Rocuronium is a new nondepolarizing neuromuscular blocking drug. Its onset of action is comparable to that of succinylcholine, with good-to-excellent intubating conditions possible 1 minute after doses two times the ED₃₅ (600 µg/kg). The ED₃₅ of rocuronium is essentially the same for children as for adults. Its duration of action is similar to vecuronium, and it is shorter for children than for adults. Rocuronium is readily reversed with conventional doses of cholinesterase-inhibiting drugs. A new agent, rocuronium possesses a very stable cardiovascular profile and a rapid onset of action. It may be useful for rapid sequence intubation without unacceptable delays in the spontaneous recovery of neuromuscular function.

Key words: Intubation, neuromuscular blockade, rocuronium.

Introduction
The past 10 years have witnessed dramatic strides in the field of anesthesiology. Developments in clinical monitoring have reduced many risks associated with anesthesia, particularly with respect to early detection of inadequate ventilation and hypoxemia.¹ Ultra-short-acting intravenous agents have been developed that foster rapid awakening and produce fewer residual effects. Continuous infusion and total intravenous anesthesia techniques have become increasingly popular because of these agents.

Research in the field of neuromuscular blockade (NMB) has been particularly fertile as well. The introduction of atracurium and vecuronium during the 1980s made two agents with intermediate onset and duration of action available to anesthetists. Neither manifests significant cardiovascular side effects. Early in the 1990s, pipecuronium and doxicurium became available for clinical use. Both are NMB drugs of long duration with stable cardiovascular profiles. However, there is still a void with regard to nondepolarizing neuromuscular blocking drugs that remains to be filled. No nondepolarizing agent that is currently available possesses a speed of onset that allows rapid control (within 60 seconds) of the airway.²³⁰⁴

Historically, succinylcholine has been the sole agent that is suitable for truly rapid sequence endotracheal intubation. A depolarizing neuromuscular blocking drug, succinylcholine has a very rapid onset (less than 1 minute) and a brief duration of action (3-5 minutes).²⁴⁵⁻⁶⁹ Unfortunately, the clinical use of succinylcholine has many relative and absolute contraindications and a variety of side effects (some of which are catastrophic).³ Recent pharmacologic developments have culminated in the clinical evaluation of two additional nondepolarizing drugs—mivacurium and rocuronium—which may allow the replacement of a number of the clinical applications of succinylcholine.

Mivacurium is a nondepolarizing NMB drug with an intermediate onset and a short duration of
action. Although it is unsuitable for rapid sequence intubation, mivacurium is ideal for routine endotracheal intubation. Its administration by continuous infusion during procedures of short or intermediate duration yields excellent neuromuscular blockade, combined with exceptionally fast spontaneous recovery. Mivacurium is metabolized by plasma esterases and, when administered appropriately, rarely requires pharmacologic antagonism. Recently published studies have suggested that the onset of rocuronium in both adults and children is comparable to that of succinylcholine, whereas its duration of action is similar to that of vecuronium.

**Review of literature: Rocuronium bromide**

- **Onset and potency.** Clinical studies in healthy children and adults suggest that the ED95 of rocuronium is approximately 300 μg/kg.5,7 Rocuronium is less potent than mivacurium, vecuronium, atracurium, doxacurium, and pipercuronium.5 Based on the results of research conducted to evaluate the relationship of neuromuscular blocking potency to the speed of onset, it would be expected that the onset of action of rocuronium would be faster than that of more potent nondepolarizing agents.8-10 Indeed, this has been found to be so. The onset of action of an NMB agent is not only a function of its potency but of other variables as well (Table I). These variables include the agent’s volume of distribution and degree of protein binding as well as its potency.

<table>
<thead>
<tr>
<th>Table I</th>
<th>Variables influencing the onset of neuromuscular blocking drugs</th>
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<tbody>
<tr>
<td>Variable</td>
<td>Change</td>
</tr>
<tr>
<td>Potency</td>
<td>Decrease</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>Increase</td>
</tr>
<tr>
<td>Protein binding</td>
<td>Increase</td>
</tr>
</tbody>
</table>

Adapted from: Stoelting RK.5-189

Min JC, Bekavac I, Glavinovic M, Donati F, Bevan DR.9

Because rocuronium is less potent than other depolarizing NMB drugs, the intubating dose (usually 1.5-2.0 times the ED95) may present a larger mass of drug to the pre- and post-junctional cholinoreceptors caused by a more substantial concentration gradient driving the drug to the receptor.11 Alternatively, some authors suggest that, because the plasma protein binding of rocuronium may be less than that of other steroid molecule muscle relaxants, a larger proportion of the injected drug is available to interact with the receptor. Unfortunately, there is much uncertainty regarding the actual protein binding of any particular NMB drug. Measures of protein binding vary from study to study and from species to species.12 Interestingly, while atracurium, metocurine, pancuronium, tubocurare, and vecuronium display widely varying degrees of protein binding, their times to maximum blockade fall uniformly in the 3-5 minute range.2p187,19 As a result, it seems unlikely that differences in protein binding alone account for the comparatively rapid onset of action of rocuronium.

Wierda and colleagues found good-to-excellent intubating conditions 1 minute after injection in a group of adults who had received 500 μg/kg (1.5 times ED95) of rocuronium during N2O/O2/fentanyl and thiopental anesthesia.11 Woelfel and associates, in a study of children 1-5 years of age who received N2O/O2/halothane anesthesia, found the ED95 of rocuronium to be approximately 300 μg/kg. They also reported excellent intubating conditions in the vast majority of children who were intubated 60 seconds after receiving rocuronium 600 μg/kg (2 times ED95) during N2O/O2/halothane anesthesia (Table II).

<table>
<thead>
<tr>
<th>Table II</th>
<th>Onset of action in children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Dose (μg/kg)</td>
</tr>
<tr>
<td>1-5</td>
<td>600</td>
</tr>
<tr>
<td>600</td>
<td>1.3 ± 0.2 (0.7-2.8)</td>
</tr>
</tbody>
</table>

Data are mean ± standard error of mean.

Adapted with permission from Woelfel SK, Brandom BW, Cook DR, Samar JB.8

Interestingly, in a fashion similar to other nondepolarizing NMBs, the time to the maximum neuromuscular blocking effect of rocuronium is relatively unchanged by increasing the dosage.2p185-189 The time from injection to the maximum neuromuscular blocking effect appears to be consistent in adults and children in doses ranging from less than one ED95 to doses up to three times the ED95 (the usual intubating dose is two times ED95). A recent study of rocuronium neuromuscular blockade in children revealed that when using sub-ED95 doses, maximum blockade occurred in about 2.4 ± 0.1 (1.7-3.8) minutes, irrespective of the
dose given. Patients received doses ranging from 120-240 μg/kg given as single boluses, and relatively few experienced 100% blockade.

In two similar studies of adults who received N2O/O2/fentanyl and thiopental anesthesia, the time to 90% blockade of T-1 was not significantly different when doses of 570 μg/kg, 710 μg/kg, or 850 μg/kg were administered as a single bolus. Similarly, Foldes and colleagues found no difference in the time to 80% block of T-1 when patients received rocuronium either as a bolus or by a priming technique (Table III). They administered an initial rocuronium priming dose of 100 μg/kg followed 4 minutes later by an additional 500 μg/kg dose. A second group received a single 600 μg/kg bolus. Patients in both groups were intubated when maximum blockade had occurred. The authors found good-to-excellent intubating conditions in all patients. The time to maximum blockade in the priming group (1.23 ± 0.14 minutes) was not statistically different from the time to maximum blockade in the bolus group (1.49 ± 0.12 minutes).

### Table III

<table>
<thead>
<tr>
<th>Dose (μg/kg)</th>
<th>Time (minutes)</th>
<th>Percentage of T-1 blocked</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolus n=20</td>
<td>600</td>
<td>0.90 ± 0.05 (0.5-1.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.49 ± 0.12 (0.7-3.0)</td>
</tr>
<tr>
<td>Priming n=20</td>
<td>600**</td>
<td>0.86 ± 0.07 (0.4-1.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.23 ± 0.14 (0.6-3.5)</td>
</tr>
</tbody>
</table>

*In the two groups combined, complete block occurred in 38 of 40 patients.
**Initial dose: 100 μg/kg, followed in 4 minutes by 500 μg/kg.
Data are mean ± standard error of mean; range in parenthesis.
Adapted with permission from Foldes FF, Hideo N, Hung DN, Schiller WS, Mason MM, Yoshio O.

Cooper and associates found that both 600 μg/kg and 900 μg/kg doses produced 100% blockade in less than 1 minute when they were administered to adult patients who were receiving either N2O/O2/fentanyl or halothane plus N2O/O2/fentanyl anesthesia. No dose-dependent difference in the time of onset was identified between the two treatment groups. Likewise, the authors did not identify an appreciable hastening of onset when halothane was added to the anesthetic.

In an interesting study of the variability of neuromuscular blockade in different muscle groups, Meistelman et al examined the speed of onset, intensity of blockade, and duration of action of rocuronium at the adductor muscles of the larynx and at the adductor pollicis muscle. They found rocuronium to have a more rapid onset, a less intense blockade, and a shorter duration of action at the adductor muscle of the larynx than at the adductor pollicis. The ED50 for the adductor muscles of the larynx was approximately 1.5 times the ED50 for the adductor pollicis. The authors suggested that monitoring the degree of blockade at the adductor pollicis may lead to overestimation of the time required for blockade of the laryngeal muscles, whereas it underestimates the dose of rocuronium required to provide maximum blockade of the laryngeal muscles. In this study, rocuronium 500 μg/kg produced 78% and 98% blockade of the laryngeal adductor muscles and adductor pollicis, respectively, while the onset of maximum effect was faster at the laryngeal adductor muscles. The implications of this study become clearer when the results of a study that compared intubating conditions in outpatients who received either succinylcholine or rocuronium are considered.

### Rocuronium and succinylcholine

In a study that compared the intubating conditions produced by succinylcholine to those produced by rocuronium, Puhringer and associates found that the time to 95% suppression of T-1 was significantly shorter for succinylcholine than for rocuronium (Table IV). However, although the onset of neuromuscular blockade was clearly faster for succinylcholine than for rocuronium, observers in this blinded study found no significant difference in intubating conditions 1 minute after administration of either drug. The authors suggest that this could be explained in part by the more rapid action of rocuronium at the adductor muscles of the larynx than at the adductor pollicis muscles. They also noted the difficulty in achieving unbiased objective measures of intubating conditions. Furthermore, it should be remembered that the ease of intubation is a function not only of neuromuscular blockade but of depth of anesthesia and the skill of the laryngoscopist as well. Nevertheless, the authors felt that satisfactory intubating conditions could be achieved consistently within 1 minute after the administration of rocuronium 600 μg/kg.

### Duration of action in adults

The duration of action of rocuronium in adults resembles that of vecuronium. As a result, it qualifies as an NMB drug of intermediate dura-
As with vecuronium, recovery parameters reflect the dose of drug administered. Recovery of T-1 to 25% of baseline (clinical duration) after an intubating dose of rocuronium (600 μg/kg) was 34 ± 7 minutes for patients during N₂O/O₂/fentanyl anesthesia and 33 ± 4 minutes for patients during N₂O/O₂/halothane anesthesia. An increase in the dose of rocuronium to 900 μg/kg prolonged the recovery of T-1 to 25% of baseline in each group by 17 and 25 minutes respectively. Similarly, Lapeyre and colleagues found that increasing the intubating dose of rocuronium from 570-850 μg/kg prolonged the recovery of T-1 to 25% of baseline by 18 minutes. Foldes and associates found the recovery index (time of recovery of T-1 from 25 to 75% of baseline) for rocuronium (600 μg/kg) to be 16.7 ± 1.2 minutes (range 4-64 minutes). They also found slight cumulative properties after successive equal doses of rocuronium.

In a similar fashion, Cooper et al found the spontaneous recovery of T-1 to 90% of baseline was prolonged by increasing the administered dose of rocuronium from 600 μg/kg (approximately 53 minutes) to 900 μg/kg (approximately 82 minutes). The rate of spontaneous recovery of T-1 was not affected by the addition of halothane to the anesthetic.

Shanks and associates studied the rocuronium infusion rates that were required to maintain 90-99% twitch suppression and found that infusion requirements decreased significantly over time for all patients and that patients receiving an isoflurane-nitrous oxide anesthesia or enflurane-nitrous oxide anesthesia required lower doses of rocuronium than patients receiving a barbiturate-nitrous oxide-opioid anesthesia (Table V). They also observed that the recovery index for all techniques averaged 20 minutes or greater, with spontaneous recovery beginning promptly at discontinuation of the infusion.

### Table IV

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>95% blockade (minutes)</th>
<th>Duration 25%* (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocuronium</td>
<td>600 μg/kg</td>
<td>1.2 ± 0.5</td>
<td>25.3 ± 5</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>1.0 mg/kg</td>
<td>0.8 ± 0.1</td>
<td>8.1 ± 2.6</td>
</tr>
</tbody>
</table>

Data are mean ± standard error of mean.
* T-1 to 25% of baseline
Adapted with permission from Puhringer FK, Khuenl-Brady KS, Koller J, Mitterschiffthaler G.17

In a similar fashion, Cooper et al found the spontaneous recovery of T-1 to 90% of baseline was prolonged by increasing the administered dose of rocuronium from 600 μg/kg, recovery of T-1 to 25% of baseline in these children occurred in 26.7 ± 1.9 (17.2-39) minutes during N₂O/O₂/halothane anesthesia. Similarly, the recovery index also was shorter for these children (11.0 ±1.6 minutes) than for adults (16.7 ± 1.2 minutes). Based on these findings, it would appear that children in this age group would require more frequent redosing with rocuronium during the maintenance phase of an anesthetic than adults.

In a study of children in three different age groups O'Kelly and colleagues found that the steady state volume of distribution was smaller for each successively older age group (Table VI). On the other hand, the rate of clearance for all three groups was similar (range 9.8-13.5 mL/kg/min). Accordingly, the authors suggested that older children would require more frequent redosing than infants, predicated on the assumption that a small volume would be cleared more quickly than a large volume, given a similar rate of clearance. Szenohradszky and associates found the steady state volume of distribution of rocuronium in healthy adults to be 207 ± 14 mL, an amount slightly smaller than that of the 4 to 8-year-old age group of O'Kelly and colleagues. The total plasma clearance they described for adults, using a three-compartment model, was 2.89 ± 0.25 mL/kg/min. Thus, the rate of clearance of rocuronium in adults is substantially less, and the elimination half time is significantly greater than for children of any age group (Table VI). The much lower rate of clearance of rocuronium in adults, despite a smaller steady state volume of distribution, may partially explain the more rapid recovery of children from rocuronium blockade.

### Table V

<table>
<thead>
<tr>
<th>Rocuronium infusion rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthesia technique</td>
</tr>
<tr>
<td>Rate (μg/kg/min)</td>
</tr>
<tr>
<td>At 30 minutes</td>
</tr>
<tr>
<td>At 60 minutes</td>
</tr>
<tr>
<td>At 90 minutes</td>
</tr>
<tr>
<td>At 120 minutes</td>
</tr>
</tbody>
</table>

Data are means ± standard deviation.
Adapted with permission from Shanks CA, Fragen RJ, Lind D.18

### Duration of action in children

The clinical duration of action of rocuronium in children 1-5 years of age is shorter than that for adults. After intubating doses of 600 μg/kg, recovery of T-1 to 25% of baseline occurred in 26.7 ± 1.9 (17.2-39) minutes during N₂O/O₂/halothane anesthesia. Similarly, the recovery index was also shorter for these children (11.0 ±1.6 minutes) than for adults (16.7 ± 1.2 minutes). Based on these findings, it would appear that children in this age group would require more frequent redosing with rocuronium during the maintenance phase of an anesthetic than adults.
**Metabolism and elimination**

Human and animal studies suggest that the route of plasma clearance of rocuronium is predominantly by hepatic uptake; the vast majority of rocuronium (greater than 75%) is subsequently excreted unchanged in the bile. Only a small fraction (8.7%) of rocuronium is excreted unchanged in the urine.\(^6\)\(^,\)\(^21\) Unlike vecuronium, the clearance of rocuronium was largely unchanged in patients undergoing renal transplantation, although the steady state volume of distribution was slightly increased. This increase in the volume of distribution of rocuronium may have been a reflection of an increase in extracellular fluid volume in endstage renal disease, or it may have been the result of other variables associated specifically with surgery, such as fluid loading or some combination of those factors.\(^20\) Although more research is needed before specific recommendations can be made, it seems very likely that rocuronium will be a suitable agent for use in patients with end-stage renal disease. Conversely, because rocuronium clearance depends on hepatobiliary function, patients with substantial hepatic disease may eliminate rocuronium poorly. In such patients, the duration of action of rocuronium may be prolonged.

**Pharmacologic antagonism.** Little has been published that specifically addresses the issue of antagonism of residual rocuronium neuromuscular blockade by the administration of cholinesterase-inhibiting drugs. Foldes and associates antagonized residual blockade using edrophonium 0.5 mg/kg combined with 0.015 mg/kg atropine and observed prompt reversal of residual effects in 85 of 95 patients within 2-5 minutes.\(^5\) Five minutes after pharmacologic reversal, the T-4/T-1 ratio for these 86 patients was 0.86 ± 0.01 (0.50-1.00). The remaining patients required brief respiratory support via mask before being transferred to the post-anesthesia care unit. Woelfel et al, in a study of 62 healthy children, allowed the ratio of T-4/T-1 to recover spontaneously to greater than 75% (41.9 ± 3.2 [26.5-57.1] minutes. Witkowski and colleagues administered neostigmine 0.04 mg/kg combined with atropine 0.015 mg/kg to reverse residual rocuronium neuromuscular blockade.\(^8\) Although specific details were not provided, no difficulty was reported with reversal using these agents. Still other authors have reported prompt reversal of residual rocuronium blockade with neostigmine.\(^22\)

Despite a lack of studies that specifically examine antagonism of residual rocuronium neuromuscular blockade, few clinical difficulties have been reported, and it seems likely that residual blockade can readily be reversed with conventional doses of cholinesterase inhibitors once spontaneous recovery has begun.

**Cardiovascular effects.** Woelfel et al observed a modest but statistically significant increase in heart rate in children shortly after they received rocuronium 600 μg/kg as a bolus (90 ± 4 beats per minute increased to 106 ± 4 beats per minute). It is noteworthy that these authors found no residual increase in heart rate 5 minutes after injection, even after 800-μg/kg bolus of rocuronium.\(^5\) Foldes and associates studied adults and found no changes in heart rate or diastolic or systolic blood pressures after either 500 μg/kg or 600 μg/kg of rocuronium. Data was collected from the beginning of injection until maximum blockade was attained.\(^8\) Similarly, other authors have reported no identifiable cardiovascular or other untoward side effects associated with bolus injections of rocuronium in doses up to three times the ED₉₅.\(^1\)\(^,\)\(^1₃\)

In addition, in a study specifically designed to detect changes in hemodynamic variables, rocuronium demonstrated little histamine-releasing potential, and no hemodynamic changes were identified after boluses of either 300 μg/kg or 900 μg/kg.\(^2₃\)

**Malignant hyperthermia.** Specific studies that address the safety of rocuronium in patients who are susceptible to malignant hyperthermia (MH) have not been published at this time. It is unlikely that rocuronium will be found to be an MH-trigging agent because, as a class, nondepolarizing agents are not included among MH triggers.\(^2₄\) This conclusion is, of course, speculative.

**Summary**

Rocuronium is a nondepolarizing neuromuscular blocking drug with a rapid onset of action, an intermediate duration of action, and a relatively uniform pharmacokinetic profile. Although the
speed of onset of rocuronium compares favorably with succinylcholine, its duration of action is similar to that of vecuronium. Administration of up to three times the ED₉₅ leads to no important hemodynamic effects in adults and results in only a transient increase in heart rate in some groups of children. Antagonism of residual blockade is possible with conventional cholinesterase inhibitors. When employed in the usual intubating doses (two times the ED₉₅), rocuronium should be useful for routine and rapid sequence intubation without causing an unacceptable prolongation of neuromuscular blockade.

REFERENCES


AUTHOR

Terry C. Wicks CRNA, MHS, is currently assistant chief anesthetist at Grace Hospital in Morgantown, North Carolina. A 1981 graduate of the University of Iowa College of Nursing, he received his anesthesia education while on active duty in the U.S. Army and is a graduate of the Fitzsimons Army Medical Center Program in Nursing Anesthesia. He earned his master's degree in Health Science from Texas Wesleyan University and later served as assistant course director of the Fitzsimons Army Medical Center Program in Nursing Anesthesia in Aurora, Colorado.

Mr. Wicks recently served on the AANA’s Regional Anesthesia Task Force. He has had original research, review articles, and case reports published in the AANA Journal and in Nurse Anesthesia and is coauthor of Spinal and Epidural Blocks, published by the AANA. With a focus on the pharmacology of new neuromuscular-blocking drugs, Mr. Wicks is a frequent speaker at anesthesia educational sessions.