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REVIEW ARTICLE

The new neuromuscular blocking agents: do they offer any advantages?

E. W. Moore* **and J. M. Hunter†**

University Department of Anaesthesia, University Clinical Department, The Duncan Building, Daulby Street, Liverpool L69 3GA, UK

**Corresponding author*

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The introduction of neuromuscular blocking drugs in 1942 marked a new era in anaesthetic and surgical practice. The anaesthetist was enabled to provide respiratory support during long and complex surgery whilst the surgeon was allowed access to body cavities without voluntary or reflex muscle movement. In recent years, a generation of anaesthetists trained since atracurium and vecuronium became available in 1982, have taken for granted the speed of onset, shorter and more predictable duration of action, and lack of cardiovascular side-effects that these drugs have in comparison with their predecessors.[56 58 59] The latest generation of neuromuscular blocking drugs aims to provide even greater advantages: as rapid an onset and offset as succinylcholine; disposition independent of organ function; and minimal adverse effects.

New neuromuscular blocking drugs

Since atracurium and vecuronium, the benzylisoquinolinium diesters, mivacurium and the 1R *cis*–1′R *cis* isomer of atracurium, cisatracurium, have become available for clinical use. The aminosteroid, rocuronium, became available in 1995. Another aminosteroid, rapacuronium (Org 9487) (Fig. 1), became available in the USA in 1999, although it was withdrawn from the market by Organon Teknika in spring 2001, for reasons which are detailed below (see Adverse events: Respiratory, p. 920). The search for other series of compounds with non-depolarizing neuromuscular blocking properties presently centres on the bis-tetrahydroisoquinolinium chlorofumarates,[17] and the tropinyl diester derivatives.[50] The most promising of the first group seems to be the asymmetrical mixed-onium chlorofumarate, GW280430A[10] (Fig. 2), which has been tested in both animal and human studies. The bis-quaternary ammonium salt of bistropinyl diester G-1-64 is the most studied of the tropinyl diester group[51] although investigations in humans have yet to be reported (Fig. 3).

GW280430A

The structure of this mixed-tetrahydroisoquinolinium chlorofumarate is given in Figure 2. The similarity in structure to mivacurium is demonstrated. The presence of three methyl groups between the quaternary nitrogen and oxygen atom at each end of the carbon chain suggests that, similar to mivacurium, this compound will not undergo Hofmann degradation. Little is known as yet about its metabolism. It is said to be degraded by chemical mechanisms *in vitro*.[77] It is possible that the chloride substituted double bond in the carbon chain is its weak point. The molecule appears to be in the *trans–trans* configuration similar to one of the active isomers of mivacurium and in contrast to cisatracurium. It is the *trans* isomers of mivacurium and atracurium that undergo ester hydrolysis.

G-1-64

This is a bis-quaternary ammonium salt of a bistropinyl diester derivative.[51] The molecule was selected from more than 200 tropinyl diester compounds. These agents are characterized by:

1. A connecting chain of acid diesters attached to the C3 atom of two tropine molecules.

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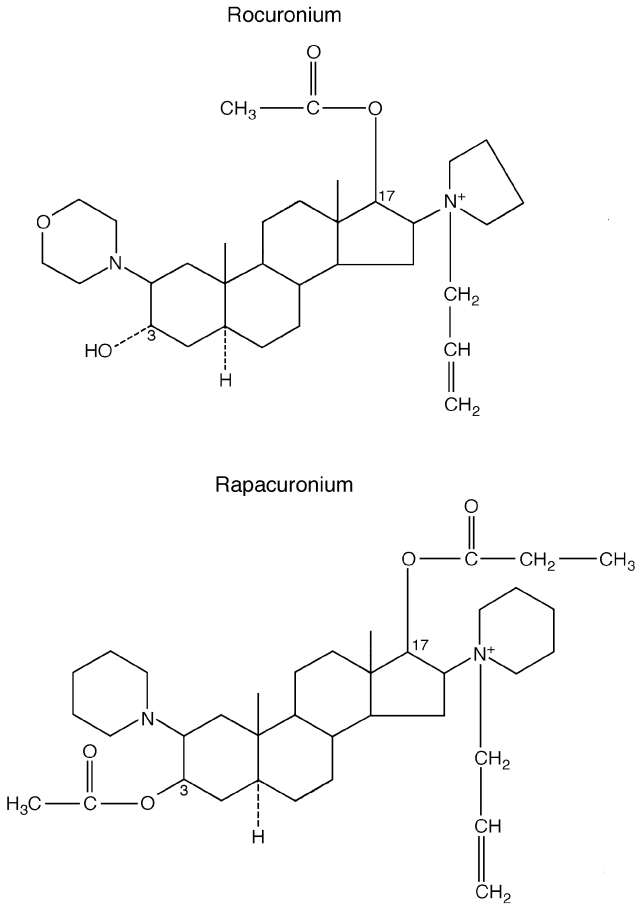


Fig 1 The structure of the aminosteroid neuromuscular blocking drugs, rocuronium and rapacuronium. Note the absence of an acetyl (CH_3COO) group at the 3-carbon position on rocuronium. The removal of this acetyl group on rapacuronium and replacement by a hydrogen ion is the first stage in its metabolism to the metabolite Org 9488, which also has neuromuscular blocking properties.

2. Bulky quaternary substitutes on the tropine N atoms.
3. Varying interonium distances between the terminal groups.

G-1-64 is the prototype of this series of compounds, with an interonium distance of 14.74 Å. It is not yet known how this compound is metabolized. Such diesters could be predicted to undergo hydrolysis in the plasma. Another tropinyl diester compound, *N*-(3,4-diacetoxybenzyl)-tropinium-3α-yl] glutarate dibromide (TAAC3), has also undergone investigation in animals and appears to undergo non-organ dependent elimination.[111 112]

Onset of action

Production of neuromuscular block depends on the presence at the post-synaptic nicotinic receptor of sufficient molecules of a neuromuscular blocking drug to produce depolarization of the endplate (depolarizing drugs), or to compete with acetylcholine to prevent it causing depolarization (non-depolarizing drugs). Bowman[19] postulated that speed of onset is inversely related to potency. When a non-depolarizing neuromuscular blocking drug is used, more than 75% of the post-synaptic nicotinic receptors must be occupied to produce clinical signs of neuromuscular block. All the agents we commonly use (even the relatively impotent ones) are sufficiently potent that the vast majority of the drug molecules within the junctional cleft are bound to a receptor. The number of molecules of a neuromuscular blocking drug which must enter the post-synaptic cleft to produce a given degree of block is, therefore, relatively constant. Within a series of compounds such as the aminosteroid or benzylisoquinolinium agents, a less potent drug is given in a higher dose; a larger number of molecules are, therefore, available to diffuse more rapidly into the neuromuscular junction than the smaller number of molecules of a more potent drug. Thus a less potent agent is more likely to produce a more rapid onset of action (Table 1). Compare the most potent benzylisoquinolinium agent, doxacurium ($2\times ED_{95}$=0.05 mg kg^{-1}), with a time to maximal neuromuscular block of 6 min with the less potent atracurium ($2\times ED_{95}$=0.4 mg kg^{-1}), which has a much shorter time to maximal block of 2.4 min.

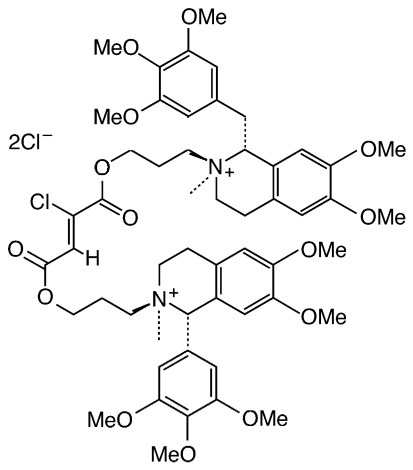
When Boros reported his investigation in rhesus monkeys of a series of bi- and mixed-tetrahydroisoquinolinium chlorofumarates, he found that the inverse relationship between potency and speed of onset of action was maintained.[18] In contrast, in studying a series of neuromuscular blocking tropinyl diesters, Gyermek found that the most potent compounds, those with the longest carbon chain attached to the nitrogen atoms of the bis-quaternary ammonium derivative, produced the more rapid onset of block.[49] Undoubtedly, Bowman did stress that this relationship of potency to onset of block was relevant only to the aminosteroid and benzylisoquinolinium compounds.[19] But Kopman demonstrated that the same effect was evident across these classes of drug with gallamine (a bis-quaternary amine), tubocurarine and pancuronium.[67]

Wright[120] proposed that as well as potency dictating the number of drug molecules available in the plasma to bind to post-synaptic nicotinic receptors and thus impact on onset time, a rapid equilibration between plasma and effect site will increase the rate of onset. Wright calculated that the rate at which the rapacuronium concentration will equilibrate between plasma and the effect site is 2.4 times that of rocuronium and 3.4 times that of vecuronium. He offers this property, perhaps because of the greater lipophilicity of rapacuronium compared with other neuromuscular blocking drugs,[120] as a further explanation for its rapid onset.

ED_{95}

The dose of a neuromuscular blocking drug required to produce 95% twitch depression (ED_{95}) is taken as a guide to the required intubating dose. It is generally considered that at least twice this dose is required to ensure adequate

GW280430A



Mivacurium

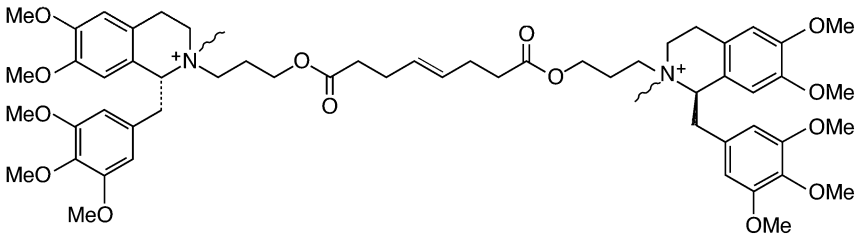


Fig 2 The structure of GW280430A, an asymmetric mixed-tetrahydroisoquinolinium chlorofumarate[17] with four stereogenic centres, two of which are quaternary ammonium, is given. The similarity in structure to mivacurium is demonstrated.

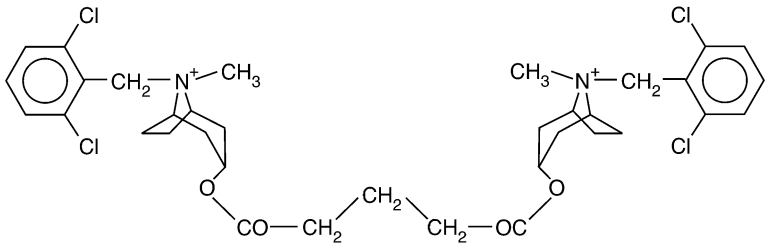


Fig 3 The structure of G-1-64, bis-[*N*-(2,6-dichlorobenzyl) tropanium-3α-yl] glutarate dibromide, which is a bis-quaternary ammonium salt of a bistropinyl diester derivative, with neuromuscular blocking properties.

intubating conditions in all patients. The ED_{95} for rapacuronium has been estimated to be 1.0 mg kg^{-1} during established nitrous oxide/oxygen/halothane anaesthesia.[116] Many of the studies comparing rapacuronium with succinylcholine 1.0 mg kg^{-1} have used rapacuronium 1.5 mg kg^{-1},[86 106] or even 2.5 mg kg^{-1},[1] (Table 2). Confusion has arisen from early studies of the ED_{95} of rapacuronium, as results varied according to whether the active moiety or the bromide salt of the drug had been used.[48] Kahwaji has calculated that 1.5 mg kg^{-1} of the active moiety of rapacuronium would be equivalent to 1.7 mg kg^{-1} of the bromide salt.[61] His studies suggest that rapacuronium 1.5 mg kg^{-1} allows intubation to be achieved as easily as with succinylcholine on more than 80% of occasions, whilst doses larger than 1.5 mg kg^{-1} provide conditions equal to those of succinylcholine (Table 2).[61] It is now standard practice with the commercial preparation to refer to the dose of rapacuronium in terms of the active moiety.

Rapacuronium, similar to rocuronium, has a greater range of effect than succinylcholine, making succinylcholine the more predictable drug.[80 119] Many authors have also reported successful rapid sequence intubation in less than 90 s with rocuronium 1.0 mg kg^{-1}.[5 84] This dose is more than three times the ED_{95} of rocuronium and thus is not a valid

Table 1 Time to maximal block of the train-of-four twitch response after approximately twice the ED_{95} (the dose required to produce a 95% reduction in twitch height), of various neuromuscular blocking drugs

Drug	Dose (mg kg^{-1})	Time to maximal block (min)	Time to 25% recovery (min)	Ref.
Quaternary amines				
Succinylcholine	1.0	0.8	7.6	52
Benzylisoquinoliniums				
Atracurium	0.4	2.4	38	21
Mivacurium	0.15	1.8	16	33, 121
Doxacurium	0.05	5.9	83	7
Cisatracurium	0.1	7.7	46	21, 72
Aminosteroids				
Pancuronium	0.08	2.9	86	63, 87
Vecuronium	0.1	2.4	44	2
Rocuronium	0.6	1.0	43	16
Rapacuronium	1.5	0.9	14.2	52

comparison with rapacuronium 1.5 mg kg^{-1}. Mivacurium and cisatracurium at doses of two to three times the ED_{95} have longer onset times of 2–8 min.[21 33 121]

Belmont has estimated the ED_{95} for the mixed-onium chlorofumarate GW280430A to be 0.19 mg kg^{-1}. Using $3\times ED_{95}$ in 11 ASA I male volunteers, its onset of action was 1.58 min.[9] Gyermek has administered the bistropinyl diester G-1-64 to rats, rabbits, cats, ferrets, pigs, and monkeys and produced 80–90% neuromuscular block in less than 2 min in each animal using $3\times ED_{80}$.[51] Although the bistropinyl diesters have not yet been studied in humans, it seems that the speed of onset of these two new groups of non-depolarizing agents may be similar to rapacuronium and rocuronium.

Response of different muscle groups

Variation in the onset and duration of response of different muscle groups to neuromuscular blocking drugs has been well-described.[37] Bragg attributes this difference in response to the effect of varying blood flow to different muscle groups, producing variable times to equilibration at the effect site.[22] Vecuronium,[46] mivacurium,[95] and rocuronium[96] all have a more rapid onset and offset at the laryngeal muscles compared with the adductor pollicis muscle. This differential onset has not been reported for cisatracurium, perhaps because of its higher potency and its longer onset time. Wright and Debaene have both shown a more rapid onset of rapacuronium at the laryngeal muscles than at the adductor pollicis. Wright administered rapacuronium 1.5 mg kg^{-1} and reported a time to maximal neuromuscular block of 0.8 min at the laryngeal adductors compared with 1.0 min at the adductor pollicis.[120] Debaene studied rapacuronium 0.75, 1.5, and 2.0 mg kg^{-1} and recorded the time from the end of injection until the first depression of the first twitch of the train-of-four response (lag time). The lag times at the larynx were 27, 23, and 20 s, respectively, compared with 42, 35, and 31 s, respectively, at the adductor pollicis muscle.[32] Debaene also found a reduced duration of effect of rapacuronium at the laryngeal muscles; he explains this laryngeal resistance by differentiating between the high density of acetylcholine receptors found in the fast contraction laryngeal muscles,[100] and the relatively low receptor density found in the slow fibres of adductor pollicis.[60] Wright[120] suggests that the more rapid onset of rapacuronium at the laryngeal muscles is a result of greater laryngeal blood flow and a more rapid equilibration between compartments with this drug. He offers the latter explanation for the difference between the onset of effect of rapacuronium and other non-depolarizing agents. Wright, however, found no evidence of laryngeal resistance with rapacuronium.

Belmont studied the onset of neuromuscular block produced by GW280430A in the laryngeal muscles and adductor pollicis. In a group of 20 volunteers, he found a more rapid onset at the laryngeal muscles compared with the adductor pollicis at all doses studied (1, 2, and $3\times ED_{95}$), whilst evidence of laryngeal resistance was only found at the lowest dose used ($1\times ED_{95}$). Time to 25% recovery T1 was similar in both groups of muscles.[10]

Effect of age

Elderly patients. An increased onset time in elderly patients has been shown with pancuronium, vecuronium, rocuronium, mivacurium, and cisatracurium.[40 29 82 30 93 105] A less dynamic circulation and increased transfer time to the effector site in the elderly are likely explanations for this effect. Ornstein compared the onset time of neuromuscular block produced by cisatracurium 0.1 mg kg^{-1} ($2\times ED_{95}$) in two groups of patients, aged 30–49 yr and 65–82 yr. He found that mean (SD) onset of block was slower in the older age group, 3.4 (1.0) min against 2.5 (0.6) min in the younger age group.[93] Sorooshian also measured speed of onset of neuromuscular block in younger (34 (9) yr) and older (74 (6) yr) patients given cisatracurium 0.1 mg kg^{-1}. He too found a slower onset of block in the older patients by about 1 min. He calculated the plasma concentration profile of cisatracurium. The predominantly different factor between the two age groups was a reduced rate of effect site equilibration in the elderly, k_{eo} being reduced to 0.06 min^{-1} in the elderly from 0.071 min^{-1} in the young.[105]

In one study[61] comparing intubating conditions in 61 elderly patients (>65 yr) and 120 younger patients (<65 yr) at 60 and 90 s after administration of rapacuronium 0.5–2.5 mg kg^{-1}, no statistically significant differences were found. However, the degree of block was greater in the younger patients at 60 s suggesting that, as for other steroidal neuromuscular blocking drugs, the pharmacodynamic behaviour of rapacuronium may be found to be altered in elderly patients, when adequate numbers have been studied.

Table 2 Studies comparing speed of onset of neuromuscular block at the adductor pollicis muscle and intubating conditions after different doses of rapacuronium and succinylcholine

Drug	Dose (mg kg^{-1})	Anaesthetic technique	Onset (s) (add poll) (SD)	Excellent (%)	Good (%)	Poor (%)	Failed (%)	Ref.
Succinylcholine	1.0	Propofol, nitrous oxide, alfentanil	51					52
Rapacuronium	1.5		54					
Rapacuronium	0.75	Propofol, fentanyl	126 (33)					32
Rapacuronium	1.5		96 (20)					
Rapacuronium	2.0		82 (21)					
Rapacuronium	1.5	Thiopental, fentanyl, halothane, nitrous oxide	96 (1.0)					102
Vecuronium	0.07		203 (46)					
Succinylcholine	1.0	Thiopental, fentanyl		88.3		9.4	2.3	86
Rapacuronium	1.5			85.9		8.6	5.5	
Succinylcholine	1.0	Thiopental and fentanyl or propofol and alfentanil		90.4		7.7	1.9	106
Rapacuronium	1.5			80.6		18.8	0.6	
Rapacuronium	0.5	Propofol, fentanyl, nitrous oxide		10	20	30	40	61
Rapacuronium	1.0			30	30	15	25	
Rapacuronium	1.5			26	42	16	16	
Rapacuronium	2.0			53	37	5	5	
Rapacuronium	2.5			77	23	0	0	
Succinylcholine	1.5	Thiopental		68	21	11	0	1
Rapacuronium	2.5			67	26	7	0	

Younger patients. A more rapid onset of neuromuscular block in children than in adults has been shown for rocuronium, mivacurium, and cisatracurium. [108 23 24] Taivainen gave 20 infants (1–11 months), 20 children (2–12 yr), and 20 adults (20–45 yr), rocuronium 0.15 mg kg^{-1} (1×ED_{50}). He recorded onset times of 2.6 (0.5), 1.9 (0.4), and 2.3 (0.5) min in infants, children and adults, respectively.[108] Bryson reviewed several paediatric studies of cisatracurium, each showing a shorter time to maximal block than in similar adult studies.[24] Brandom studied the speed of onset of neuromuscular block produced by a large dose of mivacurium 0.3 mg kg^{-1} (4×ED_{95}) in 180 children between the ages of 1 month and 13 yr. The degree of block was measured as a percentage at 90 s. More intense block was obtained in infants than in older children and those with more intense block were more likely to have intubating conditions scored as 'excellent'.[23]

Rapacuronium 0.9 mg kg^{-1} produces 100% block in children in 62 s with no adverse haemodynamic effect.[62] No data have been reported as yet for the chlorofumarates or the tropinyl diesters regarding the effect of age on their pharmacology.

Duration of block

Pharmacodynamics

After a bolus dose of rapacuronium 1.5 mg kg^{-1}, 25% recovery T1 occurs in 10–16 min (Table 4); this is slightly shorter than with mivacurium 0.15 mg kg^{-1} at 16 min.[33] Twenty-five per cent recovery T1 after succinylcholine is even shorter at 8 min.[52] Note that the times to 25% recovery after vecuronium, rocuronium, atracurium, and cisatracurium are all around 40 min following a bolus dose of 2×ED_{95} (Table 1).

Pharmacokinetics

Low potency, a high rate constant for the equilibration of the effect compartment concentration with plasma concentration (k_{eo}), and a rapid clearance are thought to be the required properties of a neuromuscular blocking drug with a fast onset and offset.[14 38 119] Several studies have shown this to be the case for rapacuronium. Wierda,[119] Schiere,[101] and Fisher[45] have all independently calculated the plasma clearance of rapacuronium to be between 7 and 8 ml kg^{-1} min^{-1}; twice the value of 4.0 ml kg^{-1} min^{-1} for vecuronium and rocuronium.[117] Schiere found the plasma equilibration constant (k_{eo}) for rapacuronium to be three times that for rocuronium, at 0.45 and 0.16 min^{-1}, respectively.[101 118] Knowledge of the elimination half-life of a neuromuscular blocking drug is of limited value after use of only a bolus dose as, with the exception of atracurium and cisatracurium, recovery from block occurs during the distribution phase. But after several doses, or an infusion of a neuromuscular blocking drug, when the plasma concentration will be higher, recovery from block may occur during the elimination phase. This variable will then have clinical significance as it takes five elimination half-lives of a drug for the plasma concentration to decrease to almost zero (3% of its original value).

Repeated boluses and infusions

Van den Broek, McCourt, and Schiere have studied the effect of repeated boluses or an infusion of rapacuronium on the duration of neuromuscular block.[110 83 102] They found that the duration of block is increased after repeated boluses, and that despite a reduction in dosage to maintain 90–95% twitch depression during an infusion, the duration of block will be almost doubled after the infusion is stopped compared with a single bolus. Two main mechanisms were suggested for this prolonged duration. First, saturation of the redistribution sites and, perhaps more importantly, the effect of the active metabolite of rapacuronium, Org 9488.

Org 9488 is the 3-desacetyl metabolite of rapacuronium and has neuromuscular blocking activity.[101] Schiere estimates that 1% of an ampoule of rapacuronium will contain Org 9488 as an impurity and that 7% of a dose of rapacuronium will be metabolized to Org 9488 after 6 h. Org 9488 has a low clearance of 1.1–1.3 ml kg^{-1} min^{-1},[101] which is one-sixth that of rapacuronium (7.28 ml kg^{-1} min^{-1}), and similar to pancuronium (1.8 ml kg^{-1} min^{-1}).[87] Org 9488 has a k_{eo} of only one-quarter that of rapacuronium, 0.11 and 0.45 min^{-1}, respectively.[101] This active metabolite is produced in the liver and excreted almost entirely in the urine,[101] in contrast to rapacuronium, which is metabolized mainly by the liver.[97] Org 9488 not only has a lower clearance but is continuously being generated after a bolus dose of rapacuronium. Thus, this metabolite may contribute to the delayed recovery from rapacuronium seen after repeated boluses or infusion of the drug.[101]

Table 3 Time to maximal block of the train-of-four twitch response and time to 25% or 90% recovery T1/T0 for the bis-onium chlorofumarate GW280430A and the bistropinyl diester G-1-64, respectively.[10 51] [a]Monkey *Macaca cynomolgus.* [b]Monkey *Macaca cyclopis* Swinehoe

Species	Dose (mg kg^{-1})	Time to maximal block (min)	Time to 25% recovery (min)
Bis-onium chlorofumarate: GW280430A			
Man	0.18	2.6	4.7
Man	0.36	1.7	7.0
Man	0.54	1.5	9.3
Species	**Dose (mg kg^{-1})**	**Time to maximal block (min)**	**Time to 90% recovery (min)**
Bistropinyl diester: G-1-64			
Rat	0.92	1.2	6.4
Rabbit	0.093	1.8	6.3
Cat	0.091	2.1	9.8
Ferret	0.062	1.6	10.5
Pig	0.41	1.3	6.5
Monkey[a]	0.3	0.9	4.6
Monkey[b]	0.86	1.3	7.3

Chlorofumarates and bistropinyl esters

The mixed-onium GW280430A given to rhesus monkeys, cats, dogs, and male human volunteers has a duration of action of less than 6 min following $1\times ED_{95}$ (0.18 mg kg^{-1} in humans; Table 3); $3\times ED_{95}$ increases the duration of action by approximately 50%.[8 9 11 18 55] Belmont investigated an infusion of GW280430A (74 ± 11 μg kg^{-1} min^{-1}) titrated to maintain 95–99% neuromuscular block for 120 min in cats. He found that the recovery time (3.6 (0.6) min) after the infusion was discontinued was not prolonged.[8]

Gyermek has studied the duration of action of the bistropinyl diester, G-1-64 in several species of animals and has recorded 90% T1 recovery times of 5–10 min using

Table 4 Time (min) to 25% recovery at the adductor pollicis muscle after a rapacuronium bolus or infusion

Rapacuronium dose (mg kg^{-1})	Anaesthetic technique	Time to 25% recovery (mean: min)	Ref.
Bolus			
1.5	Propofol, alfentanil	16.3	83
1.5	Propofol, alfentanil, nitrous oxide	14.2	52
1.5	Propofol, fentanyl	13.4	120
1.5	Propofol, fentanyl	12.8	107
1.5	Thiopental, fentanyl, nitrous oxide, halothane	10.7	102
0.75	Propofol, fentanyl	5.6	32
1.5		10.2	
2.0		13.9	
2.5	Thiopental	16.9	1
Infusion and bolus			
Bolus 1.5 mg kg^{-1}+0.049 mg kg^{-1} min^{-1} infusion	Thiopental, fentanyl, nitrous oxide, isoflurane	13.4	44
Infusion only			
0.211 mg kg^{-1} min^{-1} infusion	Thiopental, fentanyl, nitrous oxide, isoflurane	11	101

Table 5 The pharmacokinetic variables of the newer neuromuscular blocking drugs

Drug	Plasma clearance (ml kg^{-1} min^{-1})	Volume of distribution (ml kg^{-1})	$t_{1/2}$ beta (min)	k_{eo} (min^{-1})	Ref.
Benzylisoquinoliniums					
Atracurium	6.6	87	21	0.1	43,94
Mivacurium					
cis–cis	5.2	266	53		53
cis–trans	95.0	210	1.8		
trans–cis	70.0	200	1.9		
Doxacurium	2.7	220	99		26
Cisatracurium	5.7	161	24	0.179	31
Aminosteroids					
Vecuronium	4.0	199	108	0.11	79,102
Rocuronium	4.0	270	131	0.16	117
Rapacuronium	7.28	193	88	0.449	101
Org 9488	1.28	233	169	0.105	101,107

an ED_{80} dose of the drug (Table 3).[51] Recovery times are similar after an ED_{90} dose of TAAC3 in dogs and monkeys.[111 112] In his study of the family of bistropinyl diesters, Gyermek found that the more potent compounds were those with the *shortest* duration of action,[49 50] in contrast to the benzylisoquinolinium diesters and the aminosteroids. For instance, the C12 compound has an ED_{50} of 220 μg kg^{-1} and a recovery index of 1.1 min. In contrast, the much less potent C2 compound, with an ED_{50} of 1340 μg kg^{-1}, has a recovery index of 3.3 min.[49]

Effect of age

Recovery times from pancuronium,[40] vecuronium,[29] and rocuronium[82] are slower in the elderly compared with younger age groups. Kahwaji[61] has studied the effect of dosage and age on the speed of onset and duration of action of rapacuronium. Although he showed a dose dependent increase in duration of block, which was statistically significant in elderly patients, the slower speed of onset, prolongation of block and longer recovery times of any given dose in elderly patients were not statistically significant from younger patients. Szenohradszky[107] and Fisher[44 45] examined the effect of age on the pharmacokinetics of rapacuronium. Szenohradsky found a reduction in clearance of 0.9% per yr of age (compared with 30 yr); Fisher[44] found a reduction in clearance of 0.5% per yr of age (compared with 45 yr). However, in an earlier study, Fisher[45] had found that age had no effect on the clearance of rapacuronium. Fisher[44] attributed the difference in findings between the two studies that demonstrated an effect of age on the clearance of rapacuronium[107 44] and the study which did not,[45] to the smaller number and shorter duration of plasma sampling in his earlier report.

When Sorooshian studied cisatracurium 0.1 mg kg^{-1} in 31 young patients (18–50 yr) and 33 elderly patients (>65 yr) he found no increase in duration of action or recovery times between the age groups.[105] Ornstein investigated cisatracurium 0.1 mg kg^{-1} given to 12 young patients (30–49 yr) and 12 older patients (65–82 yr) and also found no difference in duration of action or recovery times between groups.[93] Dahaba used a dose-adjusted mivacurium infusion to maintain one to two twitches of the train-of-four response in 21 younger patients (18–41 yr) and 20 older patients (64–79 yr). Although he noted a significant reduction in dose requirement in the elderly compared with the younger patients, there was no difference in the recovery index between groups.[30]

Reversal of block

Difficulty with intubation is not always predictable and, therefore, rapid recovery from block is one of the major advantages of succinylcholine. The aim has been to have as rapid a recovery from a non-depolarizing agent. Following administration of succinylcholine 1 mg kg^{-1}, extubation can be achieved after 10–12 min.[57] None of the non-depolarizing agents has a similar spontaneous recovery profile. The early use of a reversal agent after rapacuronium has been investigated to assess whether this drug can be used as a short-acting agent equivalent to succinylcholine in this respect.

Although the first studies of the time course of reversal from rapacuronium induced block found a time to a train-of-four ratio of 0.7 of less than 12 min using neostigmine 0.05 mg kg^{-1},[116] these times have not been replicated by later research.[88 98] Purdy[98] reduced the time to 25% recovery T1 from 16 min to 8–9 min using neostigmine 0.05 mg kg^{-1} or 0.07 mg kg^{-1} given either 2 or 5 min after rapacuronium 1.5 mg kg^{-1}. The time to recovery of the train-of-four ratio to 0.7 was also reduced from 42 min to around 20 min. Hayes,[52] Debaene,[32] Kahwaji,[61] and McCourt[83] have studied recovery when neostigmine 0.05 mg kg^{-1} was given at a later stage after rapacuronium (T1=25%). All these studies were unable to reduce the time from administration of rapacuronium 1.5 mg kg^{-1} to a train-of-four ratio of 0.7 to less than 20 min irrespective of the reversal agent, dose or time of administration.

Lein has studied the reversibility of GW280430A induced neuromuscular block in 16 male volunteers, using 1, 2, and

Table 6 Urinary and biliary excretion of neuromuscular blocking drugs over 24 h[58]

Drug	Excretion (%)		Ref.
	Urine	Bile	
Quaternary Amine			
Succinylcholine	<10	–	58
Benzylisoquinoliniums			
Atracurium	10	–	103
Mivacurium	<10	–	27
Doxacurium	25–30	–	26
Cisatracurium	16		66
Aminosteroids			
Vecuronium	15	40	12
Rocuronium	20	54	109
Rapacuronium	<12	80	101,107

$3\times ED_{95}$ and edrophonium when T1=10%. She found recovery of 25% T1-TOF ratio of 0.9 to be 3 min in each of the three groups,[77] that is, a constant reversal time. Belmont has given GW280430A as a 2-h infusion to cats and found no increase in the recovery index compared with a single bolus of $1\times ED_{95}$.[8] This lack of prolongation of the recovery index with increasing dose suggests that GW280430A is likely to be non-cumulative, consistent with rapid degradation.

Little information is available on the reversal characteristics of G-1-64. Some of the most potent compounds in this family have been reported to have a recovery index (25–75% T1/T0) of less than 2 min in early studies in rats.[49]

New reversal agents

The well-recognized cardiovascular and intestinal side-effects of the anticholinesterases used to reverse residual neuromuscular block has prompted the search for alternative agents. The concept has recently been introduced of the use of *chemical chelation* of neuromuscular blocking drugs at the end of surgery to antagonize block. *Cyclodextrins* are a group of cyclic oligosaccharides, which are recognized to encapsulate lipophilic molecules including steroids. Org 25969 has been investigated in monkeys and been found to antagonize residual block produced by rocuronium more rapidly than neostigmine, without any significant cardiovascular changes.[15]

Hepatic and renal failure

Metabolism and excretion

Rapacuronium has been found to be eliminated mainly by the liver in both human and animal studies,[97] as is vecuronium,[13 97] and rocuronium.[64 97] Less than 12% of a dose of rapacuronium is eliminated in the urine; half is excreted unchanged and half as Org 9488.[101 107] Cisatracurium is cleared predominantly by Hofmann elimination (76.9%) to form laudanosine. Laudanosine is further metabolized to a number of conjugated metabolites which are excreted in the urine.[66] The renal clearance of cisatracurium in health was calculated to be 16% of the total clearance; thus, renal elimination accounts for most of the non-Hofmann (organ) elimination of cisatracurium.[66]

Liver disease

Fisher[44] and Duvaldestin[41] investigated the effect of cirrhosis on the pharmacokinetics of rapacuronium. Fisher studied six cirrhotic patients and found that plasma clearance and steady state volume of distribution were similar to a healthy control group.[44] In contrast, Duvaldestin found a 40% increase in plasma clearance and a 50% increase in the steady state volume of distribution in cirrhotic patients.[41] However, in both studies only a small number of patients were investigated and thus further (larger) studies will be required. No prolongation of the duration of action of rapacuronium was found following a single bolus or a 30-min infusion of the drug in cirrhotic patients.

Van Miert has compared rocuronium in normal patients and those with hepatic failure.[113] He found that although the time to maximal neuromuscular block did not differ between groups, the recovery times were prolonged in the cirrhotic group. The mean times to 25% recovery T1 after rocuronium 0.6 mg kg^{-1} were 53.7 and 42.3 min in the cirrhotic and control group, respectively ($P<0.05$).[113] Khalil[64] and Magorian[81] have also reported delayed recovery from rocuronium in hepatic failure. In van Miert's study, plasma clearance was significantly reduced in the cirrhotic group compared with healthy patients (2.66 *vs* 3.7 ml kg^{-1} min^{-1}) and the elimination half-life was significantly prolonged (143 *vs* 92 min). Steady state volume of distribution was unchanged.[113] In contrast, Khalil and Magorian did not report a reduction in the clearance of rocuronium in cirrhosis.[64 81] Van Miert attributes the differences to the failure of Khalil to normalize the results to take account of body weight; and to the use of a shorter sampling time, a smaller number of patients, and a different pharmacokinetic model in Khalil's study. Van Miert's findings are consistent with the work of Khuenl-Brady in cats.[65]

As renal excretion accounts for approximately three-quarters of the non-Hofmann elimination of cisatracurium, it is not surprising that the effect of this drug is little changed in hepatic failure.[31] After a bolus of cisatracurium 0.1 mg kg^{-1}, volume of distribution was increased by 21% and clearance by 16% in a cirrhotic group, compared with healthy patients. As the major elimination pathway for cisatracurium is organ independent, the increased clearance is probably a result of the larger volume of distribution. The mean (SD) elimination half-life was similar in both groups (26.5 (3.6) and 24.4 (2.9) min, respectively).

Kidney disease

Fisher[44] and Szenohradszky[107] found a 24% and a 32% decrease, respectively, in the clearance of rapacuronium in renal failure, with a reduced dosage required to maintain a target range of neuromuscular block in the pathological state.[44] But they found that the recovery profile after a single bolus or short infusion (30 min) was not affected in renal patients. Szenohradszky reported that 60 min after a single bolus of rapacuronium, plasma concentrations decrease more slowly in patients with renal failure. Plasma concentrations of Org 9488 decrease minimally in this group compared with healthy controls. He postulated that if repeated boluses or a prolonged infusion of rapacuronium were used in renal failure patients, recovery would be delayed. The clearance of the active metabolite of rapacuronium, Org 9488, is 15% of normal in renal failure;[107] this may be the most important factor in the increased duration of effect of rapacuronium in this disease state. Fisher suggests that monitoring neuromuscular block to adjust the dose of rapacuronium may minimize the impact of renal failure on the accumulation of Org 9488.[44]

After rocuronium 0.6 mg kg^{-1}, up to a fifth of the dose is recovered unchanged from the urine within 24 h.[109] After the same dose, Cooper found a 32% reduction in clearance, (2.5 against 3.66 ml min^{-1} kg^{-1}), with an increase in recovery time in chronic renal failure patients compared with a healthy control group.[28]

Eastwood compared cisatracurium 0.1 mg kg^{-1} in 17 patients with end-stage chronic renal failure and 15 healthy patients. He found a 13% reduction in clearance and an increase from 30 to 34 min in the elimination half-life in the renal failure group.[42]

Adverse events

Respiratory

All the studies that have recorded the incidence of adverse events have reported bronchospasm after administration of rapacuronium; it appeared to be more common in smokers and patients with a history of reversible airways disease. Kahwaji,[61] Sparr,[106] Purdy,[98] McCourt,[83] Levy,[75] and Szenohradszky,[107] found bronchospasm in 16 out of 181, 18 out of 167, nine out of 117, four out of 90, seven out of 47, and two out of 20 patients studied, respectively. Thus, bronchospasm was found in more than 9% of patients. Three of these adverse events were classed as serious and required treatment. An incidence of bronchospasm of one in 11 makes rapacuronium significantly different from the other aminosteroids in this respect.

Since rapacuronium became available for clinical use in the USA, a series of case reports published in 2001 has highlighted 21 cases of bronchospasm after its administration, 14 of which were severe.[47] Twenty of the reports occurred in children.[68 85 89] The most concerning feature of these case reports is the severity of the bronchospasm. It was associated with arterial desaturation, difficult or impossible ventilation even following tracheal intubation, and the requirement for i.v. epinephrine. In contrast to the earlier reports, there was no apparent association between the bronchospasm and a history of reversible airways disease. As a result of these reports, the sale of rapacuronium has been suspended by Organon Teknika in the USA.

Newman studied cisatracurium given by infusion to 40 critically ill patients.[92] One of the patients developed mild intermittent bronchospasm during the infusion and for 24 h following its discontinuation. There are few other reports of cisatracurium causing adverse respiratory effects.

Heerdt has studied the effect of GW280430A on the respiratory system of six male beagles; he measured pulmonary artery pressures, peak inspiratory pressure and pulmonary compliance.[54] He found no change in these variables at doses up to $25\times ED_{95}$.

Cardiovascular

Neuromuscular blocking drugs have the potential to produce adverse effects at muscarinic and nicotinic receptors resulting in an increase (vagolytic) or decrease (vagal) in heart rate. They can also, as with pancuronium, block release of norepinephrine and its reuptake at sympathetic nerve endings.[58] They may release histamine.[58] Abouleish,[1] Sparr,[106] Levy,[75] and Szenohradszky[107] all found a decrease in mean arterial pressure after rapacuronium, although none of the events required intervention, nor were the changes statistically significant. Whalley compared 20 patients given rocuronium 0.6 mg kg^{-1} with 21 patients given atracurium 0.5 mg kg^{-1} and found no differences between groups in the changes in heart rate and arterial pressure, in the 15 min after intubation and before skin incision, from control measurements obtained before induction of anaesthesia.[115] Shorten compared 15 elderly patients given rocuronium 0.9 mg kg^{-1} with 15 patients given vecuronium 0.12 mg kg^{-1} and found no significant change in heart rate, arterial pressure or plasma epinephrine, or norepinephrine concentrations in either group.[104]

Cisatracurium at doses of up to $8\times ED_{95}$ (0.4 mg kg^{-1}) has been shown to produce no significant changes in heart rate or mean arterial pressure in healthy patients.[76] In his study of cisatracurium by infusion in 40 critically ill patients, Newman found no significant haemodynamic changes in any of the patients.[92] Boyd studied two similar groups of critically ill patients who received cisatracurium or atracurium by bolus and infusion and no haemodynamic changes were reported in either group.[20] Ali[3] administered mivacurium 0.25 mg kg^{-1} to 91 patients, and Doenicke[34] administered mivacurium 0.15 mg kg^{-1} to 11 patients and mivacurium 0.21 mg kg^{-1} to 12 patients. Significant cardiovascular changes (transient tachycardia and hypotension) were only observed in Doenicke's study after the higher dose of mivacurium.

Studies of the cardiovascular properties of the tropinyl diesters have considered only the degree of vagal block produced. This is evaluated by studying the inhibition of the bradycardic response to peripheral stimulation of the cut right vagus nerve with 15–20 Hz supramaximal impulses delivered every 2 min. Gyermek found that all the tropinyl diesters studied produced vagal block in the rat.[49] The least potent compounds (which have the slowest onset of action and longest duration of effect), produced 70–90% vagal block, whereas the more potent tropinyl diesters (the most rapid onset of action and the most rapid offset) produced only 40% vagal block. Investigation of TAAC3 in anaesthetized cats also suggests that this tropinyl ester has the potential to produce changes in heart rate and arterial pressure.[4] The fact that as potency increases, the side-effect profile of these drugs becomes more favourable is encouraging, as it is these more potent agents which promise to be of most clinical benefit.

The cardiovascular side-effects of GW280430A have been investigated in dogs, cats, and human volunteers.[8 54 55 78] Heerdt measured heart rate, systemic and pulmonary artery pressures, left ventricular pressure, end-diastolic pressure, and cardiac index in beagles given increasing doses of GW280430A. Other than a transient decrease in arterial pressure at $25\times ED_{95}$, GW280430A did not alter any of the variables.[54 55] When Belmont examined the effect of GW280430A on the cardiovascular system of cats by measuring heart rate, arterial pressure and per cent vagal inhibition, he was able to give $10\times ED_{95}$ before producing a transient but significant decrease in arterial pressure and a rise in heart rate. Forty per cent vagal block was produced at $16\times ED_{95}$.[8] Lein has reported the effects of GW280430A in 16 male volunteers using doses up to $3\times ED_{95}$ and measuring maximal heart rate and arterial pressure changes in the 5 min following administration. She found that no volunteer had a maximal change in heart rate or arterial pressure of greater than 10% from baseline.[78]

Anaphylactoid reactions

The administration of a drug to a patient via the i.v. route can produce the release of vasoactive substances such as histamine, eicosanoids, and cytokines from inflammatory cells such as mast cells and basophils. The trigger for this release may be a true, immediate hypersensitivity response mediated through pre-sensitized mast cells with IgE antibody recognition.[114] However, certain drugs may directly affect inflammatory cells and the vascular system to produce adverse reactions that are often falsely labelled as allergic.[74] The clinical picture is an immediate systemic inflammatory response with hypotension, tachycardia, bronchospasm, and cutaneous flushing. The term anaphylactoid is used to describe this scenario, and when a genuine immune-mediated response can be demonstrated—anaphylactic.

Before the release of rapacuronium, it had been accepted that the aminosteroid neuromuscular blocking drugs cause less histamine release and are more cardiovascularly stable than the benzylisoquinolinium neuromuscular blocking drugs.[90] Levy,[75] McCourt,[83] Purdy,[98] Kahwaji,[61] and Abouleish[1] record skin erythema which settled without intervention in 1–2% of their patients after rapacuronium. Levy[75] studied plasma histamine levels after rapacuronium 1, 2, and 3 mg kg^{-1} and found a significant increase in histamine release at 1, 2, and 3 min post-dose in the 2 and 3 mg kg^{-1} groups; histamine levels were more than doubled in the high dose group.

Histamine release has been shown to be insignificant following doses of rocuronium up to 1.2 mg kg^{-1}, [73] and Whalley studied 20 patients given rocuronium 0.6 mg kg^{-1} and found no episodes of skin erythema.[115] Anaphylactic reactions to rocuronium have now been described, however, in many cases confirmed by positive skin prick testing.[39 70 91 99] Laxenaire has reported almost 50 cases of anaphylaxis to rocuronium over 2 yr in France.[71] Rose has investigated 54 patients in Australia with suspected anaphylaxis to rocuronium and has described rocuronium as having a propensity to cause allergy intermediate between low risk (pancuronium and vecuronium) and high risk agents (e.g. succinycholine).[99] Neal has suggested that the incidence of anaphylaxis to rocuronium may be as great as 1:3000 in the UK and that careful monitoring of reactions to rocuronium is necessary.[91] When Levy studied the production of a weal and flare response to intradermal rocuronium and cisatracurium, he found that although both drugs were capable of producing this response (at concentrations of 10^{-4} M and above), light and electron microscopy of the skin biopsies revealed mild to moderate mast cell degranulation in the cisatracurium group only and normal mast cell morphology in the rocuronium group.[74] Despite these findings, several studies have recorded no significant increase in plasma histamine levels or the presence of skin erythema after administration of cisatracurium $8\times ED_{95}$.[35 36 76] Raised plasma histamine levels have been reported after mivacurium[34 70] as has cutaneous flushing.[3 34] Anaphylaxis after atracurium,[69 70] mivacurium,[6 70] and cisatracurium[25 70] have all been reported, however.

Summary

The pharmacodynamics and pharmacokinetics of the two most recent aminosteroid neuromuscular blocking drugs to become available, rapacuronium bromide (Org 9487) and rocuronium bromide are reviewed. Two new classes of drug with neuromuscular blocking properties, the bis-tetrahydroisoquinolinium chlorofumarates and the tropinyl diester derivatives are introduced. Comparisons between these drugs and mivacurium and cisatracurium are made.

Rapacuronium 1.5 mg kg^{-1} (ED_{95} 1 mg kg^{-1}), produces maximal neuromuscular block in 54 s. Time to recovery of the train-of-four ratio to 0.7 is achieved within 20 min after neostigmine 0.05 mg kg^{-1} given at 2 min. The plasma clearance of rapacuronium is 7–8 ml kg^{-1} min^{-1}.

Rapacuronium undergoes hepatic metabolism; no prolongation of effect has been reported after a single bolus or a short infusion in patients with hepatic or renal failure. Org 9488 is the 3-desacetyl metabolite of rapacuronium, which has neuromuscular blocking properties. Its much lower clearance (1.28 ml kg^{-1} min^{-1}) and plasma equilibration constant (0.105 min^{-1}) may limit the prolonged use of rapacuronium. Rocuronium given at $2\times ED_{95}$ produces maximal neuromuscular block in 1 min. Spontaneous recovery of the train-of-four ratio to 0.7 takes over 40 min. Rocuronium has a plasma clearance of 4 ml kg^{-1} min^{-1}. Its pharmacodynamics are altered in hepatic and renal disease. A number of anaphylactoid reactions to rocuronium have been reported recently.

The bis-tetrahydroisoquinolinium chlorofumarate GW280430A has an ED_{95} of 0.19 mg kg^{-1}. Given at three times this dose, onset of neuromuscular block occurs within 100 s; the duration of block is 8–9 min. Following a 2 h infusion, the recovery index does not seem to be increased. Early studies suggest that this drug has no adverse cardiovascular or respiratory side-effects.

The tropinyl diester derivative G-1-64 will produce 80–90% neuromuscular block in less than 2 min using $3\times ED_{80}$. Ninety per cent recovery of the first twitch of the train-of-four occurs after 5–7 min using one ED_{80}. A recovery index of less than 2 min has been reported in rats. All the tropinyl diesters appear to produce vagal block.

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