the response of patients with myasthenia gravis to non-depolarising relaxants (pancuronium and tubocurarine) is variable, probably depending on the stage of the disease, preoperative control and whether the patient is in remission. The use of atracurium has been reported previously in six myasthenic patients. In the first report [115] approximately 0.18 mg kg -1 of atracurium administered incrementally was required to suppress the evoked twitch tension to 95% of control response. In the second report [116] a total dose of 0.25 mg kg -1 atracurium given in three increments was required to depress the evoked compound action potential of the adductor pollicis muscle to 90% of control and 0.1 mg kg -1 in the third report [117]. In this report, the dose required to suppress evoked thumb adduction varied between 0.33 and 0.05 mg kg -1 respectively. It appears that as with other non-depolarising relaxants, the response of myasthenic patients to atracurium (onset and depth of block) is variable. In three of eight patients who received atracurium the ED95 (the effective dose to 95% twitch suppression) was not different from that reported in normal non-myasthenic patients [34, 47] (0.2 mg kg -1). The important finding in these reports is that the myasthenic patients who were given atracurium recovered spontaneously from their neuromuscular blockade within a relatively short time. In

our first case the recovery index (25-75% recovery time) and the 5-95% recovery time were 32 minutes and 83 minutes respectively compared with approximately 12 minutes and 30 minutes respectively in normal patients [47]. The recovery time was shorter in the other myasthenic patient. This relatively rapid spontaneous recovery from atracurium neuromuscular blockade as compared with the older relaxants tubocurarine and pancuronium may be related to its mode of biodegradation and elimination.

The 5-95% recovery time of 83 minutes in our first patient followed a total dose of atracurium of 0.46 mg kg -1. The latter dose is equivalent to two times the ED95 [47]. A comparable dose of tubocurarine and pancuronium would be approximately 1.0 mg kg -1 and 0.14 mg kg -1 respectively [101]. It is conceivable that if either of the latter two doses of tubocurarine or pancuronium were administered to this myasthenic patient the recovery from neuromuscular blockade would have been markedly prolonged in comparison with atracurium. This is based on the finding that the recovery from injection of tubocurarine 0.6 mg kg -1 and pancuronium 0.1 mg kg -1 to only 25% of control is 80.5 ± 6.9 minutes and 99.3 ± 15.0 minutes (mean ± SEM), respectively, in normal patients [101].

In summary, atracurium appears to be a reasonable choice for myasthenic patients to provide surgical relaxation when clinically indicated. This is primarily because of the relatively rapid rate of recovery.

P A R T I I

BWB1090U AND BWA938U

The development of two new benzylisoquinolinium ester non-depolarising muscle relaxants.

CHAPTER 10

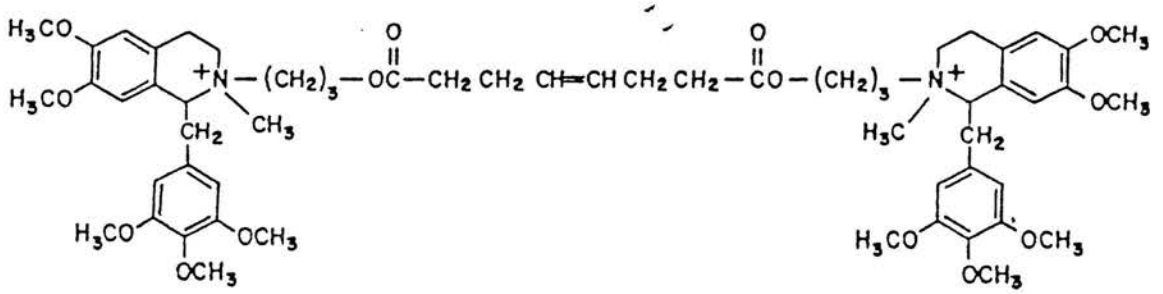
BWB1090U

Introduction

BWB1090U (Figure 14) is a unique compound developed by the Wellcome Research Laboratories in Research Triangle Park, North Carolina, in collaboration with John J Savarese, MD, of the Massachusetts General Hospital in Boston. Similar to several other experimental muscle relaxants that this group has developed, it is a bisbenzylisoquinolinium compound.

Initial pre-clinical pharmacological studies showed that BWB1090U was a potent neuromuscular blocking agent in dogs and cats. Complete paralysis was produced by intravenous doses of 0.02 to 0.06 mg kg -1. Onset was 3-5 minutes in the cat and dog. The time to 95% recovery of the ED95 dose (the dose that produces 95% suppression of the indirect twitch response) was approximately 15 minutes. These initial animal studies suggested that BWB1090U should be classified as 'short acting' with its duration in these animal models being approximately twice that of suxamethonium and one half that of the intermediate duration agents atracurium and vecuronium.

Neuromuscular blockade in the cat and dog was of the non-depolarising type as characterised by the absence of muscle fasciculations; the presence of tetanic fade; post-tetanic potentiation; and antagonism of the block by acetylcholinesterase inhibitors. The rapid recovery of neuromuscular transmission



BWB1090U

Figure 14

Chemical structure of BWB1090U

following termination of prolonged (1½ - 3 hours) 95-100% neuromuscular blockade produced by continuous intravenous infusion of BWB1090U suggests that the drug exhibits no cumulative properties in the cat or dog.

Pre-clinical animal studies also revealed that BWB1090U had no significant cardiovascular effects at doses that produce partial to complete neuromuscular paralysis in cats and dogs. Doses up to 15-20 times the ED95 dose were essentially devoid of cardiovascular and haemodynamic effects in these animals.

The effects of BWB1090U on the autonomic nervous system were evaluated in cats. Doses as high as 25-50 times the ED95 dose did not affect the contraction of the nictitating membrane in response to sympathetic nerve stimulation, and only minimally decreased (less than 10% of base line values) the cardiac and vasopressor response to parasympathetic (vagus) nerve stimulation.

Pre-clinical investigation showed that BWB1090U is a substrate for plasma cholinesterase; hence the duration of neuromuscular blockade may be influenced by the concentration and activity of this enzyme. The rate of hydrolysis of BWB1090U by purified human cholinesterase is approximately 90% of the rate of hydrolysis of suxamethonium. It is likely that the brief action of BWB1090U may be explained by rapid enzymatic breakdown in plasma; however, the relative roles of the plasma, liver and kidneys in determining the pharmacokinetic profile invivo remain to be determined. It should be noted that it is the acetyl-choline-like ester of BWA1090U that permits hydrolysis by plasma cholinesterase whereas the reversed ester group in atracurium facilitates the Hofmann reaction.

On the basis of these initial animal studies it was decided to study the effects of BWB1090U in the Rhesus monkey. This animal model probably parallels the human situation in terms of neuromuscular blockade more closely than any other model. Furthermore, the Rhesus monkey tends to be more sensitive to the histamine releasing effects of neuromuscular blocking agents, the most important side effect of the benzylisoquinolinium group of drugs.

CHAPTER 11

COMPARATIVE PHARMACOLOGY OF BWB1090U IN THE RHESUS MONKEY

In this study the neuromuscular and cardiovascular effects of BWB1090U in the Rhesus monkey are reported.

Methods

Adult Rhesus monkeys (n=6) of either sex weighing 8-13 kg were anaesthetised with thiopentone 30 mg kg -1 and diazepam 1 mg kg -1 i.m. The trachea was intubated and anaesthesia maintained with halothane (0.5 - 1.0%) in nitrous oxide and oxygen (70:30 ratio). Intermittent positive pressure ventilation was instituted using a small animal ventilator but no muscle relaxant was administered at this stage. The peroneal nerve was stimulated by a Grass S44 stimulation unit at 0.15 Hz. A small slither of tendon was dissected out and attached via silk to a Statham strain gauge (Figure 15) and the force of the indirectly elicited twitch of the tibiallis anterior muscle was measured. The intra-arterial pressure, heart rate and single twitch were recorded on a Grass polygraph (Figure 15). Ventilation was controlled to maintain normal arterial gas values. Cumulative dose response curves for neuromuscular blockade and cardiovascular effects were constructed. Appropriate statistical comparisons were made by T test, analysis of variance or linear regression on probit values.

In five separate experiments the neuromuscular and cardiovascular effects of a very large dose of BWB1090U (0.2 mg kg -1 or five times ED95) were noted when BWB 1090U was given as a first bolus to

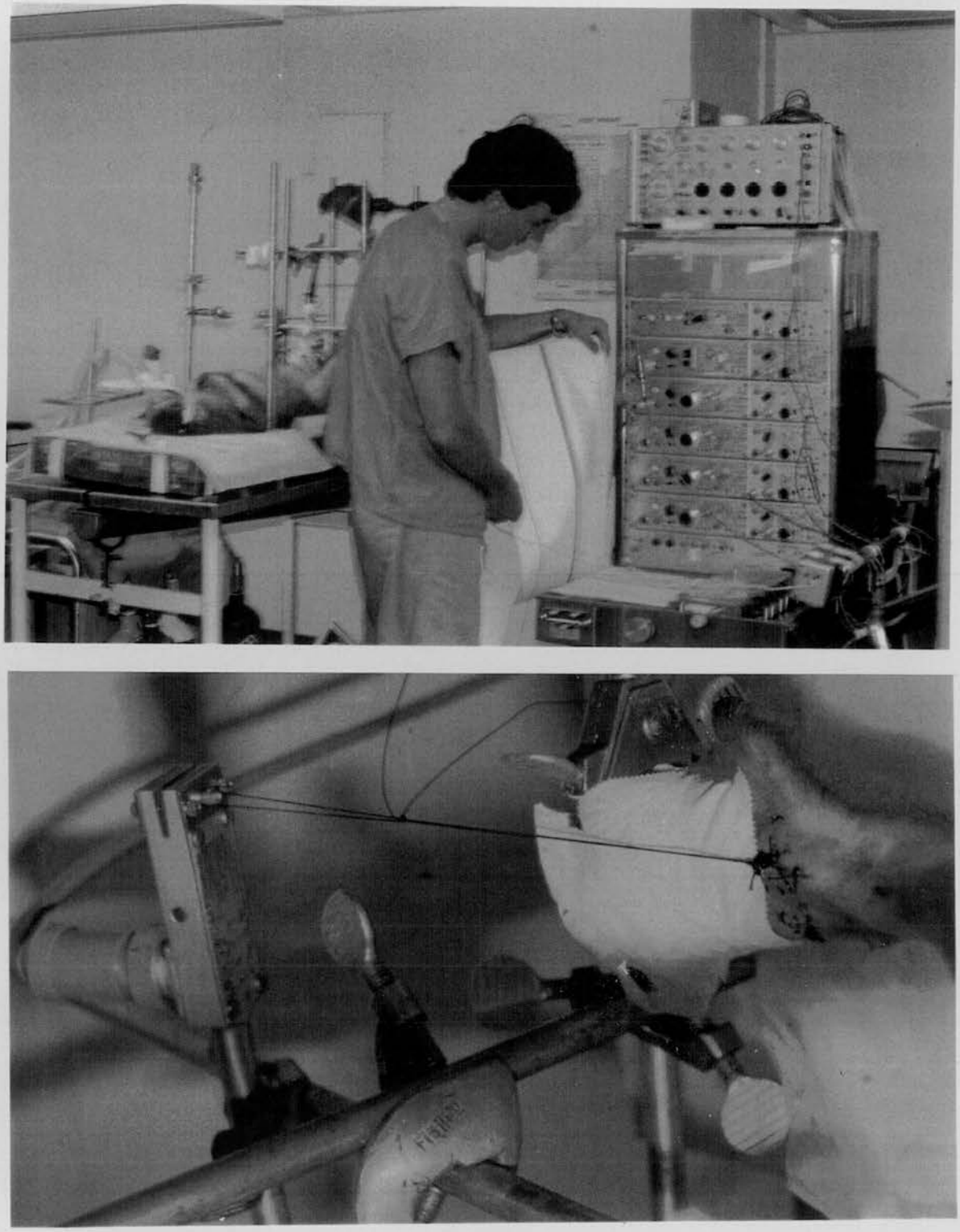


Figure 15A

The Grass neuromuscular nerve stimulator and polygraph used for recording neuromuscular and haemodynamic data derived from Rhesus monkeys.

Figure 15B

The Statham strain guage attached to a slither of tendon by silk.

virgin preparations. Ninety five percent block was then re-established and maintained by continuous infusion for two hours. Recovery times from bolus doses and infusion were compared.

Results

Using a cumulative dose response approach, the ED95 was calculated to be 0.04 mg kg -1. The duration of action at this dose was 13 minutes. At 2½ times the ED95 the duration was 17 minutes and at five times the ED95 was 21 minutes. Onset times and recovery rates are summarised in Table 23, specific details of the first bolus virgin preparation study at 0.2 mg kg -1 are given in Table 24. The continuous infusion data are reported in Table 25.

Cardiovascular changes only became significant at 0.8 mg kg -1 (20 times ED95) (Figure 16). Cardiovascular effects after five times ED95 (0.2 mg kg -1) when given either as the fourth dose in the series or as the first dose to a virgin preparation were not different and did not differ significantly from control values. However, changes at 0.8 mg kg -1 were accompanied by facial erythema, showed tachyphylaxis and were inhibited by H1 and H2 blockers.

The neuromuscular blockade showed fade of tetanus and train-of-four which was antagonised by anticholinesterases.

Discussion

In 1979 Savarese [118] and colleagues described the pre-clinical pharmacology in the Rhesus monkey of BW785U, a short acting non-depolarising ester neuromuscular blocking agent. During a

Dose mg kg -1	ED95 Multiple	% Block	Onset (min)	25-75%	Recovery Time 5-95%	Duration 0-95% (± SD)
0.01		0	-	-	-	-
0.02		68				8 ± 4
0.04	1	95	1.7	3.4	8.5	13 ± 3
0.10	2.5	100	1.4	3.5	8.6	17 ± 6
0.20	5	100	1.0	4.1	9.1	21 ± 3
0.40	10	100				27 ± 4
0.80	20	100				36 ± 5

Table 23

Part A - BWB1090U: Neuromuscular blocking effects in the Rhesus monkey. Single twitch stimulation at 0.15 Hz.

Monkey	Wt	Dose	Max %	Onset Secs	95% Recovery Mins	5-95%	5-25%	25-75%	▲BP(%C)	▲HR(%C)
Wormtongue	9.2	0.2	100	40	14	6	1	2	120/100 120%	90/100 90%
Wojo	11.2	0.2	100	60	14	6.7	1.4	3.4	100/90 111%	90/90 100%
Ectasia	14.2	0.2	100	60	20.5	12.2	1.2	4.5	100/93 107.5%	125/125 100%
Boniface	12.9	0.2	100	75	21	12.5	2.5	7	105/85 123.55%	120/125 96%
Wilhelmina	7.8	0.2	100	105	16.2	11	2.5	3.2	112/105 106.6%	95/95 100%
				68(±24)	17.14	9.68	1.72	4.02	113.7	97.2

Table 24

Part B - BWB1090U: Neuromuscular effects in the Rhesus monkey.
First bolus virgin preparation study.

Monkey	95% Blocking Rate	Duration	5-95%	5-25%	25-75%
Wormtongue	9 μg/kg/min	2 hrs	4.5	2	1.5
Wojo	13 μg/kg/min	2 hrs	8	2	2.2
Ectasia	7 μg/kg/min	2 hrs	12.5	2.7	3.2
Boniface	7.5 μg/kg/min	2 hrs	15.5	3.5	6.5
Wilhelmina	17 μg/kg/min	2 hrs	10	3	3
	10.7 (± 4.2)		10.1±4.2	2.64	3.28

Table 25

Part C - BWB1090U: Neuromuscular blocking effects in the Rhesus monkey
Infusion study.

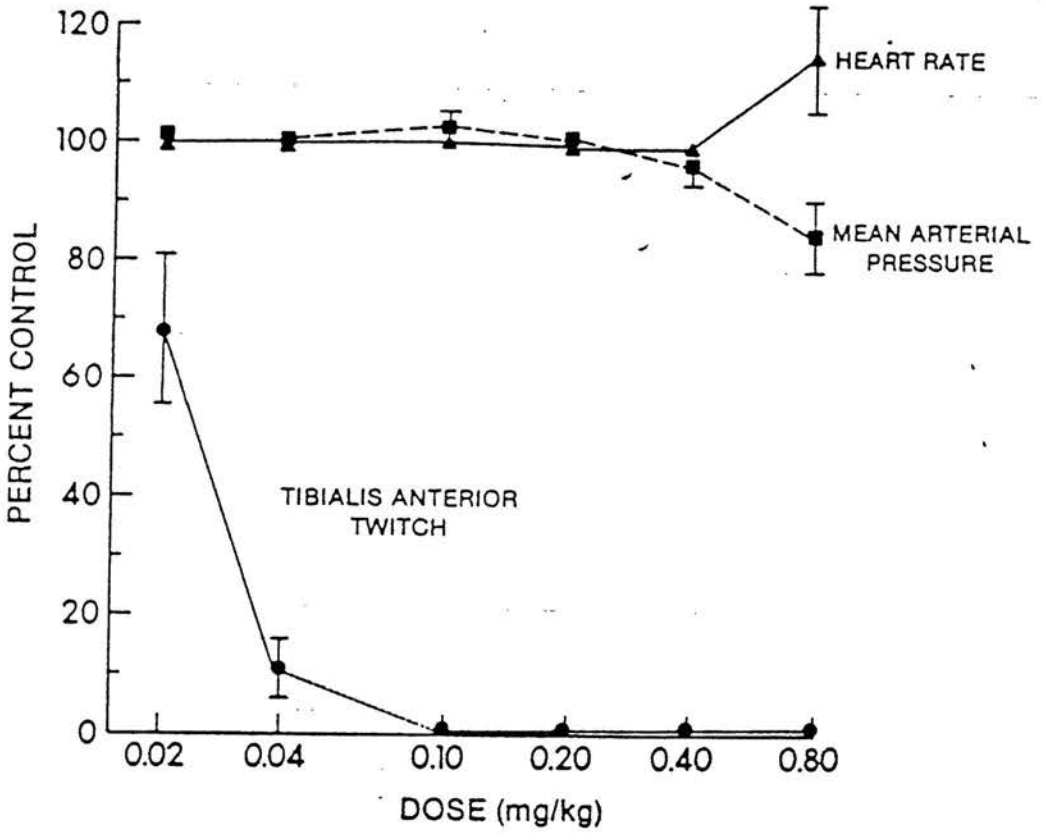


Figure 16

The effects of bolus intravenous injections of BWB1090U on mean arterial pressure, heart rate and tibialis anterior twitch in Rhesus monkeys anaesthetised with N2O/O2/halothane. The results are expressed as a percentage of the initial control values prior to drug treatment. The initial mean arterial pressure and heart rate was 88 ± 4 mm Hg and 116 ± 5 bpm, respectively. Each point represents the mean ± SE of six animals, respectively. The mean duration of neuromuscular blockade at the 0.02, 0.04, 0.10, 0.20, 0.40 and 0.80 mg kg -1 dose was 8 ± 4, 13 ± 3, 17 ± 6, 21 ± 3, 27 ± 4 and 36 ± 5 minutes.

brief clinical trial the neuromuscular blocking activity of BW785U was found to be very short. However, it had been noted to cause hypotension in animals when doses equivalent or greater than the ED95 were administered. This effect, apparently due to histamine release, was much more prominent in humans and forced the cancellation of further trials [30]. Additional structure activity studies have since led to the development of BWB1090U. Like BW785U, BWB1090U is a short acting non-depolarising agent.

From this study and other animal studies it appears that the duration of action of BWB1090U is about one third to one half of that of atracurium. The pharmacodynamics in the three animal species that have been studied, namely the cat, dog and Rhesus monkey, are similar. However, while the onset time in the cat and dog was 3-5 minutes, in the Rhesus monkey it was only 60-70 seconds, a value approaching that of suxamethonium.

The margin of safety for cardiovascular side effects would appear to be 10 times as great when compared with BW785U in the Rhesus monkey. Only supramaximal neuromuscular blocking doses (0.8 mg kg -1, 20 times ED95) of BWB1090U produced transient decreases in mean arterial pressure and transient increases in heart rate in the Rhesus monkey. The magnitude of these effects was less than 15% of baseline values. It is concluded that BWB1090U has no significant cardiovascular effects at doses that produce partial or complete neuromuscular paralysis in cats, dogs or Rhesus monkeys.

From this study and from previous animal studies it seemed that BWB1090U was worthy of clinical trial.

CHAPTER 12

NEUROMUSCULAR AND CARDIOVASCULAR EFFECTS OF BWB1090U IN ANAESTHETISED VOLUNTEERS

Introduction

Prior to the volunteer study pre-clinical safety studies were carried out. These consisted of: (a) a three week assessment of toxicity following multiple i.v. bolus and infusion doses of BWB1090U in beagle dogs; (b) a 14 day subcutaneous toxicity study in rats; (c) a seven day perivenous and intramuscular irritation study in beagle dogs; and (d) a subcutaneous teratology study over gestation days 6 to 15 in pregnant rats. No toxicopathological or teratogenic effects related to drug administration were observed.

Pre-clinical investigation shows that BWB1090U is a substrate for plasma cholinesterase; hence the duration of neuromuscular blockade may be influenced by the concentration and activity of this enzyme. It is possible that the brief action of BWB1090U may be explained by rapid enzymatic breakdown in plasma; however, the relative roles of the plasma, liver and kidneys in determining the pharmacokinetic profile in vivo remain to be determined.

On the basis of the pre-clinical studies it was concluded that BWB1090U is a neuromuscular blocking agent with potential clinical advantages over currently available agents because of its short action, rapid onset and lack of cardiovascular and autonomic nervous system effects in animal models at doses within clinically useful range. Investigation of the safety and efficacy of BWB1090U

in clinical trials was thus considered justified.

Objectives

1. To evaluate the safety of single i.v. bolus injections of BWB1090U and of single bolus injections followed by continuous i.v. infusion of BWB1090U in anaesthetised volunteers.

2. To determine whether i.v. bolus injections of BWB1090U produce suppression of muscle twitch and to estimate the onset, duration and dose response curve for neuromuscular blockade.

3. To estimate the rate of i.v. infusion of BWB1090U required to maintain 95% suppression of twitch tension for up to two hours.

4. To estimate the rate of spontaneous recovery of neuromuscular transmission following bolus injection and following cessation of infusion of BWB1090U and to determine whether neostigmine can reverse the blocking effect of BWB1090U.

Methods

Eighteen (ASA 1) male volunteers (ages 21-40) gave institutionally approved written informed consent. The volunteers were taking no medications and had no significant medical or surgical history. They received no premedication. Arterial and venous cannulae were placed under local anaesthesia.

General anaesthesia was induced with fentanyl (6-8 μg kg -1) and thiopentone (6-8 mg kg -1) and the trachea was intubated under topical anaesthesia. Ventilation was controlled with nitrous oxide and oxygen (4 litres to 2 litres) to maintain end tidal carbon dioxide in the range of 4-5 k Pa. The ulnar nerve was stimulated by needle electrodes with supramaximal pulses to elicit the single twitch adductor response of the thumb at 0.15 Hz. A Grass S44 peripheral nerve stimulator was used. Intra-arterial blood pressure, heart rate (by a tachograph) and single twitch were simultaneously recorded on a Grass polygraph. After a 15 minute stable base line period BWB1090U was injected as a rapid bolus (5-10 seconds) into a rapidly running intravenous stream.

Volunteers number 1 and 2 received graded doses spaced 15-30 minutes apart until 10-20% depression of the twitch was achieved. Volunteers number 3-18 each received a single bolus dose of BWB1090U. Dosage was increased in a graded sequence in volunteers number 3-18 from 0.04 - 0.25 mg kg -1. In volunteers numbers 7-18 a second dose of BWB1090U was given after complete recovery from the first dose in order to re-establish full paralysis of the twitch. When 5% twitch recovery was achieved from this dose an infusion of BWB1090U was begun. The infusion rate was controlled to maintain 90-95% twitch depression for 30-120 minutes. Infusion duration (30, 60, 90 and 120 minutes) was increased sequentially in pairs of volunteers. Volunteers number 13-18 received the longest infusions (120 minutes). When the infusion was terminated spontaneous recovery was observed in the odd numbered individuals. In the even numbered volunteers antagonism of residual blockade was tested by administering neostigmine (0.06 mg kg -1) and atropine

(0.03 mg kg -1).

Results were analysed where appropriate by linear regression on probit values by analysis of variance and by Students T test.

Results

The individual pharmacodynamic and haemodynamic data for each patient is displayed in Table 27. The neuromuscular data is summarised in Tables 26 and 28. Figure 17 displays the neuromuscular and cardiovascular dose response curves which were constructed for BWB1090U.

The ED95 was found to be approximately 0.07 mg kg -1. The duration of action (injection to 95% return of twitch) was 26.3 minutes at 0.1 mg kg -1, the lowest dose producing 100% block.

Spontaneous recovery time (5-95%) averaged 15.8 minutes for all doses above 0.08 mg kg -1 (n=10). Corresponding time after 1-2 hour infusions (n=5) averaged 16.9 minutes. Similarly recovery times (25-75%) averaged 7.5 minutes and 6.9 minutes after all single bolus doses producing 100% block (0.1 - 0.25 mg kg -1) and after 1-2 hour infusions respectively. The differences were not significant. In six cases where neostigmine was given to antagonise residual block at the end of an infusion, reversal from an average twitch height of 20-25% required 5.6 minutes. The 25-75% recovery time averaged 2.6 minutes.

At up to 0.15 mg kg -1 changes in heart rate and arterial pressure were less than 5%. At 0.2 and 0.25 mg kg -1 (approximately 3-4

Dose (mg kg -1)	n	% Block	Onset (min)	Average Duration to 95% (min)*	Average 5-95% Recovery (min)	
0.024	2	12	3.2	6.9	-	
0.04	2	62	4.0	15.6	-	
0.06	2	70	4.0	20.6	-	
0.08	2	75	4.3	14.6	-	
0.10	2	100	3.8	26.3	15.9	
0.15	2	100	2.7	34.6	18.7	
0.20	3	100	2.5	29.0	15.8	Average = 15.8
0.25	3	100	1.7	32.0	13.7	

* to 95% of control twitch

Table 26

BWB1090U: Pharmacodynamic data in volunteers.

Pt	Bolus mg/kg	Onset (min)	Max % Block	Duration of 100% block	Inj-95% (min)	5-95%	25-75% (%c)	MAX▲MAP (%c)	MAX▲HR	Flush
3	0.04	3.5	32	-	12.7	-	-	66-65 (98)	62-60 (97)	None
4	0.04	4.5	90	-	18.5	-	6.0	93-94 (101)	52-51 (96)	None
5	0.06	3.5	27.5	-	11.2	-	-	76-78 (103)	56-59 (105)	None
6	0.06	4.5	100	4.0	30.0	20.0	9.2	91-89 (98)	60-56 (93)	None
7	0.08	4.5	63	-	14.5	-	-	61-62 (102)	56-55 (98)	None
8	0.08	4.0	85	-	14.7	-	6.0	91-93 (102)	55-53 (96)	None
9	0.10	3.5	100	6.0	24.5	13.5	5.2	80-81 (101)	60-63 (95)	None
10	0.10	4.0	100	3.0	28.0	18.2	7.7	92-91 (99)	44-40 (91)	? Very slight
11	0.15	2.2	100	16.2	40.2	19.2	9.7	75-73 (97)	54-53 (98)	Very slight
12	0.15	3.2	100	5.7	28.7	18.2	10.2	80-75 (94)	70-71 (101)	Slight
13	0.20	2.5	100	12.5	45.0	25.0	11.5	61-46 (75)	60-76 (127)	Slight
14	0.20	3.2	100	2.7	16.0	9.0	4.0	77-59 (77)	70-74 (106)	Mild
15	0.25	1.7	100	9.2	23.2	11.0	5.7	81-72 (89)	66-73 (111)	Mild
16	0.25	1.7	100	12.0	26.7	11.7	5.5	82-58 (71)	55-66 (120)	Moderate
17	0.25	1.7	100	10.2	26.5	13.5	6.7	82-38 (46)	50-88 (176)	Slight
18	0.25	1.7	100	22.7	46.0	18.5	9.2	63-52 (83)	42-58 (138)	Mild

Table 27

BWB1090U: Volunteer study pharmacodynamic data for individual patients
(%c) = change expressed as a percentage of baseline values.

Pt	Duration of Inf (min)	% Rec at term. of Inf	Inf off - 95% (mins)	25-75% (mins)	% Rec at Reversal *	Rev - 95% Rec (mins)	25-75%
7	30	8%	13.0	5.2	-	-	-
8	32	-	-	-	18.0	2.5	2.0
9	60	2	15.0	5.2	-	-	-
10	69	-	-	-	30.0	4.0	-
11	90	7	21.2	9.5	-	-	-
12	83.5	-	-	-	22.0	5.5	2.5
13	121.0	2	28.0	12.0	-	-	-
14	120.5	-	-	-	23.0	3.0	-
15	120.0	2	9.5	4.7	-	-	-
16	121.0	-	-	-	5.0	11.5	4.5
17	120.0	5	11.0	5.0	-	-	-
18	120.0	-	-	-	28	4.2	2.5
Means		4.3	16.3	6.9	22	5.6	2.6

* Reversal with neostigmine (60 μg kg -1) and atropine (30 μg kg -1)

Table 28

BWB1090U: Volunteer study; infusion study data.

Neuromuscular and cardiovascular effects of BWB1090U in human subjects under N2O/narcotic/barbiturate anaesthesia

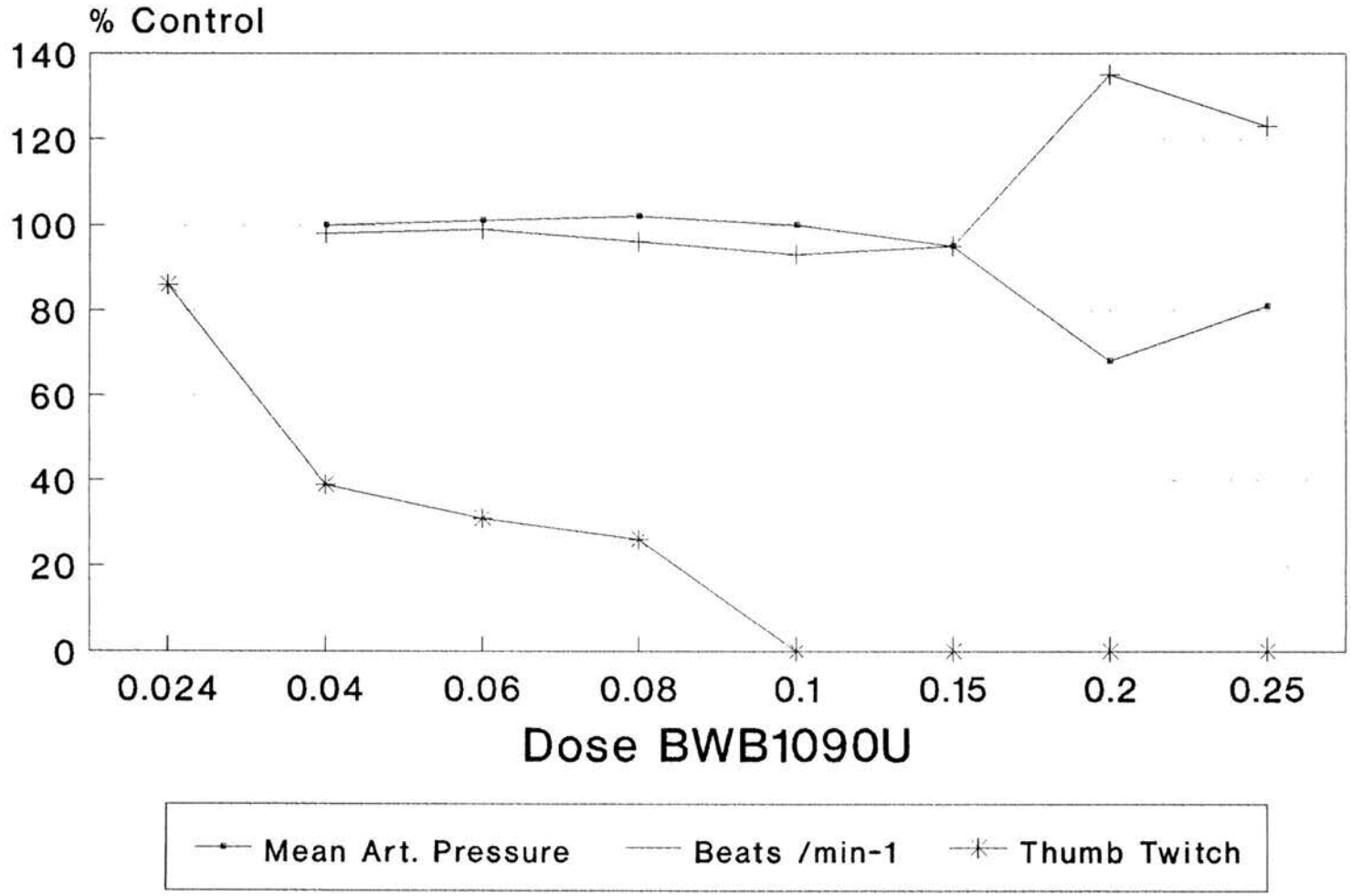


Figure 17

times the ED95) decreases in arterial pressure and increases in heart rate were noted. In the six individuals who received these highest doses heart rate increased an average of 25% and arterial pressure decreased an average of 25%. These changes were brief, lasting 1-3 minutes.

Conclusion

BWB1090U would appear to be a potent non-depolarising neuromuscular blocking drug with a short duration of action, minimal cumulative effect and reasonable cardiovascular safety. Previous experience with benzylisoquinolinium compounds would suggest that the transient change in haemodynamic parameters observed were most likely to be due to histamine release.

Because of BWB1090U's unique neuromuscular profile further studies in surgical patients seemed justified.

The author was subsequently involved in the first clinical trial of BWB1090U (Mivacurium Chloride) [135].

CHAPTER 13

BWA938U

Introduction

In 1975 Savarese and Kitz publicised the deficiencies of available neuromuscular blocking agents and identified in particular the need for a novel short acting muscle relaxant but also for intermediate and long acting non-depolarising blockers that would be free of cardiovascular effects and not show cumulative effects upon repeated administration. This thesis has examined in detail the intermediate duration muscle relaxant atracurium and has reported initial studies with the short acting agent BWB1090U.

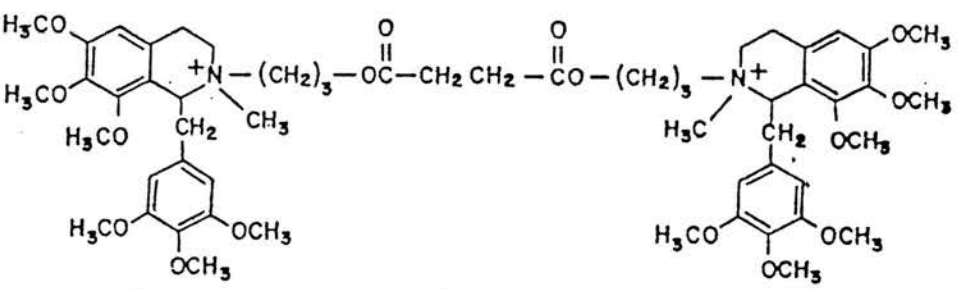
The search for a new long acting agent has continued because cardiovascular effects and cumulative properties are associated with the available long acting agents such as pancuronium, metocurine, tubocurarine and gallamine [101, 119, 120]. The well described vagolytic properties of pancuronium infrequently have clinical consequences in normal patients, but may be particularly deleterious in patients with cardiovascular disease. Metocurine lacks vagolytic effects and is frequently used to induce neuromuscular blockade in patients with cardiovascular disease in the United States. However, the histamine releasing potential of metocurine often requires that this agent be administered as a slow bolus or in divided doses to avoid adverse haemodynamic sequelae. The induction of tachycardia by gallamine and the histamine releasing and ganglion blocking activities of tubocurarine generally prevent the routine use of either agent in patients with

cardiovascular disease and may limit their use in normal patients.

The cumulative effects of the most commonly used long acting agent pancuronium have been well described. Fahey et al [121] demonstrated that the duration of action of repeated injections of pancuronium (0.02 mg kg -1) increased from 50 minutes following the first dose to 120 minutes following the fourth dose. Such cumulation makes the appropriate timing of pancuronium maintenance doses difficult to predict in the clinical setting.

The Wellcome Research Laboratories have been involved with an ongoing programme to develop novel long acting non-depolarising neuromuscular blocking agents. A result of this programme is BWA938U dichloride (Figure 18).

Pharmacological studies performed at the Wellcome Research Laboratories in cats, dogs and Rhesus monkeys have shown that BWA938U is a potent neuromuscular blocking agent. Compared with atracurium, BWA938U was more potent, had a longer onset time and a significantly longer (2-4 times) duration of action. The ED95 neuromuscular blocking dose for BWA938U in the monkey was estimated to be 0.017 mg kg -1 with a duration of action (time from injection to 95% recovery) estimated to be 50-60 minutes. Importantly, comparisons of the patterns of recovery in monkeys after single bolus injections and after a final dose in a series of five consecutive maintenance doses indicated than BWA938U had no cumulative properties. BWA938U induced neuromuscular blockade could be effectively antagonised by neostigmine and edrophonium in these studies.



BWA938U

Figure 18

Chemical structure of BWA938U

The safety of BWA938U was studied in monkeys, dogs and cats. Bolus doses approximating five times and ten times the estimated dog ED100 doses were administered to anaesthetised dogs. These doses produced no or minimal effects on arterial blood pressure and heart rate. In dogs a cumulative BWA938U dose equivalent to 62 times the ED100 resulted in minimal (less than 15-20%) transient changes in mean arterial blood pressure and heart rate immediately following the final (32 times the ED100) BWA938U dose.

In doses that produced 95-100% neuromuscular blockade BWA938U had no effect on sympathetic or parasympathetic efferent pathways in the cat. High cumulative doses (greater than 50 times the ED95) produced no or minimal inhibition of the contraction of the nictitating membrane in response to pre-ganglionic stimulation and there were no vasodepressor or bradycardic responses to vagus nerve stimulation.

BWA938U was found to be a weak substrate for plasma cholinesterase. The rate of hydrolysis by human cholinesterase was estimated to be 6% of the rate of suxamethonium hydrolysis. The relative roles of plasma enzymes, the liver, and the kidney in the disposition of BWA938U remain to be determined.

Pre-clinical toxicology studies for BWA938U consisted of:

1. A three week assessment of toxicity following multiple intravenous doses of BWA938U in beagle dogs.

2. A perivenous and intramuscular irritation study in beagle dogs.

3. A 14 day subcutaneous toxicity study in rats.

4. A subcutaneous teratology study over gestation days six through 15 in pregnant rats.

No toxicopathological or teratogenic effects relating to BWA938U were observed in these studies. However, during the subacute intravenous toxicity study, dogs receiving BWA938U often produced a thick viscous saliva during recovery from anaesthesia that was not observed in control dogs. The mechanism and significance of this effect remain to be determined.

On the basis of these pre-clinical studies it was concluded that BWA938U is a long acting neuromuscular blocking agent with potential advantages over currently available agents (eg, pancuronium, tubocurarine, metocurine) because its effects are non-cumulative upon repeated administration and would appear to be devoid of cardiovascular effects at several multiples of the estimated clinically useful dose.

These properties justified investigation of BWA938U in a volunteer study.

CHAPTER 14

A PILOT STUDY OF THE SAFETY AND EFFICACY OF BWA938U IN VOLUNTEERS UNDER NITROUS OXIDE/NARCOTIC ANAESTHESIA

Objectives

1. To evaluate the safety of intravenous bolus injections of BWA938U at several dose levels in anaesthetised volunteers.

2. To determine the dose of BWA938U required to produce muscle twitch suppression; to estimate the onset, depth and duration of neuromuscular blockade produced by several BWA938U doses; and to estimate the BWA938U dose-response relationship.

3. To estimate the spontaneous recovery rate from BWA938U induced neuromuscular blockade and obtain initial estimates of the reversibility of BWA938U induced neuromuscular blockade.

This was an open escalating dose study in which healthy volunteers received one or more intravenous bolus injections of BWA938U while under steady state nitrous oxide/oxygen narcotic anaesthesia. The initial eight volunteers were studied in order to obtain a preliminary estimate of the BWA938U dose response relationship and safety. The safety and efficacy of BWA938U administered at increasing multiples of the estimated ED95 was subsequently studied in five further volunteers.

Methods

Each volunteer received 2-5 ug kg -1 of fentanyl prior to the induction of general anaesthesia with 4-6 mg kg -1 of thiopentone intravenously. The volunteers were maintained on nitrous oxide (4 litres per minute) and oxygen (2 litres per minute) for the duration of the base line and treatment phases. Thiopentone (2-3 mg kg -1) and/or fentanyl (0.5 - 2.0 ug kg -1) were administered intravenously as required to maintain the desired depth of anaesthesia.

Blood pressure was monitored using intra-arterial cannulae, 12 lead electrocardiographs were obtained and plasma histamine levels were measured before and after bolus administration of BWA938U.

The ED50, ED75 and ED95 doses were estimated using the observed responses to BWA 938U using a cumulative dose response technique for volunteers 1-2, 1-4 and 1-6 respectively. The first eight volunteers were each allowed to spontaneously recover from the BWA938U induced neuromuscular blockade.

Once recovery was complete, (T4:T1 ratio 0.75 or greater) each of these volunteers received the same bolus dose which was initially administered (ie, estimated ED50, ED75, ED95). Once the response to this second BWA 938U dose was maximal each volunteer received sufficient cumulative doses (as required) of BWA938U to approach the 95% twitch suppression range. Once 90-99% twitch suppression was obtained one volunteer from each pair (ie, numbers 3, 5 7) was allowed to undergo spontaneous recovery to greater than 95% recovery. The second volunteer of each pair (ie, number 4, 6 8)

was allowed to spontaneously recovery to approximately the 25% recovery level. At approximately this level of recovery reversal of neuromuscular blockade in each of these volunteers was attempted with an intravenous bolus dose of neostigmine (0.06 mg kg -1) in conjunction with atropine (0.03 mg kg -1).

Volunteers 9-13 received single i.v. bolus doses of BWA 938U according to an escalating design (ie, an ED95 multiple) each volunteer was allowed to spontaneously recover to at least 25% twitch height. No additional doses were administered. The decision to proceed to each successive dose level was based on the investigators and medical monitors clinical evaluation of responses observed at previous dose levels.

Intra-arterial blood pressure, heart rate and single twitch were continuously recorded on a Grass polygraph.

Results

Table 29 shows the efficacy data from this study. Onset and duration of neuromuscular blockade following BWA938U administration appeared to be dose dependent. Neuromuscular blockade was reversible with neostigmine once spontaneous recovery was underway. There were no consistent or clinically significant effects on mean arterial pressure or heart rate (Table 30) after administration of BWA938U at doses up to approximately four times the estimated ED95.

Conclusion

BWA938U was found to have a long duration of action in volunteers receiving nitrous oxide narcotic anaesthesia. Increasing the

BWA938U Dose (μg kg -1)	no	Maximum Block %	Onset Maximum Block (min)	Duration* 25% (min)	Recovery* 95% (min)
12	2	70	11.9	27.8	61.7 +
18	2	68	13.8	32.5	81.2 +
25	2	97	9.5	47.3	70.0 +
36	2	100	4.9	87.5	216.5 +
48	2	99	5.6	58.2	104.0
72	2	100	3.7	151.0	-
96	1	100	2.5	204.0	-

* Indicates time from injection to 25% and 95% recovery

+ Indicates recovery data available from one volunteer only

Table 29

Neuromuscular effects of BWA938U in volunteers

BWA938U Dose (μg kg -1)	no	HR (% Control)	MAP (% Control)	Plasma Histamine (% Control)
25	2	100	105	144
36	2	98	99	66
48	2	96	98	66
72	2	100	101	73
96	1	100	93	163

Table 30

Maximum percent change in heart rate (HR), mean arterial pressure (MAP), and plasma histamine 2 minutes following BWA938U administration.

BWA938U dose produced dose related increases in the depth and duration of neuromuscular blockade as well as decreases in onset time.

BWA938U appears to be devoid of effects on mean arterial pressure and heart rate at doses greater than three times the ED95. No patient was observed to develop a precipitous blood pressure decrease consistent with histamine release. There was no significant rise in histamine levels following administration of BWA938U. This data indicates that BWA938U is devoid of haemodynamic effects when administered in clinically useful doses. This profile may represent an important safety advantage for BWA938U when compared to other long acting neuromuscular blocking agents that have the potential for significant haemodynamic effects in individual patients (ie, pancuronium, tubocurarine).

CHAPTER 15

DOXACURIUM CHLORIDE: A PRELIMINARY CLINICAL TRIAL

As a result of the initial animal studies and of the volunteer study reported in the previous chapter, preliminary clinical studies were commenced in the USA. These investigations suggested that doxacurium was a potent, long acting drug, devoid of cardiovascular and histamine releasing side effects at clinically effective doses [122, 123]. The ED95 dose to block contraction of the adductor pollicis muscle was reported to be approximately 25 ug kg -1.

The following study was the first investigation of doxacurium chloride performed in Europe. The study was designed to assess its onset, intubation conditions, effect of multiple increments and ease of antagonism with edrophonium and neostigimine. A preliminary report of this study was presented to the Anaesthetic Research Society.

Methods

Twenty seven ASA Class 1 or 2 adult patients (weights 45 - 100 kg) scheduled to undergo elective surgery expected to last 120 minutes were studied. Each patient gave written, informed consent for this study, which was also approved by the local hospital ethics committee.

The patients were premedicated with papaveretum (15-20 mg kg -1), and hyoscine (0.3 - 0.4 mg kg -1) i.m. one hour before surgery.

Before induction of anaesthesia, the skin over one forearm and the hand was degreased using an alcohol solution. Five silver-chloride electrodes were placed, two over the ulnar nerve, one over the midpoint of the distal skin crease at the wrist, one over the palmer aspect of the head of the fifth metacarpal, and one over the belly of the adductor pollicis muscle. These were connected to a Datex Relaxograph. Anaesthesia was induced with thiopentone (5 mg kg -1) iv, and fentanyl (2-3 μg kg -1) iv

Neuromuscular monitoring was commenced using train-of-four stimuli (2 Hz at 20 second intervals) to the ulnar nerve and the gated rectified and integrated EMG from the adductor pollicis was recorded. The size of the gain setting, supramaximal stimulus and the stimulus artefact were noted. Anaesthesia was maintained with 66% nitrous oxide in oxygen, and the lungs were ventilated artificially to maintain normocapnia. The patients were allocated to three groups of nine and patient order was randomised. Following randomisation, the first 18 patients studied (and hence the last nine also) were equally divided between the three groups. When an initially stable record was obtained, doxacurium 37.5 ug kg -1 i.v. (1.5 x ED95) was administered to group A, and 62.5 ug kg -1 i.v. (2.5 x ED95) to groups B and C with the bolus being given either into a continuous infusion or flushed through a cannula with a 5 ml bolus of saline. The bolus was given to coincide with a train-of-four sequence to give an accurate time mark on the record.

Intubation conditions were assessed by the same investigator (RPFS) each time at four minutes after the administration of doxacurium in groups A and B and at three minutes in group C. The conditions

were graded on a scale of 1-4 (excellent, good, poor or not possible) [124].

The onset of block was determined as the time from injection to the appearance of either complete block or the maximum degree of block. Following maximal block, anaesthesia was maintained with nitrous oxide in oxygen plus 0.5% halothane. Additional doses of fentanyl and thiopentone were administered as required. When the first response of the train-of-four (T1) had recovered to 20% of control, a bolus of doxacurium 5 ug kg -1 was given; this was repeated when T1 had recovered again to 20%. The duration and degree of block produced by each increment were noted.

At the end of surgery, when T1 had recovered to greater than 10% of control, the residual block was antagonised with edrophonium 1 mg kg -1 intravenously in the first 18 patients (six in each of groups A, B and C) and neostigmine 50 μg kg -1 i.v. in the last nine patients (n=3 in each group). Glycopyrrolate or atropine intravenously in an appropriate dose was given concurrently. The percentage recovery of T1 following the injection of the anticholinesterase agent was continuously recorded.

Heart rate was observed continuously from a Hewlett Packard ECG monitor and the arterial pressure measured every two minutes using a Hewlett Packard noninvasive monitor. To detect decreases in core and hand temperatures during the operation, nasopharyngeal temperature was measured. All infusions were warmed to body temperature, a condensor humidifier was used in the breathing system and the forearm was insulated by wrapping in towelling.

Neuromuscular monitoring was stopped when the patient was awake and neuromuscular function was evaluated clinically during the recovery period by assessing patients' grip strength and ability to headlift for five seconds [38]. Each patient was reassessed 24-48 hours after surgery and questioned with regard to any adverse experience noted.

Non-parametric and Students T test were used as appropriate to assess statistical significance.

Results

There were no significant differences between the ages, weights or ASA categories of the three groups of patients studied (Table 31). The duration of surgery was defined as the time from administration of the initial bolus of doxacurium until administration of the antagonising agent. Intubation conditions ranged between grades excellent and poor in all three groups, but only one patient in each group achieved excellent conditions (Table 32). Intubation was accomplished successfully in all patients, although 100% block of adductor pollicis was not achieved before intubation was performed.

Because patients in groups B and C all received doxacurium 62.5 ug kg -1, these two groups were analysed together and compared with group A (doxacurium 37.5 ug kg -1) (Table 33). Three patients in group A failed to achieve 80% block following the initial bolus and one patient was antagonised at 10% recovery. In the remaining five, it took an average of 51 minutes to recover to T1 of 20%. With the higher dose, in one patient the initial block was only to

	n	Age (yr)	Weight (kg)	Duration of surgery (min)	Sex (M/F)
Group A Doxacurium 37.5 μg kg -1	9	52.5 (11.8)	67.3 (10.7)	127.8 (58.4)	5/4
Group B Doxacurium 62.5 μg kg -1	9	60.7 (11.2)	69.8 (15.8)	161.4 (48.6)	7/2
Group C Doxacurium 62.5 μg kg -1	9	49 (14.0)	74.5 (15.0)	139.6 (38.7)	6/3

Table 31

Patient characteristics (mean (SD))

	Time of intubation (min)	Intubation score (no. patients)						Reduction in T1 at intubation (%)
		1	2	2.5	3	4	Mean (SD)	
Group A Doxacurium 37.5μg kg -1	4	1	4	1	3	0	2.27 (0.66)	55.2 (32.9)
Group B Doxacurium 62.5μg kg -1	4	1	6	1	1	0	2.0 (0.5)	80.1 (15.5)
Group C Doxacurium 62.5μg kg -1	3	1	6	0	2	0	2.1 (0.6)	67.1 (26.0)

Table 32

Intubation data. Score 1 = excellent, 2 = good, 3 = poor, 4 = not possible.

	n	Max block achieved (T1%)	Time to max block (min)	Duration to 20% recovery of T1 (min)
Group A Doxacurium 37.5 μg kg -1	9	83.6(18.3)[55-100]	10.5(2.2)[6-14]	N/A*
Group B Doxacurium 62.5 μg kg -1	18	97.6(5.2)[78-100]	9.85(6.17)[5-31]	101.7(41.8) [31-75] (n = 15)

* Three patients failed to achieve 80% block.

Table 33

Onset and duration data (mean (SD) [range]).

75% and in two, the recording was lost following movement of the patient by theatre staff and loss of electrode placement. In the remaining 15, the time to 20% T1 recovery was on average 102 minutes after the initial dose (Table 33). There was no significant correlation between the age of the patients and the duration of block at the higher dose.

Only 13 patients received increments of doxacurium as, in the remainder, the initial bolus dose of doxacurium was adequate to last throughout the operation. The incremental doses administered at 20% recovery of T1 produced a moderately wide between patient variation in response, both with regard to percent increase in block of T1 and time to return to 20% T1. However, the response in any one patient was consistent, with increments producing the same increase in paralysis and a constant duration of effect (Table 34).

Two patients with poor recovery recordings were omitted from the antagonism data analysis. The mean percent recovery of T1 at the time of administration of the antagonist was almost the same in the edrophonium and neostigmine groups (Table 35). The first twitch of the train-of-four was antagonised well after giving neostigmine. The T1 antagonism response to edrophonium was rapid in onset but was incomplete and subsequently appeared to be similar to that of a spontaneous recovery. In eight (47%) patients in the edrophonium group, a train-of-four (TOF) ratio less than 0.5 was still present when recording had to be stopped. Only four (24%) patients achieved a TOF ratio greater than 0.7. One patient with a TOF ratio of 0.6 at the end of recording failed a five second head lift 30 minutes after administration of edrophonium. Ten minutes later

No patients receiving increments at 20% recovery	Increase in block T1 (%)	Duration to return to 20% (min)	No increments
Total 13*	8(3.3)[2.5-15]	31.3(31.1)[9.5-42]	3.9(3.8)[1-12]

* Group A n = 4; group B n = 4; group C n = 5

Table 34

Response to increments of 5μg kg -1 Doxacurium (mean (SD) [range]).

	n	Drug admin	Recovery of T1 (%) at 1 min	3 min	5 min	10 min
Edrophonium	17	23.8(8.8)[10-37]	59.2(22.8)	70.9(17.3)	76.4(17.4)	78.0(16.7)
Neostigmine	8	22.5(6.7)[10-32.5]	40.6(21.2)	70.5(28.2)	81.8(21.0)	94.3(12.2)

Table 35

Data on antagonism of block by edrophonium or neostigmine (mean (SD) [range])

he had a successful head lift following administration of neostigmine 2.5 mg. In the neostigmine group, no neuromuscular block could be detected by clinical assessment in the recovery room. One patient had a TOF ratio less than 0.5 following antagonism at the end of the recording. Four patients (50%) achieved a TOF ratio greater than 0.7. The mean period of recording following administration of both agents was approximately 14 minutes.

Twelve (44.4%) patients required administration of an intravenous anticholinergic agent during operation to correct a heart rate of less than 50 beats per minute.

The bradycardias were gradual in onset and generally occurred 30 to 60 minutes after induction of anaesthesia and seemed unrelated to the administration of doxacurium.

No adverse experiences were reported by the patients on follow up at 24 hours.

Discussion

This study confirms that doxacurium is a potent, long acting neuromuscular blocking agent. Although a formal dose response study was not carried out in these patients, the drug appeared to be less potent than might have been anticipated from the volunteer study reported in the previous chapter and also other reports. Other studies suggest that the ED95 lies between 13.6 and 25 ug kg -1, depending on the anaesthetic conditions [122, 123, 125, 126].

The dose regime in this study was based on the initial report by Basta and colleagues which suggested that the ED95 under balanced anaesthesia was 25 μg kg -1 [122]. In this study, group A received 1.5 times the ED95 and groups B and C received 2.5 times the ED95. This study, however, showed that at 37.5 μg kg -1 (1.5 x ED95) the maximum block achieved was 83.6% T1. This apparent difference in potency may result from the fact that we compared EMG responses to mechanomyographic forms of measurement [122, 123]. In addition, the drug may appear less potent because of the lighter depth of anaesthesia during induction. The effect of anaesthetic agents on the pharmacodynamics of a muscle relaxant was noted in one of the author's previous studies on high dose atracurium. Alternatively, there may be an Anglo-American difference in potency for doxacurium as has been described previously for tubocurarine [127].

Intubating conditions were similar to those described by other workers [128, 129] and could only be described as excellent in one patient in each group; in no patient was 100% blockade of T1 achieved before intubation. In two patients the intubating conditions were between groups two and three by the intubation criteria of Twohig and his colleagues [124], and therefore they scored 2.5. Even at the high dose (62.5 ug kg -1) the mean onset time to 90% block of T1 was some 4.9 minutes (n=17). Nevertheless, in no patient was intubation impossible and the mean conditions in all three groups could be said to be good.

In the patients receiving multiple maintenance increments of doxacurium, there was no evidence of an increase in duration or degree of block following each bolus.

In all patients except the two with poor recordings in whom antagonism was blind, the block was antagonised between 10 and 37% recovery of T1. It could be argued that the poor antagonism with edrophonium was related to base line drift of the electromyographic recording, which has been well documented by other authors [130, 131]. However, the antagonism of T1 by neostigmine was complete; this would confirm a real difference in ability to antagonise doxacurium by these two anticholinesterase agents. As a result of time constraints imposed on this clinical study, TOF fade was still present in several patients when stimulation had to be stopped as the patient awakened. Nevertheless, with the exception of one patient who received edrophonium, all other patients appeared to have appropriate clinical antagonism of block and had satisfactory grip strength and five second head lift when tested between 20 and 40 minutes after admission to the recovery ward.

It is unlikely that the gradual onset of bradycardia could be attributed to doxacurium; the measurements of heart rate and arterial pressure confirm the findings of the volunteer study and other reports that doxacurium is a haemodynamically stable agent [122, 132]. There was no clinical evidence of histamine release. Konstadt [133] also noted a decrease in heart rate and attributed this to progressive reduction in sympathetic tone resulting from anaesthesia. The effect of opioids and volatile agents on heart rate is well documented [134].

In conclusion, we found doxacurium to be a potent, long acting haemodynamically stable, non-depolarising neuromuscular blocker. Although intubation was possible in all patients in the three

groups studied, with the dosage used in this study, doxacurium did not provide intubating conditions which could be described as excellent. In common with vecuronium and atracurium, this drug does not have the protective vagolytic effect of pancuronium and it is recommended that an anticholinergic agent be availabe immediately if vagal stimuli are likely to be encountered during surgery. Neostigmine would appear to be more suitable than edrophonium as an antagonist for doxacurium.

CONCLUSION AND UPDATE

Most of the important research into new muscle relaxants can be divided into two distinct chemical groups, namely the benzylisoquinolinium compounds, and the steroids.

For a number of years now, Savarese and colleagues at the Massachusetts General Hospital, USA, have been collaborating with pharmacologists and molecular chemists at Burroughs Wellcome, Research Triangle Park, North Caroline, USA. They have been particularly interested in the bisbenzylisoquinolinium diester non-depolarising compounds known to undergo hydrolysis in the presence of plasma cholinesterase. While a number of prototypes offered many features of 'the ideal muscle relaxant', the major stumbling block with this class of experimental drugs has been histamine release. This side effect, well recognised in other benzylisoquinolines, notably tubocurarine, metocurine, and to a lesser extent atracurium, has resulted in the withdrawal of some otherwise potentially useful agents following volunteer studies.

Benzylisoquinoline ester compounds can be readily chemically manipulated to undergo more rapid metabolism or degradation, thereby shortening the neuromuscular effect. Atracurium was the first to find clinical success in which the ester linkage facilitates both the Hofmann elimination and ester hydrolysis pathways of breakdown. With BW81090U (mivacurium) the basic benzylisoquinOline structure provides good potency, while two ester linkages allow rapid breakdown by plasma cholinesterase at about 88% of the rate of suxamethonium hydrolysis [135]. Preliminary

data in vitro and in the cat, however, suggest that mivacurium might also undergo liver uptake and metabolism. This could explain the poor correlation of the duration of action of bolus doses of mivacurium with the plasma cholinesterase activity of individual subjects. The metabolites have been identified in the bile and urine of both cat and dog, as well as in human urine [135].

Since enzymatic hydrolysis is most likely the major route of clearance, the duration of action of mivacurium may be longer in people with low cholinesterase activity. Savarese et al [135] postulate that the relative increase in duration of action, however, may not be as great as in the case of suxamethonium for three reasons:-

1. The upper limit of the clinical dose range is greater with suxamethonium than mivacurium, and therefore represents a relatively greater overdose, and consequently higher clearance load;

2. Other clearance pathways for mivacurium seem likely; and

3. The complicating process of phase two block cannot occur in the case of mivacurium.

Mivacurium's duration of action is about one third to one half that of an equipotent dose of atracurium or vecuronium, or about one and a half to two times longer than suxamethonium. Its onset time, however, is more similar to atracurium or vecuronium than suxamethonium. Rather than engage in the often discussed

definition of cumulation, it is simpler to say that mivacurium's recovery indices are relatively short and do not change over a wide dose range, nor after prolonged continuous administration by infusion [136]. The addition of isoflurane may, however, prolong the recovery index [137]. Interestingly, Ali et al [136] noted a significant correlation between the infusion rate of mivacurium required to maintain 95% twitch depression and the plasma cholinesterase activity of individual subjects.

Antagonism of mivacurium induced block by anticholinesterase agents would seem at least as easy as reversal of any other non-depolarising drug. It is likely that during reversal hydrolysis of mivacurium may be slowed for a brief period due to a short lasting inactivation of plasma cholinesterase. Nevertheless, moderate levels of mivacurium block are readily antagonised by neostigmine due to acetylcholinesterase inhibition. Presumably, within about 20 minutes following neostigmine administration, plasma cholinesterase activity should have recovered sufficiently to destroy any residual mivacurium ester material.

Since mivacurium is a benzylisoquinolinium substance, it shares the generic side effect of this group of compounds, namely histamine release. This side effect would seem to be relatively mild and its cardiovascular effects are similar to those of atracurium [135]. Like atracurium, the transient, haemodynamic response to a high bolus can be attenuated by slowing the speed of injection to about 60 seconds.

BWA938U (doxacurium) would appear to be the most potent, non-depolarising relaxant ever studied in man [132].

This long acting bisquarternary benzylisoquinolinium diester was identified as a byproduct of the programme to develop a short acting agent. It has a similar duration of effect to pancuronium given in equipotent doses and provided there is some evidence of recovery, as assessed by using a peripheral nerve stimulator, the drug may be reversed satisfactorily with neostigmine. Edrophonium, however, would appear to be an unsatisfactory antagonist for this agent.

The onset time is slow and probably slower than that of pancuronium in equipotent dose [122, 132]. Thus, doxacurium would seem to be an unsuitable agent for rapid tracheal intubation.

Its major advantage is its haemodynamic stability in both healthy adult patients and those with cardiac disease [138]. Although some decrease in heart rate [138] may be observed over time, this is unlikely to be an effect of doxacurium. The vagal effects of anaesthesia and certain surgical stimuli which are concealed by the vagolytic effect of pancuronium, may occasionally be exposed with this drug. A similar phenomenon is seen not infrequently with vecuronium, which is also stable on the circulatory system.

Unlike other benzylisoquinoline analogues, it does not release histamine in the clinical dose range [122]. This is almost certainly due to its high potency making the margin of safety between the neuromuscular blocking dose and the dose at which

histamine release is observed, that much wider.

Although the drug has been identified in human bile, it is thought that doxacurium is largely eliminated unchanged by the kidney. The hydrolysis rate in vitro as catalysed by purified pooled human plasma cholinesterase is only 6% of the rate of suxamethonium.

It will have become apparent from the foregoing discussion that there is still a need for a rapid onset, non-depolarising drug, or if you like, a suxamethonium substitute without the depolarising side effects. That is effectively where most research into muscle relaxant molecular chemistry will be directed from now on. It would seem that there are two philosophies on how to achieve this ideal agent. Chemists working with the benzylisoquinoline structure believe that a highly potent ultra short acting drug is the answer; their hypothesis being that it will be possible to give large doses to improve onset time without an undue prolongation of blockade. Furthermore, the more potent the drug is regarding neuromuscular blocking activity, the greater the margin of safety for histamine will be: this chemical group's major side effect.

Steroidal chemists, however, are working on an entirely different hypothesis. They believe that highly potent drugs by definition have a high affinity for receptors and therefore rapid onset can only be achieved at the expense of a very prolonged duration of action. An analysis of the relationship between neuromuscular blocking potency and duration of action has revealed that it is reciprocal, suggesting that a non-depolarising equivalent of suxamethonium, when discovered, may necessarily be a drug of low

potency [139]. Work in this area has already produced some encouraging results, albeit in animals [140, 141].

Two fast onset short duration steroids, ORG7617 and ORG9616, although significantly less potent that vecuronium, have demonstrated a pharmacodynamic profile similar to suxamethonium. The problem with reducing potency of steroidal compounds is that vagolytic and autonomic side effects begin to appear. Initial animal studies suggest these two experimental agents may not be haemodynamically stable, at least at higher doses.

However, two fast onset intermediate duration steroids, ORG9426 and ORG9273, are being investigated and have produced only minor changes in blood pressure and heart rate in all species at three times EC90 blocking doses. Although, once again, considerably less potent than vecuronium, they display a similar duration and faster onset of action at equipotent dose.

It should be borne in mind that the duration of drug action is briefer, the smaller the species of animal, presumably because of faster blood flow and metabolism. Nevertheless, the relative time course of action in the cat of these new drugs compared with suxamethonium and vecuronium, is encouraging.

We await the results of the full clinical trials.

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1. Scott R P F, Goat V A. Atracurium: Its speed of onset. A comparison with suxamethonium. Br J Anaesth 1982; 54: 909.

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Br. J. Anaesth. (1982), 54, 909

ATRACURIUM: ITS SPEED OF ONSET. A COMPARISON WITH SUXAMETHONIUM

R. P. F. SCOTT AND V. A. GOAT

SUMMARY

Forty healthy patients were randomly selected to receive either atracurium 0.6 mg kg^{-1}, or suxamethonium 1 mg kg^{-1}. Onset of neuromuscular blockade and the time to full peripheral paralysis were measured using a train-of-four stimulus repeated once every 12 s. Atracurium appeared to be a potent non-depolarizing muscle relaxant, with a rapid onset of action. However, full peripheral paralysis took longer to achieve than with suxamethonium. There were no significant problems with recovery.

Atracurium dibesylate is reported to be a potent non-depolarizing muscle relaxant in both laboratory animals (Hughes and Chapple, 1980; Hughes and Chapple, 1981) and man (Hunt, Hughes and Payne, 1980). It is a short-acting agent and a qualitative evaluation of the drug has suggested that it has a rapid onset of action (Payne and Hughes, 1981).

There have been many studies to evaluate the speed of action of muscle relaxants. In some, judgement of paralysis has been largely subjective, using clinical criteria such as jaw relaxation, ease of tracheal intubation and the absence of response to laryngoscopy and intubation (Harrison and Feldman, 1981; Hey, 1973). Despite all efforts to eliminate bias, ease of intubation will depend not only upon the degree of neuromuscular blockade, but also upon the depth of anaesthesia, the anatomical configuration of the patient and not least upon the skill of the anaesthetist. An objective comparison of the rate of onset of neuromuscular blocking drugs can best be obtained by recording the response of a muscle to stimulation of its motor nerve.

In this study the speed of action of atracurium was monitored using a repeated 2-Hz train-of-four stimulus, and compared with suxamethonium. This comparison was chosen since the fast onset time reported in a preliminary study (Payne and Hughes, 1981) had suggested to the investigators that this new non-depolarizing muscle relaxant could well be used as an alternative to suxamethonium.

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METHOD

Forty healthy patients undergoing minor dental surgery requiring intubation were studied. The patients, who gave informed consent to the trial, were between 18 and 45 years of age. Any patient receiving concurrent medication, apart from the contraceptive pill, or in whom pregnancy was suspected, was excluded. Ethical consent for this study was obtained and the trial was conducted with the authority of a clinical trial certificate issued by the Committee on the Safety of Drugs.

After premedication with papaveretum and hyoscine, a modified Elcomatic transducer (Armstrong, Goat and Loach, 1977) was attached to the patient's dominant hand and positioned to achieve maximal mechanical response to thumb adduction. Anaesthesia was induced with fentanyl 3 μg kg^{-1} and thiopentone 5 mg kg^{-1}, and maintained with nitrous oxide and oxygen; ventilation of the lungs was assisted via a face-mask. Stimulation of the ulnar nerve at the wrist was carried out via cutaneous electrodes, using a Grass S48 nerve stimulator and S1U5 isolation unit. The stimulus width was 0.2 ms. Once it was certain that the stimulus was supramaximal, the stimulator was set to produce a 2-Hz train-of-four stimulus, repeated once every 12 s. The mechanical response to nerve stimulation was measured by the transducer and displayed on an Elcomatic recorder.

The patients had been randomly selected to receive either atracurium 0.6 mg kg^{-1} of suxamethonium 1 mg kg^{-1}, diluted to the same volume for injection. All drugs were administered via a peripheral indwelling needle, and the relaxant injected at the time of nerve stimulation, the start of

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injection coinciding with the first stimulus of the train. The time from the administration of the muscle relaxant to the first depression of any response in the train was noted. This was called the onset time. The time at which full peripheral paralysis occurred was also noted. At this time no recorded response was obtained from the stimulus. Tracheal intubation was attempted by one of the authors (V.A.G.) at full peripheral paralysis, using the nasal route under direct vision.

During induction of anaesthesia, the e.c.g. was monitored continuously to detect changes in heart rate. After intubation 1% halothane was added to the anaesthetic; this concentration was reduced during surgery to allow a rapid return of consciousness at the end of the procedure. Neuromuscular monitoring was not continued during surgery, and at the completion of the operation, those patients who had received atracurium were given neostigmine 2.5 mg with atropine 1.2 mg. The time of administration of these drugs was noted, and reversal of paralysis shown by the ability of the patient to maintain a head-lift for 5 s (Dam and Guldmann, 1961).

After operation all patients received standard analgesic and antiemetic drugs and were interviewed at 24 h. They also received a questionnaire which they were asked to return after 72 h, in order to detect any major problems.

Results were analysed using the unpaired two-tailed Student *t* test.

RESULTS

The results are summarized in table I. Patients were evenly distributed according to age and weight in both groups. The onset of neuromuscular block was faster by almost 15 s in those patients receiving suxamethonium, and this difference in onset time is significant.

Full peripheral paralysis occurred in all patients in both groups. A highly significant difference was seen in the time to full peripheral paralysis, with atracurium taking nearly twice as long as suxamethonium.

Retrospective analysis of the data showed that in several cases in both groups full peripheral paralysis had been anticipated, and intubation had commenced on the penultimate train-of-four. This gave an inconsistent starting point for intubation and intubating conditions between the drugs could not be compared reliably.

Changes in heart rate were minimal in both groups and there was no significant difference between the two groups (table II). No specific problems were encountered after operation in those patients receiving atracurium, although 11 patients in the suxamethonium group complained of moderate to severe muscle pains.

TABLE II. *Heart rate change*

	No. patients	No. with heart rate change	
		>10 beat min^{-1}	<10 beat min^{-1}
Suxamethonium	20	2	2
Atracurium	20	2	2

DISCUSSION

The speed of onset of atracurium has been studied by others (Payne and Hughes, 1981), who followed the time course of blockade by using the response of the adductor pollicis muscle to repeated tetanic stimulation. The mean onset of maximal effect was reported to be 1.2 min at a dose of 0.6 mg kg^{-1}. The time to full peripheral paralysis in this study was just over 2 min (129 s). The discrepancy between these

TABLE I. *Patient characteristics and neuromuscular blockade data. Significance (Student's* t *test): *P <0.01, **P <0.001*

	No. of patients	Mean age (yr)	Mean wt (kg)	Male	Mean time to onset of paralysis (s)	Mean time to full peripheral paralysis (s)
Suxamethonium	20	24.9 (SD 5.4)	64.9 (SD 11.9)	10	34.8 (SD 11.6)	69.9 (SD 18.5)
Atracurium	20	24.3 (SD 6.8)	63.8 (SD 11.1)	7	49.8* (SD 8.9)	129.0** (SD 24.3)

results could be explained by the mode of stimulation used. Although the response to tetanic stimulation is a more sensitive indication of receptor occlusion than either the single twitch response or the train-of-four, tetanic stimulation may distort subsequent neuromuscular transmission (Lee and Katz, 1980) and increase the apparent degree of neuromuscular blockade. The train-of-four stimulus was chosen for this study since it is slightly more sensitive to receptor occlusion than is the single twitch (Lee, 1975). It also lacks the equivalent of post-tetanic distortion of the subsequent muscle response, and is therefore suitable for repeated application up to once every 12 s.

The use of volatile anaesthetic agents was avoided until after monitoring had been discontinued, because of the well documented interaction between volatile and neuromuscular blocking agents (Waud and Waud, 1979).

In this study, atracurium appeared to be a potent competitive neuromuscular blocking agent, and its effect at the neuromuscular junction is readily reversed. Although the onset of paralysis is rapid, with full peripheral paralysis occurring in just over 2 min, this is significantly slower than the action of suxamethonium. No significant changes in heart rate were seen and no perioperative problems encountered.

ACKNOWLEDGEMENTS

The authors would like to thank the Oral Surgeons for their co-operation and patience; Mrs Bridget Harrison B.SC., M.I.S., for her help in analysing the data obtained, and also Miss Jennifer Hill and Miss Sarah Edwards for their secretarial assistance. The muscle relaxants used were kindly provided by the Wellcome Research Laboratories, Beckenham, Kent.

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ATRACURIUM: SA RAPIDITE D'ACTION. UNE COMPARAISON AVEC LE SUXAMETHONIUM

RESUME

Quarante sujets en bonne santé ont été choisis de façon aléatoire pour recevoir soit 0,6 mg kg^{-1} d'atracurium, soit 1 mg kg^{-1} de suxaméthonium. L'apparition de bloc neuromusculaire et le temps d'obtention d'une paralysie périphérique totale ont été mesurés en utilisant un stimulus par train de quatre répété toutes les 12 s. L'atracurium s'est montré un curare non dépolarisant puissant, d'action rapide. Cependant, l'obtention d'une paralysie périphérique complète a été plus longue qu'avec le suxaméthonium. Il n'y a pas eu de problèmes significatifs de décurarisation.

ATRACURIUM, DIE GESCHWINDIGKEIT SEINES WIRKUNGSEINTRITTS IM VERGLEICH ZU SUXAMETHONIUM

ZUSAMMENFASSUNG

Vierzig gesunde Patienten wurden randomisiert ausgewählt, um entweder 0,6 mg kg^{-1} Suxamethonium zu erhalten. Der Beginn der neuromuskulären Blockade und die Zeit der vollen peripheren Blockade wurde gemessen, indem ein train of four-Stimulus alle 12 Sekunden gesetzt wurde. Atracurium schien ein potentes nicht-depolarisierendes Muskelrelaxans zu sein, mit schnellem Wirkungseintritt. Die volle periphere Lähmung jedoch trat später ein als bei Suxamethonium. Es wurden keine Schwierigkeiten bei der Antagonisierung oder in Zusammenhang mit der Operation beobachtet.

ATRACURIO: SU VELOCIDAD INICIAL. UN ESTUDIO COMPARATIVO CON EL SUXAMETONIO

SUMARIO

Se seleccionaron cuarenta pacientes sanos de forma aleatoria para administrárseles 0,6 mg kg^{-1} de atracurio ó 1 mg kg^{-1} de suxametonio. Se midió el inicio del bloqueo neuromuscular y el tiempo transcurrido hasta alcanzar una parálisis periférica total, haciendo uso de una serie de cuatro estímulos que se repitieron una vez cada 12 segundos. El atracurio pareció ser un potente relajante muscular de carácter no despolarizante que presentó una temprana actividad. Sin embargo, el tiempo necesario para alcanzer la parálisis periférica total fue mayor que en el caso del suxametonio. No se presentaron problemas de importancia en lo tocante a la recuperación.

Br. J. Anaesth. (1985), 57, 550–553

ATRACURIUM: CLINICAL STRATEGIES FOR PREVENTING HISTAMINE RELEASE AND ATTENUATING THE HAEMODYNAMIC RESPONSE

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SUMMARY

This study was designed to determine the effects of a rapid bolus dose of atracurium 0.6 mg kg^{-1} on arterial pressure, heart rate and plasma histamine concentration (n = 9), and to compare these values with those obtained by (a) giving the same dose of atracurium slowly (over 75 s) (n = 9), or (b) pre-treating with H_1- and H_2- antagonists (n = 9). The rapid (5-s) bolus dose of atracurium i.v. resulted in a significant increase in plasma histamine concentration (P < 0.05) and was associated with a decrease in mean arterial pressure and an increase in heart rate. Administering the same dose of atracurium slowly (over 75 s) prevented the increase in plasma histamine concentration, and abolished the subsequent haemodynamic response. Pretreatment with cimetidine 4 mg kg^{-1} i.v. and chlorpheniramine 0.1 mg kg^{-1} i.v. abolished the haemodynamic response despite a moderate increase in histamine concentration (0.1 > P > 0.05).

All basic compounds may disrupt mast cells and cause the release of histamine if the dose is large enough (Paton, 1957). Among the neuromuscular blocking drugs, this effect appears to be most pronounced with tubocurarine, possibly because of its free hydroxyl groups which are thought to enhance histamine-releasing potency (Buckett and Frisk-Holmberg, 1970). Unfortunately, the lack of a sensitive and reliable assay for plasma histamine has made it difficult to document the role of the histamine so released in drug-induced cardiovascular changes. The recent development of a radioenzymatic technique (Snyder, Baldasserarini and Axelrod, 1966; Beavan, Jacobsen and Horakova, 1972; Beavan and Horakova, 1978; Iverson, Iverson and Snyder, 1979) and its improvement by the discovery of renal histamine-n-methyltransferase (Shaff and Beavan, 1979) have greatly enhanced our ability to detect histamine in clinically important situations.

The histamine-releasing property of tubocurarine occurs within the clinical dose range, and a close correlation between the dose of tubocurarine administered and the amount of histamine released has been documented in man (Moss et al., 1982). In addition, a correlation exists between the plasma histamine concentration and the extent of systemic arterial hypotension. When plasma concentrations are increased by about 200% of control, significant changes are noted in heart rate and arterial pressure (Moss et al., 1982).

More recently, it has been shown that atracurium will also release histamine at the upper end of its clinical dose range (0.6 mg kg^{-1}) and this is associated with corresponding changes in cardiovascular indices (Basta et al., 1983, 1984). The ability of atracurium to release histamine relative to its neuromuscular blocking potency is approximately one-half that of dimethyltubocurarine and less than one-third that of tubocurarine.

A number of clinical strategies have been used to attenuate the adverse reactions to the histamine released by certain drugs. It has been shown that even small time differences in the rate of administration of i.v. agents can lead to significant changes in the likelihood of generating clinically significant histamine release (Rosow et al., 1980; Basta et al., 1981). Furthermore, there is abundant evidence suggesting that the prophylactic use of H_1- and H_2-

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antagonists can also attenuate the haemodynamic responses to certain histamine-releasing drugs, including morphine (Philbin et al., 1981), BW 785U (Rosow et al., 1980), Haemaccel (Lorenz et al., 1980) and tubocurarine (Moss et al., 1982).

This study was designed to determine the effects of a rapid bolus dose of atracurium 0.6 mg kg^{-1} on arterial pressure, heart rate and plasma histamine concentration, and to compare these values with those obtained by (a) giving the same dose of atracurium slowly over 75 s and (b) pretreating with H_1- and H_2-antagonists.

PATIENTS AND METHODS

Twenty-seven (ASA Class I or II) patients gave institutionally approved informed consent to the study, and were assigned to one of three subgroups at the discretion of the investigator. All the patients were aged between 18 and 60 yr, weighed 45–110 kg, and were undergoing elective surgical procedures. Any patient with recent exposure to antihistamines or antidepressants was excluded from the trial.

Premedication consisted of morphine 0.1 mg kg^{-1} i.m. and diazepam 0.2 mg kg^{-1} by mouth. Anaesthesia was induced with fentanyl 3–4 μg kg^{-1} and thiopentone 5 mg kg^{-1} i.v., and maintained with nitrous oxide in oxygen via a face mask. Heart rate (by tachograph), ECG and intra-arterial pressure were recorded continously on a Grass Model 7 polygraph. After a stable 10-min baseline period, a single bolus of atracurium 0.6 mg kg^{-1} was administered over 5 s to patients in group I. Patients in group II received the same dose of atracurium slowly (over 75 s). The patients in group III were pretreated with cimetidine 4 mg kg^{-1} and chlorpheniramine 0.1 mg kg^{-1} i.v. 15 min before induction. They were then given atracurium 0.6 mg kg^{-1} as 5-s bolus. Maximum changes in heart rate and arterial pressure were noted. Intubation of the trachea was delayed for 10 min following the administration of atracurium, to avoid the cardiovascular response to laryngoscopy. Arterial blood samples were drawn immediately before the injection of atracurium and at 2 and 5 min after injection; these samples were analysed for histamine by an isotope radioenzymatic assay technique (Moss et al., 1981). End-tidal carbon dioxide concentration was kept within the normal limits during the course of the study.

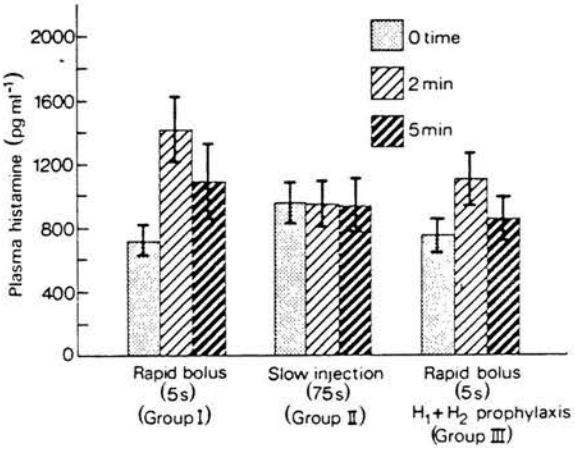

FIG. 1. Mean plasma histamine concentrations in the three groups at control, 2 min and 5 min following administration of atracurium 0.6 mg kg^{-1} i.v.

RESULTS

The results are summarized in tables I and II: the data displayed are mean values. The changes in mean arterial pressure and heart rate are the maximum changes that occurred in the 10 min following the administration of atracurium, calculated as a percentage of the baseline values. The absolute values at baseline, 2 min and 5 min for mean arterial pressure and heart rate are displayed in parentheses in table I. Figure 1 illustrates the mean changes in

TABLE I. *Effect of atracurium 0.6 mg kg^{-1} on mean arterial pressure and heart rate. *Actual values at baseline, 2 and 5 min for mean arterial pressure (MAP) (mm Hg) and heart rate (HR) (beat min^{-1}) are shown in parentheses*

	n	MAP (% of baseline)	HR (% of baseline)
Group I: 5-s bolus	9	82.1±6.4 (78.4;63.5;74.8)*	108.6±4.6 (65;70.1;64.1)*
Group II: 75-s dose	9	95.7±2.6 (75.1;71.8;73.5)*	97.7±2.3 (66;64.2;62.4)*
Group III: $H_1 + H_2$ prophylaxis	9	96.2±2.2 (65.7;63.0;65.2)*	102.3±2.2 (60.2;62.1;60.4)*

TABLE II. *Effect of atracurium 0.6 mg kg^{-1} on plasma histamine concentration.* *P<0.05 *(one way analysis of variance)*

	Plasma histamine (pg ml^{-1})		
	Control	+2 min	+5 min
Group I 5-s bolus	715.3±93.6	1415.1±203.5*	1086.3±237.9
Group II 75-s slow injection	954.1±131.7	949.9±154.1	939.4±162.7
Group III $H_1 + H_2$ prophylaxis	751.1±113.3	1107.0±160.4	854.1±146.0

plasma histamine concentration in the three groups, and figure 2 the changes in plasma histamine concentration in the individual patients. Patients in group I demonstrated a significant increase in plasma histamine concentration at 2 min ($P < 0.05$; analysis of variance). Seven patients (77%) in this group showed clinical signs of histamine release, with the development of mild to moderate erythema over the trunk and face. The changes in heart rate and arterial pressure in this group were all transient and had almost returned to baseline values by 5 min.

A moderate increase in histamine concentration at the 2-min sample in group III approached, but did not reach, statistical significance ($0.1 > P > 0.05$).

None of the patients in groups II or III showed clinical signs of histamine release nor any haemodynamic changes of statistical or clinical significance.

DISCUSSION

Simple histamine release by many drugs, including neuromuscular blocking agents, does not involve immunological mechanisms but rather a non-specific displacement of histamine and possibly other vasoactive substances from vascular mast cells. The transient nature of the changes in arterial pressure and heart rate following a bolus dose of atracurium 0.6 mg kg^{-1} i.v. and the significant increases in plasma histamine concentration would seem to confirm that this haemodynamic response results from the release of endogenous histamine. Atracurium has a very high margin of safety for ganglionic blockade (Hughes and Chapple, 1981), the duration of which tends to parallel neuromuscular blockade (Savarese, 1976). Thus, a hypotensive response to atracurium mediated via ganglionic blockade would seem unlikely.

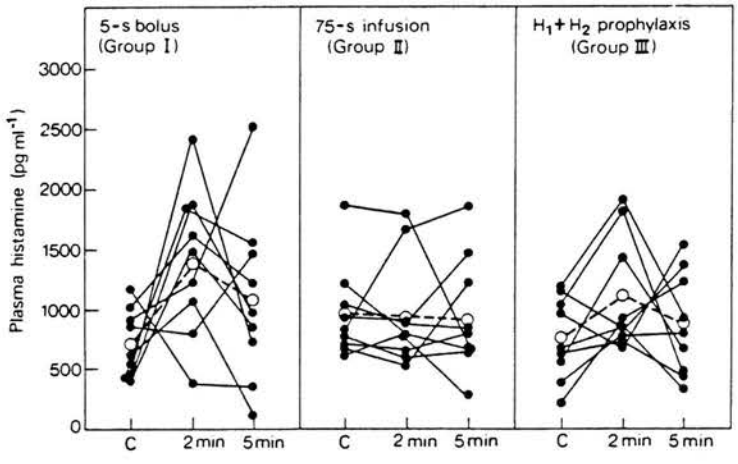

FIG. 2. Plasma histamine concentrations in individual patients in the three groups at control, 2 min and 5 min following administration of atracurium 0.6 mg kg^{-1} i.v.

It appears that small differences in the plasma concentration of a histamine-releasing drug can produce large changes in the amount of histamine liberated. In this study, slowing the administration of atracurium appeared to prevent the increase in histamine concentration and the subsequent change in haemodynamic variables.

The wide variety of agents with which combined histamine–receptor blockade is effective, demonstrates the clinical importance of histamine release as well as the effectiveness of combined blockade. In the present study the patients receiving a rapid bolus of atracurium i.v. who were pretreated with H_1- and H_2-antagonists did show increases in plasma histamine concentration. The haemodynamic response, however, was markedly attenuated.

It should be noted that not all patients will release histamine at high doses of atracurium, as indicated by the large standard error. However, as the size of the bolus dose increases, there is a greater likelihood of this response occurring (Basta et al., 1981). Although this transient haemodynamic response is probably of little clinical significance in the healthy patient, the effect may be more important in the haemodynamically unstable patient who is hypovolaemic, or has cardiovascular disease.

We conclude that the release of histamine by large bolus doses of atracurium (0.6 mg kg^{-1}), and any associated haemodynamic response, can be prevented by administering the dose slowly (over 75 s). In addition, the haemodynamic response to a rapid (5-s) bolus can be minimized by pretreatment with H_1- and H_2-receptor antagonists such as chlorpheniramine and cimetidine i.v., given 15 min before the atracurium.

ACKNOWLEDGEMENTS

This study was funded in part by the Medical Department, Burroughs Wellcome Company, Research Triangle Park, North Carolina.

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Br. J. Anaesth. (1986), 58, 834–838

CLINICAL PHARMACOLOGY OF ATRACURIUM GIVEN IN HIGH DOSE†

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SUMMARY

The safety and efficacy of atracurium 0.8 mg kg^{-1} was determined in healthy patients with particular attention to the speed of onset of blockade, and to changes in haemodynamic variables. Atracurium 0.8 mg kg^{-1} had a shorter onset time than atracurium 0.5 mg kg^{-1}, and satisfactory intubating conditions were achieved earlier. "Priming" produced no significant improvement in onset time or intubating conditions. Onset times were significantly shorter with nitrous oxide–opioid anaesthesia than following thiopentone alone. Although a 0.8-mg kg^{-1} bolus resulted in a significant reduction in mean arterial pressure to 75% of control and was associated with a significant increase in plasma histamine concentrations, this response could be prevented by injecting the drug over 75 s. "Priming" or a 30-s injection produced no haemodynamic protection. The protection achieved by pretreatment with anti-histamines was incomplete: mean arterial pressure decreased to 83% of control.

The newer neuromuscular blocking drugs have come closer to the ideal (Savarese and Kitz, 1973, 1975) in terms of duration of action and cardiovascular stability than the earlier agents. However, the onset times of atracurium and vecuronium, although similar in equipotent doses (Gramstad, Lilleaasen and Minsaas, 1983), are significantly slower than that of suxamethonium in the clinical dose range (Scott and Goat, 1982; Gyasi et al., 1983). For rapid sequence induction, suxamethonium remains the drug of choice.

Since the speed of onset of the intermediate duration neuromuscular blocking drugs is dose dependent (Agoston et al., 1980; Payne and Hughes, 1981; Basta et al., 1982; Durant, 1982), their administration in high doses should provide a more rapid onset of action without the excessively prolonged duration of action that may be observed following high doses of the longer-acting agents. Indeed, Waldburger, Nielsen and Mulroy (1984) have suggested that atracurium 0.8 mg kg^{-1} will allow satisfactory intubating conditions in all patients within 90 s of injection without prolonged blockade or significant variation in haemodynamic indices. However, other studies have shown that atracurium 0.6 mg kg^{-1} causes a moderate reduction in mean arterial pressure as a result of histamine release (Basta et al., 1983)—an effect which may be prevented by injecting the drug slowly over 75 s or by pretreating with i.v. H_1- and H_2-antagonists (Scott et al., 1985).

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† Presented at the International Anaesthesia Research Society Congress, Las Vegas, U.S.A. on March 19, 1986.

More recently, it has been demonstrated that the speed of onset and degree of blockade of competitive neuromuscular blocking drugs may be enhanced if the agents are administered in divided doses (Schwartz et al., 1985; Mehta et al., 1985). From these data it is postulated that an initial subparalysing dose (priming dose) may occupy 70–75% of cholinoceptors without causing unpleasant symptoms in awake patients. Tracheal intubation might then be performed more rapidly after a second larger dose that increases receptor occupancy quickly to the 90–95% necessary for paralysis. Furthermore, priming may improve the haemodynamic profile by releasing less histamine, as divided dosing is another form of slow injection.

The present study was designed to determine the safety and efficacy of administering atracurium 0.8 mg kg^{-1} to healthy patients. The speed of onset and the haemodynamic response were studied in an attempt to find modes of administration that would combine fast onset times with haemodynamic stability. Some of these data are compared with previously unpublished data obtained using the same investigative procedure, but with the lower dose of 0.5 mg kg^{-1}, the highest recommended in the United States.

PATIENTS AND METHODS

Fifty-six (ASA Class 1 or 2) patients gave informed consent for the study and were assigned to one of seven sub-groups at the discretion of the investigator. The patients were aged 18 to 60 yr, weighed between 45 and 110 kg, and were undergoing elective surgical procedures. Any patient with recent exposure to anti-histamines, anti-depressants, or aminoglycoside antibiotics was excluded.

Premedication consisted of morphine 0.1 mg kg^{-1} i.m. and diazepam 0.2 mg kg^{-1} orally. In groups I–V, anaesthesia was induced with fentanyl 5 μg kg^{-1} and thiopentone 5 mg kg^{-1} i.v. The trachea was intubated without the use of a neuromuscular blocking drug, additional increments of thiopentone being administered when appropriate to facilitate this procedure. Ventilation of the lungs was controlled to produce normocapnia and anaesthesia was maintained with nitrous oxide in oxygen. Volatile agents were not used. Heart rate, ECG, radial arterial pressure, and the single twitch adductor response at the thumb were recorded continuously on a Grass polygraph. A Grass S44 stimulator with subcutaneous needle electrodes and a Statham strain gauge were used. The single twitch was produced at a frequency of 0.15 Hz with a stimulus duration of 2 ms. After a stable baseline period (10 min) a bolus dose of atracurium 0.8 mg kg^{-1} was administered in 5 s to patients in groups I and IV. This dose was given over 30 s to patients in group II and over 75 s to patients in group III. Group V patients received a priming dose of 0.08 mg kg^{-1} followed 6 min later by a 0.72-mg kg^{-1} bolus. Patients in group IV were pretreated with cimetidine 4 mg kg^{-1} and chlorpheniramine 0.1 mg kg^{-1} i.v. 15 min before induction. Maximum changes in heart rate and arterial pressure were noted. Arterial blood samples were drawn immediately before the administration of the atracurium, and at 2 and 5 min after injection. These samples were analysed for histamine concentration by a radioenzymatic assay technique (Moss et al., 1981).

In groups VI and VII, anaesthesia was induced with thiopentone 5 mg kg^{-1} only. Group VI patients received a priming dose of atracurium 0.08 mg kg^{-1} 5 min before induction, followed by a bolus of 0.72 mg kg^{-1} 30 s after induction. Group VII patients received a bolus of atracurium 0.8 mg kg^{-1} given in 5 s, 30 s after induction. In these two groups the trachea was intubated 90 s following this large dose of atracurium, and the intubating conditions were classified as 1 (excellent), 2 (satisfactory), 3 (fair), or 4 (poor) according to the criteria of Lund and Stovner (1970).

Blood samples were not analysed for histamine concentrations in these two groups as it would be difficult to correlate any changes in plasma histamine concentrations with the inevitable haemodynamic response to intubation. Furthermore, the histamine response to these two dose regimens had already been analysed in groups I and V under stable haemodynamic conditions.

RESULTS

The results are summarized in tables I, II and III. The data displayed are mean values with standard errors of the mean (SEM). The changes in mean arterial pressure and heart rate are the maximum changes, calculated as a percentage of the baseline values, that occurred in the 10 min after the administration of the atracurium. The actual values at control, 2 min and 5 min for mean arterial pressure and heart rate are displayed in parentheses in table I. The data on mean arterial pressure, heart rate and histamine concentration (table II) at baseline and 2 min were analysed according to a 3-factor analysis of variance with group and time crossed and patient (a random factor) nested within group. In order to stabilize their variability and more closely satisfy the assumptions underlying the analysis of variance, the histamine data were analysed on a logarithmic scale. Tests of significance for the change from baseline to 2 min within each group then used t statistics, setting the critical value according to Bonferroni's inequality so that the simultaneous significance level would not exceed 0.05 (or 0.01, as appropriate).

There were significant decreases in mean arterial pressure in groups I, II and V ($P < 0.05$)

TABLE I. *Cardiovascular data. Effect of atracurium 0.8 mg kg^{-1} on mean arterial pressure (MAP) and heart rate (HR). Actual values at baseline, 2 and 5 min for mean arterial pressure (mmHg) and heart rate (beat min^{-1}) are shown in parentheses. The range of the maximum per cent change in MAP and HR is shown in square brackets. By* t *test:* * $P < 0.05$ *(simultaneous)*

	n	MAP (% of baseline)	HR (% of baseline)
Group I (5-s bolus)	8	74.6±5* (80.8/60/76.5) [52–97]	113.25±3.75 (64.25/72.1/65.8) [100–138]
Group II (30-s dose)	8	77±7.5* (67.25/50.75/64.75) [49–104]	114.75±10.8 (60/67.5/58.8) [89–191]
Group III (75-s dose)	8	95.7±1.2 (71.1/68.5/70.1) [90–100]	102.6±1.17 (55.2/56/55.7) [96–107]
Group IV (anti-hist.)	8	83.3±7.1 (77.3/65.6/75.1) [38–100]	109.9±3.65 (59.1/64.7/60) [96–125]
Group V (prime)	8	76±7.6* (68.5/52.5/64.7) [43–103]	109.3±2.83 (63.5/69.3/65) [100–126]

(table I). The moderate decrease in group IV approached, but did not reach, statistical significance ($0.1 > P > 0.05$). In all patients the changes in arterial pressure and heart rate were transient and had returned to baseline values by 5 min.

Patients in groups I, IV and V demonstrated significant increases in plasma histamine concentration at the 2-min sample (table II).

There were no significant differences in onset time (table III) between any of the techniques of administration when atracurium 0.8 mg kg^{-1} was administered during nitrous oxide and fentanyl anaesthesia. Nor was there a significant difference between groups VI and VII in which atracurium was administered following induction with thiopentone. Atracurium 0.8 mg kg^{-1} produced a significantly shorter onset time ($P < 0.05$) than 0.5 mg kg^{-1} under nitrous oxide–opioid anaesthesia. Atracurium 0.8 mg kg^{-1} also produced a significantly more rapid onset than 0.5 mg kg^{-1} following induction with thiopentone alone ($P < 0.05$).

The depth of anaesthesia appeared to have an effect on onset time, and both the bolus (group I) and prime (group V) groups had significantly shorter onset times ($P < 0.05$) under nitrous oxide–fentanyl anaesthesia when compared with the bolus (group VII) and prime (group VI) groups, respectively, receiving thiopentone alone.

There were no significant differences between the recovery times or the durations of action in the four groups in which these were recorded.

The intubation score was slightly better in the prime group (VI) than in the bolus group (VII), but this was not significant. The intubation score produced by the 0.8-mg kg^{-1} bolus group at 90 s was the same as that produced by 0.5 mg kg^{-1} at 150 s.

DISCUSSION

We have shown previously that atracurium 0.6 mg kg^{-1} given over 5 s is associated with a doubling of plasma histamine concentrations and a 21 % reduction in mean arterial pressure. These changes can be prevented by administering the drug over 75 s or by pretreating with antihistamines (cimetidine 4 mg kg^{-1} and chlorpheniramine 0.1 mg kg^{-1} i.v.) 15 min before the injection of the neuromuscular blocker.

In this study, decreasing the rate of injection of

TABLE II. *Effect of atracurium 0.8 mg kg^{-1} on plasma histamine concentrations. By* t *test:* * $P < 0.05$ *(simultaneous);* ** $P < 0.01$

	n	Plasma histamine (pg ml^{-1}) Control	+2 min	+5 min
Group I (5-s bolus)	8	557±232 [177–2110]	1646+419* [710–4070]	721±167 [100–1552]
Group II (30-s dose)	8	453±81 [230–1023]	2137±984 [247–8999]	1030±268 [308–2127]
Group III (75-s dose)	8	669±171 [182–1347]	791±123 [466–1500]	541±86 [147–972]
Group IV (anti-hist.)	8	485±100 [192–922]	6154±4063** [105–34064]	2251±1436 [59–12016]
Group V (prime)	8	203±44 [94–470]	1874±804** [95–6871]	558±158 [60–1259]

TABLE III. *Pharmacodynamic data (mean ± SEM). All data in parentheses refer to atracurium 0.5 mg kg^{-1} (n = 10)*

	Onset (min) (end injection to complete block)	5–95% Recovery (min)	Duration (min) (injection to 95% recovery)	Intubating conditions at 90 s
Group I (5-s bolus)	1.82 ± 0.25 (2.3 ± 0.2)	20.8 ± 1.22 (24)	70 ± 1.49 (59 ± 1.9)	
Group III (75-s dose)	1.71 ± 0.21	24 ± 2.1	69.7 ± 5.4	
Group IV (anti-hist.)	2.0 ± 0.17	30.75 ± 3.6	83.1 ± 6.6	
Group V (prime)	1.9 ± 0.21	29.8 ± 1.2	81.25 ± 6.6	
Group VI (prime thiopentone only)	3.0 ± 0.5			1.62 ± 0.26
Group VII (5-s bolus thiopentone only)	3.48 ± 0.54 (4.6 ± 0.4)			1.9 ± 0.26 (1.9 ± 0.4 at 150 s)

atracurium 0.8 mg kg^{-1} to 75 s also minimized the haemodynamic changes and prevented the increase in histamine concentration. However, in the anti-histamine group, the haemodynamic protection was incomplete and was associated with a highly significant increase in plasma histamine concentration. The patient with the most marked increase in plasma histamine concentration and the greatest decrease in mean arterial pressure was in this group. This large increase in mean plasma histamine concentration may have been the result of the known inhibitory effect of cimetidine on histamine-N-methyltransferase, the enzyme responsible for one of the major catabolic pathways of histamine. The substantial increase in plasma histamine concentration in this group probably overcame the protection offered by the anti-histamines by a simple dose–response effect.

Although there was almost a 5-fold increase in plasma histamine concentrations following the 30-s injection, this was not found to be statistically significant because of the large between-patient variation and, hence, the large standard deviation in this group. Considerable variability for histamine release among subjects is well recognized. Not all patients will release histamine after high doses of atracurium but, as the size of the bolus dose increases, there is a greater likelihood of this occurring in most individuals. In animal studies, mast cells from different species and even individual tissues within a single animal are shown to vary markedly in their response to a given inducer of histamine release (Pearce, 1982).

This histamine-releasing response to the higher doses of atracurium must be kept in perspective. Basta and colleagues (1983) have shown that the ability of atracurium to release histamine, relative to its neuromuscular blocking potency, is only one-half that of di-methyl tubocurarine and less than one-third that of tubocurarine. Nevertheless, this response could be of significance in the hypovolaemic patient or the patient with cardiovascular disease.

Several studies have demonstrated more rapid onset of blockade and superior intubating conditions when the priming principle was used (Hutton et al., 1983; Bevan et al., 1984; Nagashima et al., 1984; Mehta et al., 1985; Schwartz et al., 1985). However, there is little uniformity among these studies in terms of the drugs used, the priming dose, the intubating dose, the time between priming and intubating dose and the anaesthetic technique used. These variables may require proper adjustment for each competitive neuromuscular blocking agent. We can only conclude that, with the dose regimen and time interval used in this study, priming does not improve onset times or intubating conditions; nor does it have any protective haemodynamic effect.

A wide variety of onset times at a number of

different doses has been reported for atracurium (Payne and Hughes, 1981; Scott and Goat, 1982; Foldes et al., 1983; Gergis et al., 1983). However, standardization of anaesthetic technique is very important before any effective comparison can be made. In particular, the starting point and end point in the measurement of onset time, the mode of peripheral nerve stimulation and the anaesthetic agents used should all be defined clearly. This is emphasized in this study by the significantly shorter onset times under nitrous oxide–opioid anaesthesia compared with those associated with thiopentone alone.

We conclude that atracurium 0.8 mg kg^{-1} will produce a significantly more rapid onset of blockade than 0.5 mg kg^{-1} with a similar intubation score 1 min earlier (at 90 s compared with 150 s). This may be associated with a transient but significant decrease in mean arterial pressure. This effect, which is probably of little importance in the healthy patient can, however, be attenuated by injecting the drug more slowly—over 75 s.

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2

Histamine Release by Muscle Relaxants

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I. INTRODUCTION

Histamine is distributed throughout the human body and is present in potentially lethal quantities in organs that are particularly vulnerable to its action (e.g., the airways, blood vessels, and heart). Most of it is sequestered with heparin in small membrane-bound granules in mast cells (3–20 pg of histamine per cell). These cells are imbedded in the mucosal linings, skin, connective tissue, and the tissue of small blood vessels and the conducting bundles of the heart.

Histamine was one of the first vasoactive substances to be identified in the body. It is formed by the decarboxylation of the amino acid L-histidine, a reaction which is catalyzed in mammalian tissue by a pyridoxal-requiring enzyme, histidine-decarboxylase (Fig. 1).

In mammals, histamine is metabolized by two routes. One involves deamination in the presence of diamine oxidase; the other, the methylation of the imidazole ring in the presence of the enzyme, histamine N-methyltransferase.

The widespread distribution of histamine in the mast cell is observed only in terrestrial vertebrates, but whatever the benefit of this particular development in vertebrate evolution, the mast cell is of practical importance to the clinician because of its ability to degranulate in response to allergic reactions and to a wide variety of drugs.

II. ETIOLOGY OF HISTAMINE RELEASE

Anesthesiologists encounter both immunologically mediated reactions and chemically mediated reactions associated with the administration of muscle relaxants. The explosive release of histamine from tissue mast cells and blood basophils by an energy-dependent mechanism may be in response to immunological or chemical stimuli.

The immunological reactions may be divided into:

1. Type 1 hypersensitivity response
2. Classic complement-mediated reaction
3. Alternate pathway activation of complement component C_3.

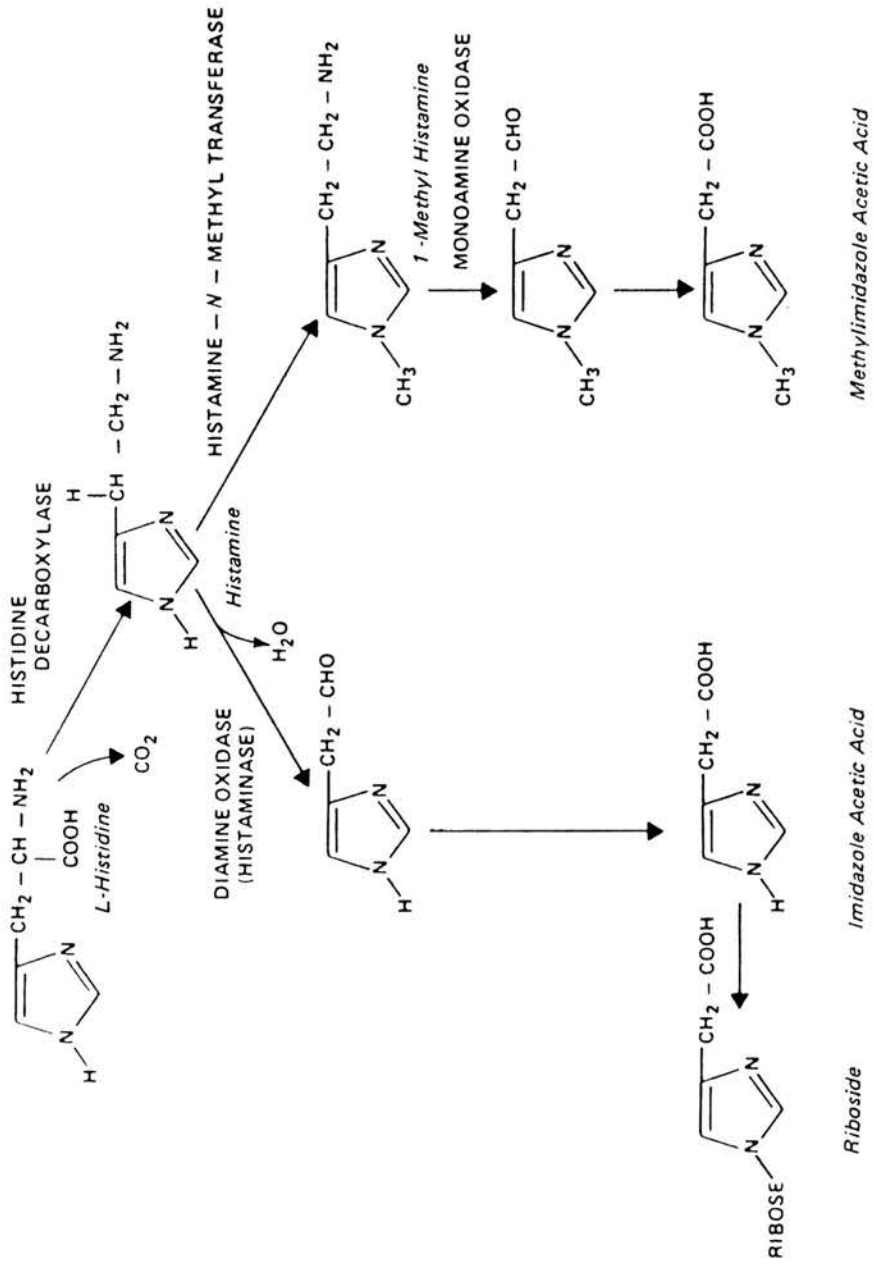

Figure 1 Histamine metabolism.

Immunological reactions to muscle relaxants have never attracted as much notice as those to intravenous induction agents. They are rarer but no less dangerous in their manifestations, since many may be severe enough to necessitate cardiopulmonary resuscitation. Reactions to succinylcholine are more common than with any other muscle relaxant.

Chemically mediated reactions happen much more frequently, and occur when the injected substance acts directly on the tissue mast cells and basophil leukocytes, leading to the release of histamine without antibody or complement involvement. Most organic bases may destruct mast cells and cause histamine release by this mechanism when sufficiently large doses or concentrations are used.

Several experimental studies have shown that histamine is released following the administration of certain neuromuscular-blocking agents, and that the histamine release is an important aspect in the hemodynamic response to the drug. This proposition is based partly upon preclinical and animal experiments in which various agents can elicit the release of histamine. However, the high dose of drugs required to effect histamine release in various in vitro studies as well as the species-specific characteristic of histamine release render extrapolation difficult. Thus, d-tubocurine can be demonstrated to cause histamine release from rat peritoneal mast cells (1), but the concentrations required to elicit this release is significantly higher than is achieved in clinical practice. The term species variability of drug-induced histamine release means that the animal models may not be a valid paradigm for histamine release in man. The rhesus monkey probably provides the closest parallel to the human situation, but even in this animal muscle relaxants tend to be more potent for the neuromuscular junction and less potent for histamine release, making the margin of safety for histamine release rather higher than in man. The margin of safety for histamine release by neuromuscular-blocking agents can be described for each drug. This indicates the number of multiples of the dose of relaxant producing 95% neuromuscular blockade that must be administered in order to produce the side effects associated with histamine release. That is,

$$\frac{ED_{50}\ \text{(histamine release}}{ED_{95}\ \text{(neuromuscular block)}}$$

In addition to the in vitro studies and animal experiments, there are a plethora of case reports (3) and clinical studies which demonstrate that the administration of neuromuscular-blocking drugs in usual doses can cause hemodynamic effects mimicked by the infusion of histamine (4).

III. HISTAMINE RELEASE BY MUSCLE RELAXANTS IN MAN

Most of the commonly used nondepolarizing muscle relaxants in the United States tend to fall into two groups. The steroids (pancuronium and vecuronium) and the benzylisoquinolinium compounds (d-tubocurarine, metocurine, and atracurium). Although histamine release by pancuronium has been described, it is classically a problem associated with the latter group.

In a study in healthy patients, Moss et al. (2) analyzed histamine levels with a radioenzymatic assay technique following administration of d-tubocurarine. While higher doses of d-tubocurarine caused increases in the mean levels of plasma histamine 2 min following administration, there was a significant variability between patients. It should be noted that mast cells from different species and even from individual tissues within a single animal are shown to vary markedly in their responses to given histamine inducers (5). However, it appears that there is a dose-response curve for d-tubocurarine-induced histamine release (i.e., as the dose of d-tubocurarine is increased there is an increased likelihood that the patient will release histamine). This ability to generate a dose-response relationship provides further evidence for a chemically mediated phenomenon rather than an immunologically mediated mechanism. Similar dose-response curves and similar variability for histamine release have been noted with other experimental benzylisoquinolinium neuromuscular-blocking agents, notably BW785 (6) and BWA444U (7). BW785 and BWA444U are interesting nondepolarizing compounds metabolized by plasma cholinesterase. BW785 has a significantly shorter duration of action than atracurium or vecuronium. Unfortunately, its margin of safety for histamine release was considered to be too low to be used safely. BWA444U had pharmacodynamic properties similar to that of

atracurium, but again, its margin of safety for histamine release was considered to be too low.

The histamine liberated by muscle relaxants may produce a number of pharmacological effects dependent on plasma histamine levels. When plasma histamine levels are only marginally elevated (1000–1500 pg/ml) all that may be observed is a transient increase in blood pressure related to an increase in myocardial contractility. However, at higher levels (1500 pg/ml), histamine acts as a potent vasodilator. Thus, hypotension occurs, as does tachycardia, either as a reflex effect related to the hypotension or as a direct effect. Dilatation of cutaneous blood vessels with increased microvascular permeability results in flushing of the skin and increases in skin temperature. Stimulation of bronchial musculature results in bronchoconstriction. All of these effects are dependent on plasma histamine levels. Histamine also exerts effects on other organ systems, including the gastric mucosa, ileum, uterus, and the central and sympathetic nervous systems. The most frequent clinical signs observed by the anesthesiologist, however, are facial flushing, hypotension, and tachycardia. Therefore, the emphasis in this chapter will be on the hemodynamic effects of histamine release following the administration of muscle relaxants.

IV. HEMODYNAMIC EFFECTS OF HISTAMINE RELEASE

There is an abundant body of pharmacological literature on the effects of histamine in animals. More recently, a number of studies have investigated the effects of histamine on the human cardiovascular system. In vitro studies as well as a number of in vitro studies have demonstrated effects on the heart and systemic vasculature (8). Administration of histamine causes:

1. A chronotropic effect (H_2 directly and through catecholamine liberation)
2. An inotropic effect (H_1 negative, H_2 positive)
3. An effect on coronary vasoconstriction (H_1 constricts, H_2 dilates)
4. Changes in conductivity
5. Changes in fibrillation threshold (doses as low as 10 pg/ml)

In addition to the changes in the heart itself, there are important effects on the systemic vascular resistance which appears to be a direct effect of histamine (9). Recent studies have shown that histamine methyltransferase, one of the major catabolic enzymes for histamine, is located within arterioles, particularly in the kidney. The ability to maintain vascular integrity may depend upon the ability to metabolize endogenous histamine. It has been postulated that anesthetic drugs may interfere with histamine metabolism and thereby potentiate its effects.

Despite the significant variability in d-tubocurarine-induced histamine release, the increased levels of plasma histamine observed 2 min after d-tubocurarine administration correlates well with the observed hypotension (10). Multiple linear regression analysis demonstrates a tight correlation between the amount of drug administered and the amount of histamine released, and between the level of plasma histamine and the extent of hypotension (Fig. 2). The relationship between the dose of d-tubocurarine and the extent of hypotension is more tenuous. While d-tubocurarine has been shown to have ganglionic-blocking activity in animals, the contemporaneous restoration of hemodynamic variables and plasma histamine within 5 min of administration suggests that simultaneous ganglionic blockade is not involved and that histamine release is of more importance in terms of hemodynamic changes. Measurement of ganglionic blockade is difficult in the clinical setting, so that it is virtually impossible to establish how important a role it plays in normal anesthetized humans. Savarese (11), using the chloralose-anesthetized cat, established that ganglionic blockade induced by d-tubocurarine occurred at 1.31 mg/kg, whereas the delayed depressor response was transient and occurred at 0.4 mg/kg. Data accumulated during these experiments suggest that the duration of ganglionic blockade secondary to d-tubocurarine administration was similar to the duration of neuromuscular blockade. Classically, the histamine release observed with muscle relaxants is a transient phenomenon, with the associated hemodynamic changes returning to baseline within about 5 min. Histamine has a plasma half-life of less than 1 min.

Experiments with BWA444U (7), a muscle relaxant devoid of ganglionic-blocking activity, have also demonstrated a similar relationship between hypotension and plasma histamine 2 min following administration. It appears from these studies that the

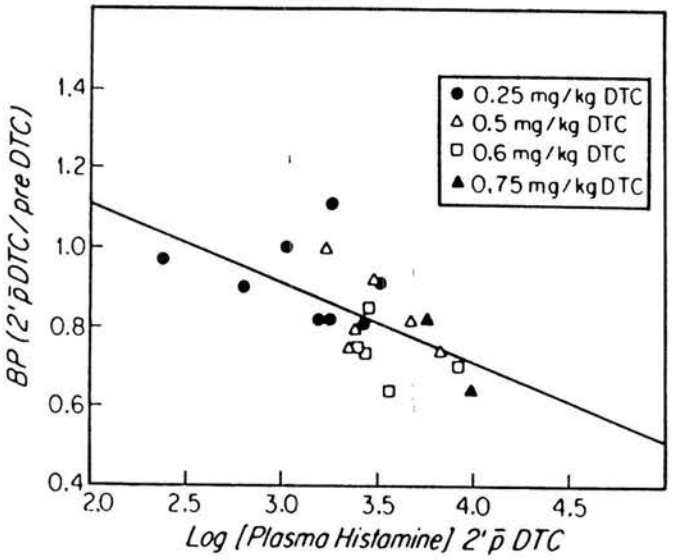

Figure 2 Relationship between the decrease in blood pressure and plasma histamine concentration 2 min after the administration of indicated doses of d-tubocurarine in 21 patients. (From Ref. 2, used with permission.)

dose of neuromuscular-blocking agent which increases plasma histamine to about 200% of control values will result in clinically and statistically significant changes in heart rate and arterial pressure in healthy patients.

Basta et al. (12) compared the histamine-releasing potency of atracurium to those of metocurine and d-tubocurarine. Atracurium produced a transient but significant reduction in mean arterial blood pressure at the upper end of its clinical dose range (0.6 mg/kg) (Fig. 3). However, when compared with other commonly used benzylisoquinolinium muscle relaxants, the ability of atracurium to release histamine relative to its neuromuscular-blocking potency was found to be approximately one-half that of metocurine and less than one-third that of d-tubocurarine (Table 1).

The other new intermediate-duration muscle relaxant, vecuronium, shows no histamine-releasing potential within the

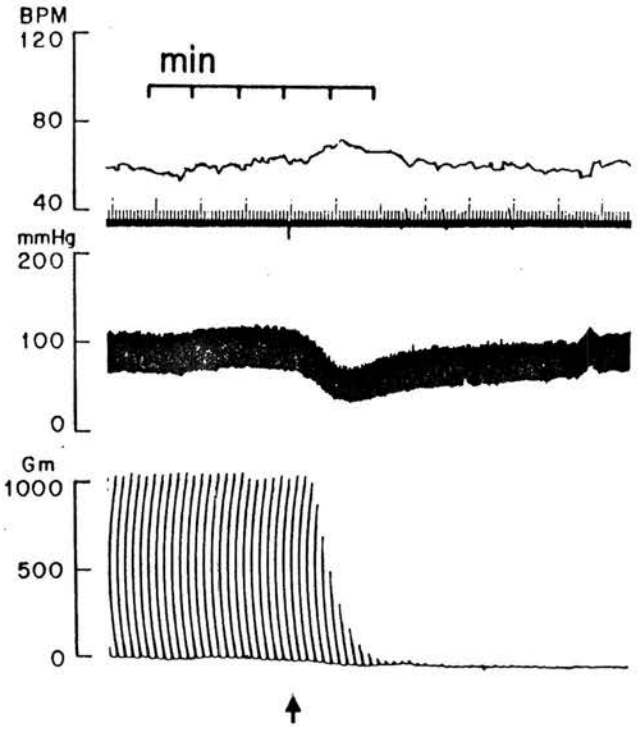

Figure 3 The transient hemodynamic response occasionally observed following a 0.6-mg/kg bolus of atracurium. Illustrated are the heart rate (by tachograph), intra-arterial blood pressure, and the single twitch at 0.15 Hz. Atracurium, 0.6 mg/kg, was injected as a rapid bolus at the arrow mark.

clinical dose range. Even at 0.2 mg/kg, three and one-half times its ED_{95}, there was no histamine release and hemodynamic parameters were stable. In a clinical study that measured skin redness and induration caused by the intradermal injection of d-tubocurarine, metocurine, pancuronium, and vecuronium, vecuronium caused the smallest reaction and d-tubocurarine and metocurine the largest (13).

Table 1 Histamine-Releasing Potencies of Neuromuscular-Blocking Agents

Drug	Dose (mg/kg)	x ED_{95}	Percent of control		
			MAP	HR	Histamine
d-Tubocurarine	0.5	1	78	116	318
Metocurine	0.5	2	79	119	212
Atracurium	0.6	3	80	108	192
Vecuronium	0.2	3.5	99	102	87

Abbreviations: MAP, mean arterial pressure; HR, heart rate.
Doses of drugs associated with significant changes from control values. Note that even at 3.5 x ED_{95}, vecuronium has no significant change in cardiovascular parameters or plasma histamine levels.
Source: From Ref. 12, used with permission.

Succinylcholine has a histamine-liberating capacity of about 1% that of d-tubocurarine. Gallamine and pancuronium have minimal potential for histamine release within the clinical dose range.

V. STRATEGIES FOR THE ATTENUATION OF HISTAMINE-MEDIATED HEMODYNAMIC CHANGES

While the rapid administration of a neuromuscular-blocking drug can evoke hemodynamically significant histamine release, it has been shown that a variety of clinical strategies may be employed to attenuate the hemodynamic responses.

A. Injection Rate

In a study with d-tubocurarine, Rosow and colleagues found dose-related increases in plasma histamine occurring 2 min after injection in the groups receiving boluses but not in those receiving a slow infusion (Fig. 4). Even a 0.75-mg/kg dose of d-tubocurarine administered over 105 sec caused no clinically significant histamine release or hypotension (10).

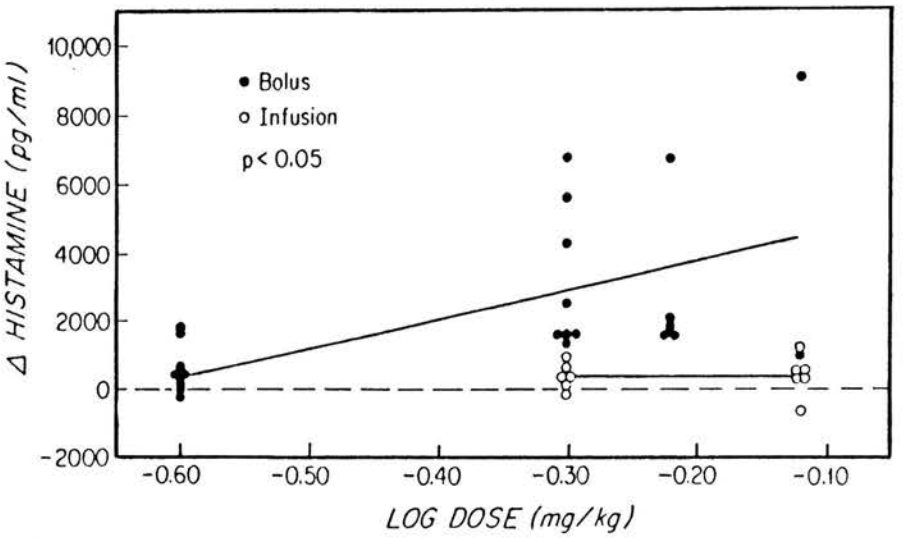

Figure 4 Slowing the injection rate of d-tubocurarine minimizes histamine release. In a study with d-tubocurarine, dose-related increases in plasma histamine occurring 2 min after injection in the groups receiving boluses but not in those receiving a slow infusion were found (10). (From Ref. 10, used with permission.)

In a similar study, a comparison of the alterations in hemodynamics and histamine release for BW785 following either a bolus or a 1-minute infusion of the drug demonstrated that when the drug was administered as a 1-min infusion it had significantly less hemodynamic effect than when administered as a bolus (6).

In a further study, the administration of BWA444U (1.2 mg/kg) as a 5-sec bolus caused significant increases in plasma histamine in several patients, whereas no detectable change was seen in any of the patients receiving the same dose in a 15- to 30-sec slow bolus (7).

More recently, it has been shown that the transient histamine release and associated hemodynamic response to high-dose atracurium (0.6 mg/kg) may also be prevented by administering this dose slowly over 75 sec (14) (Fig. 5).

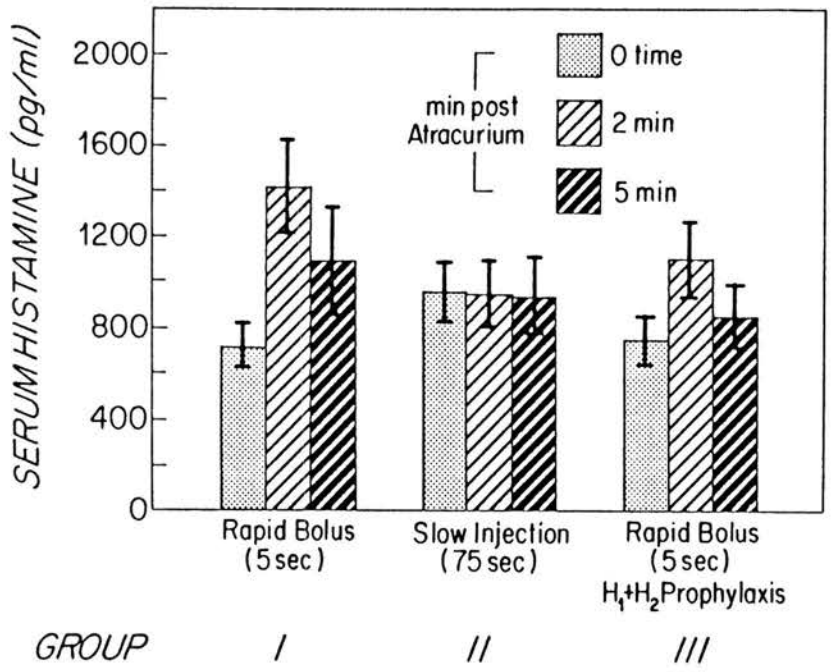

Figure 5 Histamine release by atracurium (0.6 mg/kg) and the subsequent hemodynamic response is prevented by administering this dose slowly over 75 sec. Pretreatment with intravenous H_1 and H_2 antagonists does not prevent histamine release but does attenuate the hemodynamic response. (From Ref. 14, used with permission.)

It thus appears that small time differences in the rate of administration of intravenous muscle relaxants can lead to significant changes in the likelihood of generating clinically significant histamine release. Small differences in plasma levels of a histamine-releasing drug can produce large changes in the amount of histamine liberated. Transiently high drug levels are more likely to degranulate mast cells.

B. Histamine Receptor Blockade

Aside from altering the rate of infusion, abundant data suggest that the prophylactic use of H_1 and H_2 antagonists can also attenuate the cardiovascular responses caused by various histamine-releasing drugs such as morphine (15), BW785 (6), haemaccel (16) and d-tubocurarine (10).

When cimetidine (4 mg/kg) and diphenhydramine (0.1 mg/kg) were administered intravenously 15 min prior to injection of a rapid bolus of BW785 significant cardiovascular protection could be achieved. It should be noted, however, that the rise in histamine levels following this approach was even higher than that seen following the injection of a single rapid bolus without antihistamine pretreatment. This effect is presumably due to the known capacity of cimetidine to inhibit histamine N-methyltransferase, which is possibly the principle route of histamine catabolism. Despite these high histamine levels, the cardiovascular effects were significantly less than in the nonpretreated subjects.

Similarly, when patients were pretreated intravenously with H_1 and H_2 antagonists prior to administration of atracurium, 0.6 mg/kg^{-1}, the hemodynamic response was attenuated (14), again despite a moderate rise in plasma histamine (Table 2) and (Fig. 5).

Table 2 Effect of 0.6 mg/kg^{-1} Atracurium on Mean Arterial Pressure and Heart Rate

	n	MAP % of Baseline	HR % of Baseline
Group I 5-sec bolus	9	82.1±6.4% (78.4/63.5/74.8)	108.5±4.6% (65/70.1/64.1)
Group II 75-sec bolus	9	95.7±2.6% (75.1/71.8/73.5)	97.7±2.3% (66/64.2/62.4)
Group III $H_1 + H_2$ prophylaxis before 5-sec bolus	9	96.2±2.2% (65.7/63.0/65.2)	102.3±2.2% (60.2/62.1/60.4)

Abbreviations: MAP, mean arterial pressure; HR, heart rate.
Actual values at baseline, 2 and 5 min for mean arterial pressure and heart rate are shown below in brackets. The units are mmHg and beats/min, respectively.
Source: From Ref. 14, used with permission.

The results of these studies using antihistamines are supported by pharmacological studies carried out in healthy subjects using systemic histamine (17). Exogenous histamine by rapid injection appears to stimulate only H_1 receptors. Chlorpheniramine alone antagonizes this response to histamine. The effects of cardiovascular H_2-receptor stimulation are demonstrated best by a sustained and a large dose of histamine given by infusion.

Experiments have been made in anesthetized cats and dogs and in healthy human volunteers to compare the changes in blood pressure and heart rate during the systemic administration of histamine (4).

Histamine (1×10^{-9} to 1×10^{-7} mmol/kg/min) lowered blood pressure in a similar dose-dependent fashion in all three species. In man and the cat, this was accompanied by a clear dose-dependent tachycardia, whereas in the dog, heart rate changes were minimal.

Pharmacological analysis of the depressor responses to histamine in all three species and the reduction in total peripheral resistance in the cat and dog showed that the immediate responses to histamine in all three species involved H_1 receptors, and that sustained responses involved H_2 receptors. Abolition of responses to histamine throughout infusions required H_1- and H_2-receptor blockade.

Therefore, in order to antagonize all the cardiovascular responses to endogenous histamine, pharmacological data suggest that this is best achieved by a combination of H_1- and H_2-receptor antagonists.

C. Drug Design

A third strategy in preventing histamine release involves structure activity relationships. Small variations in molecular design can radically alter the autonomic side effects of neuromuscular-blocking agents.

The histamine-releasing group of drugs includes a wide variety of different compounds. Indeed, the structures of these drugs are so diverse that Paton was forced to conclude that in addition to polymeric substances, any compound with two or more basic groups separated by a sufficient aromatic or aliphatic

scaffold is liable to have this property. Even today, our knowledge of histamine-releasing structure activity relationships is still elementary.

The histamine-releasing properties of d-tubocurarine are probably due to the presence of the tertiary amine. In general, bisquarternary compounds do not possess strong ganglionic-blocking or histamine-releasing properties. Methylation of d-tubocurarine to produce metocurine or dimethyl tubocurarine (a bisquarternary compound) reduces the histamine-releasing and ganglion-blocking activities associated with d-tubocurarine.

VI. CONCLUSIONS

Since Alam et al. (1939) first detected the histamine release caused by curare, several thousand studies have been devoted to the question of whether or not histamine plays a significant role in adverse reactions to intravenous agents, and whether this role can be distinctly defined both qualitatively and quantitatively.

Unfortunately, the lack of a sensitive and reliable assay for plasma histamine had made it difficult to document the role of histamine release in drug-induced cardiovascular changes. The recent development, however, of a radioenzymatic technique and its improvement by the discovery of renal histamine N-methyltransferase has greatly enhanced our ability to detect histamine in clinically important situations.

The importance of histamine release in relation to the hemodynamic changes associated with the administration of d-tubocurarine and other benzylisoquinolinium compounds is now well recognized. One of the characteristics of an ideal muscle relaxant (18) is that this side effect be avoided.

Even atracurium has been criticized for its mild histamine-releasing effect when administered as a bolus at the high dose end of its spectrum. This side effect of atracurium must be kept in perspective. Atracurium has only one-third the histamine-releasing potential of d-tubocurarine, which has been used successfully for several decades. Also as outlined in this chapter, there are clinical strategies for preventing this response. In the health ASA (American Society of Anesthesiologists Classification) I or II patient, this transient hypotensive effect is probably of little clinical significance.

Nevertheless, in the hemodynamically unstable patient who is hypovolemic or has cardiovascular disease, this effect could well be of more importance.

There is no doubt that where a "clean" cardiovascular profile is required, vecuronium has to be the drug of choice. Certainly, with the new hemodynamic standards set by this drug, it is unlikely that the anesthesiologist will ever again see a new muscle relaxant introduced with a histamine-releasing potential greater than that of atracurium.

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5

New Muscle Relaxants and the Cardiovascular System

In the early 1980s the most commonly used muscle relaxants in anesthetic practice in the United States were succinylcholine, tubocurarine, metocurine, pancuronium and, to a lesser extent, gallamine. However, these agents have certain cardiovascular side effects that limit their use. These effects are generally due to stimulation or inhibition of peripheral autonomic sites, to the release of histamine and possibly other vasoactive substances from vascular mast cells, or to increases in serum potassium levels secondary to motor end-plate depolarization. A major reason for developing new neuromuscular blocking agents is to produce drugs that avoid these well-known side effects. A careful examination of the advantages and disadvantages of the above agents will lead to the conclusion that a nondepolarizing muscle relaxant such as pancuronium, without cardiovascular side effects, would provide a significant improvement.

The accumulated knowledge of structure-activity relationships in the field of neuromuscular blockade allows chemists to produce effective neuromuscular blocking drugs more predictably, with less reliance on chance, than is the case with any other class of drugs. Consequently, most kinds of unwanted activity can be avoided by appropriate molecular design; and new compounds that produce unwanted effects can be discarded at an early stage in preclinical testing. The development of atracurium and vecuronium has marked an exciting stage in the production of drugs with improved cardiovascular stability. These two drugs fall into the intermediate duration class, but research is continuing to find agents of similar cardiovascular stability with shorter and longer durations of action.

PHARMACOLOGY OF THE AUTONOMIC NERVOUS SYSTEM

In order to understand the autonomic responses to existing muscle relaxants and the developmental pharmacology of new agents, it is important to have a working knowledge of the autonomic nervous system, and, in particular, the possible sites of interaction between muscle relaxants and cholinoceptors.

Acetylcholine acts on both muscarinic and nicotinic receptors (Table 5-1). Muscarinic receptors are present in various smooth muscles, cardiac muscle, and exocrine glands. They are termed "muscarinic" because muscarine, a quaternary amine alkaloid, has

CARDIAC ANESTHESIA, SECOND EDITION
ISBN 0-8089-1848-6

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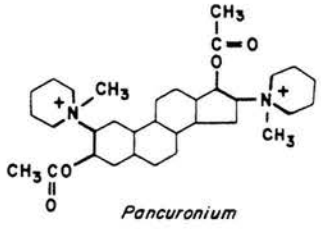
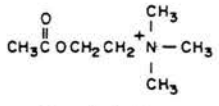
Table 5-1
Cholinoceptive Sites

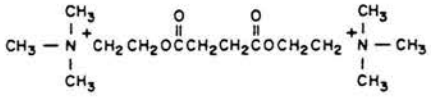
Site	Activator or Substrates	Inhibitor
Nicotinic receptors	Nicotine, tetramethylammonium,	d-tubocurarine
Neuromuscular junction	succinylcholine, decamethonium	All nondepolarizing neuromuscular blocking agents
Autonomic ganglia	Dimethylphenylpiperazinium	Hexamethonium, d-tubocurarine
Muscarinic receptors, (bowel, bladder, bronchi, sinus node of the heart, pupillary sphincter)	Muscarine	Atropine, gallamine, pancuronium
Esteratic receptors		
Active site of acetylcholinesterase	Acetylcholine, methacholine	Neostigmine, pyridostigmine, benzoquinonium
Active site of plasmacholinesterase	Benzoylcholine, butyrylcholine, succinylcholine	Hexaflurenium, tetrahydroaminacrine, pancuronium



Pancuronium



Acetylcholine



Succinylcholine
(diacetylcholine)

Fig. 5-1. Structural relationship of acetylcholine to two neuromuscular blocking agents. Succinylcholine (diacetylcholine) is simply two molecules of acetylcholine linked through the acetate methyl groups. Pancuronium may be viewed as two acetylcholine-like fragments (outlined in dark print) properly orientated conformationally on a bulky, rigid, inflexible steroid nucleus.

actions similar to those of acetylcholine at the sites indicated. The muscarinic receptor is blocked by atropine and related drugs. The nicotinic receptors of acetylcholine are located in autonomic ganglia and at the skeletal neuromuscular junction. They are termed "nicotinic" because nicotine also acts on these receptors. However, the nicotinic receptors in the autonomic ganglia and skeletal muscle are not identical. The effect of acetylcholine on autonomic ganglia is blocked by tubocurarine and related compounds. Further cholinoceptive sites are found on the esteratic receptors of acetylcholinesterase and plasma cholinesterase. Crystalographic analysis of acetylcholine and related agonists provides a tentative answer to the nature of the cholinergic receptor. Acetylcholine is a flexible molecule, and rotation is possible at two different bonds (Fig. 5-1). Muscarinic and nicotinic drugs differ from acetylcholine in the degree of rotation at the sites of torsion. Thus, acetylcholine has both muscarinic and nicotinic effects, whereas the purely muscarinic or nicotinic congeners have constraints imposed on them by conformational factors. In order for neuromuscular blocking drugs to interact with the recognition sites of the cholinoceptors at the neuromuscular junction, the drugs must bear some chemical relationship to acetylcholine. Consequently, there is the possibility that they might compete with or mimic acetylcholine at other sites (eg, cholinesterases, nicotinic autonomic ganglionic receptors, and muscarinic receptors).

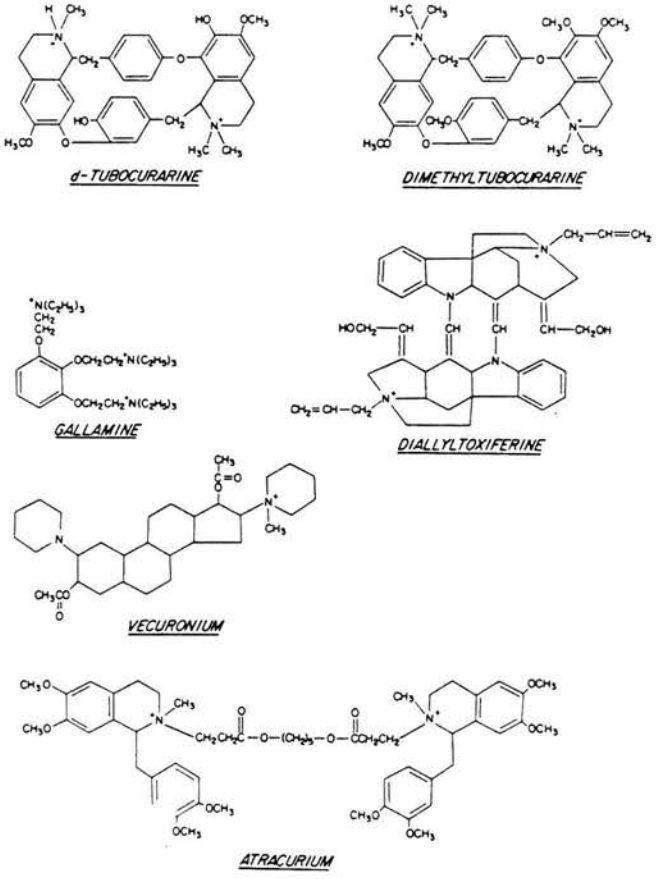


Fig. 5-2. The chemical structure of some common nondepolarizing neuromuscular blocking agents.

Interaction of Neuromuscular Blocking Agents at Different Cholinoceptive Sites

AUTONOMIC GANGLIA

Tubocurarine (Fig. 5-2) blocks ganglionic nicotinic receptors and produces some ganglionic blockade in a dose range similar to that required to produce neuromuscular blockade. It may have a slightly more powerful action on parasympathetic than on sympathetic ganglia.[1] Autonomic reflexes arising in the course of surgical operations may be impaired by the ganglionic blocking action, and this action may contribute to hypotension.[2,3] Recent evidence, however, suggests that the role of ganglionic blockade in the hypotensive action of tubocurarine is possibly less important than its ability to release histamine.[4]

Metocurine (dimethyltubocurarine) and alcuronium (diallyltoxiferine) are weaker ganglionic blockers; and other neuromuscular blocking drugs (eg, gallamine, pancuronium, atracurium, and vecuronium) have no ganglionic blocking activity in the doses used clinically (Fig. 5-2). Succinylcholine has a weak autonomic ganglion stimulant action that may have some clinical importance, since a hypertensive response is occasionally observed (Fig. 5-3).[5]

MUSCARINIC RECEPTORS

Evidence has accumulated in recent years that muscarinic receptors are probably not a homogeneous group.[6] By definition they are all stimulated by muscarine and they are all blocked by atropine, but they may differ with respect to their interactions with

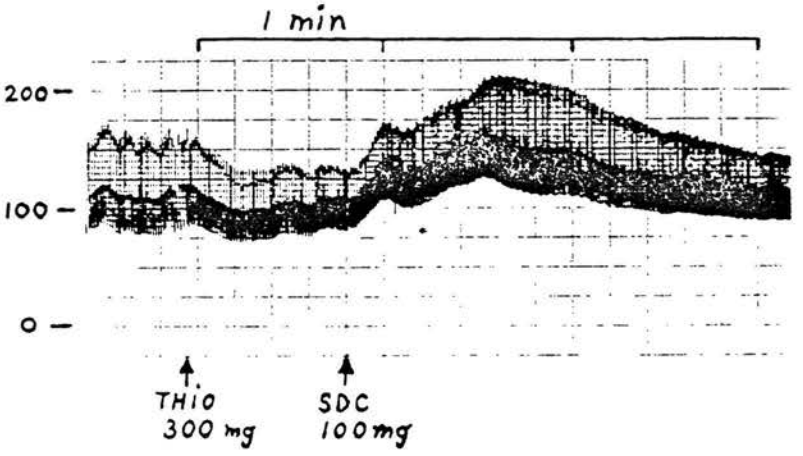


Fig. 5-3. Hypertensive response to succinylcholine (SDC). Increased arterial pressure after succinylcholine administration may represent a clinical manifestation of its ganglion stimulating action. This patient had a hypertensive response to succinylcholine. There was no other anesthetic or surgical intervention.

other agonists and antagonists. Figure 5-4 is a diagramatic representation of the main components of the autonomic nervous system with respect to the heart. For the purpose of the diagram, the muscarinic cholinoceptors have been labeled "M1," "M2," and "M3" receptors, but this is not a strict classification and is probably an oversimplification.[7]

The first indication that muscarinic receptors may not all be identical in character came from Riker and Wescoe[8] who showed that gallamine, although generally free from atropine-like activity in smooth muscle, nevertheless blocked muscarinic receptors in the cat heart, and, consequently, inactivated the cardiac vagus nerve. In Figure 5-4 the cardiac muscarinic receptors are included in the "M2" group to distinguish them from the more usual type labeled "M1." Other workers have since shown that pancuronium,[9] fazadinium,[10] alcuronium,[11] and stercuronium[12] also block the cardiac muscarinic receptors in doses approximating those required to produce muscle relaxation. Tubocurarine, metocurine, vecuronium, and atracurium block cardiac muscarinic receptors and other muscarinic receptors only in doses that greatly exceed the neuromuscular blocking dose.[13-15]

Arterioles also have muscarinic receptors, but

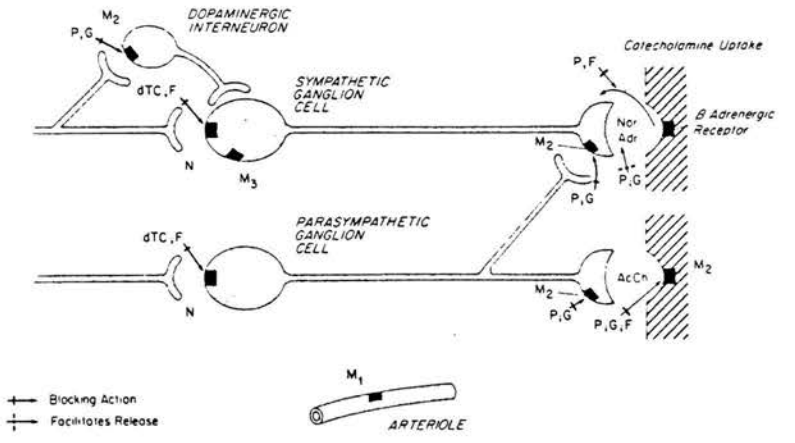


Fig. 5-4. Diagrammatic representation of the autonomic nervous system with respect to the heart, and sites of action of some neuromuscular blocking drugs on this system. The muscarinic receptors have been divided into three subclasses (M_1, M_2, M_3). By permission of the authors. N = nicotinic receptor, P = pancuronium, G = gallamine, F = fazadinium, dTc = *d*-tubocurarine.

these receptors are not innervated. They resemble most of the noncardiac muscarinic receptors in their agonist and antagonist selectivity, and are labeled "M1" in Figure 5-4. The vasopressor response to methacholine, although blocked by atropine, is not affected by pancuronium, showing that the muscarinic receptors involved in the arterioles are not the same type as those in the sinoatrial node.

Experiments have shown that cardiac muscarinic receptors are not the only muscarinic receptors that are blocked by certain neuromuscular blocking drugs. Stimulation of the vagus nerve has been shown to reduce the release of norepinephrine from concomitantly stimulated sympathetic nerves to the heart.[16] It is, therefore, believed that vagus nerve terminals impinge not only on the nodal and atrial cells of the heart, but also on the sympathetic nerve endings where they act to inhibit the release of norepinephrine. The cholinergic receptors on the sympathetic nerve endings are of the muscarinic type, and there is indirect evidence that they are blocked by gallamine and pancuronium, but much less effectively by vecuronium.[17] This effect would enhance the tachycardia arising from blockade of the cardiac muscarinic receptors. Because the muscarinic receptors on the sympathetic terminals resemble the cardiac muscarinic receptors in being blocked by gallamine and pancuronium, they have both been labeled "M2," but the evidence of similarity is not very strong.

Another location of muscarinic cholinoceptors that are blocked by pancuronium and gallamine and are, therefore, indicated as "M2" receptors in Figure 5-4 is on the small dopaminergic interneurons on sympathetic ganglia. These cells are activated through muscarinic receptors stimulated by acetylcholine that is released from collaterals of the preganglionic cholinergic nerve fibers. Dopamine released from these cells onto the ganglion cells hyperpolarizes them and, therefore, suppresses ganglionic transmission.[18] Blockade of these inhibitory cells by gallamine or pancuronium may, therefore, at appropriate stimulation frequencies, facilitate transmission through the ganglia by inactivating the inhibitory modulating influence of the dopaminergic cell loop.[19]

Transmission through sympathetic ganglia is mediated by acetylcholine acting on nicotinic receptors. There are, however, muscarinic cholinoceptors present on sympathetic ganglia whose physiological function is as yet unknown. These are labelled "M3" receptors in Figure 5-4. They differ from those labeled "M2" in that they are not blocked by gallamine or pancuronium; and, they differ from those labeled "M1" and "M2" in that they are especially sensitive to certain unusual muscarinic agonists.[20] It should be noted that gallamine causes norepinephrine release in guinea pig and cat atria and in anesthetized cats by a mechanism that may be quite independent of muscarinic blockade.[21] Similarly, very large concentrations of pancuronium produce norepinephrine release in isolated guinea pig atria under conditions in which parasympathetic block could not be involved.[22] Pancuronium and fazadinium have also been shown to block norepinephrine reuptake into sympathetic nerve endings both in cardiac muscle and in smooth muscle in guinea pigs and rats.[22-24] In the cat, the main mechanism through which certain neuromuscular blocking drugs depress cardiovagal activity is by blocking postjunctional muscarinic cholinoceptors as described above. However, Lee Son and Waud calculated that the concentrations of pancuronium and gallamine that block responses to postjunctional vagal stimulation are too low to exert significant blocking action on the postjunctional muscarinic receptors; they concluded that the main site of action of these two drugs in blocking the guinea pig cardiac vagus is on the postganglionic nerve terminals.[25]

It can be concluded from the foregoing discussion that a combination of any of the above actions of gallamine, pancuronium, and fazadinium may account for the cardiovascular effects of these drugs. There is considerable species difference with regard to the relative importance of these effects. It is not known which effect is the most predominant in humans, but it is likely that the relative importance varies from patient to patient according to such factors as the pre-existing autonomic balance, the type of premedication, the anesthetic, and any concurrent drug therapy.

The Demonstration of Autonomic Effects of Neuromuscular Agents in Whole Animals

There are no appropriate means for testing the autonomic effects of relaxants in man, and most of the knowledge of these actions is derived from experiments performed in isolated organ systems or in whole animals such as the cat. In the cat, measurements of neuromuscular and autonomic functions may be accomplished simultaneously. Neuromuscular function is assessed by recording the twitch response of the tibialis anterior (or other appropriate muscle) evoked indirectly via the sciatic or peroneal nerve. Vagal function is determined by quantitation

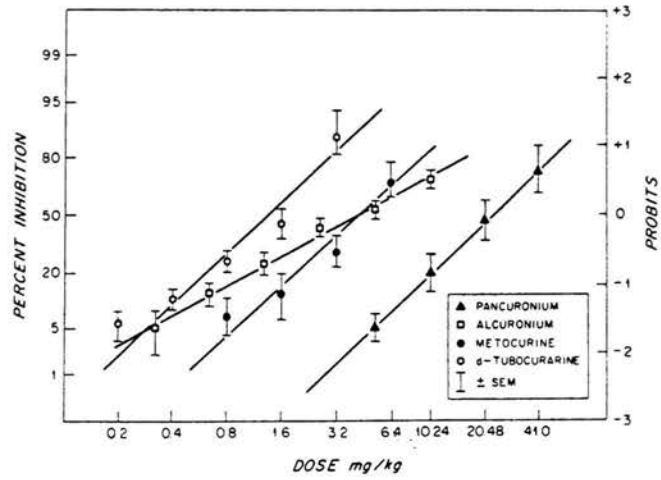


Fig. 5-5. Sympathetic (ganglionic) inhibition by nondepolarizing relaxants in the cat. (JJ Savarese, unpublished data).

of the bradycardia and hypotension elicited by stimulation of the nerve. Sympathetic ganglionic responses (Fig. 5-5) are assayed by preganglionic stimulation of the sympathetic trunk, central to the superior cervical ganglion, and recording the evoked contraction of the nictitating membrane (Fig. 5-6).

The separation of neuromuscular blocking action from autonomic effects can be described for each drug as its *autonomic margin of safety.* This indicates the number of multiples of a dose of relaxant, producing 95 percent neuromuscular blockade, that must be administered in order to produce side effects. The higher the autonomic margin of safety, the lower the probability of occurrence of a side effect. The following quotients are used:

1. $\frac{ED_{50}\text{ (Ganglion block)}}{ED_{95}\text{ (Neuromuscular block)}}$
2. $\frac{ED_{50}\text{ (Cardiac vagal block)}}{ED_{95}\text{ (Neuromuscular block)}}$
3. $\frac{ED_{50}\text{ (Histamine release)}}{ED_{95}\text{ (Neuromuscular block)}}$

Calculation of autonomic margins of safety for neuromuscular blocking drugs in man is not possible because suitable methods for quantitating autonomic responses in humans are not available. There is considerable indication, however, that when a neuromuscular blocking drug produces an autonomic effect in the cat within or near the neuromuscular dose range, the neuromuscular blockade in humans will be accompanied by cardiovascular changes corresponding to those autonomic actions (Table 5-2).

The ED_{95} for neuromuscular blockade for some of the nondepolarizing relaxants in humans, under nitrous oxide, has been determined. These values, together with the ED_{50} for ganglion and vagal block derived in the cat (since these cannot be determined in humans), were used to calculate the values in the table. The ED_{50} for histamine release can, however, be calculated in humans, using an isotope radioenzymatic assay. The relative importance of ganglion block, vagal block, and histamine release for each of the nondepolarizing relaxants is outlined in Table 5-3.

Anesthesiologists encounter both immunologically mediated reactions and chemically mediated reactions associated with the administration of muscle relaxants. Immunological reactions to muscle relaxants have never attracted as much attention as those to intravenous induction agents. These reactions are rare but no less dangerous in their manifestations, since many have been severe enough to necessitate cardiopulmonary resuscitation. Reactions to succinylcholine are more common than with any other muscle relaxant.

Chemically mediated reactions happen much more frequently and occur when the injected substance acts directly on tissue cells and basophil leukocytes, leading to the release of histamine without antibody or complement involvement. Most organic bases can release histamine, and most neuromuscular blocking drugs have been shown to produce this effect when sufficiently large doses or concentrations

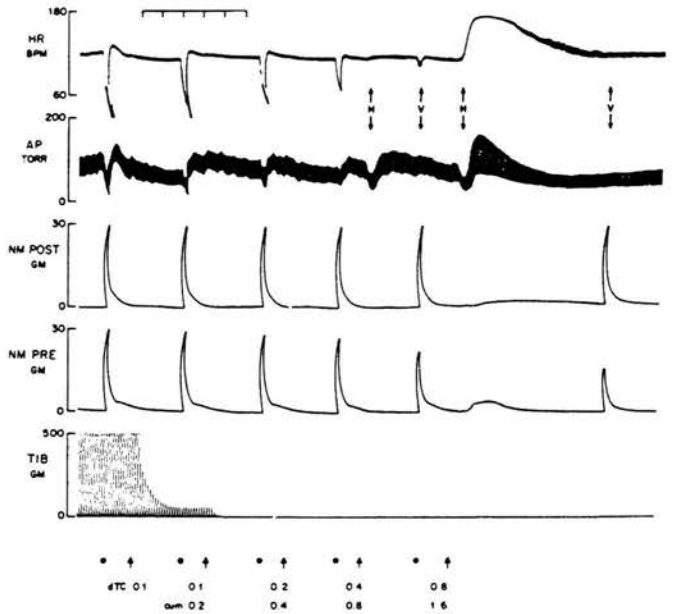


Fig. 5-6. Simultaneous recording of autonomic and neuromuscular function in a cat anesthetized with chloralose. Recordings are (top to bottom) of heart rate, femoral arterial pressure, contractions of the left and right nictitating membranes elicited preganglionically and postganglionically, and tibialis anterior muscle twitch. At times indicated by dots below the graphs, stimulation of the right vagus nerve and both sympathetic trunks (left postganglionically, and right preganglionically) was applied at 20 Hz for 10 seconds. At times indicated by arrows below graphs, *d*-tubocurarine in doses indicated (mg/kg) was given intravenously. Lower figures indicate cumulative dosage. Note that vagal response (bradycardia and hypotension), ganglionic response (preganglionically stimulated nictitating membrane) and neuromuscular response are all inhibited at a cumulative dose of 0.8 to 1.6 mg/kg. Marker H between the upper two graphs indicates cardiovascular changes suggestive of histamine release. Marker V indicates points of vagal stimulation with little or no response. (From Savarese JJ: The autonomic margins of safety of metocurine and d-tubocurarine in the cat. Anesthesiology 50:40, 1979, with permission.)

Table 5-2
Autonomic Margin of Safety of Nondepolarizing Relaxants in Man

Drug	Neuromuscular Block*	Autonomic Margin of Safety		Margin of safety for histamine release
	ED_{95} in Man	*Ganglion block*	*Vagal block*	
d-tubocurarine	0.51	2.94	0.59	1
Metocurine	0.28	18.6	2.86	2
Pancuronium	0.07	328.6	2.86	High
Alcuronium	0.25	18.0	1.84	High
Vecuronium	0.056	89.2	40.6	High
Atracurium	0.28	35.7	8.7	3

*ED_{95} in humans (mg/kg)

$$\text{Autonomic margin of safety} = \frac{ED_{50} \text{ for autonomic inhibition in the cat}}{ED_{95} \text{ for neuromuscular block in man}}$$

$$\text{Margin of safety for histamine release} = \frac{ED_{50} \text{ for histamine release in man}}{ED_{95} \text{ for neuromuscular block in man.}}$$

Table 5-3
Effects of 1.5–2 × ED_{95} Blocking Dose of Nondepolarizing Muscle Relaxants in Humans Under Halothane Anesthesia

	Ganglion block	(Muscarinic) vagal block	Histamine release	Under Anesthesia			
				SVR	*CO*	*BP*	*HR*
Tubocurarine	*	–	***	↓	↓	↓	–
Metocurine	–	–	*	↓	–	↓	–
Pancuronium	–	**	–	–	↑	↑	↑
Gallamine	–	***	–	–	↑	↑	↑
Alcuronium	*	*	–	↓	↑	↓	↑
Fazadinium	**	**	–	↓	↑	↓	↑
Vecuronium	–	–	–	–	–	–	–
Atracurium	–	–	(– to *)	(– or ↓)	(– or ↑)	(– or ↓)	–

SVR = Systemic Vascular Resistance, CO = Cardiac Output, BP = Blood Pressure (Mean arterial pressure), HR = Heart Rate

* = Mild

** = Moderate

*** = Major

are used.[26] It is important to know, however, whether the effect is likely to occur with the dosage used in clinical practice. It has been recognized that tubocurarine is a potent liberator of histamine, and this is possibly the major cause of the hypotension occurring in most patients given clinical doses.

Recent work has demonstrated that the release of histamine by muscle relaxants in humans is dose-dependent (Fig. 5-7), and that the release is well-correlated with significant hemodynamic effects (Fig. 5-8).[4] Further studies, however, have shown that there are clinical strategies, such as slowing the injection rate (Fig. 5-7), or administering histamine receptor blockers (H1 and H2), that can blunt these effects in humans.[27]

The ability of atracurium to release histamine relative to its neuromuscular blocking potency is approximately one-half that of dimethyltubocurarine, and about one-third that of tubocurarine.[28] Succinylcholine has a histamine-liberating activity about 1

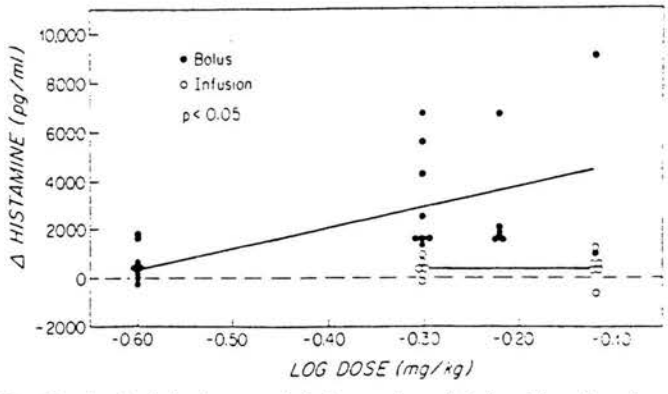


Fig. 5-7. Slowing the injection rate of *d*-tubocurarine minimizes histamine release. In a study with *d*-tubocurarine, Moss et al found dose-related increases in plasma histamine occurring 2 minutes after injection in the groups receiving boluses, but not in those receiving a slow (60–90 sec) infusion. (From Moss J, Rosow CE, Savarese JJ, et al: Role of histamine in the hypotensive action of d-tubocurarine in humans. Anesthesiology 55:19, 1981, with permission.)

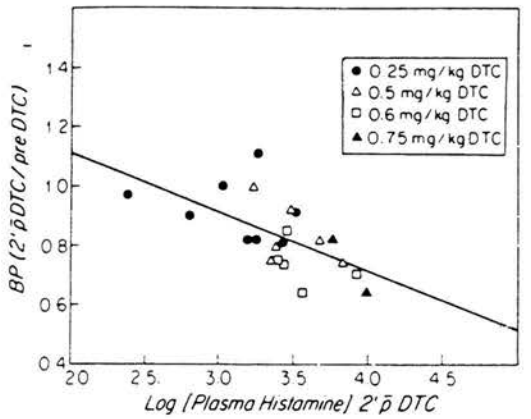


Fig. 5-8. Relationship between the decrease in blood pressure and plasma histamine concentration 2 minutes after the administration of indicated doses of *d*-tubocurarine in 21 patients. (From Moss J, Rosow CE, Savarese JJ, et al: Role of histamine in the hypotensive action of d-tubocurarine in humans. Anesthesiology 55:19, 1981, with permission.)

percent that of tubocurarine, while gallamine, pancuronium, and vecuronium have minimal potential for releasing histamine in clinical doses.

STRUCTURE-ACTIVITY RELATIONSHIPS

The natural transmitter at the neuromuscular junction, acetylcholine, has a positively charged ammonium group, which is attracted to the negatively charged cholinergic receptor sites. This feature is also common to the neuromuscular blocking drugs that contain at least one quaternary ammonium group (Figs. 5-1 and 5-2).

The neuromuscular blocking agents show certain structural similarities to acetylcholine. Succinylcholine is essentially two molecules of acetylcholine linked through the acetate-methyl groups. Depolarizing agents, such as succinylcholine, generally stimulate nicotinic and muscarinic receptors in imitation of the role of acetylcholine. The depolarizing action of succinyl choline is due to the presence in the molecule of the trimethyl ammonium group and the carboxyl groups in a linear flexible chain (Fig. 5-1). The separation of the quaternary ammonium functions from the carboxyl groups by a distance of 4.5 Å, as occurs with acetylcholine, also contributes to the agonist (depolarizing) action of succinylcholine.[29] Removal of the carboxyl groups of succinylcholine results in decamethonium, which has much weaker autonomic stimulating properties than succinylcholine.[30]

The shape and flexibility of the molecule is important. Most agonists such as succinylcholine are flexible, long, and slender. Bulky molecules such as pancuronium with a rigid ring system cannot activate or stimulate the receptors themselves, but block the approach of acetylcholine, and, therefore, produce a nondepolarizing block by antagonism or receptor inhibition.

Tubocurarine (Fig. 5-2) has now been shown to have only one quaternary ammonium group and a tertiary amine group in equilibrium with a proton at physiological pH.[31] The new formula supports the autonomic ganglionic properties of tubocurarine as a monoquaternary structure, which is more likely to produce ganglionic blockade than a bisquaternary compound. The histamine-releasing properties of tubocurarine are probably due to the presence of the tertiary amine.[32] In general, bisquaternary compounds do not possess strong ganglionic blocking or histamine-releasing properties. Methylation of tubocurarine to produce metocurine or dimethyltubocurarine (a bisquaternary compound) reduces the histamine-releasing and ganglion-blocking activities associated with tubocurarine, and results in a muscle relaxant that is three times less potent than tubocurarine in blocking sympathetic and parasympathetic ganglia.[11,13] Gallamine (a trisquaternary compound) has marked vagolytic properties probably due to the presence of the three positively charged nitrogen atoms.[8,11]

THE DEVELOPMENTAL CHEMISTRY OF THE NEW DRUGS

In 1973, a model of the perfect relaxant was described by Savarese and Kitz[33] as a drug having a brief, noncumulative, nondepolarizing neuromuscular blocking action with a rapid onset and recovery. It should be readily reversible by an appropriate antagonist, cause neither histamine release nor ganglionic blockade, and give rise to minimal cardiovascular side effects. It should be highly potent and its metabolites should neither accumulate nor have any pharmacologic activity or toxicity.

In 1851, coincidentally in the same year that Claude Bernard first described the action of curare on the neuromuscular junction, A.W. Hofmann described his method of degrading quaternary ammonium compounds, now known as "Hofmann elimination," which required strong alkaline conditions and

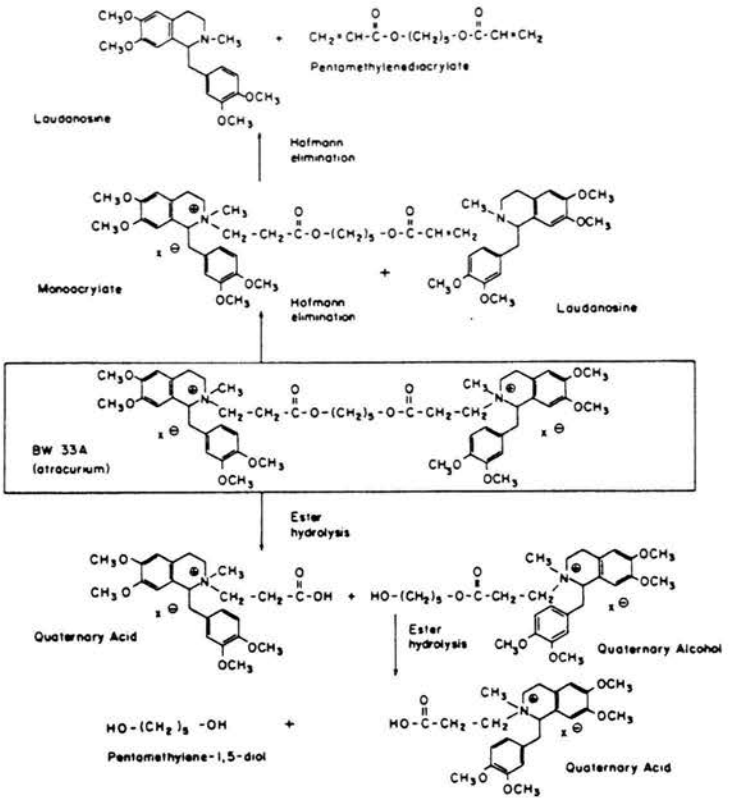


Fig. 5-9. Proposed pathways of inactivation of atracurium by Hofmann elimination reaction and ester hydrolysis. (From Basta SJ, Ali HH, Savarese JJ, et al: Clinical pharmacology of atracurium besylate (BW 33A): A new non-depolarizing muscle relaxant. Anesth Analg 61:723, 1982, with permission.)

very high temperatures. More than 100 years later these two apparently unrelated events were brought together and led to the development of atracurium. Professor J.B. Stenlake of the University of Strathclyde, Glasgow, had the novel idea of incorporating these features into the chemical structure of a neuromuscular blocking agent that would allow the Hofmann elimination to proceed under physiological conditions at body pH and temperature.[34] The idea was that the incorporation of this self-destructing mechanism would provide a drug that was not dependent on hepatic or renal function for the termination of its action. This nonenzymatic biodegradation mechanism (Fig. 5-9) is promoted by the combined electron-withdrawing properties of the two beta-linked estercarbonyl groups and the positively charged nitrogens of the quaternary ammonium groups. Nucleophylic attack by hydroxyl ions occurs readily at physiological pH and temperature. It results in the destruction of the bisquaternary structure essential for neuromuscular blocking activity through molecular fragmentation to laudanosine and other products without significant neuromuscular or cardiovascular effects.[35] Hydrolysis of the ester groupings is similarly promoted by the electron-withdrawing effects of the positively charged quaternary ammonium groups. Hofmann elimination is, therefore, accompanied by ester hydrolysis, which further fragments the molecule to inactive components. Breakdown and loss of potency of atracurium in human plasma is independent of plasma esterase activity. The time course of action is unaffected by hepatic metabolism or renal function.

The rates of Hofmann elimination and ester hydrolysis of atracurium control the stability and life of the intact molecule both in vivo and in vitro. Both reactions are base-catalyzed so that potency and duration of the full block are reduced and recovery is hastened by alkalosis. Ester hydrolysis is also acid catalyzed, but Hofmann elimination is increasingly

inhibited with the decreasing pH. Stability of the molecule, as a whole, is, therefore, achieved at about pH 3.5, and aqueous injection solutions at this pH stored under refrigerated conditions have a shelf life adequate for clinical use. It follows that artificial lowering of body temperature in vivo as in open heart surgery may, therefore, slow the inactivation of atracurium to advantage; whereas rewarming should enhance this decomposition and hasten recovery.

Hofmann elimination was originally postulated to be the major route of in vivo degradation of atracurium, although a recent in vitro study in human plasma has demonstrated that ester hydrolysis is possibly of more importance as the major metabolic pathway.[36] If these findings can be confirmed, the hypothetical potential adverse effects from the acrylate end-products of Hofmann elimination would be lessened. A further hypothetical side effect of an atracurium metabolite is the known convulsant effect of laudanosine. This, however, occurs at blood levels unlikely to be achieved even by prolonged atracurium administration.[37]

Savage et al are responsible for the manipulation of the steroid nucleus that resulted in the development of many neuromuscular blocking drugs, the most successful being the bisquaternary compound, pancuronium (Fig. 5-1).[38] In order to provide a nondepolarizing neuromuscular blocker with a more rapid onset of action and a shorter duration of action, the monoquaternary vecuronium bromide (Fig. 5-2) was developed from a continuation of the research that originally resulted in pancuronium. Extensive studies of many analogues of pancuronium identified the importance of retaining an intact ring D-acetylcholine-like fragment to ensure high neuromuscular blocking activity.[39] However, when the acetylcholine moiety involving ring A is modified, resulting in a tertiary nitrogen atom at position 2, the remaining monoquaternary derivative, vecuronium bromide, exhibits an unusually high selectivity for the postjunctional cholinoceptors at the neuromuscular junction. It is considered that the high selectivity for the postjunctional cholinoceptors that vecuronium and pancuronium display can be attributed to the unique hydrogen-bonded, cagelike structure of this particular ring D-acetylcholine fragment.

Although vecuronium differs from pancuronium only in the nature of its 2-piperidine nitrogen atom, which is tertiary, as distinct from quaternary, this single apparently minor molecular modification results in a drug molecule that is significantly different in both physical and chemical properties and in chemical reactivity. Although both vecuronium and pancuronium are hydrophilic, vecuronium is slightly more lipophilic because it is a monoquaternary rather than a bisquaternary compound. Increased lipophilicity should enhance penetration into membranes and could alter vecuronium's route of elimination, as compared with pancuronium, which has proved to be the case. In short, vecuronium is a significantly different chemical entity from pancuronium.

COMPARATIVE PHARMACOLOGY OF VECURONIUM AND ATRACURIUM

Potency

When dose-response curves are constructed, the ED_{95} (ie, the mean dose of neuromuscular blocking drug that depresses twitch tension by 95 percent) can be derived. This dose usually provides adequate relaxation in an anesthetized patient. The ED_{90} and ED_{95} reported by different investigators[40–49] have varied because of several factors, including the anesthetic and the method of peripheral nerve stimulation used (eg, single twitch tension, train of four). However, an approximate ED_{95} value for atracurium is 0.28 mg/kg, for vecuronium, 0.056 mg/kg, and for pancuronium, 0.07 mg/kg. Vecuronium is the most potent muscle relaxant currently available for use in clinical practice. The log dose-response curves for vecuronium, pancuronium, and atracurium are essentially parallel (Fig. 5-10).

Volatile anesthetic agents will enhance a nondepolarizing neuromuscular block more than a nitrous oxide-narcotic technique. Studies have shown that enflurane is the most potent volatile agent, followed by isoflurane, and then halothane in enhancing neuromuscular blockade.[50] The potencies of atracurium and vecuronium appear to be influenced less by the choice or concentration of volatile anesthetic than are the potencies of tubocurarine and pancuronium. Enflurane and isoflurane augment tubocurarine and pancuronium neuromuscular blockade about twice as much as does an equipotent concentration of halothane.[51–53] In contrast, the augmentation of a vecuronium- or atracurium-induced neuromuscular blockade by enflurane or isoflurane is only 20–30 percent greater than the augmentation produced by halothane or nitrous oxide-narcotic anesthesia.[54–56] Changes in the end-tidal concentration of inhaled anesthetics also have a lesser influence on neuromuscular blockade produced by vecuronium or atracurium than those produced by other nondepolarizing neuromuscular blockers. The reasons for vecuronium

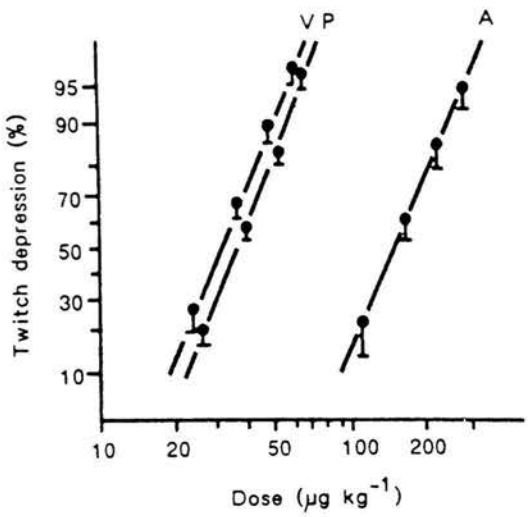


Fig. 5-10. The log dose-response curves for vecuronium (V), pancuronium (P), and atracurium (A). (From Gramstad L, Lilleaason P, Minsaas B: Comparative study of atracurium, vecuronium (Org NC 45) and pancuronium. Br J Anaesth 55(Suppl 1):95S, 1983, with permission.)

and atracurium being less influenced by the specific anesthetic and its dose or concentration are unknown.

Pharmacokinetics

Both vecuronium and atracurium have distinct pharmacokinetic properties as compared with currently used nondepolarizing muscle relaxants. For example, unlike pancuronium, metocurine, tubocurarine, or gallamine, neither vecuronium nor atracurium depends heavily on the kidney for elimination. Because atracurium is metabolized nearly completely through Hofmann elimination and ester hydrolysis, it should be excreted either in the urine or bile mostly in the form of metabolites. Although urinary and biliary excretion have not been determined in humans, the elimination half-life has been shown to be about 20–30 minutes.[57-58] Further confirmation of rapid metabolism is the appearance of laudanosine in the blood within 5–20 minutes.[57]

Only 10–25 percent of an injected dose of vecuronium is excreted in the urine.[59-61] The predominant route of elimination is almost certainly the bile.[59] Although vecuronium should be metabolized into its 3-hydroxy, 17-hydroxy, and 3,17-hydroxy metabolites as is pancuronium, only small amounts of these metabolites have been detected by methods such as thin layer chromatography.[60] The precise extent to which vecuronium is metabolized has not yet been determined, although most of the drug seems to be excreted unchanged in the urine and bile.[59] The proposed metabolites have little or no cardiovascular or neuromuscular effects, and, therefore, are of little concern.[62-63] In humans, vecuronium has a more rapid clearance (5.2 ml/kg/min) and a shorter elimination half-life (71 min) than pancuronium (1.8 ml/kg/min; 140 min).[64] These two characteristics probably account for the shorter duration of action of vecuronium compared to pancuronium.

Although atracurium and vecuronium produce neuromuscular blockade of similar duration, calculated values for their pharmacokinetic variables are quite different. For example, the elimination half-life is about 22 minutes for atracurium, and 71 minutes for vecuronium.[64] It appears that the inter-relationship between pharmacokinetic variables and neuromuscular blockade differs for these two drugs. All previous pharmacokinetic models, including that for vecuronium, assume that elimination of a drug occurs from only one compartment. This approach is obviously inappropriate for atracurium because Hofmann elimination can occur from all body compartments.

Onset Time and Priming

The onset time (time from administration of muscle relaxant to its peak effect) is similar for both vecuronium and atracurium. The doses of atracurium and vecuronium that depress twitch height less than 100 percent have onset times ranging from 4 to 8 minutes, and the speed of onset of these intermediate-duration muscle relaxants is dose dependent.[41,48,49] By using high doses of these intermediate-duration drugs it is possible to achieve a more rapid onset without the excessively prolonged duration of action that may be observed following high doses of the longer-acting agents. For example, four times the ED_{95} of vecuronium has an onset time of 1.3 minutes.[65] When three times the ED_{95} of atracurium was given, onset times were 1.2[48] and 1.3[66] minutes. The onset times of atracurium and vecuronium, however, although similar in equipotent doses, are significantly slower than succinylcholine in the clinical dose range.[67]

Several authors have recently shown that it is possible to accelerate the onset of the nondepolarizing block by administering a small "priming" dose about 3–6 minutes before the full dose in order to more rapidly produce intubating conditions. Foldes et al advocate administration of 0.015 mg/kg of vecuronium or 0.08 mg/kg of atracurium 6 minutes before giving 0.05–0.06 mg/kg of vecuronium or 0.25–0.3 mg/kg of atracurium, respectively, for intu-

bation.[68] They claim that intubation can be easily accomplished within 60–90 seconds using this priming principle. Later studies, however, most of them still in progress, indicate that in order to ensure good intubating conditions within 90 seconds, the doses given for intubation should be at least twice as large as recommended by Foldes et al, ie 0.5–0.6 mg/kg of atracurium or 0.12–0.15 mg/kg of vecuronium. There is no doubt that priming will become an important maneuver, but for a rapid sequence induction, succinylcholine is still the drug of choice.

Duration and Recovery of Action

When equipotent doses are compared, both vecuronium and atracurium have a similar duration of action, about one-third to one-half that of pancuronium.[41,42,44,45,47,49] For doses depressing twitch tension less than 100 percent, duration of action is about 15–30 minutes.[40,41,44,45,47,49] When three times the ED_{95} of these drugs is given, duration of action is between 50 and 76 minutes.[41,48,49] In contrast, when only two times the ED_{95} of pancuronium was given, the time from administration of the muscle relaxant to only 25 percent recovery of control twitch tension was 158 minutes. Recovery time (time from 25 to 75 percent recovery of control twitch tension) is also 30–50 percent shorter for vecuronium and atracurium than for pancuronium;[40,42,46,47,49] these times range from 9 to 12 minutes for both atracurium and vecuronium.[40–42,44,45,49]

After a single dose of vecuronium or pancuronium, plasma concentration falls rapidly because of redistribution from the central to the peripheral compartment. With subsequent doses, muscle relaxant in the peripheral compartment limits this distribution phase, and the decrease in plasma concentration results from elimination or metabolism. Thus, both pancuronium and, to a lesser extent, vecuronium can be demonstrated to have cumulative effects. This is not the case for atracurium. For although biphasic pharmacokinetic models have been described, there is not a distinct distribution phase with a rapid decrease in plasma concentration. Recovery from the effects of atracurium depends predominantly upon elimination (in this case metabolism by Hofmann elimination and ester hydrolysis) rather than redistribution. As a result, recovery from the neuromuscular effects of atracurium is similar for the first and all subsequent doses. This lack of accumulation makes atracurium the ideal agent for use as an infusion. Gargarian et al found that a mean infusion rate of 8.4 μg/kg/min produced excellent muscle relaxation and maintained 90–99 percent suppression of the single twitch.[69] There was no difference in recovery rates following a single bolus administration or continuous infusion.

Hepatic and Renal Failure

Because of its unique degradation pathways, the pattern of neuromuscular blockade produced by atracurium has been shown to be remarkably little affected by renal or hepatic failure.[70] Hofmann elimination is a nonbiological process, so atracurium is not dependent on the liver or kidney for its removal from the body and does not accumulate even in renal or hepatic failure, where its behavior is much the same as in normal patients. Atracurium is therefore the nondepolarizing relaxant of choice in these patients because of this advantage.

Vecuronium is the first and only relaxant to be eliminated mainly via the liver. Most of this elimination seems to be as the unchanged molecule with the kidney a secondary route. Some authors have postulated spontaneous deacetylation of vecuronium to account for its relative lack of cumulative property, but this is not yet proven. Since vecuronium is excreted mainly by the liver, it is a good second choice in renal failure where the pharmacokinetic profile of a single bolus is very similar to the profile in normal subjects.[61] There is a small cumulative effect after 1½ to 2 hours of vecuronium administration to patients in renal failure. Although statistically significant, this cumulative effect is probably of minor clinical importance. In cirrhotic patients, however, the duration is approximately double.[71]

THE CARDIOVASCULAR EFFECTS OF THE NEW MUSCLE RELAXANTS

Atracurium

Dose-response curves for atracurium obtained from results in anesthetized cats, dogs and rhesus monkeys (Fig. 5-11) demonstrate that there is a wide separation between the doses required for neuromuscular paralysis and those that inhibit autonomic mechanisms.[72,73] In cats, significant hypotension and slight bradycardia were evident after 4 mg/kg IV, but this dose was 16 times that required for full neuromuscular paralysis. Similar results were found in rhesus monkeys. In dogs, atracurium, 2 mg/kg, reduced mean arterial pressure to 53 percent of the control value, but this dose was 8 times that required for full neuromuscular paralysis. Atracurium at high concen-

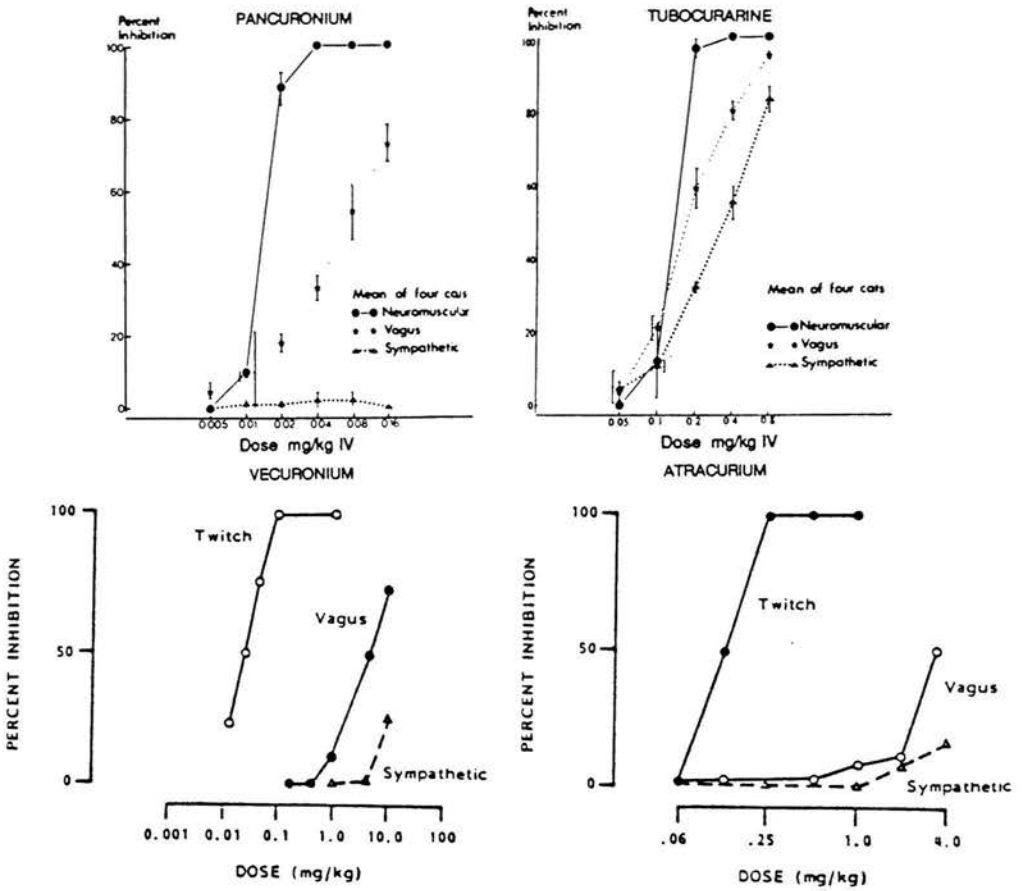


Fig. 5-11. Dose-response curves for neuromuscular and autonomic function inhibition in cats following pancuronium, tubocurarine and vecuronium; and in monkeys following atracurium. Note that vecuronium and atracurium cause insignificant autonomic inhibition at doses considerably in excess of that required to produce 100 percent depression of the single twitch. (Data modified from Durant NW, Marshall IG, Savage DS, et al: The neuromuscular and autonomic blocking activities of pancuronium, ORG NC 45, and other pancuronium analogues in the cat. J Pharm Pharmacol 31:831, 1979, and from Hughes R, Chapple DJ: The pharmacology of atracurium, a new competitive neuromuscular blocking agent. Br J Anaesth 53:31, 1981, with permission.)

trations had no inotropic or chronotropic effects on spontaneously beating guinea pig atria.

Cardiovascular studies in man have been carried out under halothane, enflurane and isoflurane anesthesia. During halothane anesthesia (0.7–0.9 percent end-tidal), maximum changes in mean arterial blood pressure and mean heart rate following intravenous doses of 0.2 and 0.4 mg/kg of atracurium were 6 and 8 percent, respectively, in one study;[74] and changes averaged less than 5 percent in another study.[75] Hilgenberg et al investigated the hemodynamic effects of 0.2 and 0.4 mg/kg of atracurium during enflurane anesthesia (1.0 to 1.25 percent inspired) and found no change in heart rate, cardiac index, stroke index, central venous pressure, or systemic mean arterial pressure.[76] Systemic vascular resistance was decreased by 7 percent, compared with the control value, following both doses of atracurium. Similarly, Ramsey et al found no significant changes in heart rate and arterial blood pressure during enflurane anesthesia (1.16 end-tidal) after administration of 0.36 mg/kg of atracurium.[55] During isoflurane anesthesia (1.25 percent), Sokoll et al reported that there were no clinically significant changes in mean arterial blood pressure, mean heart rate, systemic vascular resistance, cardiac index, or central venous pressure after 0.2 and 0.4 mg/kg doses of atracurium.[77]

In man, under nitrous oxide/narcotic anesthesia, mean arterial pressure and heart rate first showed significant changes from control values at 0.6 mg/kg, double the full paralyzing dose (Fig. 5-12).[28] Maxi-

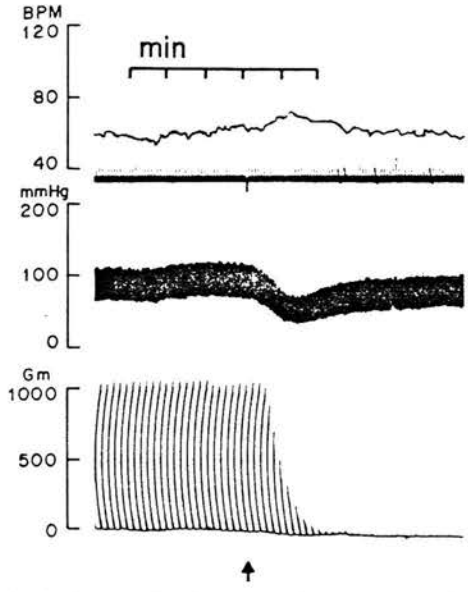


Fig. 5-12. The transient hemodynamic response occasionally observed following a bolus of 0.6 mg/kg of atracurium. Illustrated are the heart rate (by tachograph), intra-arterial blood pressure, and the single twitch at 0.15 Hz. Atracurium, 0.6 mg/kg, was injected as a rapid bolus at the arrow mark to a patient under balanced anesthesia.

mum heart rate and arterial pressure changes occurred 1–2 minutes after drug injection, and returned to normal within approximately 5 minutes. These changes have been shown to be due to a dose-dependent release of histamine, and the increase in plasma histamine levels correlates with the heart rate and arterial pressure changes. Scott et al have shown that these changes can be abolished by either slowing the rate of injection of atracurium to 75 seconds or by intravenous pretreatment with H1 and H2 blockers (chlorpheniramine and cimetidine) (Fig. 5-13).[78] A subsequent study by the same group has shown that doses as high as 0.8 mg/kg of atracurium can be administered safely, with hemodynamic stability, provided the injection rate is slowed.[79] Although atracurium will release histamine when high doses are bolused intravenously, it is important to keep this side effect in perspective. The ability of atracurium to release histamine relative to its neuromuscular blocking potency is only one-half that of dimethyltubocurarine, and less than one-third that of tubocurarine.[28]

Vecuronium

Since initial testing with vecuronium, it has been apparent that the margin between the neuromuscular

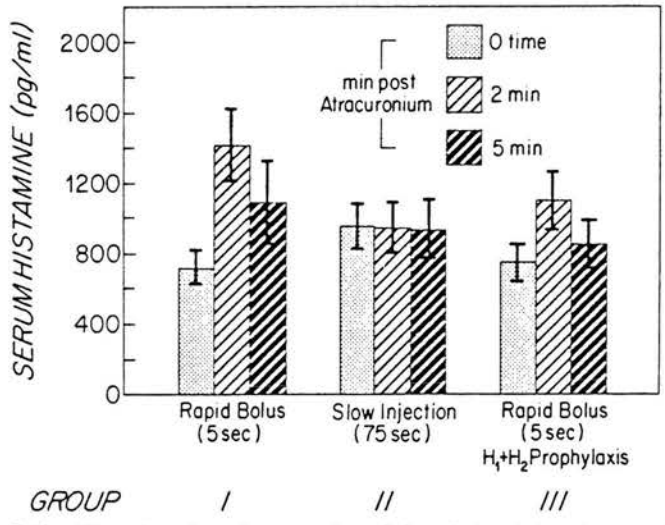


Fig. 5-13. Histamine release by atracurium (0.6 mg/kg) and the subsequent hemodynamic response is prevented by administering this dose slowly over 75 seconds. Pretreatment with intravenous H_1 and H_2 antagonists does not prevent histamine release but does attenuate the hemodynamic response. (From Scott RPF, Savarese JJ, Basta SJ, et al: Atracurium: Clinical strategies for preventing histamine release and attenuating the haemodynamic response. Br J Anaesth 57:550, 1985, with permission.)

blocking dose of this drug and the dose producing cardiovascular and autonomic effects is very wide. Results obtained in anesthetized cats and dogs (Fig. 5-11) have demonstrated that vecuronium, even in doses 20 times greater than those required for neuromuscular blockade, has no effect on heart rate, arterial pressure, autonomic ganglia, alpha- or beta-adrenoreceptors, or baroreceptor reflex activity.[72,80] Studies in pithed rats and guinea pig atria have further shown that vecuronium has little effect on cardiac muscarinic receptors or on norepinephrine reuptake mechanisms.[80] In contrast to its analogue, pancuronium, vecuronium appears to have far less indirect sympathomimetic activity.[81]

Eighteen adult patients studied under nitrous oxide-narcotic anesthesia demonstrated no significant changes in heart rate or arterial pressure with doses of vecuronium up to 150 μg/kg, which is nearly 3 times the 95 percent blocking dose.[82] Equipotent doses of pancuronium and vecuronium were compared in 20 patients receiving halothane anesthesia. Pancuronium (0.08 mg/kg) caused a significant increase in heart rate, insignificant change in arterial pressure, and significant changes in systolic time intervals.[83] The roughly equipotent dose of vecuronium, 0.057 mg/kg, caused no significant changes in heart rate, arterial pressure, or systolic time intervals. In both experimental animals and in humans, vecuronium has shown minimal potential for histamine release.[82,83]

In a clinical study that measured skin redness and induration caused by the intradermal injection of tubocurarine, metocurine, pancuronium, and vecuronium, vecuronium caused the smallest reaction, and tubocurarine and metocurine the largest. These results indicate that vecuronium had the least tendency to release histamine of the drugs tested. In a comparative study with tubocurarine, metocurine, and atracurium, Basta demonstrated that following 0.2 mg/kg of vecuronium (2 times the normal intubating dose) the heart rate, mean arterial pressure, and serum histamine levels were not altered.[84]

CARDIAC SURGERY AND CARDIOPULMONARY BYPASS

Since they have little or no cardiovascular effects, vecuronium and atracurium may be appropriate neuromuscular blocking drugs for cardiac surgery or noncardiac surgery on patients with cardiac disease. Very large doses of vecuronium (eg, 0.28 mg/kg) can be given with no cardiovascular effects.[85] As already indicated, however, large doses of atracurium may occasionally cause hypotension. Pokar and Brandt administered atracurium in doses of 0.6–1.0 mg/kg into right atrial catheters in patients who had undergone coronary artery bypass surgery.[86] Of the 9 patients, 4 had a decrease of more than 10 percent in arterial blood pressure. In a further study, when atracurium, 0.3 mg/kg, was given to 8 patients about to undergo elective coronary artery surgery, 1 patient had a decrease in mean arterial pressure (from 70 to 55 mm Hg) and other signs consistent with histamine release.[87] It is possible that prior diuretic therapy had made this patient more susceptible to even the slight histamine release associated with atracurium administration.

The hemodynamic stability of vecuronium may be a disadvantage when high-dose fentanyl or sufentanil anesthesia is used. The vagolytic action of pancuronium often protects against the tendency of the narcotics to produce bradycardia. When vecuronium is used with high-dose narcotic anesthesia, however, the heart rate often decreases.[88] This effect may be more apparent in patients who are receiving beta-blocker therapy during anesthesia for cardiac surgery.

Hypothermia and cardiopulmonary bypass can also affect the amount of atracurium or vecuronium required for neuromuscular blockade. Flynn et al found that 43 percent less atracurium was required to maintain a 90–95 percent neuromuscular blockade during the hypothermic cardiopulmonary bypass period.[89] They attributed the apparent increased potency of atracurium to the fact that hypothermia reduces the rate of Hofmann degradation. Buzello et al compared pancuronium and vecuronium before and after cardiopulmonary bypass.[90] Before bypass, pancuronium acted about twice as long as vecuronium. However, during hypothermic bypass, the durations of action of pancuronium and vecuronium increased 1.8-fold and 5-fold, respectively. It thus appears that during hypothermic bypass, pancuronium and vecuronium have similar durations of action. It may therefore be concluded that hypothermic cardiopulmonary bypass is associated with a marked increase in the duration of the neuromuscular blockade of both atracurium and vecuronium.[91] This point is, however, largely academic as the majority of patients requiring cardiopulmonary bypass will be ventilated postoperatively for a period longer than the duration of any muscle relaxant.

EFFECTS OF MUSCLE RELAXANTS ON CARDIAC RHYTHM

Nondepolarizing Agents

The nondepolarizing agents generally do not produce cardiac dysrhythmias. In fact, there is evidence that tubocurarine increases the dose threshold for the production of epinephrine-induced dysrhythmias in dogs under halothane and nitrous oxide anesthesia.[92,93]

Dysrhythmias after administration of pancuronium and gallamine may occur as a result of the following factors:

1. A sudden shift of autonomic balance towards the adrenergic side due to the vagal blocking effect of these drugs
2. A possible indirect sympathomimetic effect
3. A relatively greater inhibition of the AV node than the sinus node

These mechanisms may manifest themselves clinically as single or multifocal premature ventricular contractions, ventricular tachycardia, or nodal (junctional) tachycardia. In the case of gallamine, there is a higher incidence of ventricular dysrhythmias under light halothane or cyclopropane anesthesia probably because of the lowering of the threshold for ventricular excitability caused by these anesthetics.[94] In patients with sinus node disease, a vagolytic effect might cause a relatively greater increase in the spontaneous rate of activity of the atrioventricular node than the sinus node, the result being nodal tachycardia.

Succinylcholine

In man, succinylcholine is probably the only neuromuscular blocking agent that may itself precipitate cardiac dysrhythmias during anesthesia. It stimulates all cholinergic autonomic receptors, nicotinic receptors in both sympathetic and parasympathetic ganglia, and muscarinic receptors in the sinus node of the heart. The development of cardiac dysrhythmias is a clinical manifestation of this generalized autonomic stimulation; and sinus bradycardia, junctional rhythms, and ventricular dysrhythmias ranging from unifocal premature ventricular contractions to ventricular fibrillation have all been documented. However, many authors have noted these dysrhythmias in the presence of intense autonomic stimuli, most notably including tracheal intubation; and it is not always clear whether the cardiac irregularities are due to the action of succinylcholine alone or to the presence of extraneous autonomic stimulation.

Sinus bradycardia after succinylcholine occurs most commonly in nonatropinized, relatively sympathotonic individuals (eg, children), and is due to stimulation of cardiac muscarinic receptors in the sinus node.[95] Sinus bradycardia has also been noted in adults, and appears more commonly after a second dose of the drug given approximately 5 minutes after the first.[96,97] It has been suggested that the higher incidence of bradycardia after a second dose of succinylcholine may be due to the hydrolysis products sensitizing the heart.[98] Thiopental, atropine, ganglion-blocking drugs, and nondepolarizing relaxants have all been used to prevent the bradycardia.

Nodal rhythms commonly occur as bradycardias and are probably due to the relatively greater stimulation of the sinus node than the atrioventricular node. The result is suppression of the sinus mechanism and the emergence of the atrioventricular node or even a ventricular focus as the pacemaker. The incidence of a junctional rhythm is higher after a second dose of succinylcholine, but is prevented by prior administration of tubocurarine.[96,99,100]

Succinylcholine lowers the threshold of the ventricle to catecholamine-induced dysrhythmias in the monkey[101] and the dog[92] under stable anesthetic conditions. Other autonomic stimuli, such as endotracheal intubation, hypoxia, hypercarbia, and surgery are probably additive to the effect of succinylcholine and may provoke ectopic activity. Ventricular escape may also occur after severe sinus and atrioventricular nodal slowing, secondary to succinylcholine administration.

The depolarizing nature of the drug encourages ventricular dysrhythmias by releasing potassium from skeletal muscle.[102] The rise of potassium in normal people following a 1-mg/kg dose of the drug is about 0.5 mEq/1.[102] However, marked increases may occur within 1–2 minutes of succinylcholine administration in the following groups:

1. Burned patients[99]
2. Patients with extensive denervation of skeletal muscle due to injury or disease of the central nervous system
3. Massively traumatized patients[103]
4. Patients with severe intra-abdominal infection [104]

The period of danger in these groups begins within a few days in the burned and denervated patients, and within a few hours in the traumatized

patient. Studies in baboons have shown that hyperkalemia following surgical denervation begins as early as 4 days after the establishment of the lesion, and reaches a peak within 14 days.[105] Whether the hyperkalemic response to succinylcholine in these 4 groups represents a permanent lesion is not known. Uremic patients and patients at least 6 months past complete healing of burns are probably not at risk.[106] A study in dogs has suggested that immobilization atrophy does not seem to provoke the hyperkalemic response either.[107] The use of succinylcholine is probably contraindicated in these various groups. A modest dose of a nondepolarizing relaxant (6 mg of tubocurarine, 40 mg of gallamine, 3 mg of metocurine, or 1 mg of pancuronium) administered 3 minutes before succinylcholine may attenuate but will not guarantee the absence of the hyperkalemic response.

DRUG INTERACTIONS WITH THE CARDIOVASCULAR EFFECTS OF THE RELAXANTS

Succinylcholine lowers the threshold of the ventricle to catecholamine-induced dysrhythmias. To this must be added the possible influence of drugs such as digitalis, tricyclic antidepressants, monoamine-oxidase inhibitors, catecholamines, and anesthetic drugs such as halothane and cyclopropane, all of which may lower the ventricular threshold for ectopic activity or increase the dysrhythmogenic effect of the catecholamines.

The nondepolarizing agents may also produce cardiovascular effects upon interaction with other drugs. Edwards et al showed that simultaneous administration of pancuronium and imipramine caused a tachycardia in an additive manner.[108] An 80-μg/kg dose of pancuronium produced premature ventricular contractions and ventricular tachycardia, which rapidly progressed to ventricular fibrillation in 2 of the 10 dogs given imipramine, 8 mg/kg/day, and 4 of 10 dogs given 16 mg/kg/day. The authors concluded that severe ventricular dysrhythmias may occur as a result of administration of pancuronium in dogs anesthetized with halothane and chronically receiving imipramine. Since vecuronium is much less potent than pancuronium in blocking norepinephrine uptake, the possibility of ventricular dysrhythmias arising during halothane anesthesia in patients on tricyclic antidepressants would presumably be reduced.

In another study, neither pancuronium nor tubocurarine affected the dysrhythmogenic dose of epinephrine during halothane anesthesia in dogs.[109] This finding indicates that the usual guidelines for the administration of adrenaline during halothane anesthesia are not affected by concomitant administration of these two nondepolarizing muscle relaxants. Gallamine and tubocurarine may decrease the incidence of epinephrine-induced dysrhythmias, in contrast to succinylcholine, which may enhance epinephrine's effects.[92]

Occasionally, drug interactions may be advantageous. Combinations of pancuronium and metocurine not only potentiate neuromuscular blockade,[110] but minimize the heart rate change associated with pancuronium on its own. At twice the ED_{95}, the heart rate increased significantly more in the pancuronium group than in the pancuronium/metocurine combination group.

THE CARDIOVASCULAR EFFECTS OF THE ANTAGONISTS

Cardiovascular complications have been associated with the use of anticholinesterase drugs as antagonists of nondepolarizing neuromuscular blockade. Dysrhythmias and cardiac arrest following the administration of neostigmine and atropine have been reported.[111,112] As a result, various techniques have been described to improve the safety of reversal. These include hyperventilation to produce mild respiratory alkalosis, simultaneous injection of atropine and neostigmine, slow administration of neostigmine and atropine in a ratio of 2.5:1, and maintenance of adequate oxygenation throughout the period of reversal.[113,114]

The cardiac arrests have been attributed to cholinergic (muscarinic) stimulation of the heart by neostigmine combined with insufficient atropine. The relationship of dysrhythmias such as inverted P waves, Wenckebach phenomena, premature atrial contractions, junctional rhythms, atrioventricular dissociation, premature ventricular contractions, and bigeminy to atropine, neostigmine, or their combination is less clear.[115-118] Many of these reports occurred during emergence from anesthesia when changing anesthetic concentrations, surgical stimulation, and ventilation may have caused the dysrhythmias. However, dysrhythmias may occur even when these variables are held constant.[119] A decrease in the amount of atropine or replacement of it with another anticholinergic drug, such as glycopyrrolate, have

been used to attenuate the tachycardia and reduce the frequency of dysrhythmias.[120]

Patients receiving glycopyrrolate with neostigmine have smaller changes in heart rate than those who receive atropine.[121] Glycopyrrolate also decreases the frequency of dysrhythmias when combined with neostigmine, pyridostigmine, or edrophonium.[119,120,122] Although a greater frequency of dysrhythmias occurs with atropine, there is insufficient evidence to implicate it as the etiological agent. It is possible that glycopyrrolate blocks the dysrhythmogenic stimulus of the anticholinesterase agents more effectively than atropine.

In view of this, the antagonist that requires the least amount of vagal blockade to prevent a bradycardia may provide an advantage clinically in terms of dysrhythmias. Edrophonium has two distinct advantages:[123] It has a shorter onset time than neostigmine or pyridostigmine; and it requires about half as much atropine to block adverse cardiac muscarinic effects as neostigmine. In order to minimize changes in heart rate, the rapidly acting edrophonium and atropine should be given together, and the slower acting neostigmine and glycopyrrolate together. Edrophonium has fewer muscarinic actions than neostigmine, and its predominant mechanism of action is probably presynaptic.

4-Aminopyridine has no muscarinic properties.[124] When it is combined with neostigmine or pyridostigmine, approximately 5 μg/kg of atropine is required to prevent bradycardia.[125] The atropine dose must be increased to 15 μg/kg when either neostigmine or pyridostigmine is used alone. 4-Aminopyridine is devoid of anticholinesterase activity and acts by increasing the amount of acetylcholine released by nerve impulses. However, the facilitatory actions of 4-aminopyridine are not confined to the neuromuscular junction. Transmission is also facilitated at autonomic, adrenergic, and cholinergic junctions including sympathetic ganglia and central synapses. In animal studies, 4-aminopyridine produced increases in left ventricular systolic pressure and dP/dt_{max}, right atrial pressure, stroke volume, myocardial blood flow, myocardial oxygen consumption, external cardiac work, arterial oxygen content, and blood hemoglobin.[126] These effects were attributed to facilitation of sympathetic transmission to the blood vessels, heart and spleen. Heart rate was not greatly affected because facilitation of vagal transmission to the sinoatrial node counteracted the increased sympathetic effect. While 4-aminopyridine may be useful in certain relatively rare conditions of neuromuscular transmission failure, such as botulism, myasthenia gravis, and Eaton-Lambert syndrome, its actions are too widespread for routine use as an antagonist to nondepolarizing drugs.

Reversal of neuromuscular blockade after prolonged tricyclic antidepressant therapy can also lead to electrocardiographic disturbances. Results of one study demonstrated that minor ST-T wave and myocardial conduction changes observed in cats under chloralose anesthesia during chronic amitriptyline treatment markedly intensified during reversal of tubocurarine blockade with neostigmine alone or with a mixture of neostigmine and atropine.[127] This is probably due to the effect of neostigmine on the heart, coupled with the quinidine-like activity and direct action of tricyclic drugs on the myocardium.

Because of the relatively rapid recovery pattern of the new intermediate duration drugs, it may be possible in many cases to avoid the necessity of antagonism of residual blockade if dosing is carefully judged, properly timed, and monitored. When the new drugs have been employed, reversal should be done on clinical indication rather than as a routine. Anticholinesterases need not be administered, particularly if patients show no fade on train of four, are ventilating adequately, are responsive, and can demonstrate adequate head lift or grip strength.

MUSCLE RELAXANTS OF THE FUTURE

Pipecuronium

Pipecuronium bromide is an analogue of pancuronium with the quaternary nitrogen groups situated at the more remote nitrogen of the piperazine groups substituted at the 2 and 16 positions of the androstane skeleton (Fig. 5-14). In contrast to pancuronium it has no acetylcholine-like fragments, and the interonium distance is considerably larger than in pancuronium.

In isolated nerve-muscle preparations (rat phrenic-nerve diaphragm and chick biventor cervicis muscle), pipecuronium produced a pure nondepolarizing type of neuromuscular blockade, showing a relative potency of 1.7–3 times that of pancuronium under similar experimental conditions.[128] The nondepolarizing mode of action has been further demonstrated in experiments in vivo in cats, rabbits, and dogs.[128] Further observations in animals suggest that this new compound possesses remarkable cardiovascular stability.[129]

The initial clinical data on pipecuronium has been generated and reported mainly in Hun-

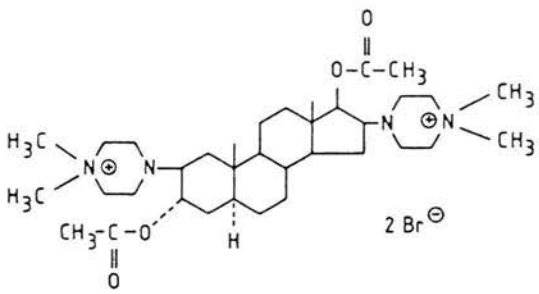


Fig. 5-14. The structural formula of pipecuronium bromide. (From Agoston S, Richardson FJ: Pipecuronium bromide—a new long-acting nondepolarizing neuromuscular blocking drug. Clin Anesthesiol 3:361, 1985, with permission.)

gary.[130,131] In many respects pipecuronium is similar to pancuronium. In man, neuromuscular blocking potency is equal to or slightly greater than that of pancuronium and, consequently, its routine use in clinical practice should follow the existing pattern for pancuronium. A dose of 0.05 mg/kg after intubation with succinylcholine will provide adequate muscle relaxation for 40–50 minutes. For intubation, however, the dose should be increased to 0.08–0.1 mg/kg, which will give satisfactory intubating conditions in 2.5–3 minutes and adequate surgical relaxation for 80–120 minutes. As with pancuronium, cumulative effects after repeated doses and potentiation of inhalational anesthetic agents, particularly enflurane, can be expected.

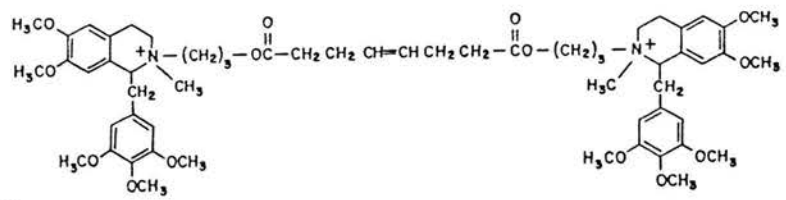
Pipecuronium appears to be free from histamine-releasing properties. The most important advantage of this compound in comparison with other long-acting drugs like pancuronium or alcuronium is that it is devoid of circulatory effects. Pipecuronium does not cause a tachycardia as does pancuronium, and in patients undergoing abdominal surgery there was no significant changes in blood pressure, central venous pressure, pulmonary capillary wedge pressure, or cardiac index.[132]

Pipecuronium, like vecuronium, has a minor disadvantage in that it has to be dissolved in solvent before use. The ampules currently used contain 4 mg of the agent that should be dissolved in 2 ml of solvent. Pipecuronium should be stored in a refrigerator at 4°C and should be used shortly after dissolving the powder.

BWB1090U

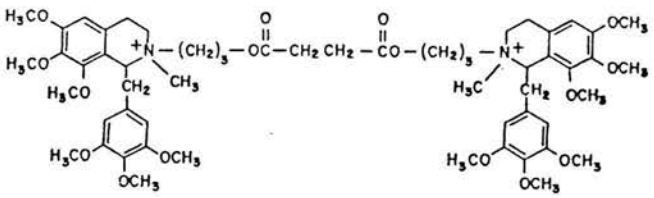
For a number of years, workers have been investigating a series of nondepolarizing bulky diester compounds that are metabolized by plasma cholinesterase. In 1979, BW785U, a short-acting nondepolarizing ester neuromuscular blocking agent was described. During a brief clinical trial, neuromuscular blocking activity of BW785U was indeed found to be very short.[133] A hypotensive response, however, first noted in animals and apparently due to histamine release, was found to be much more prominent in humans and forced the cancellation of further trials. BWA444U was another compound in the benzylisoquinolinium series.[134] Pharmacodynamically this agent's neuromuscular blocking effect was very similar in duration to that of atracurium, but its margin of safety for histamine release was somewhat less, so that it was withdrawn from further studies. Additional structure activity studies have since led to the development of BWB109OU.

BWB109OU (Fig. 5-15) is another short-acting nondepolarizing benzylisoquinolinium ester. The duration of action in the rhesus monkey was found to be about one-third that of atracurium and vecuronium. Its safety margin for histamine release was found to be about 10 times as great as that of BW785U. In initial clinical studies, the ED_{95} has been estimated to be approximately 0.08 mg/kg. The duration of action (injection to 95 percent return of twitch) is 25–30 minutes at 0.15–0.25 mg/kg, doses that produce 100 percent block. Spontaneous recovery time (5–95 percent) averages 14–15 minutes for all doses above 0.10 mg/kg. There is no significant



BWB1090U

Fig. 5-15. Chemical structure of BWB109OU.



BWA938U

Fig. 5-16. Chemical structure of BWA938U.

difference in recovery times between single bolus doses or after 1–3 hour infusions. Neuromuscular blockade is readily reversed with neostigmine. In a further trial of 53 ASA class I and II patients, the cardiovascular effects and histamine-releasing properties of large doses were studied.[135,136] Brief decreases in arterial pressure after 2.5 and 3.1 times the ED_{95}, given as a rapid bolus, corresponded with elevations in plasma histamine levels. Cardiovascular changes were less after a second identical dose of BWB109OU or after slower bolus administration. The cardiovascular effect of BWB109OU, therefore, seems attributable to a relatively weak histamine-releasing property. The safety margin for this side effect is 2.5 to 3 times greater than that of tubocurarine or roughly similar to that of atracurium (2.5 to 3 times ED_{95}).

BWA938U

BWA938U (Fig. 5-16) is another benzylisoquinolinium ester.[137] Preclinical pharmacological studies in cats, dogs and rhesus monkeys showed that BWA938U is a very potent and rather safe nondepolarizing neuromuscular blocking agent. Compared with BWB109OU and atracurium, BWA938U is more potent, has a longer onset time, and longer duration of action. The ED_{95} for BWA938U in the monkey is estimated to be 0.017 mg/kg; the ED_{95} in man is 0.025–0.03 mg/kg. Bolus doses of 9 times the ED_{95} of BWA938U produced no significant cardiovascular effects in dogs. In patients under balanced anesthesia, doses of 0.08 mg/kg (three times ED_{95}) produced no significant cardiovascular effect.

In summary, BWA938U is a very potent, long-acting nondepolarizing neuromuscular blocking agent, about three times as potent as pancuronium. Preclinical data suggests that two properties of BWA938U may significantly distinguish it from other long-acting agents. These properties are a lack of cardiovascular effects at several multiples of the ED_{95} dose for neuromuscular blockade, and a lack of cumulative effects following repeated dosing. These properties have been confirmed recently in volunteer studies and clinical trials evaluating the safety and efficacy of this drug. This agent has a small advantage over pipecuronium in that it is stable in solution and may be stored at room temperature.

CONCLUSIONS

The history and development of neuromuscular blocking agents have been characterized by a progressive reduction in side effects and improvement in pharmacodynamic profiles. Atracurium and vecuronium have set new standards in this field, and several of the older drugs would be unlikely to pass the animal testing stage today. This is certainly true in terms of cardiovascular side effects

Most of the commonly used nondepolarizing muscle relaxants can be classified as either steroids (pancuronium, vecuronium) or benzylisoquinolinium compounds (tubocurarine, metocurine, atracurium); and further research is continuing with both of these groups of substances. In the future, there will probably be more published about pipecuronium, a pancuronium analogue with a similar duration to its parent compound but without the tachycardia. Research with the benzylisoquinoliniums is also producing a number of interesting new agents. This group of compounds has a wide variety of pharamacodynamic profiles (BWB109OU and BWA938U). Work on the structure-activity relations on both types of compounds has resulted in three new drugs reaching full-scale clinical trials; with successful completion of human studies, the new drugs should be available for general use in the United States within 2–3 years.

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Br. J. Anaesth. (1988), **61**, 292–296

EFFECT OF SUXAMETHONIUM GIVEN DURING RECOVERY FROM ATRACURIUM

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Summary

Suxamethonium was given in varying doses when twitch response had returned to 50% of control following the administration of atracurium in anaesthetized patients. Small doses of suxamethonium produced antagonism, enhancement of the block, or a combination showing a biphasic response. A dose of 3 mg kg^{-1} was needed to produce consistently 100% block of the twitch. The subsequent recovery rate for T1 was as fast as that seen normally after suxamethonium and was not enhanced by neostigmine.

At the end of an abdominal operation, muscle relaxation may be inadequate and a transient increase in block may be needed to facilitate closure. Suxamethonium is the only agent of short duration available currently [1] and has been used in these circumstances. Whilst interactions with long acting competitive agents have been described [2–5], there are no descriptions of its effect on recovery from the block produced by atracurium. This study was designed to assess the effects of increasing doses of suxamethonium on the recovery of block produced by atracurium and on the subsequent interaction with neostigmine.

PATIENTS AND METHODS

Thirty-eight patients (18–70 yr, 45–110 kg) undergoing elective surgical procedures were studied after they had given informed consent. No patient who had received aminoglycoside antibiotics was studied. The study was approved by the local Ethics Committee.

Diazepam 10–20 mg and metoclopramide 10 mg were given by mouth 1 h before anaesthesia was induced with thiopentone 4–6 mg kg^{-1} and fentanyl 2–4 μg kg^{-1}. Anaesthesia was maintained with 66% nitrous oxide and 0.5% enflurane in oxygen supplemented by additional doses of fentanyl and thiopentone as required. End-tidal carbon dioxide tension was maintained at 4–5 kPa.

The integrated, rectified and gated electromyographic response of the hypothenar muscles was recorded in response to supramaximal train-of-four stimuli delivered to the ulnar nerve at 20-s intervals using a Datex Relaxograph. Control records were obtained after induction of anaesthesia but before a block was produced with an initial dose of atracurium 0.4 mg kg^{-1}.

The first twitch (T1) of the train-of-four was allowed to recover to 50% of the control value in 22 patients. Suxamethonium 0.25, 0.5, 1, 1.5, 2 or 3 mg kg^{-1} was given i.v. and the subsequent course of paralysis noted. When the first twitch had recovered to 100% (in some patients in whom the train-of-four ratio remained less than 0.6 after several minutes of monitoring), the additional effect of neostigmine 35 μg kg^{-1} was noted (table I).

In order to provide comparative recovery data, three further groups were studied: atracurium 0.4 mg kg^{-1} with spontaneous recovery, atracurium 0.4 mg kg^{-1} with antagonism by neostigmine 35 μg kg^{-1} at T1 10–25%; and spontaneous recovery of suxamethonium 1.5 mg kg^{-1} without any preceding atracurium.

In order to mimic a possible clinical situation, in a further four patients the initial dose of atracurium was allowed to recover to 50% T1 and suxamethonium 3 mg kg^{-1} was given in the same manner as in the first study, but neostigmine 35 μg

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TABLE I. *Study groups. *Suxamethonium administered at 50% T1 recovery from a 0.4-mg kg^{-1} atracurium block*

n	Atracurium (mg kg^{-1})	Suxamethonium (mg kg^{-1})	Neostigmine (μg kg^{-1})
1	0.4	0.25 at 50% T1*	±35 at 100% T1
4	0.4	0.5 at 50% T1	±35 at 100% T1
4	0.4	1.0 at 50% T1	±35 at 100% T1
3	0.4	1.5 at 50% T1	±35 at 100% T1
6	0.4	2.0 at 50% T1	±35 at 100% T1
4	0.4	3.0 at 50% T1	±35 at 100% T1
4	0.4	3.0 at 50% T1	+35 at 25% T1
4	0.4	—	—
4	0.4	—	+35 at 10–25% T1
4	—	1.5	—

TABLE II. *Effect of suxamethonium on a recovering (50% T1) atracurium block. *Four patients received neostigmine at 25% T1 after suxamethonium (see table III). **A 50% change in block represents 100% block of T1*

Dose of Sux. (mg kg^{-1})	*n*	No. with biphasic response	Mean (SD) change in block (%)	T1 100% block time (min)
0.25	1	0	−10	
0.5	4	2	−1.25 (10.3)	
1.0	4	2	−1 (12.5)	
1.5	3	2	34 (17.7)	
2.0	6	4	40.5 (13.5)	
3.0	8*	3	50**	8

kg^{-1} was given when the T1 had returned again to 25%. The response to suxamethonium 3 mg kg^{-1} in this study ($n = 4$) is included in table II with the results of the first study of the effect of suxamethonium on a recovering atracurium block ($n = 4$) so that overall, $n = 8$. However, the recovery data for these two groups were different and are tabulated separately (table III).

TABLE III. *Reversal data (mean (SD)). AS = Suxamethonium 3 mg kg^{-1} administered at a 50% T1 atracurium recovery; AS+N = neostigmine administered at 25% T1 recovery of AS block; S = suxamethonium 1.5 mg kg^{-1}; A = atracurium 0.4 mg kg^{-1}; A+N = neostigmine reversed (at 10–25% T1) atracurium blockade*

Group	*n*	25–75% recovery (min)	5–95% recovery (min)
AS	4	2.75 (0.28)	8.25 (0.95)
AS+N	4	7.25 (3.6)	12.3 (5.9)
S	4	3 (0)	7.75 (0.5)
A	4	13.1 (1.8)	38.3 (7.6)
A+N	4	4.5 (0.57)	14.5 (1.73)

RESULTS

Giving suxamethonium when T1 had recovered to 50% after the administration of atracurium produced no effect on the block, a mild increase in recovery rate, an enhancement of the block, or a biphasic response. Figure 1 shows a biphasic response in which there was an initial reversal, followed by the development of full block and later recovery. There were marked variations between patients for each dose of suxamethonium, but the net effect of the lower doses was to antagonize the block and of higher doses to enhance it. Only with suxamethonium 3 mg kg^{-1} was it possible consistently to produce a complete block: this lasted some 8 min before recovery (table II).

When atracurium was given alone the mean recovery index (25–75% T1 recovery) was 13.1 min, and when neostigmine was given at 10–25% T1 this time was shortened, on average to 4.5 min. When suxamethonium 3 mg kg^{-1} was given at 50% T1 recovery after atracurium, the recovery index following the period of 100% block was

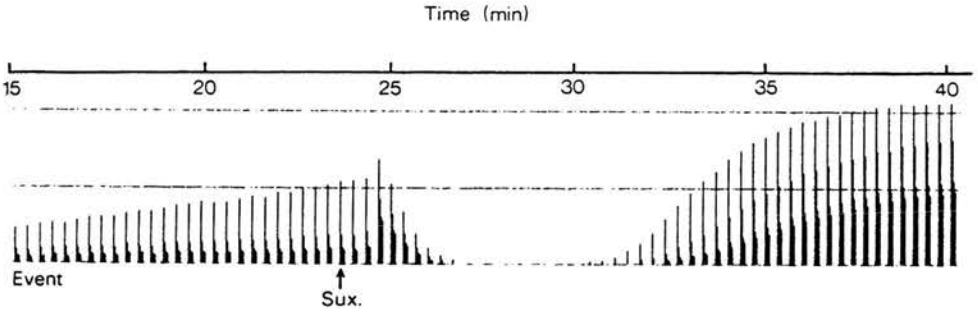

FIG 1. Effect of suxamethonium on a recovering atracurium block. Suxamethonium 2 mg kg^{-1} (Sux.) was administered at 50% T1 recovery from an atracurium 0.4 mg kg^{-1} blockade. Subsequent biphasic response followed by a brief period of 100% T1 block and a rapid recovery.

2.75 min and the 5–95 % recovery time was 8.25 min. These times are very similar to those recorded following a spontaneous suxamethonium 1.5 mg kg^{-1} recovery (3 and 7.75 min, respectively). However, fade always persisted following the block induced by suxamethonium after atracurium, despite the rapid recovery of T1; but this fade was always reversed when neostigmine was administered at 100 % T1 recovery (table III).

When suxamethonium 3 mg kg^{-1} was administered at a 50 % T1 recovery from atracurium, and neostigmine was administered subsequently at the earlier stage of 25 % T1 of this combination block, fade was reversed. The mean recovery index, however, was prolonged to 7.25 min and in one patient neostigmine transiently increased the block by 10 %, prolonging the 5–95 % recovery time to 19 min. Thus the fastest recovery times were observed after suxamethonium 1.5 mg kg^{-1} alone, or during the recovery stage of a suxamethonium 3 mg kg^{-1}-potentiated atracurium block. While the addition of neostigmine reversed fade when administered at 100 % T1 after the combination block, neostigmine slowed recovery of this block when administered at the earlier stage of recovery (T1 25 %).

Suxamethonium given after atracurium did not produce muscle fasciculations.

DISCUSSION

This study was designed to mimic a clinical problem. The blockade produced by atracurium was allowed to wear off to a point at which T1 had recovered to 50 % and where all four responses to train-of-four stimulation were apparent. This level of recovery is usually too great to allow closure of the abdomen without deep general anaesthesia, and the anaesthetists should intensify the block. It was common to use a small dose of suxamethonium for this rather than give an increment of a long acting competitive blocker.

Our results show that small doses of suxamethonium may antagonize the partial block seen during recovery from atracurium, but that larger doses usually enhance the block. The subsequent pattern of recovery of a combination block is faster than that seen with atracurium alone or when antagonized by neostigmine. However, during the recovery of a combination block, fade of the train-of-four response is seen. Similar results have been reported with the interaction of suxamethonium with longer acting competitive blocking drugs [2–5]. Young [4] and Walts [2] demonstrated similar patterns of dose-related effect with tubocurarine, as did Katz for pancuronium [3]. The biphasic pattern has been described by Walts [2] and in more detail by Buzello and his colleagues [5]. This last study demonstrated that, with a constant dose of suxamethonium 0.5 mg kg^{-1}, the proportional relationship between reversal and subsequent increase of blockade depends on the stage of recovery from non-depolarizing neuromuscular blockade at the time of administration of suxamethonium. Young [4] reported similar findings.

What are the mechanisms which produce these interactions? The traditional view would be that atracurium produces mainly a competitive block of the post-synaptic receptors. Such a block may be overcome by increasing the concentration of agonist usually, in clinical practice, by the administration of neostigmine. However, suxamethonium also acts as an agonist and interacts with the post-synaptic receptors, leading to the opening of ionic channels and depolarization of the membrane. In turn, this may initiate a muscle action potential and contraction. If the amount of suxamethonium is too great, depolarization is maintained and the muscle membrane becomes inexcitable. Hence small doses may act as antagonists, but larger ones produce a block as the depolarization develops.

We still need to explain why the recovery index is quicker during recovery from the combination block, why neostigmine slows it and why fade of the train-of-four response persists. Again, the traditional view of block may provide an explanation. The enhanced recovery index by itself may be misleading. It is likely that what we are observing is a simple competitive displacement by the law of mass action at the post-junctional receptor: the dose–response curve of suxamethonium is shifted to the right because of the presence of atracurium molecules on the receptor.

It appears from Buzello's study [5] that, when suxamethonium is administered during a pancuronium recovery phase, 100 % T1 recovery was not achieved at 30 min following suxamethonium when administered at 25 % or 75 % recovery of T1. In our study every patient had recovered to 100 % T1 from a combination block (suxamethonium 3 mg kg^{-1}) within 20 min of administration of suxamethonium. This observation supports our hypothesis. As suxamethonium is catabolized and the local concentration declines at

the end-plate, the post-junctional receptors may be occupied by the longer acting pancuronium molecules, which are eliminated more slowly. This does not occur with atracurium, which has intermediate duration of action, because elimination is occurring more rapidly than with pancuronium during the time that suxamethonium is being hydrolysed. Thus the fast recovery index reflects the fact that most of the block is produced by suxamethonium. The fact that neostigmine slowed recovery after suxamethonium may be a result of its effect on plasma, in addition to true cholinesterase, thereby delaying the breakdown of suxamethonium.

Fade is now believed to result either from a block of pre-junctional acetylcholine receptors by competitive drugs or from a use-dependent occlusion of the post-junctional ion channel [6]. However, the latter hypothesis ignores the findings of Hutter [7] and Otsuka and colleagues [8] that tubocurarine-induced fade is associated with diminished release of acetylcholine and, certainly, the evidence for drugs used in clinical circumstances favours the first of these two mechanisms. The fade demonstrable during the recovery from suxamethonium following atracurium is accounted for most probably by the residual pre-junctional action of atracurium. It may result from development of a phase 2 block [9] by suxamethonium, but this would seem unlikely because of the rapid recovery time. Furthermore, neostigmine did not shorten the recovery time, and on one occasion actually increased block, adding substance to the hypothesis that a depolarizing block is present. In any event, all these explanations are speculative, especially with the difficulties inherent in comparing the evoked electromyographic responses demonstrable in man with the precise studies now possible in the laboratory. A detailed study of the interactions would presumably need voltage [10] and patch clamp studies to ascertain which effects result from interaction with acetylcholine receptors on the muscle and which from effects on receptors on the nerve terminals.

The data generated by the indirectly evoked EMG should be used with some understanding of its limitations as a predictor of mechanical response. Although Carter and colleagues [11] found a good correlation between the two methods of measurement for both twitch height and train-of-four ratio (correlation coefficients 0.93 and 0.97, respectively), Kopman [12] found that the simultaneously evoked (hypothenar) EMG and MMG did not give identical information. The regression line for the T1 : Tc (twitch depression/control twitch) ratio was parallel to the line of identity, but showed an absolute offset of 15%. Furthermore, the EMG baseline may drift with time as a result of a number of possible factors and return to T1 : Tc control values does not always occur.

The Datex EMG was chosen in this study because it is a compact and convenient tool, providing information on the nature of the response to be expected from certain drug interactions, rather than a precise quantification of effect. Where significant baseline drift was observed (T1 : Tc < 0.85) the data were excluded from the study. These limitations do not detract from our conclusions.

Although we did not see prolonged block when suxamethonium 3 mg kg^{-1} was given after recovery from atracurium to a 50% T1 level, we would not recommend giving such a dose to enhance neuromuscular blockade in clinical practice unless a peripheral nerve stimulator were used to monitor the degree and duration of block. If such a technique is used, neostigmine appears not to accelerate the subsequent recovery and should not be used. It is important to remember that we gave the suxamethonium at 50% T1, at which time all four responses to train-of-four stimulation were present. An alternative clinical solution would be to increase the block with a small increment of atracurium. The intensity, duration and subsequent recovery of the block would then depend on the size of dose used.

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EDITORIAL III

DO WE NEED MORE MUSCLE RELAXANTS?

In 1975 Savarese and Kitz [1] suggested that three new types of neuromuscular blocking drug were required. All should be non-depolarizing agents capable of antagonism and all should be free from cardiovascular side effects in therapeutic doses. The first type would replace suxamethonium, the second was to have a duration of action shorter than the competitive agents available at that time, and the third a longer action to replace pancuronium and tubocurarine. Since then two drugs, atracurium and vecuronium, have been introduced and have gained wide acceptance. It seems that we are about to be offered a further selection. Do we need the drugs on offer and do we still need further developments?

Atracurium and vecuronium were developed and marketed as drugs of intermediate durations of action. They were tested thoroughly in animal preparations to ensure that the doses necessary to show vagolytic, sympathomimetic or ganglion blocking actions were well in excess of those needed to produce neuromuscular blockade. They exhibit remarkably similar durations of action in equipotent doses and these durations are less than those possessed by the competitive agents hitherto available. Atracurium achieves this by having the, so far unique, property of Hofmann degradation whereby it degrades spontaneously when warmed to body temperature and placed at physiological pH. The fact that one of the end products is laudanosine, which is a central nervous system excitant in high doses does not appear to be clinically important even with prolonged use in intensive care patients in renal failure [2]. The absence of significant prolongation of action in renal or liver disease is a significant advantage [3, 4]. One disadvantage may be the dose-related release of histamine seen on occasion, although this and the associated haemodynamic response may be attenuated simply by slowing the speed of injection [5, 6]. In contrast, the short duration of action of vecuronium appears to result from rapid uptake by the liver, with elimination mainly in the bile but also by the kidney [7]. Some prolongation of the action of vecuronium may be seen with renal failure, with obstructive jaundice and with cirrhosis, but the extent is usually much less than is seen with conventional doses of pancuronium in healthy patients [8]. One additional problem is seen with both drugs. Neither shows vagolytic actions nor has sympathomimetic properties. Thus when they are used with opioids, with volatile agents such as halothane or when anaesthesia is insufficiently deep to prevent vagal responses to traction of viscera, there is a likelihood of bradycardia which may be severe enough to present as sinus arrest. The virtues of the drugs, however, have led to their wide acceptance for operations of intermediate duration.

In the past decade, there has also been a much better understanding of pharmacokinetics and pharmacodynamics. Both atracurium and vecuronium were marketed as being "non-cumulative", which appeared to imply that when increments were given at a constant level of block, each increment produced a constant duration of block; but each drug was usually given as an initial large bolus and increments became necessary only to replace drug being lost by elimination. Thus "non-cumulation" could be expected and may be seen if the traditional agents such as tubocurarine and pancuronium are studied in the same way. Nevertheless, the idea of non-cumulation led to the use of both drugs by infusion which may lead to relatively easy maintenance of a constant level of block with easy antagonism when the operation has been completed [9]. By using either incremental bolus techniques or by using infusions, both drugs can be used satisfactorily for long operations. In effect they can be used as the Savarese–Kitz type III drugs. Atracurium seems effective and safe in those few patients who need paralysis in intensive care; it is not yet clear if vecuronium is equally effective and shows a rapid recovery.

What new drugs are on offer? On the West and East sides of the Atlantic there is some progress with developments of the benzylisoquinoliniums and the steroids, respectively. Two long acting drugs are available which appear devoid of cardiovascular side effects. Doxacurium (BW A938U) [10] and pipecuronium [11] are under-

going clinical trials in a number of centres. Their pharmacodynamic properties resemble those of pancuronium and they are probably also excreted largely by the kidney. Presumably, conditions which diminish glomerular filtration delay elimination, but they fit the bill should a replacement for pancuronium be needed. The absence of cardiovascular side effects may allow bradycardia to develop as a result of the vagotonic effect of certain anaesthetic agents and surgical stimuli. Their prolonged actions may also pose problems in antagonism of blockade, and anaesthetists will have to decide if they wish to use a single injection of the newer drugs compared with the ease of repeated bolus injections or infusions of atracurium or vecuronium. As for all prolonged operations, the use of a nerve stimulator will aid their safe administration.

There is one new drug with an action significantly shorter than that of atracurium or vecuronium. Mivacurium [12, 13] is another benzylisoquinolinium compound but, unlike atracurium, it is thought to undergo active hydrolysis by cholinesterase in addition to metabolism by hepatic microsomal enzyme systems. Its plasma clearance is faster than that of atracurium and with equipotent doses its action is 33–50 % that of atracurium or approximately twice that of suxamethonium. Further, the recovery rate seems to be almost independent of the initial dose, and recovery times upon discontinuation of infusions have not differed significantly from times after single bolus doses. Its action is antagonized by neostigmine and it seems a better drug to use for those operations too long for a single dose of suxamethonium and too short for an intubating dose of atracurium or vecuronium. The temporary problem of the weak and floppy patient in the recovery room following attempted antagonism of drugs of intermediate duration of action after, say, 10–15 min, may be resolved but, as with more effective drugs, it possesses a disadvantage: its potential to release histamine seems to be equivalent to that of atracurium.

However, we still seem no nearer to replacing suxamethonium. Its unique triad of producing complete paralysis within 1 min of injection for a relatively short period of time implies that we shall continue to use it, although perhaps more sparingly than before. When there is an urgent need to facilitate tracheal intubation, to break laryngospasm and perhaps for short procedures such as electroconvulsive therapy, there is no equivalent substitute. It does, of course, have significant dangers: it can trigger malignant hyperpyrexia and it may produce life-threatening anaphylactoid reactions. It may lead to dangerous hyperkalaemia in the recently injured, in the burnt and in patients with upper and lower motor neurone lesions. It may not paralyse all patients, it provokes increases in intraocular pressure and it produces muscle pains. Can we identify why it remains so useful? Why do the other neuromuscular blocking agents not act so quickly [14], so well and for so short a time? There seem to be two features. First, we accept that there is a large margin of safety at the neuromuscular junction; the competitive blockers have to block all the spare receptors and most of the remaining 20–30 % to produce complete block. In contrast, being a depolarizing drug, suxamethonium may need to produce depolarization only via the 20–30 % to make the junction insensitive. Thus it may not need as high a concentration gradient to produce the effect. Second, because it has such a short half-life (of the order of 2–3 min at most in the normal patient) it can be given in a huge overdose, thus increasing the concentration gradient driving the drug towards the junction. The short half-life is associated with a very rapid decrease in concentration and, hence, rapid elimination. It remains to be seen if it is possible to produce a competitive blocker with a similar short half-life, but the signs are encouraging with the development of mivacurium.

To return to the question posed at the head of this editorial: "Do we need more muscle relaxants?" The answer is "yes". One reason is that, as with most drugs containing quaternary nitrogen groups, anaphylactoid reactions occur to muscle relaxants and alternatives are needed. The introduction of new drugs always stimulates a critical examination of current practice and that is also an advantage. It is an open question if we need the long-acting replacements for pancuronium and tubocurarine, and this may be answered perhaps when we have more details of the variability in response to doxacurium and pipecuronium and an understanding of what factors predict prolonged responses. As described in this issue [15], mivacurium appears to be useful as a "short–intermediate" drug which may have a role in procedures such as those seen commonly in day-case centres. We still await the replacement for suxamethonium.

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Br. J. Anaesth. (1989), **62**, 373–377

DOXACURIUM CHLORIDE: A PRELIMINARY CLINICAL TRIAL

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SUMMARY

The onset, duration of action and reversibility of doxacurium were studied in 27 anaesthetized patients, using doses of 37.5 μg kg^{-1} (1.5 × ED_{95}) and 62.5 μg kg^{-1} (2.5 × ED_{95}). Onset was slow and, whilst tracheal intubation was always possible 3 or 4 min after injection, the conditions were not ideal. With the higher dose a mean 97.6 (SD 5.2)% block of the response of adductor pollicis to ulnar nerve stimulation was obtained in 9.85 (6.17) min and recovery of the integrated EMG response to 20% of control took 102 min (42 min). After these initial doses, when incremental doses were given there was no sign of cumulation of effect. Antagonism of block with edrophonium 1 mg kg^{-1}, whilst fast in onset, was rarely complete; with neostigmine 50 μg kg^{-1} antagonism was satisfactory. No adverse haemodynamic effect was seen, although a gradual onset of bradycardia, which responded to atropine or glycopyrrolate, was noted in 12 of the patients. No histamine release or other adverse effects were noted.

Doxacurium, in common with atracurium, is a benzylisoquinolinium, non-depolarizing neuromuscular blocking drug containing two quarternary nitrogen groups. Initial clinical studies in the U.S.A. suggest that it is a potent, long acting drug devoid of cardiovascular and histamine releasing side effects at clinically effective doses [1, 2]. The ED_{95} dose to block contraction of the adductor pollicis muscle is approximately 25 μg kg^{-1} [1]. Unlike atracurium, it is not susceptible to Hofmann degradation, and is probably excreted largely unchanged by the kidney.

This study of doxacurium was designed to assess its onset, intubation conditions, effect of multiple increments and ease of antagonism with edrophonium and neostigmine. A preliminary report of this study was presented to the Anaesthetic Research Society.

PATIENTS AND METHODS

We studied 27 ASA I or II adult patients (weights 45–100 kg) scheduled to undergo elective surgery expected to last 120 min. Each gave written informed consent for the study which was also approved by the local Hospital Ethics Committee.

The patients were premedicated with papaveretum 15–20 mg and hyoscine 0.3–0.4 mg i.m. 1 h before surgery. Before induction of anaesthesia the skin over one forearm and the hand was degreased using an alcohol solution. Five silver–silver chloride electrodes were placed, two over the ulnar nerve, one over the mid-point of the distal skin crease at the wrist, one over the palmar aspect of the head of the fifth metacarpal and one over the belly of the adductor pollicis muscle. These were connected to a Datex Relaxograph. Anaesthesia was induced with thiopentone 4–5 mg kg^{-1} i.v. and fentanyl 2–3 μg kg^{-1} i.v.

Neuromuscular monitoring was commenced using a train-of-four stimuli (2 Hz at 20-s intervals) to the ulnar nerve and the gated, rectified and integrated EMG from the adductor pollicis was recorded. The size of the gain setting, supramaximal stimulus and the stimulus artefact were noted. Anaesthesia was maintained with 66% nitrous oxide in oxygen and the lungs were ventilated artificially to maintain normocapnia. The patients were allocated to three groups of nine and patient order was randomized. Following randomization the first 18 patients studied (and hence the last nine also) were equally divided

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between the three groups. When an initially stable record was obtained, doxacurium 37.5 μg kg^{-1} i.v. ($1.5 \times ED_{95}$) was administered to group A, and 62.5 μg kg^{-1} i.v. ($2.5 \times ED_{95}$) to groups B and C, with the bolus being given either into a continuous infusion or flushed through a cannula with a 5-ml bolus of saline. The bolus was given to coincide with a train-of-four sequence, to give an accurate time mark on the record.

Intubation conditions were assessed by the same investigator (R.S.) each time at 4 min after the administration of doxacurium in groups A and B and at 3 min in group C. The conditions were graded on a scale of 1–4 (excellent, good, poor or not possible) [3].

The onset of block was determined as the time from injection to the appearance of either complete block or the maximum degree of block. Following maximal block, anaesthesia was maintained with nitrous oxide in oxygen plus 0.5% halothane. Additional doses of fentanyl and thiopentone were administered as required. When the first response of the train-of-four (T1) had recovered to 20% of control, a bolus of doxacurium 5 μg kg^{-1} was given; this was repeated when T1 had recovered again to 20%. The duration and degree of block produced by each increment were noted.

At the end of surgery, when T1 had recovered to greater than 10% of control, the residual block was antagonized with edrophonium 1 mg kg^{-1} i.v. in the first 18 patients (six in each of groups A, B and C), and neostigmine 50 μg kg^{-1} i.v. in the last nine patients ($n = 3$ in each group). Glycopyrrolate or atropine i.v. in an appropriate dose was given concurrently. The percentage recovery of T1 following the injection of the anticholinesterase agent was continuously recorded.

Heart rate was observed continuously from a Hewlett–Packard ECG monitor and the arterial pressure measured every 2 min using a Hewlett–Packard non-invasive monitor. To minimize decreases in core and hand temperatures during the operation, nasopharyngeal temperature was measured, all infusions were warmed to body temperature, a condenser humidifier was used in the breathing system and the forearm was insulated by wrapping in towelling.

Neuromuscular monitoring was stopped when the patient was awake, and neuromuscular function was evaluated clinically during the recovery period by assessing patient's grip strength and ability to head lift for 5 s [4]. Each patient was reassessed 24–48 h after surgery and questioned with regard to any adverse experience noted.

Non-parametric and Student's t test were used as appropriate to assess statistical significance.

RESULTS

There were no significant differences between the ages, weights or ASA groups of the three groups of patients studied (table I). The duration of surgery was defined as the time from administration of the initial bolus of doxacurium until administration of the antagonizing agent. Intubation conditions ranged between grades excellent and poor in all three groups, but only one patient in each group achieved excellent conditions (table II). Intubation was accomplished successfully in all patients, although 100% block of adductor pollicis was not achieved before intubation was performed.

Because patients in groups B and C all received doxacurium 62.5 μg kg^{-1}, these two groups were analysed together and compared with group A

TABLE I. *Patient characteristics (mean (SD))*

	n	Age (yr)	Weight (kg)	Duration of surgery (min)	Sex (M/F)
Group A Doxacurium 37.5 μg kg^{-1}	9	52.5 (11.8)	67.3 (10.7)	127.8 (58.4)	5/4
Group B Doxacurium 62.5 μg kg^{-1}	9	60.7 (11.2)	69.8 (15.8)	161.4 (48.6)	7/2
Group C Doxacurium 62.5 μg kg^{-1}	9	49 (14.0)	74.5 (15.0)	139.6 (38.7)	6/3

TABLE II. *Intubation data. Score 1 = excellent, 2 = good; 3 = poor; 4 = not possible*

	Time of intubation (min)	Intubation score (No. patients)						Reduction in T1 at intubation (%)
		1	2	2.5	3	4	Mean (SD)	
Group A Doxacurium 37.5 μg kg^{-1}	4	1	4	1	3	0	2.27 (0.66)	55.2 (32.9)
Group B Doxacurium 62.5 μg kg^{-1}	4	1	6	1	1	0	2.0 (0.5)	80.1 (15.5)
Group C Doxacurium 62.5 μg kg^{-1}	3	1	6	0	2	0	2.1 (0.6)	67.1 (26.0)

(doxacurium 37.5 μg kg^{-1}) (table III). Three patients in group A failed to achieve 80% block following the initial bolus and one patient was antagonized at 10% recovery. In the remaining five it took an average of 51 min to recover to T1 of 20%. With the higher dose, in one patient the initial block was only to 75%, and in two the recording was lost following movement of the patient by theatre staff and loss of electrode placement. In the remaining 15, the time to 20% T1 recovery was on average 102 min after the initial dose (table III). There was no significant correlation between the age of the patients and duration of block at this higher dose.

Only 13 patients received increments of doxacurium as, in the remainder, the initial bolus dose of doxacurium was adequate to last throughout the operation. The incremental doses administered at 20% recovery of T1 produced a moderately wide between-patient variation in response, both with regard to percent increase in block of T1 and time to return to 20% T1. However, the response in any one patient was consistent, with increments producing the same increase in paralysis and a constant duration of effect (table IV).

Two patients with poor recovery recordings were omitted from the antagonism data analysis. The mean percent recovery of T1 at the time of administration of the antagonist was almost the same in the edrophonium and neostigmine groups (table V). The first twitch of the train-of-four was antagonized well after neostigmine. The T1 antagonism response to edrophonium was rapid

TABLE III. *Onset and duration data (mean (SD) [range]). *Three patients failed to achieve 80% block*

	n	Max. block achieved (T1%)	Time to max. block (min)	Duration to 20% recovery of T1 (min)
Group A Doxacurium 37.5 μg kg^{-1}	9	83.6 (18.3) [55–100]	10.5 (2.2) [6–14]	N/A*
Groups B+C Doxacurium 62.5 μg kg^{-1}	18	97.6 (5.2) [78–100]	9.85 (6.17) [5–31]	101.7 (41.8) [31–175] (n = 15)

TABLE IV. *Response to increments (5 μg kg^{-1}) (mean (SD) [range]), †Group A* n = 4; *group B* n = 4; *group C* n = 5

No. patients receiving increments at 20% recovery T1		Increase in block T1 (%)	Duration to return to 20% (min)	No. increments
Total	13†	8 (3.3) [2.5–15]	31.3 (31.1) [9.5–42]	3.9 (3.8) [1–12]

TABLE V. *Data on antagonism of block by edrophonium or neostigmine (mean (SD) [range])*

		Recovery of T1 (%) at				
	n	Drug admin.	1 min	3 min	5 min	10 min
Edrophonium	17	23.8 (8.8) [10–37]	59.2 (22.8)	70.9 (17.3)	76.4 (17.4)	78.0 (16.7)
Neostigmine	8	22.5 (6.7) [10–32.5]	40.6 (21.2)	70.5 (28.2)	81.8 (21.0)	94.3 (12.2)

in onset but was incomplete and subsequently appeared to be similar to that of a spontaneous recovery. In eight (47%) patients in the edrophonium group a train-of-four (TOF) ratio less than 0.5 was still present when recording had to be stopped. Only four (24%) patients achieved a TOF ratio greater than 0.7. One patient, with a TOF ratio of 0.6 at the end of recording, failed a 5-s head lift 30 min after administration of edrophonium. Ten minutes later he had a successful head lift following administration of neostigmine 2.5 mg. In the neostigmine group, no neuromuscular block could be detected by clinical assessment in the recovery room. One patient had a train-of-four ratio less than 0.5 following antagonism at the end of the recording. Four patients (50%) achieved a TOF ratio greater than 0.7. The mean period of recording following administration of both agents was approximately 14 min.

Twelve (44.4%) patients required administration of an i.v. anticholinergic agent during operation to correct a heart rate of less than 50 beat min^{-1}.

The bradycardias were gradual in onset and generally occurred 30–60 min after induction of anaesthesia and seemed unrelated to the administration of doxacurium.

No adverse experiences were reported by the patients on follow-up at 24 h.

DISCUSSION

This study confirms that doxacurium is a potent, long acting neuromuscular blocking agent. Although a formal dose–response study was not carried out in our patients the drug appeared to be less potent than might have been anticipated from previous reports. Other studies [1, 2, 5, 6] suggest that the ED_{95} lies between 13.6 and 25 μg kg^{-1}, depending on the anaesthetic conditions. The dose regimen in this study was based on the initial report by Basta and colleagues which suggested the ED_{95} under balanced anaesthesia was 25 μg kg^{-1} [1]. In our study, group A received 1.5 times this ED_{95} and groups B and C received 2.5 times the ED_{95}. Our data, however, showed that at 37.5 μg kg^{-1} ($1.5 \times ED_{95}$) the maximum block achieved was 83.6% T1. This apparent difference in potency may result from the fact that we compared EMG responses to mechanomyographic forms of measurement [1, 2]. In addition, the drug may appear less potent because of the lighter depth of anaesthesia during induction. Alternatively, there may be an Anglo–American difference in potency for doxacurium, as had been described previously for tubocurarine [7].

Intubating conditions were similar to those described by other workers [8, 9] and could only be described as excellent in one patient in each group; in no patient was 100% blockade of T1 achieved before intubation. In two patients the intubating conditions were between grades 2 and 3 by the intubation criteria of Twohig and his colleagues [3] and therefore they scored 2.5. Even at the high dose (62.5 μg kg^{-1}) the mean onset time to 90% block of T1 was some 4.9 min ($n = 17$). Nevertheless, in no patient was intubation impossible and the mean conditions in all three groups could be said to be good.

In the patients receiving multiple maintenance increments of doxacurium there was no evidence of an increase in duration or degree of block following each bolus.

In all patients except the two with poor recordings, in whom antagonism was blind, the block was antagonized between 10 and 37% recovery of T1. It could be argued that the poor antagonism with edrophonium was related to baseline drift of the electromyographic recording, which has been well documented by other authors [10, 11]. However, the antagonism of T1 by neostigmine was complete; this would confirm a real difference in ability to antagonize doxacurium by these two anticholinesterase agents. As a result of time constraints imposed on this clinical study, TOF fade was still present in several patients when stimulation had to be stopped as the patient

awakened. Nevertheless, with the exception of one patient who received edrophonium, all other patients appeared to have appropriate clinical antagonism of block and had satisfactory grip strength and 5-s head lift when tested between 20 and 40 min after admission to the recovery ward.

It is unlikely that the gradual onset of bradycardia could be attributed to doxacurium; our measurements of heart rate and arterial pressure confirm the findings of others that doxacurium is a haemodynamically stable agent [1, 12]. There was no clinical evidence of histamine release. Konstadt also noted a decrease in heart rate and attributed this to progressive reduction in sympathetic tone resulting from anaesthesia [13]. The effect of opioids and volatile agents on heart rate is well documented [14].

In conclusion, we found doxacurium to be a potent, long acting, haemodynamically stable, non-depolarizing neuromuscular blocker. Although intubation was possible in all patients in the three groups studied and with the doses used in this study, doxacurium did not provide intubating conditions which could be described as excellent. In common with vecuronium and atracurium, this drug does not have the protective vagolytic effect of pancuronium and it is recommended that an anticholinergic agent be available immediately if vagal stimuli are likely to be encountered during surgery. Neostigmine would appear to be more suitable than edrophonium as an antagonist for doxacurium.

ACKNOWLEDGEMENT

This study was supported by the Department of Clinical Therapeutics, Wellcome Research Laboratories, Beckenham, Kent.

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Current Opinion in ANAESTHESIOLOGY

Reprinted from Volume 2 1989

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SCIENCE

Newer agents

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Current Opinion in Anaesthesiology 1989, **2**:493–496

Introduction

Important research into new muscle relaxants can be divided into two distinct chemical groups, namely the benzylisoquinolinium compounds and the steroids.

The benzylisoquinolinium agents

For a number of years now, Savarese and colleagues at the Massachusetts General Hospital, USA have been collaborating with pharmacologists and molecular chemists at Burroughs Wellcome, Research Triangle Park, North Carolina, USA. They have been particularly interested in the bis-benzylisoquinolinium diesters, a group of non-depolarizing compounds known to undergo hydrolysis in the presence of plasma cholinesterase. While a number of prototypes offered many features of 'the ideal muscle relaxant', the major stumbling block with this class of experimental drugs has been histamine release. This side effect, well recognized in other benzylisoquinolines, notably d-tubocurarine, metocurine and to a lesser extent atracurium, has resulted in the withdrawal of some otherwise potentially useful agents following volunteer studies.

Two drugs, doxacurium chloride (BWA 938 U) [1], and mivacurium chloride (BWB 1090 U) [2], have, however, recently come to full scale clinical trials in both the USA and Europe.

Doxacurium [1,3,4] would appear to be the most potent non-depolarizing muscle relaxant ever studied in man. At an estimated ED_{95} of 30 μg/kg doxacurium is two to two and a half times more potent than pancuronium, and over 16 times more potent than d-tubocurarine.

This long-acting bis quarternary benzylisoquinolinium diester was identified as a byproduct of the programme to develop a short-acting agent. It has a similar duration of effect to pancuronium given in equipotent doses [1,3] and provided there is some evidence of recovery as assessed by using a peripheral nerve stimulator, the drug may be reversed satisfactorily with neostigmine [1,3]. Edrophonium, however, would appear to be an unsatisfactory antagonist for this agent [5].

The onset time is slow, and probably slower than that of pancuronium in equipotent dose [1,3]. At 80 μg/kg ($2.7 \times ED_{95}$) the mean onset to maximum suppression was only 3.5 min [1]. Thus doxacurium would seem to be an unsuitable agent for rapid tracheal intubation.

Its major advantage is its haemodynamic stability in both healthy adult patients and those with cardiac disease [1,6]. Although some decrease in heart rate [5,6] may be observed over time, this is unlikely to be an effect of doxacurium. The vagal effects of anaesthesia and certain surgical stimuli, which are concealed by the vagolytic effect of pancuronium, may occasionally be exposed with this drug. A similar phenomenon is seen not infrequently with vecuronium, which is also stable on the circulatory system.

Unlike other benzylisoquinoline analogues, it does not release histamine in the clinical dose range [1]. This is almost certainly due to its high potency making the margin of safety between the neuromuscular blocking dose and the dose at which histamine release is observed, that much wider.

Early pharmacokinetic studies in humans show elimination half-lives (1–2 h) and clearance values (1–2 ml/kg per min) typical of other long-acting agents such as pancuronium or d-tubocurarine. Although the drug has been identified in human bile, it is thought that doxacurium is largely eliminated unchanged by the kidney. The hydrolysis rate *in vitro*, as catalyzed by purified pooled human plasma cholinesterase, is only 6% of the rate of suxamethonium [1].

Benzylisoquinoline ester compounds can be readily chemically manipulated to undergo more rapid metabolism or degradation, thereby shortening the neuromuscular effect. Atracurium was the first to find clinical success in which the ester linkage facilitates both the Hofmann elimination and ester hydrolysis pathways of breakdown. With mivacurium, the basic benzylisoquinoline structure provides good potency, while two ester linkages allow rapid breakdown by plasma cholinesterase at about 88% of the rate of suxamethonium hydrolysis [2]. Preliminary data *in vitro* and in the cat, however, suggests that mivacurium might also undergo liver uptake and metabolism. This could explain the poor correlation of the duration of action of bolus doses of mivacurium, with the plasma cholinesterase activity of individual subjects. The metabolites have been identified in the bile and urine of both cat and dog, as well as in human urine [2].

Since enzymatic hydrolysis is most likely the major route of clearance, the duration of action of mivacurium may be

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longer in people with low cholinesterase activity. Savarese *et al.* [2] posit that the relative increase in duration of action, however, may not be as great as in the case of suxamethonium for three reasons:

(1) the upper limit of the clinical dose range is greater with suxamethonium than mivacurium, and therefore represents a relatively greater overdose and consequently higher clearance load;
(2) other clearance pathways for mivacurium seem likely, and
(3) the complicating process of phase II block cannot occur in the case of mivacurium.

Mivacurium's duration of action is about one-third to one-half that of an equipotent dose of atracurium of vecuronium, or about one and a half to two times longer than suxamethonium. Its onset time, however, is more similar to atracurium or vecuronium than suxamethonium. The calculated ED_{95} for neuromuscular blockade is 0.08 mg/kg. At a dose of 0.3 mg/kg ($3.8 \times ED_{95}$), onset can be shortened to the 2 min range, but there is still a spontaneous recovery to 95% twitch height in some 36 min [2]. This pharmacodynamic pattern, where an increase in dose is accompanied by a disproportionately small extension of duration of effect, is unlike that of any other non-depolarizing blocker, with the possible exception of atracurium. Rather than engage in the often discussed definition of cumulation, it is simpler to say that mivacurium's recovery indices are relatively short, and do not change over a wide dose range, nor after prolonged continuous administration by infusion [7]. The addition of isoflurane may, however, prolong the recovery index [8]. Interestingly, Ali *et al.* [7] noted a significant correlation between the infusion rate of mivacurium required to maintain 95% twitch depression, and the plasma cholinesterase activity of individual subjects.

Antagonism of mivacurium-induced block by anticholinesterase agents would seem at least as easy as reversal of any other non-depolarizing drug. It is likely that during reversal, hydrolysis of mivacurium may be slowed for a brief period, due to a short-lasting inactivation of plasma cholinesterase. Nevertheless, moderate levels of mivacurium block are readily antagonized by neostigmine, due to acetylcholinesterase inhibition. Presumably within about 20 min following neostigmine administration, plasma cholinesterase activity should have recovered sufficiently to destroy any residual mivacurium ester material.

Since mivacurium is a benzylisoquinoline substance, it shares the generic side effect of this group of compounds, namely histamine release. This side effect would seem to be relatively mild, and its cardiovascular effects are similar to those of atracurium [2]. Like atracurium, the transient haemodynamic response to a high dose bolus can be attenuated by simply slowing the speed of injection to about 60 s

Mivacurium will be supplied as a solution that is stable at room temperature.

Steroidal agents

The concept of fusion of acetylcholine-like fragments with a steroidal skeleton was stimulated following the discovery of malouetine, a naturally occurring extract of a jungle plant found in Zaire. Although this substance had neuromuscular blocking properties, its cardiovascular side effects made it unsuitable for clinical trials. Nevertheless, subsequent molecular design led to the development of pancuronium. The observation in 1974 that the vagolytic effect of pancuronium was due to the A ring acetylcholine-like moiety and its $\alpha\beta$ stereochemistry, resulted in the emergence of two further steroid analogues namely vecuronium and pipecuronium bromide.

Pipecuronium was originally synthesized 10 years ago in Hungary, and indeed has now been approved for clinical use in a number of Eastern European countries. Despite this experience, progress through the clinical trials stage in Western Europe and the USA has been slow. More recently however, Gideon Richter Ltd (Hungary) have licensed Organon Technika (Belgium) to manufacture and market the drug, and one would anticipate it being available for routine anaesthetic practice in the near future.

In contrast to pancuronium, it has no acetylcholine-like fragments and the interonium distance is considerably larger. Although slightly more potent than pancuronium (ED_{95}, 0.06 mg/kg), all other pharmacodynamic parameters, in particular onset, duration, recovery and reversibility are remarkably similar (Agoston and Richardson, *Clin Anaesth* 1985, 3:361–369; Biaon and Szpomy, *World Congress of Anaesthesiologists* 1988, 2:A0532).

Renal excretion as the unchanged parent molecule appears to be the most important route of elimination, so it is assumed that impaired renal function may prolong the duration of action. As with pancuronium, cumulative effects after repeated doses and potentiation by volatile anaesthetic agents, especially enflurane, can be expected.

Pipecuronium appears to be free from histamine-releasing properties. Like doxacurium, the most important advantage of this drug over other long-acting agents is its freedom from circulatory side effects [9].

Pipecuronium will be supplied as a freeze-dried powder, for storage at room temperature and dilution before use.

Future research

It will have become apparent from the foregoing discussion that there is still a need for a rapid-onset non-depolarizing drug, or, if you like, a suxamethonium substitute without the depolarizing side effects. This is, effectively, where most research into muscle relaxant molecular chemistry will be directed from now on.

It would seem that there are two philosophies on how to achieve this ideal agent.

Chemists working with the benzylisoquinoline structure believe that a highly potent, ultra short-acting drug is the answer; their hypothesis being that it will then be possible to give large doses, to improve onset time with-

out an undue prolongation of blockade. Furthermore, the more potent the drug is regarding neuromuscular blocking activity, the greater margin of safety for histamine release will be; this chemical group's major side effect.

Steroidal chemists however, are working on an entirely different hypothesis. They believe that highly potent drugs, by definition, have a high affinity for receptors, and therefore rapid onset can only be achieved at the expense of a very prolonged duration of action. An analysis of the relationship between neuromuscular blocking potency and duration of action has revealed that it is reciprocal, suggesting that a non-depolarizing equivalent of suxamethonium, when discovered, may necessarily be a drug of low potency [10]. Work in this area has already produced some encouraging results, albeit in animals [11,12].

Two fast onset short-duration steroids, Org 7617 and Org 9616, although significantly less potent than vecuronium, have demonstrated pharmacodynamic profiles similar to suxamethonium. The problem with reducing potency of steroidal compounds, is that vagolytic and autonomic side effects begin to appear. Initial animal studies suggest these two experimental agents may not be haemodynamically stable, at least at the higher doses.

However, two fast onset intermediate duration steroids, Org 9426 and Org 9273, are being investigated and have produced only minor changes in blood pressure and heart rate in all species, at three times EC_{90} blocking doses. Although, once again, considerably less potent than vecuronium, they display a similar duration and faster onset of action at equipotent dose.

It should be borne in mind that the duration of drug action is briefer the smaller the species of animal, presumably because of faster blood flow and metabolism. Nevertheless, the relative time course of action in the cat of these new drugs, suxamethonium and vecuronium, is encouraging.

We eagerly await the results of the initial volunteer studies.

Annotated references and recommended reading

- • Of interest
- •• Of outstanding interest

1. •• BASTA SJ, SAVARESE JJ, EMBREE PB, ALI HH, SCHWARTZ AF, RUDD GD, WASTILA WB: **Clinical pharmacology of doxacurium chloride — a new long-acting nondepolarizing muscle relaxant.** *Anesthesiology* 1988, 69:478–486.

A pharmacodynamic and haemodynamic study of 81 ASA I or II patients. Pancuronium has a marginally faster onset time, but otherwise the pharmacodynamics are similar in equipotent doses. Doxacurium was devoid of dose-related effects on heart rate, at up to and including 2.7 × ED_{95} for twitch suppression.

2. •• SAVARESE JJ, ALI HH, BASTA SJ, EMBREE PB, SCOTT RPF, WEAKLY JN, SUNDER N, WASTILA WB, EL-SAYAD HA: **The clinical neuromuscular pharmacology of mivacurium chloride (BW B1090U): a short-acting nondepolarizing ester neuromuscular blocking drugs.** *Anesthesiology* 1988, 68:723–732.

A pharmacodynamic study in 72 ASA I or II patients. This may constitute a versatile new addition to anaesthetic practice, since its administration seems particularly adaptable to short procedures or to maintenance of relaxation by infusion. Mivacurium chloride would appear to have similar onset times and histamine-releasing potential to atracurium.

3. • MURRAY DJ, MEHTA MP, CHOI WW, FORBES RB, SOKOLL MD, GERGIS SD, RUDD GD, ABOUDONIA MM: **The neuromuscular blocking and cardiovascular effects of doxacurium chloride in patients receiving nitrous oxide narcotic anesthesia.** *Anesthesiology* 1988, 69:472–477.

Pancuronium had a significantly faster onset than doxacurium. The decreases in blood pressure and heart rate noted may be related to study design.

4. • SARNER JB, BRANDOM BW, COOK DR, DONG M-L, HORN MC, WOELFEL SK, DAVIS PJ, RUDD GD, FOSTER VJ, MCNULTY BF: **Clinical pharmacology of doxacurium chloride (BW A938U) in children.** *Anesth Analg* 1988, 67:303–306.

At equipotent doses of doxacurium, both the time to onset of maximum blockade and time to recovery of neuromuscular transmission to T25 are shorter in children, during halothane anaesthesia, than in adults during narcotic anaesthesia. No significant effects on heart rate or blood pressure were observed.

5. • SCOTT RPF, NORMAN J: **Doxacurium chloride: a preliminary clinical trial.** *Br J Anesth* 1988, 61:505.

In this UK study, doxacurium appeared less potent than had been anticipated from North American studies. Edrophonium was an unsatisfactory antagonist of the doxacurium-induced blockade. A gradual onset of bradycardia was observed, but was probably unrelated to doxacurium administration.

6. • STOOPS CM, CURTIS CA, KOVACH DA, MCCAMMON RL, STOELTING RK, WARREN TM, MILLER D, ABOU-DONIA MM: **Hemodynamic effects of doxacurium chloride in patients receiving oxygen sufentanil anesthesia for coronary artery bypass grafting or valve replacement.** *Anesthesiology* 1988, 69:365–370.

Doxacurium showed no clinically significant effect on measured or derived haemodynamic variables, at doses up to 3 times its ED_{95}, in ASA III or IV patients undergoing cardiac surgery.

7. • ALI HH, SAVARESE JJ, EMBREE PB, BASTA SJ, STOUT RG, BOTTROS LH, WEAKLY JN: **Clinical pharmacology of mivacurium chloride (BW-B1090U) infusion — comparison with vecuronium and atracurium.** *Br J Anaesth* 1988, 61:541–546.

Recovery times following infusions of mivacurium did not differ significantly from those following single bolus doses, and were approximately 50% of those for equivalent durations of infusion of atracurium or vecuronium. There was a significant correlation between the infusion rate of mivacurium required to maintain 95% twitch depression, and the plasma cholinesterase activity of individual subjects.

8. • WEBER S, BRANDOM BW, POWERS DM, SARNER JB, WOELFEL SK, COOK RD, FOSTER VJ, MCNULTY BF, WEAKLY JN: **Mivacurium chloride (BW B1090U)-induced neuromuscular blockade during nitrous oxide-isoflurane and nitrous oxide-narcotic anesthesia in adult surgical patients.** *Anesth Analg* 1988, 67:495–499.

The addition of isoflurane (0.5–0.75% end-tidal concentration) to nitrous oxide narcotic anaesthesia, augments the degree of neuromuscular blockade from a given dose of mivacurium, and also prolongs the recovery index.

9. • TASSONYI E, NEIDHART P, PITTET J-F, MOREL DR, GEMPERLE M: **Cardiovascular effects of pipecuronium and pancuronium in patients undergoing coronary artery bypass grafting.** *Anesthesiology* 1988, 69:793–796.

In patients about to undergo coronary artery bypass grafting, pipecuronium in doses up to 3 × ED_{95} was associated with haemodynamic stability. Previous reports of bradycardia could not be confirmed.

10. •• BOWMAN WC, RODGER IW, HOUSTON J, MARSHALL RJ, MCINDEWAR I: **Structure/action relationships among some desacetoxy analogues of pancuronium and vecuronium in the anesthetized cat.** *Anesthesiology* 1988, 69:57–62.

The greater neuromuscular blocking potency of pancuronium and vecuronium is lost after removal of 1 or both of the acetylcholine moieties. An analysis of the relationship between neuromuscular blocking dose and duration of action revealed that it is reciprocal and it is suggested that a non-depolarizing equivalent of suxamethonium, when discovered, may necessarily be a drug of relatively low potency.

11. BOOIJ LHDJ, MARSHALL IG, CRUL JF, MUIR AW: **(Abstracts) Pharmacology of four steriod muscle relaxants.** *World Congress of Anaesthesiologists* 1988, 2:AO533.

The pharmacodynamics in animals of 2 rapid-onset, short-duration steroids and 2 rapid-onset, intermediate-duration steroids is reviewed.

12. MARSHALL RJ, MUIR AW, BOOIJ L, CRUL J, MARSHALL IG: **The cardiovascular effects of four new non-depolarising neuromuscular blocking drugs in rats, cats dogs, pigs and monkeys.** *World Congress of Anaesthesiologists* 1988, 2:AO534.

The rapid-onset, short-duration steroidal muscle relaxants may have a vagolytic and/or autonomic side effects in the clinical dose range, in animals. The rapid-onset, intermediate-duration steroids look more promising haemodynamically.