REVIEW ARTICLE

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Newer Neuromuscular Blocking Agents

How do They Compare with Established Agents?

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Contents

Abstract

Rapacuronium bromide (rapacuronium; ORG-9487) is a nondepolarising muscle relaxant (NMBA) with a low potency [90% effective dose (ED_{90}) 1 mg/kg], which to some extent is responsible for its rapid onset of action. Because of the high plasma clearance (5.3 to 11.1 mg/kg/min) of rapacuronium, its clinical duration of action following single bolus doses up to 2 mg/kg in adults is short (i.e. <20 minutes). Rapacuronium forms a pharmacologically active 3-desacetyl metabolite, ORG-9488, which may contribute to a delay in spontaneous recovery after repeat bolus doses or infusions. After rapacuronium 1.5 mg/kg clinically acceptable intubating conditions are achieved within 60 to 90 seconds in the majority of adult and elderly patients undergoing elective anaesthesia. However, in a rapid-sequence setting, intubating conditions are less favourable after rapacuronium 1.5

to 2.5 mg/kg than after succinylcholine. The most prominent adverse effects of rapacuronium (tachycardia, hypotension and bronchospasm) are dose-related, and in particular pulmonary adverse effects are observed more frequently under conditions of a rapid-sequence induction in adults. Therefore, it seems worthwhile to consider only doses of rapacuronium ≤1.5 mg/kg to facilitate rapid tracheal intubation, and to use succinylcholine or rocuronium rather than rapacuronium in a rapid-sequence setting. Rapacuronium, however, is a suitable alternative to mivacurium chloride (mivacurium) and succinylcholine for short procedures (e.g. ambulatory anaesthesia).

Rocuronium bromide (rocuronium) is a relatively low-potent, intermediate-acting NMBA. Its main advantage is the rapid onset of neuromuscular block whereby good or excellent intubating conditions are achieved within 60 to 90 seconds after rocuronium 0.6 mg/kg (2 x ED_{95}), and within 60 to 180 seconds after smaller doses (1 to 1.5 x ED_{95}). Larger doses of rocuronium (≥1 mg/kg) seem to be suitable for rapid-sequence induction under relatively light anaesthesia. However, it is still a matter of controversy whether, in the case of an unanticipated difficult intubation, the long duration of rocuronium administered in such large doses outweighs the many adverse effects of succinylcholine. Rocuronium has mild vagolytic effects and does not release histamine, even when administered in large doses. Rocuronium is primarily eliminated via the liver and its pharmacokinetic profile is similar to that of vecuronium bromide (vecuronium). Unlike vecuronium, rocuronium has no metabolite.

Cisatracurium besilate (cisatracurium), the 1*R-cis*, 1'*R-cis* isomer of atracurium besilate (atracurium) is approximately 4 times more potent than atracurium. The onset time of cisatracurium is significantly slower than after equipotent doses of atracurium. The recommended intubating dose is 0.15 to 0.2 mg/kg (3 to 4 times ED_{95}). Over a wide range of clinically relevant doses the recovery properties of cisatracurium are affected by neither the size of the bolus dose nor by the duration of infusion. Unlike atracurium, cisatracurium does not trigger histamine release. Like atracurium, cisatracurium undergoes Hofmann elimination. In contrast to atracurium, cisatracurium does not undergo hydrolysis by nonspecific plasma esterases. Moreover, about 77% of the drug is cleared by organ-dependent mechanisms.

The introduction of atracurium besilate (atracurium) and vecuronium bromide (vecuronium) into anaesthetic practice in the early 1980s was a milestone in the development of neuromuscular blocking agents (NMBAs). They were the first non-depolarising NMBAs with an intermediate duration of action, that is, duration 25% following twice a 95% effective dose (ED_{95}) of 20 to 40 minutes, and hence useful drugs for relatively short surgical procedures. The major advantage of atracurium and vecuronium is a reduced incidence of residual neuromuscular block at the end of anaesthesia. After the use of long-acting NMBAs, such as pancuronium bromide (pancuronium) and d-tubocurarine chloride (tubocuraine), the incidence of residual neuromuscular block is approximately 40% compared to about 5% after atracurium and vecuronium.[1,2]

A train-of-four (TOF) ratio of >0.7 at the thumb has been considered to be a cut-off value at which recovery of neuromuscular function is adequate for extubation of the trachea in the absence of an un-

derlying disease.[3] However, recent studies in human volunteers indicate that a TOF ratio of >0.9 may be necessary for full recovery of pharyngeal muscle function and for airway protection mechanisms to be intact.[4,5]

Residual paralysis after pancuronium has been identified as a significant risk factor for the development of postoperative pulmonary complications.[6] In addition, the use of long-acting NMBAs is associated with prolonged postoperative recovery and may therefore result in higher costs than the use of intermediate NMBAs.[7,8] In the future, the use of long-acting NMBAs in anaesthetic practice is therefore expected to further decline in favour of quantitative neuromuscular transmission monitoring (e.g. acceleromyography) in order to prevent residual neuromuscular block and possible pulmonary complications.

The problem of residual paralysis and the adverse effects of the depolarising NMBA succinylcholine have stimulated the search for short- and intermediate-acting NMBAs with a fast to intermediate onset of action.[9] Since 1994 three NMBAs, the monoquaternary aminosteroids rocuronium bromide (rocuronium) and rapacuronium bromide (rapacuronium), and the benzylisoquinolinium diester cisatracurium besilate (cisatracurium), have been introduced into clinical practice. This review compares these newer NMBAs with established agents.

1. Rapacuronium Bromide

Rapacuronium, the 16-*N*-allyl 17-β-propionate analogue of vecuronium, was approved for clinical use in the US in 1999.[10] Like rocuronium, rapacuronium (ORG-9487) is a monoquaternary aminosteroidal NMBA with a fast onset of action and is considered to be a potential alternative to succinylcholine to facilitate endotracheal intubation within 1 minute.[9,11-15] When neostigmine is given 2 or 5 minutes after the recommended intubation dose of rapacuronium 1.5 mg/kg for adults, or at 25% twitch recovery, the time to a TOF ratio of 0.7 is about 20 minutes in adults.[16-19] This recovery rate is faster than with currently available intermediate-acting NMBAs.[20] For patients undergoing a Caesarean section and children (aged 1 month to 12 years) rapacuronium 2.5 and 2.0 mg/kg, respectively, is recommended for tracheal intubation.[10]

1.1 Neuromuscular Effects

1.1.1 Potency and Onset of Block

Rapacuronium is a neuromuscular blocking agent of low potency, which is consistent with its rapid onset of action (maximum twitch depression at approximately 1 to 1.6 minutes after the administration of a dose of 1.5 mg/kg).[12-14,21]

In the 1994 article by Wierda et al.,[22] a 90% effective dose (ED_{90}) for free base of the drug of 1.01 mg/kg (= bromide salt 1.15 mg/kg) was reported. A similar value may be estimated from the data of a modelling study done by Schiere et al.[23] In contrast, Kopman et al.[24] found ED_{95} values of 0.75 [standard deviation (SD) 0.16] mg/kg using a single dose technique in female patients. There is, however, some evidence that muscle relaxants are more potent on a milligram per kilogram basis in women than in men.[25] Thus rapacuronium may be considered to be 2.5 to 3 times less potent than rocuronium. The ED_{50} for adults, elderly patients (≥65 years) and infants (1 month to <1 year) is approximately 0.3mg/kg, for paediatric patients (1 to 12 year) the ED_{50} is 0.4 mg/kg.[10,22,24,26]

The onset of action of rapacuronium is faster at the laryngeal adductor muscles than at the adductor pollicis muscle.[12,27] The laryngeal muscles resist the action of rapacuronium. In one study complete block was not attained even after a dose of 2 mg/kg.[12] In another study, however, similar sensitivities in both muscles were reported.[27]

1.1.2 Duration of Block

Depending on the dose, rapacuronium has a short to intermediate duration of action.[9] Clinical duration (time from end of injection to recovery of twitch response to 25% of baseline) is 10.2 to 19 minutes using a dose of 1.5 mg/kg versus 25 minutes using a dose of 2.5 mg/kg in adults.[12-14,28-30]

The clinical duration of rapacuronium 1.5 mg/kg is shorter than that of mivacurium chloride (mivacurium) 0.25 mg/kg (15.4 *vs* 21 minutes),[13]

rocuronium 0.45 or 0.6 mg/kg (16.5 *vs* 27.2 or 38.1 minutes)[31] or vecuronium 0.07 mg/kg (10.7 *vs* 28.8 minutes).[23] The shorter duration of action after an intubating dose of rapacuronium compared with rocuronium and vecuronium seems primarily to be due to a higher rate of (initial) plasma clearance.[32,33] The recovery index of rapacuronium is similar to that of atracurium and vecuronium.

In patients with end-stage renal failure and liver cirrhosis (Child Pugh score 7 to 10), the clinical duration of a single dose of rapacuronium 1.5 mg/kg is not prolonged.[14,30] Clinical duration and time to a TOF ratio of 0.7 did not significantly differ between elderly patients and adults.[29] In infants and children, however, recovery from the same doses of rapacuronium seemed to be about 2 to 2.5 times faster than in adults (table I).[29,34]

1.1.3 Early Versus Late Reversal of Block

In the cat, the administration of neostigmine 1 minute after a rapacuronium dose of 3 x ED_{90} significantly decreased reversal times.[35] This concept of early reversal was also successful in a phase II clinical study using rapacuronium 1.3 mg/kg in which the time to a TOF ratio of 0.20 (where diaphragmatic breathing is expected to be reasonably restored,[36] for example, in the case of an unexpectedly difficult intubation) was significantly shortened by early reversal compared with spontaneous recovery (mean time = 6.6 *vs* 12.0 minutes).[15] In addition, the time to 90% twitch recovery did not differ between patients receiving rapacuronium 1.3 mg/kg reversed with neostigmine after 2 minutes and those receiving succinylcholine (mean time = 10.6 *vs* 11.6 minutes).[15]

Table I. Spontaneous recovery from neuromuscular block following a single, intravenous dose of rapacuronium bromide. All times are from end of drug administration and all end-point values are means. Anaesthesia was induced with thiopental alone[34], or supplemented by fentanyl.[29] In the study with paediatric patients, time to reappearance of T3 was determined by acceleromyography as an estimation of clinical duration.[34] Values for children presented in the table are weighted means calculated from raw data from the study of Meakin et al.[34] generously provided by Dr. Meakin upon request.

Reference	Population	Maintenance of anaesthesia	Dose (mg/kg)	Spontaneous recovery (min)	
				Clinical duration	Time to TOF ratio = 0.7
Kahwaji et al.[29]	Adults (<65 yr)	Propofol, N_2O,	0.5	6	12
		fentanyl	1.0	11	26
			1.5	14	30
			2.0	18	45
			2.5	25	57
	Elderly		0.5	10	20
	(>65 yr)		1.0	13	32
			1.5	17	36
			2.0	23	56
			2.5	33	70
Meakin et al. [34]	Infants (<1 yr)	N_2O, alfentanil	0.5	2.9	6.3
			1.0	6.5	11.9
			1.5	8.9	16.8
			2.0	10.5	20.9
	Children		1.0	4.8	10.7
	(1-12 yr)		1.5	7.2	15.5
			2.0	8.3	17.2
			2.5	10.3	22.2

T3 = reappearance of the third response to TOF stimulation; **TOF** = train of four ratio at the thumb.

This original concept of early or escape reversal of small doses of rapacuronium (<1.5 × ED_{90}) is based on 2 considerations: (i) the reduction of the gap between the very short duration of action of succinylcholine (<8 minutes) and the short duration of action of rapacuronium; and (ii) the time from administration of neostigmine until its peak effect (i.e. 10 minutes).

More recent publications have focused on the influence of the timing of administration of neostigmine on the recovery from neuromuscular block. After rapacuronium 1.5 or 2.0 mg/kg, the time until reaching a TOF ratio of 0.7 or 0.8 did not differ whether neostigmine was given at 2 minutes or at 25% recovery of the first response of the TOF (T1),[15-18] whereas the time to 25% and 75% twitch recovery was shortened by about 50% by early reversal.[16,17] These studies are in agreement with the prediction of computer simulations with rocuronium and rapacuronium showing that early reversal will not shorten the time until recovery to a TOF ratio >0.7.[15,37]

As with rapacuronium, neostigmine may also be administered as soon as there is no further need for relaxation after small doses (1.5 x ED_{95}) of rocuronium and vecuronium in adults and children, as the times to a TOF ratio of 0.7 will be similar whether neostigmine is given early during intense block or later when recovery is well established.[38] However, the times to a TOF ratio of 0.7 are considerably longer with rocuronium or vecuronium 1.5 x ED_{95} than with rapacuronium 1.5 mg/kg in adults (27.6 or 27.2 *vs* 18.1 minutes).[19,38]

In general, recovery times after rapacuronium 1.3 to 2.5 mg/kg are shortened by about 50% using reversal with neostigmine.[15,18,19] After rapacuronium 1.5 mg/kg, the time to 25% twitch recovery decreased from a mean of 16 minutes in control patients allowed to recover spontaneously to mean values of 8 to 10 minutes in patients given neostigmine 0.05 or 0.07 mg/kg at 2 or 5 minutes, respectively; the time to a TOF ratio of 0.7 decreased from 38 minutes to 17 to 19 minutes.[19] Recovery times were not different among the groups that received different doses and timing of administration of neostigmine[19] (fig. 1). After an initial dose of rapacuronium 1.5 mg/kg followed by maintenance doses of 0.5 mg/kg, the time to a TOF ratio of 0.7 was shorter after neostigmine 0.05 mg/kg (given 2 minutes after the final dose of rapacuronium) than after edrophonium 1 mg/kg [19.8 (SD 6.3) *vs* 35.1 (SD 11.4) minutes].[39]

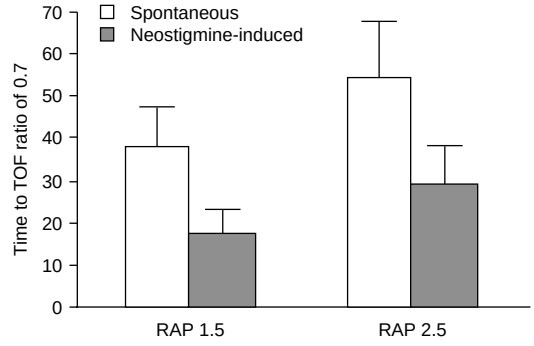

Fig. 1. Concept of early reversal. Spontaneous and neostigmine-induced (50 %g/kg at 2 or 5 minutes) recovery from neuromuscular block induced by rapacuronium bromide 1.5 (RAP 1.5) or 2.5 mg/kg (RAP 2.5).[19]

1.1.4 Cumulative Effects

In contrast to the fast recovery after a single intubating dose of rapacuronium, the administration of rapacuronium by repeat bolus doses or infusion was associated with slow spontaneous recovery.[32,40] After an initial dose of rapacuronium 1.5 mg/kg followed by three maintenance doses (0.5 mg/kg) the recovery time (T1-25% to TOF 0.8) was 72.4 (SD 16.5) minutes, which was shortened by neostigmine reversal (0.05 mg/kg) to 9.9 (SD 4.5) minutes.[40] After a 1-hour infusion, rapacuronium changed its time course characteristics gradually from that of a short-acting NMBA to that of a muscle relaxant with an intermediate duration. The spontaneous recovery from a twitch height of 25% to a TOF ratio of 0.7 was 32.5 minutes after a 1-hour infusion of rapacuronium (mean block of 83%) compared with 16.1 minutes after a single intubation dose of 1.3 mg/kg.[15,32]

These cumulative properties of rapacuronium are in part due to the action of its 3-desacetyl me-

tabolite.[33] This metabolite, however, has no influence upon the duration of action after a single dose of rapacuronium.[33]

1.1.5 Intubating Conditions Provided

In a phase II clinical study, intubating conditions 60 seconds after the administration of rapacuronium 1.3 mg/kg were similar to those after succinylcholine 1 mg/kg.[15] However, intubation was performed about 5 to 10 minutes after induction of anaesthesia, that is, under conditions that are quite different from the clinical practice of rapid-sequence induction.[15]

In pharmacodynamic studies of neuromuscular blocking agents, intubating conditions are now most frequently evaluated according to the guidelines for good clinical research practice.[41] These guidelines were used in 4 intubating studies with rapacuronium[42-45] and a comparable scoring system was applied in 2 other studies.[29,34] Good and excellent intubating conditions are considered to be clinically acceptable.[41]

Intubating Conditions in Elective Cases

A range of different doses of rapacuronium has been evaluated for rapid tracheal intubation in paediatric, adult and elderly patients undergoing elective surgery.[29,34,42,44] In all of these studies neuromuscular monitoring was applied in an uncalibrated fashion[34] or using only a short stabilisation period (i.e. less than 3 minutes).[29,42,44] These studies may therefore be considered to reflect the normal clinical practice of administering an NMBA soon after induction of anaesthesia.

Fleming et al.[44] reported clinically acceptable (good or excellent) intubating conditions in 87% of patients with rapacuronium 1.5 mg/kg and in 95% of patients with succinylcholine 60 seconds after induction of anaesthesia with fentanyl and propofol ($p < 0.05$). In contrast, at 60 seconds, Kawhaji et al. observed acceptable intubating conditions only in 68% of adult patients given rapacuronium 1.5 mg/kg compared with 90 and 100% of patients after doses of 2.0 and 2.5 mg/kg.[29] In the elderly, however, the 1.5 mg/kg dose provided clinically acceptable intubating conditions in 100% at 60 seconds.[29] In a small study with patients undergoing elective Caesarean section, intubating conditions after rapacuronium 2.5 mg/kg were similar to those after succinylcholine 1.5 mg/kg.[42] In children (1 to 12 years) intubating conditions at 60 seconds were clinically acceptable after rapacuronium doses of 2.0 mg/kg or more, and in infants (<1 year) after doses of 1.5 mg/kg or more.[34]

Intubating Conditions During a Rapid-Sequence Induction (RSI)

Rapacuronium at doses of 1.5, 2.0 and 2.5 mg/kg has been evaluated for use in rapid sequence induction (RSI) in 2 large multi-centre studies (335 and 600 patients, respectively).[43,45] The overall frequency of acceptable (good and excellent) intubating conditions was 89.4% after rapacuronium 1.5 mg/kg and 97.4% after succinylcholine 1 mg/kg ($p < 0.001$). Neither anaesthetic technique (thiopental and fentanyl *vs* propofol and alfentanil) nor patient group (obese patients *vs* normal-weight patients) had an influence on intubating conditions.[45]

On the basis of the results of that study,[45] rapacuronium 2.0 or 2.5 mg/kg was compared to succinylcholine 1 mg/kg during RSI with thiopental and fentanyl.[43] As equivalence was not expected, this study was designed to prove that rapacuronium is not inferior to a standard dose of succinylcholine.[43] Intubating conditions were clinically acceptable in 91.8% of patients receiving succinylcholine, and in 84.1 and 87.6% of patients receiving rapacuronium 2.0 and 2.5 mg/kg, respectively. The estimated difference [and the upper limit of the one-sided 97.5% confidence interval (CI)] between succinylcholine and rapacuronium 2.0 mg/kg was 7.8 (14.4) %, and that between succinylcholine and rapacuronium 2.5 mg/kg was 4.0 (10.2) %, that is, the upper limit of the one-sided CI exceeded the predefined 10% difference in both cases. Hence, non-inferiority could not be proven for rapacuronium 2.0 and 2.5 mg/kg when compared with succinylcholine.[43] However, the incidence of adverse effects with rapacuronium increased in a dose-related manner, which may limit the use of rapacuronium for RSI. In particular, the

incidence of pulmonary adverse effects (mainly short-lasting bronchospasm) of 18.5% after rapacuronium 2.5 mg/kg may be considered unacceptable.[43]

1.2 Adverse Effects

1.2.1 Cardiovascular

Rapacuronium was shown to cause a moderate decrease in blood pressure and a concomitant increase in heart rate in animals and, in an early clinical study, in humans.[22,35] In contrast to rapacuronium, vecuronium has no and rocuronium only mild, cardiovascular adverse effects. There is evidence that the rate of cardiovascular adverse effects of aminosteroidal NMDAs increases with decreasing potency because of vagolytic effects, calcium channel blocking properties and probably non-immunological histamine release.[35,46,47]

In cats, the ratio between the rapacuronium dose required for vagal and that for neuromuscular block was approximately 3, which is markedly less than that for vecuronium and similar to that for pancuronium.[35] In contrast to pancuronium, however, rapacuronium does not inhibit noradrenaline re-uptake,[35] but may increase the release of norepinephrine from cardiac tissue by antagonistic action at cardiac M_2 muscarinic receptors.[48] The direct vasodilator action of rapacuronium is 20 to 50 times greater than that of vecuronium.[35,47] This action may induce arterial hypotension, but it may also increase blood flow to skeletal muscle and contribute to the rapid onset of action of rapacuronium. Rapacuronium 2 to 3 mg/kg led to an increase in plasma histamine levels (≥1.0 μg/L).[49] However, changes in heart rate and blood pressure following rapid (i.e. within 5 seconds) injection of rapacuronium 1 to 3 mg/kg did not correlate with plasma histamine levels.[49]

The cardiovascular adverse effects of rapacuronium have been studied under conditions of a constant plane of anaesthesia without any stimulation as well as during rapid-sequence induction.

During isoflurane nitrous oxide anaesthesia without any noxious stimuli, heart rate increased to an average of 10, 15 and 18% above baseline after rapacuronium 1.0, 2.0 and 3.0 mg/kg, respectively, in American Society of Anesthesiologists' (ASA) class I and II patients. Systolic and diastolic blood pressure decreased by 9 and 19%, respectively, after rapacuronium 3.0 mg/kg.[50] More pronounced haemodynamic changes may be expected in patients with cardiovascular disease. McCourt et al.[51] studied the haemodynamic effects of rapacuronium 1.5 mg/kg in 56 patients with good left ventricular function, who underwent coronary artery bypass graft or valve replacement surgery, using a fentanyl-based anaesthetic technique. Rapacuronium was associated with a significant increase in heart rate (17%) and cardiac index (15%) as well as a significant decrease in mean arterial blood pressure (MAP; 11%) and systemic vascular resistance (18%), whereas vecuronium 0.1 mg/kg and placebo were associated with significant decreases in heart rate only.

The heart rate and blood pressure responses to intubation following a rapid-sequence induction are determined by several factors. Laryngoscopy and tracheal intubation are strong noxious stimuli. In addition, the sympathoadrenal response to intubation is influenced by the anaesthetic technique used for induction (premedication, choice and dose of intravenous anaesthetic and opioid, time point of administration, choice and dose of the NMBA).

After RSI, the maximum increase in heart rate was higher after rapacuronium 1.5, 2.0 or 2.5 mg/kg than after succinylcholine 1.0 mg/kg (fig. 2).[43,45] In patients who were given rapacuronium 1.5 mg/kg, heart rate increased by an average of 11% after induction with alfentanil and propofol, and by an average of 36% after induction with fentanyl plus thiopental.[45] The increase in heart rate after rapacuronium during tracheal intubation seems to be dose-dependent. Significant increases in heart rate (i.e. >30% *vs* baseline) were observed more commonly after rapacuronium 2.5 mg/kg than after rapacuronium 1.5 mg/kg, succinylcholine or mivacurium (26 *vs* <10%).[13] In patients scheduled for elective Caesarean section the maximum increase in heart rate following intubation

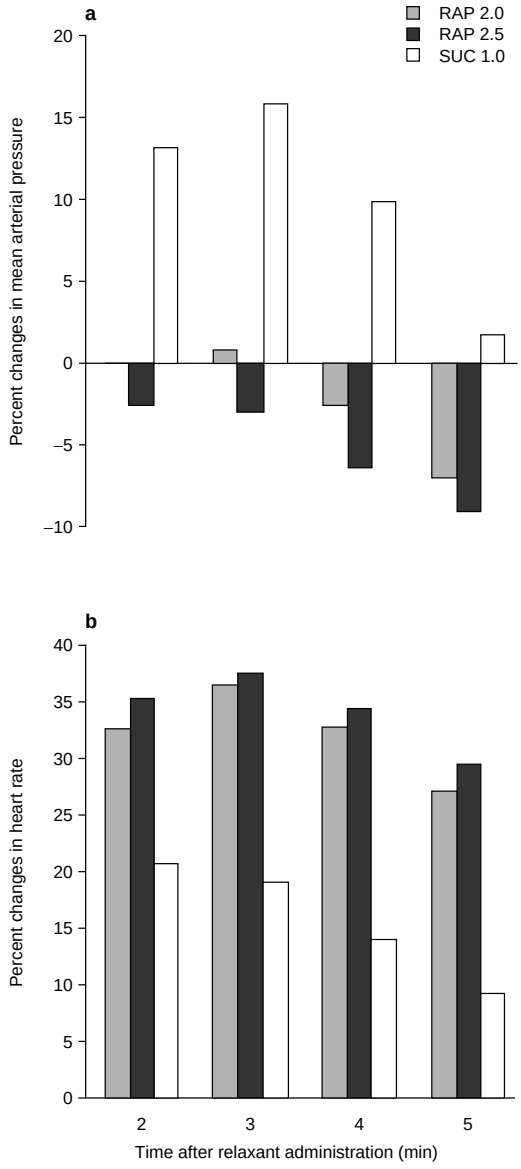

Fig. 2. Percent changes compared to baseline in (**a**) mean arterial pressure and (**b**) heart rate during rapid-sequence induction with rapacuronium (RAP) 2.0 and 2.5 mg/kg, or succinylcholine (SUC) 1.0 mg/kg. Intubation was performed 1 minute after relaxant administration. Both parameters responded significantly diferently after succinylcholine compared to both doses of rapacuronium (ANOVA for repeated meausrements; $p < 0.01$ for the interaction term between treatment group and time of assessment).[43]

was 48% with rapacuronium 2.5 mg/kg compared with 19% with succinylcholine 1.5 mg/kg.[42]

1.2.2 Pulmonary

The overall incidence of bronchospasm was 3.4% in 1956 patients treated with rapacuronium.[10] However, a higher incidence of pulmonary adverse effects (bronchospasm or transient increase in airway pressure during controlled ventilation without wheezing on auscultation) has been observed after administration of rapacuronium under conditions of a RSI. Pulmonary adverse effects were observed in 10.7, 13 and 18.5% of patients after rapacuronium 1.5, 2.0 and 2.5 mg/kg, respectively, and in 3.5 to 4.1% of patients after succinylcholine.[43,45]

There is some evidence that bronchospasm after rapacuronium occurs more frequently in patients with a history of bronchial hyperreactivity and/or smoking.[43] The occurrence of bronchospasm did not significantly correlate with increased histamine levels after large doses of rapacuronium.[49] However, a selective inhibition of M_2 muscarinic receptors of the smooth muscles of airways might be responsible for short-lasting bronchospasm after administration of rapacuronium.[52] In addition, tracheal intubation is more likely to trigger a bronchospasm than insertion of a laryngeal mask.[53]

1.3 Pharmacokinetics and Pharmacokinetic/Pharmacodynamic Relationship

The pharmacokinetics of rapacuronium have been studied using the classical kinetic analysis[22,30,32,33] and the population analysis (NONMEM).[14,39,54] With one exception,[39] all these pharmacokinetic studies available revealed a high plasma clearance ranging from 5.3 to 11.1 ml/kg/min, which is higher than that of other NMBAs except mivacurium.[55-58] The volume of distribution at steady state ranges from 193 to 457 ml/kg, and the mean residence time (MRT) between 28 and 58 minutes.[14,22,30,32,54] In contrast to these results, Mills[39] reported lower values for clearance (4.4 and 2.7 ml/kg/min in males and females, respectively), and a very large volume of

distribution (V_3 was 9900 ml/kg). The MRT calculated from these values would approximate 2500 minutes. The authors did not discuss their results in the light of previous pharmacokinetic studies of rapacuronium.[39] Because of the relatively short sampling period (i.e. 4 samples between 120 and 360 minutes) and the lack of concentration-time data, a final conclusion cannot be drawn.

Rapacuronium is mainly eliminated by the liver. The fraction of a given dose of rapacuronium recovered from the urine of patients with normal renal function was 6.2 to 22%.[14,22,33] The 3-desacetyl metabolite, ORG-9488, is the primary metabolite of rapacuronium. The potency of ORG-9488 was estimated to be 2.5 times greater than that of rapacuronium [modelled concentration in the biophase at 50% effect (EC_{50}) 1.83 *vs* 4.7 μg/ml].[33] Compared to its parent compound, a higher proportion of a given dose of ORG-9488 was recovered from urine (6.2 *vs* 51.9 or 53.5%).[33] The clearance of ORG-9488 is markedly lower than that of rapacuronium in adults with normal renal function (7.28 *vs* 1.28 or 1.06 ml/kg/min), and it is 85% lower in patients with renal failure compared with healthy volunteers.[14,33] The lower clearance of ORG-9488 may gradually prolong the duration of action during maintenance with rapacuronium, particularly in patients with renal failure.[14]

The rate constant of transport between the plasma and the biophase (k_{e0}) of rapacuronium is higher than that of rocuronium and vecuronium at the adductor pollicis muscle (0.405 or 0.449 *vs* 0.17 and 0.12 min^{-1}).[27,33,59,60] In addition, the k_{e0} of rapacuronium is larger at the laryngeal adductor muscles than at the adductor pollicis muscle.[27] A larger k_{e0} indicates a more rapid establishment of effect, that is, neuromuscular block.

1.4 Clinical Use

Rapacuronium 1.5mg/kg is a short-acting nondepolarising NMBA that provides clinically acceptable intubating conditions within 60 to 90 seconds in the majority of adult patients. The duration of action of rapacuronium can be shortened by about 50% by the administration of an anticholinesterase, whereas the time until a TOF ratio of ≥0.70 is reached does not depend on whether rapacuronium is reversed early (i.e. at 2 or 5 minutes) or at 25% recovery of the first response of the TOF (T1).

Under conditions of elective anaesthesia the use of rapacuronium is associated with a low incidence of adverse effects (tachycardia 3.2%, mild hypotension 5.2%, and transient bronchospasm 3.2%).[10,61] The adverse effects are considered to be dose-related, and, in particular, pulmonary adverse effects were observed more frequently (in 10.7 to 18.5% of patients after rapacuronium 1.5 to 2.5mg/kg) under the conditions of rapid-sequence induction.[43,45]

The short duration of action of rapacuronium results from its rapid initial clearance, whereas the fast termination of action of succinylcholine and mivacurium is dependent on a normal function of pseudocholinesterase. Therefore, rapacuronium 1.5 mg/kg in adult and elderly patients and rapacuronium 2.0 to 2.5 mg/kg in paediatric patients is a suitable alternative to mivacurium and succinylcholine for short surgical procedures (<30 minutes), particularly in ambulatory anaesthesia. In a rapid-sequence setting, however, succinylcholine or rocuronium rather than rapacuronium should be considered as the preferred NMBA.

(See Addendum at end of article)

2. Rocuronium Bromide

Rocuronium (ORG-9426), is a monoquaternary aminosteroidal NMBA. Rocuronium differs structurally from vecuronium in 4 positions, that is, it has a 2β-morpholino group, a 3α-hydroxy group and a 16-pyrrolidino function attached to a 16-N-allyl group. Except for the rapid onset of neuromuscular block, the pharmacodynamics of rocuronium ≥1.0 mg/kg resemble those of vecuronium. The rapid onset makes rocuronium a candidate for RSI in nonfasted patients. Rocuronium is supplied in aqueous solution nd it is incompatible with thiopental and may precipitate in an intravenous line.

2.1 Neuromuscular Effects

2.1.1 Potency and Onset of Block

Rocuronium is a neuromuscular blocking agent with a relatively low potency, that is, approximately one sixth that of vecuronium. The single bolus dose of rocuronium producing a 95% neuromuscular block at the adductor pollicis (ED_{95}) is approximately 0.3 mg/kg in adults[62-65] and 0.35 to 0.4 mg/kg in children.[66,67] After doses of 0.6 mg/kg (2 x ED_{95}), maximal block at the thumb occurs already within 1 to 2 minutes.[11,64,68,69] At the adductor pollicis muscle the onset of block after rocuronium is about 2.5 times faster than after an equipotent dose of vecuronium and atracurium.[70] Similar to vecuronium, the onset of action of small doses of rocuronium (0.4 and 0.5 mg/kg) at the laryngeal adductor muscles is faster than at the adductor pollicis muscle, but the block is less intense.[71,72] However, even after the administration of higher doses of rocuronium (0.8 and 1.2 mg/kg), the onset of action at the laryngeal adductor muscles is slower than after succinylcholine (96 and 54 *vs* 34 seconds).[71] In a recent study, no difference in the onset times of rocuronium at laryngeal compared to peripheral muscles could be demonstrated.[73] A high dose of vecuronium (0.3 to 0.4 mg/kg, i.e. 6 to 8 x ED_{95})[74,75] results in onset times similar to those of a 2 x ED_{95} dose of rocuronium, but such onset times are obtained at the cost of a much longer duration of action (208 and 40 minutes for vecuronium and rocuronium, respectively).[74,75]

2.1.2 Duration of Block

After spontaneous recovery, the mean clinical duration, mean recovery index and mean recovery to TOF 0.7 of rocuronium 0.6 mg/kg are 24 to 43, 9 to 14, and 47 to 72 minutes, respectively.[64,76-80] The duration of equipotent doses (1.5 to 2 x ED_{95}) of rocuronium and vecuronium is similar.[38,80] The mean infusion rate for maintenance of a 95% neuromuscular block was 10 and 6 μg/kg/min during intravenous and inhalational anaesthesia, respectively.[81-84] The recovery index after an infusion of rocuronium under intravenous anaesthesia averaged 20 minutes,[83] whereas it was 26 minutes after a 2-hour infusion of vecuronium under a similar anaesthesia. During surgery, a neuromuscular block maintained with rocuronium appears to have little advantage over one maintained with vecuronium.[83]

The duration of block of an equipotent single dose of rocuronium may be longer and more variable in patients with liver and kidney failure and elderly patients when compared to adults[85-88] and in infants when compared to children.[67]

2.1.3 Reversal of a Block

A rocuronium-induced neuromuscular block can be antagonised safely and rapidly using neostigmine 0.035 mg/kg at recovery of T1 = 10% or greater, although reversal may be slightly more rapid when carried out at a T1 = 25%.[89] Using neostigmine 0.07 mg/kg, it has been suggested that reversal of an intense rocuronium- or vecuronium-induced block does not have to be delayed until return of appreciable neuromuscular function has been demonstrated. After the same dose of neostigmine, the rate of recovery of neuromuscular function was similar for rocuronium and vecuronium.[38]

2.1.4 Cumulative Effects

The clinical duration of the first maintenance doses of rocuronium 0.1, 0.15 and 0.2 mg/kg administered upon return of T1 to 25% of control were 11.0 ± 1.0, 18.3 ± 1.6 and 28.1 ± 6.3 minutes, respectively (mean ± SEM).[62] In the case of repeated administration, there was no significant increase in the clinical duration of successive doses. After an initial dose of rocuronium 0.6mg/kg, no overt cumulative effects were observed after up to 6 doses of 0.225 mg/kg.[90] In contrast, the duration of vecuronium (0.04 mg/kg, 0.8 x ED_{95}) was 39% longer after the fourth than after the first maintenance dose.[91] In patients in intensive care units (ICUs), effect-controlled administration of rocuronium (median duration 39 hours, total dose 938mg) resulted in moderately prolonged recovery compared with surgical patients. Interindividual and time-related differences in the dose requirement for rocuronium in these patients make the use of neuromuscular monitoring mandatory.[92]

2.1.5 Intubating Conditions Provided

Intubating Conditions in Elective Cases

The intubating conditions provided by rocuronium have been assessed in a large number of studies. Under conditions of elective anaesthesia and using various anaesthetic techniques, rocuronium 0.6 mg/kg facilitated tracheal intubation under good or excellent conditions within 60 to 90 seconds in most adult[11,68,93-97] and paediatric patients.[98-100] Lower doses of rocuronium (0.03 to 1.5 x ED_{95}) allow tracheal intubation under clinically acceptable conditions within 60 to 180 seconds.[101-104]

Intubating Conditions During a RSI

Because of its rapid onset of action, rocuronium has been considered to be a suitable alternative to succinylcholine for rapid tracheal intubation in elective and in emergency cases, although even at large doses its onset of action at the laryngeal muscles is slower than that of succinylcholine.[71] Therefore, with rocuronium 0.6 mg/kg, an appropriate anaesthetic technique, in particular the use of opioids, may be essential in order to achieve smooth intubating conditions within 60 seconds at a similar frequency to that with succinylcholine.[95] When anaesthesia is induced with thiopental alone in unpremedicated adult patients, intubating conditions produced by rocuronium 0.6 mg/kg are in fact less favourable than those produced by succinylcholine.[105] In addition, there is good evidence that satisfactory intubating conditions after rocuronium 0.6 mg/kg can be achieved faster after propofol or ketamine than after thiopental or etomidate,[106-109] although others found that the intravenous anaesthetic had no influence of on intubating conditions.[95] After rocuronium 0.6 mg/kg satisfactory intubating conditions in 90% of patients can be expected within 61 and 101 seconds using propofol 2.5 mg/kg and thiopental 5 mg/kg, respectively (fig. 3).[107]

Even so, the majority of anaesthesiologists do not seem to use opioids (not even in small doses) as part of RSI (97% according to a recent questionnaire in the UK).[110] In the case of a relatively light anaesthesia, larger doses of rocuronium may be necessary in order to produce smooth intubating conditions within 60 seconds. Rocuronium ≥1 mg/kg should be administered to facilitate tracheal intubation in a RSI setting, that is, using a relatively light anaesthesia with no or only low doses of an opioid (e.g. fentanyl 1 to 2 μg/kg) in adults[111-117] and in children.[118] In 2 recent studies a probability-based approach was used to predict doses of rocuronium giving 90% and 95% probability of successful intubation within 60 seconds.[115,116] In the study by Kirkegaard-Nielsen et al.,[116] patients were premedicated with intravenous midazolam 2mg, and anaesthesia was induced with fentanyl 2 μg/kg and propofol 2 mg/kg followed randomly by rocuronium 0.0, 0.4, 0.8 or 1.2 mg/kg. The dose versus fraction of patients with successful intubation was analysed by logistic regression. In that study, rocuronium 1.04 (95% confidence limits 0.76 to 1.36) mg/kg was defined as the dose that provides a 95% probability of intubation under perfect or acceptable conditions at 60 seconds.[116] Heier et al.[115] calculated that a dose of 2 mg/kg of rocuronium results in a 90% probability of achieving perfect intubating conditions winthin 60 seconds following induction of anaesthesia with

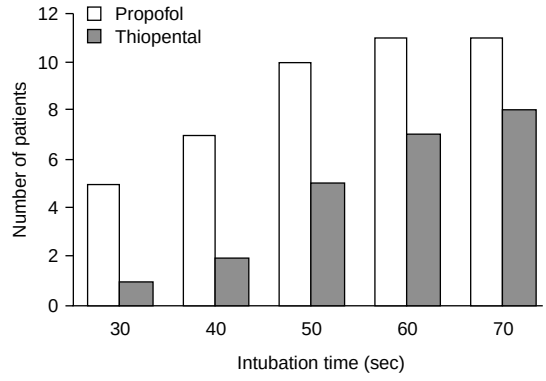

Fig. 3. The number of patients with satisfactory (good and excellent) intubating conditions after rapid sequence induction of anaesthesia with either propofol 2.5 mg/kg or thiopental 5 mg/kg and rocuronium bromide 0.6 mg/kg in patients undergoing elective surgery. Fentanyl 1 %g/kg was administered 3 minutes before induction (reproduced from Dobson et al.,[107] with permission).

thiopental 4 mg/kg and alfentanil 10 μg/kg.[115] Doses of rocuronium up to 2 mg/kg were administered in that study without significant cardiovascular adverse effects.[115] Doses of rocuronium up to 2 mg/kg were administered that study without significant cardiovascular adverse effects.[115] Intubating conditions provided by rocuronium in non-fasted patients in emergency situations have been evaluated in only a small number of studies so far (table II).[111,118-121]

Whether rocuronium can replace succinylcholine in RSI is a matter of debate, which focuses on the long duration of the required rocuronium dose.[114,122-125] The main argument in favour of succinylcholine is its shorter duration in the situation of unanticipated difficult intubation, whereas the main argument in favour of rocuronium is the avoidance of the many adverse effects of succinylcholine. But even the very short duration of action of succinylcholine may be too long to prevent desaturation in a 'cannot-ventilate, cannot intubate' situation,[126] and immediate airway management, for example, insertion of a laryngeal mask airway, will be mandatory to save the patient's life. Therefore, it has been suggested that the issue of safe conduct for induction of anaesthesia in a patient with an increased risk of pulmonary aspiration should not only be a discussion of rocuronium *vs* succinylcholine. In each individual patient, it is up to the anaesthesiologist to judge which of the alternatives represents the safest method.[124]

2.2 Adverse Effects

2.2.1 Cardiovascular

In general, rocuronium has minimal cardiovascular effects.[127] The autonomic margin of safety for vagal blockade is 5 for rocuronium and 41 for vecuronium, and for ganglion block it is 89 and >100, respectively.[128] A clinically significant cardiovascular effect was not observed after doses up to 1.2 mg/kg.[129-132] After RSI with thiopental alone changes in heart rate and blood pressure were not related to rocuronium 0.4 to 2.0 mg/kg.[115] Rocuronium 2 x ED_{95} administered to patients paralysed with vecuronium resulted in a limited increase in heart rate from 67 to 72 beats/min, which is most probably due to vagolytic effects; there was no change in MAP.[133] In elderly patients with left

Table II. Intubating conditions under rapid sequence induction in non-fasted patients for emergency procedures following various doses of rocuronium under various anesthetics

Reference	Anaesthesia	No. of pts	NMBA dose (mg/kg)	Time to intubation (s) mean ± sd	Acceptable intubating conditions (% of pts)
Mazurek et al.[118]	TPL	13	1.2	42 ±3[a]	92 [1 pt fair[b]]
		13	1.5 SUC	40 ± 4[c]	92 [1 pt fair[d]]
Abouleish et al.[119]	TPL	40	0.6	79.3 ± 2.9[e]	90 [5 pts required 2nd dose (0.12 mg/kg)]
Hanowell et al.[120]	ETO	15	0.9	84 ± 33[f]	100
		15	1.2	84 ± 33[f]	100
Sakles et al.[121]	ETO/BENZO/NONE	34	1.0 ± 0.2[g]	45 ± 15.5 (20-90)[h] range	100
	ETO/BENZO/NONE	24	1.0 ± 0.2[g]	46-60	100

a Range 33-48 seconds.

b Moving vocal cords and poor jaw relaxation.

c Range 36-45 seconds.

d Moving vocal cords and severe coughing/bucking.

e Mean ± standard error.

f Time from injection of induction drugs to confirmation of intubation by capnometry.

g Range 0.6-1.1 mg/kg.

h Figures in brackets indiate range.

Benzo = benzodiazipime; **ETO** = etomidate; **None** = on induction agent administered; **sd** = standard deviation; **SUC** = succinylcholine; **TPL** = thiopental.

ventricular dysfunction and in ASA 3 and 4 patients scheduled for cardiac surgery, rocuronium ≤0.9 mg/kg produced only minor haemodynamic changes.[134,135] The haemodynamic effects of rocuronium 2 to 3 x ED_{95} were compared with those of vecuronium, using different anaesthetic regimens. The results were either no relevant haemodynamic differences[131] or a decrease in heart rate and MAP following vecuronium, and an increase in heart rate following rocuronium.[132] Rocuronium was associated with a lower requirement for vasopressors[136] and may attenuate the fall in MAP in absence of surgical stimulation.[132]

In outpatients undergoing laparoscopic gynaecological procedures, episodes of profound bradycardia (heart rate <30 beats/min) occurred less frequently after rocuronium 20mg than after vecuronium 4mg (0% *vs* 5%).[137] The margin of safety for histamine release is high for both rocuronium and vecuronium.[128] There was no significant histamine release after doses of rocuronium ≤1.2 mg/kg.[129,138] Recently, 3 histaminoid reactions have been suggested to be associated with rocuronium.[139]

2.2.2 Pain on Injection

The incidence of withdrawal movements of the limbs after administration of rocuronium is variable but high; however, none of the anaesthetised patients complained of pain or recalled the induction of anaesthesia.[140] In paediatric and adolescent patients, who were probably under light planes of anaesthesia, the incidence of pain was 84%.[140] In awake patients, the incidence was 47%,[141] with 12% describing it as severe.[142] In another study, 8 out of 10 awake patients receiving rocuronium 10mg complained of severe pain, which lasted for approximately 10 to 20 seconds.[143] In awake patients receiving rocuronium 0.6 mg/kg followed by induction of anaesthesia 30 seconds later, the incidence of pain was 77%.[144]

Apart from 1 study with low levels of anaesthesia at injection of rocuronium, movements were always limited to the extremity where the injection was given.[140,141] The mechanism that is responsible for the withdrawal reaction is unknown, but does not seem to be due to the low pH of 4 since NaCl 0.9% with a pH of 4 was not associated with pain.[143] Another explanation may be the local release of mediators. Both lidocaine (10mg and, more effectively, 30mg) 10 seconds and fentanyl (2 μg/kg) 45 second before the administration of rocuronium significantly reduced the incidence and severity of pain or the incidence of spontaneous movements associated with rocuronium administration.[144,145]

The withdrawal of limbs in anaesthetised patients may be sufficient to displace the venous catheter. There is, however, no need to administer rocuronium to awake patients, as rapid tracheal intubation can be achieved by administering rocuronium without applying the priming and timing principles, both of which may compromise neuromuscular transmission and, consequently, lung function and protective airway reflexes.[6,146,147]

2.3 Pharmacokinetics

The pharmacokinetics of rocuronium resemble those of vecuronium. However, in contrast to vecuronium, rocuronium lacks an ester group at position 3 of the steroid skeleton. Consequently, hydrolysis, which in the case of vecuronium results in the pharmacologically active 3-OH metabolite, cannot occur with rocuronium. So far, metabolites of rocuronium have not been shown in humans.[55,148] Rocuronium is mainly eliminated by the liver, and 33% of a single dose of 1.0 mg/kg was recovered from urine within 24 hours.[55]

Pharmacokinetic analysis in patients receiving rocuronium 2 x ED_{95} under different anaesthetic regimens revealed a volume of distribution of approximately 200 ml/kg, a plasma clearance of 4 to 5 mg/kg/min and a MRT of 45 to 65 minutes.[148-150] Clearance of rocuronium may be reduced and MRT may be prolonged in the presence of hepatic and renal failure.[88,150,151] After prolonged administration of rocuronium in patients in ICU (median duration 39 hours, total dose 938mg) volume of distribution, MRT, and elimination half-life differed from data obtained after rocuronium infusion of moderate duration in surgical patients; volume

of distribution was increased (769 ml/kg), and MRT and elimination half-life were prolonged (263 and 337 minutes, respectively).[92]

2.4 Clinical Use

Rocuronium 0.6 mg/kg (2 x ED_{95}) is an intermediate-acting nondepolarising NMBA that provides clinically acceptable intubating conditions within 60 to 90 seconds under various anaesthetic conditions in children, adults and elderly patients. The main advantage rocuronium has over vecuronium is the rapid onset of neuromuscular block, which allows tracheal intubation under clinically acceptable conditions 60 to 180 seconds after low doses of rocuronium (1 to 1.5 x ED_{95}).[101-104,152] Using an anaesthetic technique with propofol and remifentanil (0.5 μg/kg/min) intubating conditions were good or excellent at 180 seconds in all but one patient given rocuronium 0.3, 0.45 or 0.6 mg/kg, but in only 60% of patients receiving no muscle relaxant.[104] The clinical duration and time to TOF 0.8 after rocuronium 0.3 mg/kg was 16 and 35 minutes, respectively.[104] Low doses of rocuronium may, therefore, be suitable to facilitate tracheal intubation for short procedures.

Rocuronium, if administered in large doses (≥1 mg/kg), seems to be a drug that can replace succinylcholine in a rapid-sequence setting provided that the airway has been carefully assessed and no difficulty is anticipated.[111,114] Although difficulty in obtaining a satisfactory view at direct laryngoscopy, cannot be predicted with 100% accuracy by any scoring system.[123] The cardiovascular response to intubation under light thiopental anaesthesia was not dependent on the dose of rocuronium which ranged from 0.4 to 2 mg/kg, that is, up to approximately 7 x ED_{95}.[115] This is in contrast to rapacuronium, which is associated with dose-dependent respiratory adverse effects that limit the use of doses higher than 1.5 x ED_{95} and hence the use of rapacuronium in a rapid-sequence setting.[43] Compared to the use of rocuronium in doses ≤2 x ED_{95} in combination with an appropriate induction technique (i.e. including an opioid) or the use of larger doses of rocuronium under a relatively light anaesthesia, the timing and priming principles offer no advantage with respect to rapid tracheal intubation, but may potentially be harmful to the patient.[6,146,147] Finally, rocuronium administered immediately before an induction agent may be the best nondepolarising NMBA to reduce fasciculations and muscle pain induced by succinylcholine.[153]

3. Cisatracurium Besilate

Cisatracurium is a benzylisochinolinium nondepolarising NMBA. Unlike atracurium, which is a mixture of 10 stereoisomers, cistracurium is a single isomer, that is, 1R-cis, 1'R-cis isomer; atracurium consists of about 15% cistracurium. Cisatracurium has a similar neuromuscular blocking profile to atracurium, except that the onset of action of cisatracurium is somewhat slower and its propensity to release histamine is significantly reduced.

3.1 Neuromuscular Effects

3.1.1 Potency and Onset of Block

A comparison of the onset properties and the potency of different stereoisomers of atracurium supports the hypothesis that onset of neuromuscular block is inversely related to the potency of the compound.[154] The neuromuscular potency of cisatracurium is approximately 4 times that of atracurium and its ED_{95} is 0.05 mg/kg compared with 0.2 to 0.25 mg/kg for its parent compound. Thus, the onset was expected to be slower after cisatracurium than after atracurium. And in fact, after equipotent doses (2 x ED_{95}) the onset of maximum neuromuscular block was significantly slower with cisatracurium than with atracurium (5.2 ± 0.3 minutes *vs* 3.2 ± 0.3 minutes).[155] Further studies confirmed this finding.[156-158]

The slow onset properties may limit the use of cisatracurium in clinical practice. Therefore 2 different approaches have been proposed to decrease the onset time of cisatracurium: (i) increasing the size of the bolus dose; and (ii) applying the priming principle. Belmont et al.[155] demonstrated that increasing the dose of cisatracurium actually de-

creases its onset time; the onset time of 5.2 ± 0.3 minutes after cisatracurium 0.1 mg/kg (2 x ED_{95}) decreased to 2.7 ± 0.1 minutes after cisatracurium 0.2 mg/kg (4 x ED_{95}) and to 1.9 ± 0.1 minutes after a dose of 0.4 mg/kg (8 x ED_{95}). Whereas for most other NMBAs, 2 x ED_{95} of the compound is proposed as the intubating dose, 3 to 4 x ED_{95} (0.15 to 0.2 mg/kg) is recommended for cisatracurium.[159] The clinical value of the priming principle to decrease the onset time of cisatracurium was first investigated by Stevens et al.[160] They reported an onset time of 4.6 ± 1.4 minutes after a bolus dose of cisatracurium 0.1 mg/kg; a priming dose of 0.01 mg/kg followed by an intubating dose of cisatracurium 0.1 mg/kg 5 minutes later significantly shortened the onset time to 2.9 ± 0.8 minutes. Similar findings were recently presented by Pühringer et al.[161]

3.1.2 Duration of Neuromuscular Block

In comparative studies no difference in the duration of action between equipotent doses of cisatracurium and atracurium have been reported. Neuromuscular block induced by 2 x ED_{95} cisatracurium is characterised by an intermediate duration of action. Depending on the anaesthetic technique and the neuromuscular monitoring technique used, values between 44.8 minutes and 50 minutes were reported.[155,157,158] However, increasing the size of the cisatracurium bolus dose from 0.1 to 0.2 mg/kg, as recommended to facilitate endotracheal intubation, led to a increase in clinical duration to 68.3±2.4 minutes.[155] Thus, in this context the profile of the compound changes from an intermediate-acting NMBA to a long-acting one.[9]

3.1.3 Recovery from Neuromuscular Block

The spontaneous recovery from cisatracurium-induced neuromuscular block is unrelated to dose or duration of administration. The recovery indices for a T1 recovery from 25 to 75% and from 5 to 95% did not differ whether a bolus dose of cisatracurium 0.1, 0.2 or 0.4 mg/kg was given or whether the compound was administered by a continuous infusion (mean infusion time 109.2 minutes). The 25 to 75% and the 5 to 95% recovery intervals were 13 to 15 minutes and 30 to 33 minutes, respectively.[155]

Carroll et al.[157] compared the recovery characteristics of cisatracurium and atracurium. They reported that spontaneous and neostigmine-induced recovery from both compounds were comparable. After atracurium 0.5 mg/kg the 25 to 75% recovery interval (mean and range) was 12.0 (10.5 to 13.3) minutes; when neostigmine (0.05 mg/kg) was given at a T1-recovery of 10% this interval was reduced to 3.3 (21 to 6.2) minutes. After cisatracurium 0.1 mg/kg, these intervals were 13.5 (7.7 to 16.6) minutes and 3.4 (2.2 to 4.4) minutes and after cisatracurium 0.15 mg/kg the respective values were 12.4 (9.1 to 23.5) minutes and 3.2 (2.0 to 7.1) minutes.

3.1.4 Intubating Conditions

The intubating conditions provided by cisatracurium have been investigated in a limited number of studies.[162-164] At 2 minutes post administration, clinically acceptable (good or excellent) intubating conditions were achieved less frequently using cisatracurium 2 x ED_{95} than after equipotent doses of atracurium (67 *vs* 95%).[162] Therefore, larger doses of cisatracurium are recommended to facilitate tracheal intubation.[159,163] Two minutes after cisatracurium 3 x ED_{95} or 4 x ED_{95}, intubating conditions were clinically acceptable in 80 to 90% and in 97% of patients, respectively.[162,164] Whether modifications of the anaesthetic technique (use of propofol instead of thiopentone or addition of fast onset opioids such as remifentanil to the induction regimen) may improve intubating conditions 2 minutes after cisatracurium 2 x ED_{95} has not been assessed in comparative studies to date.

3.2 Adverse Effects

3.2.1 Cardiovascular

In clinically relevant doses, atracurium has no effect on autonomic ganglia and the haemodynamic aberrations observed after atracurium are mainly the result of the histamine-releasing properties of the compound.[165,166] In doses larger than 0.5 mg/kg, atracurium may cause histamine re-

lease, which can result in (facial) flushing and hypotension.[167-169] These effects are usually of short duration and related to the dose and the speed of injection. They can be prevented by the injection of divided doses, slow injection or premedication with histamine H_1 and histamine H_2 receptor blockers.[170] In healthy adults, the histamine releasing properties of atracurium are clinically insignificant, however, they may be disadvantageous in special patient populations such as cardiovascular, neurosurgical or ICU patients.

Cisatracurium is characterised by a remarkable haemodynamic stability; in doses up to 8 x ED_{95} it did not cause histamine release or clinically significant haemodynamic changes.[171-173] Moreover, like atracurium, cisatracurium has no effect on autonomic ganglia. This facilitates handling of the compound, as slow injection over a period of 30 to 60 seconds, divided doses or premedication with histamine H_1 or H_2 receptor blockers is not required, and, if need be, larger doses of cisatracurium can be administered without running the risk of histamine release or haemodynamic consequences.

3.2.2 Laudanosine

Laudanosine is the primary metabolite of atracurium and cisatracurium, and is formed by Hofmann elimination. It is a potent cerebral stimulant, which, unlike atracurium, freely crosses the blood-brain-barrier.[174] In addition, it also has cardiovascular effects. Unlike atracurium and cisatracurium, laudanosine is dependent on the liver and kidney for its elimination and accumulates in patients with impaired function of these organs.[175,176]

After the administration of atracurium, laudanosine concentrations up to 440 μg/L have been reported in cerebrospinal fluid of patients in ICU and, in patients undergoing cerebral aneurysm clipping, values up to 570 μg/L have been measured.[174,177] Laudanosine at these concentrations has been suspected to contribute to an increased incidence of seizures.[178] Following the administration of cisatracurium, the measured plasma laudanosine concentrations are 5 to 10 times lower than after atracurium; hence, laudanosine accumulation and cerebrospinal fluid passage are unlikely to occur with the use of cisatracurium in clinical practice.[171,179,180]

3.3 Pharmacokinetics

Like atracurium, cisatracurium undergoes Hofmann elimination to yield laudanosine and a monoquaternary acrylate metabolite. The monoquaternary acrylate is then further hydrolysed to monoquaternary alcohol which again undergoes Hofmann degradation to form laudanosine. Unlike atracurium, cisatracurium does not undergo hydrolysis by nonspecific plasma esterases.[58,181] Moreover, 23% of the drug is cleared by organ-dependent mechanisms, with renal elimination accounting for 16%.[58] In healthy adults, the clearance of cisatracurium 2 x ED_{95} ranges from 4.7 to 5.3 ml/kg/min.[179,180] This is comparable to values reported for atracurium (5.5 to 6.1 ml/kg/min), vecuronium (5.3 to 5.6 ml/kg/min) and rocuronium (2.9 to 5.0 ml/kg/min). The volume of distribution at steady state of cisatracurium in healthy adults ranges from 141 ± 34 to 190 ± 47 ml/kg and the elimination half-life ranges from 22 to 35 minutes compared with 21 minutes for atracurium.[171,182]

The peak plasma laudanosine concentration after administration of cisatracurium 0.1 mg/kg ranges from 20 to 38 mg/L in healthy patients compared to 190 to 233 mg/L after equipotent doses of atracurium.[182]

In patients with chronic renal failure the volume of distribution of cisatracurium was unchanged but clearance was reduced by 13%.[179] Clinical duration and recovery properties remained unchanged.[179] In patients with liver disease the volume of distribution of cisatracurium was increased by 21% and clearance by 16%, whereas the elimination half-life remained unchanged; onset of block was delayed but no alteration in the recovery profile was observed;[165,182,183] see also table III.

After continuous infusions of cisatracurium in patients in ICU, clearance and volume of distribution vlaues were increased, which may best be explained by the oedema found in these patients.[187] However, the fact that the elimination half-life was

unchanged (28 minutes) suggests that cisatracurium is noncumulative.[187]

3.4 Clinical Use

Compared to atracurium, cisatracurium is characterised by a remarkable haemodynamic stability and a significantly reduced laudanosine production. Like atracurium, cisatracurium undergoes Hofmann elimination. When administered in doses up to 3 x ED_{95} the compound has an intermediate duration of action. Recovery after cisatracurium-induced neuromuscular block is fast and predictable. However, the major weakness of this NMBA is its relatively slow onset of action. Especially after cisatracurium 2 x ED_{95}, techniques such as the priming principle or an induction regimen including propofol and fast onset opioids (alfentanil or remifentanil) are needed to ensure acceptable intubating conditions within 2 to 3 minutes. However, acceptable intubating conditions may be achieved within 90 to 120 seconds after cisatracurium 3 x ED_{95} (0.15 mg/kg) and 4 x ED_{95} (0.2 mg/kg).

Only limited data on the pharmacology of cisatracurium in paediatric patients are available.[188-192] The estimated ED_{95} of cisatracurium in children aged 2 to 12 years is 0.04 mg/kg; after a bolus dose of 0.08 mg/kg, neuromuscular blockade is of intermediate duration.[188,189,191] More data are required to determine the place of cisatracurium in paediatric patients; in particular, specific dose-finding studies for this patient population are needed.

In the following patient groups cisatracurium may be of particular interest.

3.4.1 Elderly Patients

Neither the pharmacokinetics nor the pharmacodynamics of cisatracurium are altered in elderly patients compared with younger patients; in particular, the recovery characteristics do not differ between these groups.[184] Therefore, cisatracurium may be of particular interest in this patient population. However, it remains to be proven in prospective studies whether cisatracurium is associated with a lower incidence of residual paralysis in elderly patients than other intermediate-acting NMBAs.

3.4.2 Patients with Hepatic or Renal Failure, and in Intensive Care

The clinical duration and the recovery profile of cisatracurium are largely independent of hepatic and renal functions, which makes the pharmacodynamics of cisatracurium predictable in patients with severe hepatic or renal failure.[156,183] This is of particular importance in situations in which repeated bolus doses or even a continuous infusion technique are used to ensure deep neuromuscular blockade. The use of NMBAs to facilitate mechanical ventilation in patients in ICU has declined during the last 10 years. In the past, cumulation of the potentially neurotoxic metabolite laudanosine and subsequent passage into the cerebrospinal fluid have been observed after continuous infusion of atracurium in such patients.[177]

Table III. Pharmacodynamics of cisatracurium in healthy patients and patients with liver or kidney failure. Values are presented as means

	Onset (min)[a]	Clinical duration (min)[b]	DUR 0.7 (min)[c]	References
Healthy				155,156,158,160,183-186
0.10 mg/kg	2.7-7.7	44.8-50	66.7-82.5	
0.15 mg/kg	2.2	51.0	NA	
0.20 mg/kg	2.7	68.3	89.9	
Liver failure	2.4	53.5	79.0	183
Renal failure	8.8	44.0	72.0	156

a Time from injection of cisatracurium to maximum neuromuscular block.

b Time from injection to 25%-T1 recovery.

c Time from injection to recovery of the TOF-ratio to 0.7.

NA = data not available; **T1** = first response of the TOF; **TOF-ratio** = train of four ratio at the thumb.

Significantly reduced laudanosine production as well as increased haemodynamic stability are the major advantages of cisatracurium over atracurium. In addition, compared to vecuronium, recovery from neuromuscular block seems to be more rapid after prolonged infusion of cisatracurium in critically ill patients.[193] However, in predisposed patients in ICU (e.g. receiving treatment with high-dose corticosteroids) cisatracurium may produce prolonged paralysis just like any other NMBA.[194]

4. Conclusion

The 3 newer nondepolarising NMBAs, rocuronium (introduced in 1994), cisatracurium (1995) and rapacurium (1999), offer several advantages over the established NMBAs.

Rapacurium is a new, nondepolarising NMBA with a rapid onset of and short duration of action and may therefore be a suitable alternative to mivacurium and succinylcholine for short procedures (<30 minutes), particularly in ambulatory anaesthesia. The most prominent adverse effects of rapacurium (tachycardia, hypotension and bronchospasm) are dose-related and limit the use of rapacuronium in a rapid-sequence setting. As a consequence of a series of recent reports on bronchospasm following administration of rapacurium (see Addendum below) the dose recommendations will probably be changed by the manufacturer.

From all currently available nondepolarising muscle relaxants, rocuronium in doses ≥1 mg/kg is the most suitable alternative to succinylcholine in a classical rapid-sequence setting, that is, under a relatively light anaesthetic depth. In contrast to rapacurium, the use of rocuronium in a rapid-sequence setting is not associated with dose-dependent respiratory adverse effects.

Unlike atracurium, cisatracurium does not trigger histamine release even when administered in large doses and it has only minimal cardiovascular adverse effects. The elimination of cisatracurium from the body is mainly independent of organ function making the pharmacodynamics of cisatracurium predictable in patients with impaired renal and hepatic function such as geriatric patients and critically ill patients.

Addendum

In premarketing clinical trials, rapacuronium bromide caused bronchospasm in 3.2% of patients. In clinical practice in the USA several serious adverse bronchospasm events were reported to Organon Inc, of West Orange, N.J., including a few fatalities. Therefore, on March 27, 2001 Organon Inc. voluntarily withdrew rapacuronium bromide (trade name Raplon) from the US market (see http://www.fda.gov/medwatch/safety/2001/raplon_DDL.htm for more detailed information) until a more restricted package insert comes into place. Raplon and its possible association with the occurrence of severe bronchospasm have led to this decision.

Three case reports dealing with bronchospasm following administration of rapacuronium and an accompanying editorial has been published in the May issue of Anesthesiology 2001.[195-198]

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