■ CLINICAL INVESTIGATIONS

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Intramuscular Rocuronium in Infants and Children

Dose-ranging and Tracheal Intubating Conditions

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Background: **Rocuronium's rapid onset and intermediate duration of action with intravenous administration suggests that intramuscular administration might facilitate tracheal intubation without producing prolonged paralysis. Accordingly, in infants and children, the authors measured onset at the adductor pollicis and respiratory muscles to determine the optimal dose (phase I), then gave this optimal dose to determine the optimal time for tracheal intubation (phase II).**

Methods: **The authors studied 45 unpremedicated patients aged 3 months to 5 yr. In phase I, 25 patients were anesthetized with nitrous oxide and halothane and breathed spontaneously; twitch tension and minute ventilation were measured. Rocuronium (800–2,400 μg/kg) was injected into the quadriceps or deltoid muscle; doses varied, using an "up–down" technique, the goal being to bracket the dose depressing twitch 75–90% within 5 min. In phase II, deltoid injections of the optimal dose from phase I (infants: 1,000 μg/kg; children: 1,800 μg/kg) were given to 20 patients anesthetized with 0.82–1.0% halothane. Tracheal intubation was attempted 1.5–3.0 min later; time to tracheal intubation was varied, using an "up–down" technique.**

Results: **In phase I, 5 of 7 patients given quadriceps injections (1,200–2,200 μg/kg) had slow onset of twitch and ventilatory depression. With deltoid injections (800–2,400 μg/kg), all patients developed complete twitch depression; median time to 50% depression of minute ventilation was 3.2 min in infants and 2.8 min in children. In phase II, intubating conditions were consistently adequate or good–excellent at 2.5 min in infants and 3.0 min in children. Initial twitch recovery was at 57 ± 13 min (mean ± SD) in infants and 70 ± 23 min in children.**

Conclusions: **Deltoid injections of rocuronium, 1,000 μg/kg in infants and 1,800 μg/kg in children, rapidly permit tracheal intubation in infants and children, despite a light plane of anesthesia. Duration of action of these large doses might limit clinical utility. (Key words: Anesthesia: pediatric, intubation. Injection: intramuscular. Muscle relaxants: rocuronium. Respiratory effects: muscle relaxants.**

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DURING inhalation induction of anesthesia in pediatric patients, succinylcholine is often given intramuscularly to facilitate elective tracheal intubation before venous access is secured. This technique provides excellent conditions for tracheal intubation, thereby obviating the need to administer high concentrations of inhaled anesthetics, with their potential for hypotension. However, a recent report[1] of cardiac arrest and death in children given succinylcholine during induction of anesthesia led the Food and Drug Administration to advise Burroughs Wellcome to revise succinylcholine's package insert. An initial revision contraindicated administration of succinylcholine to children "except when used for emergency tracheal intubation or in instances where immediate securing of the airway is necessary."‖ This controversial change[2] was later replaced with a warning that "Since there may be no signs or symptoms to alert the practitioner to which patients

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‖ Package insert for succinylcholine, Burroughs Wellcome, November 1992.

Package insert for succinylcholine, Burroughs Wellcome, November 1994.

are at risk, it is recommended that the use of succinylcholine in children should be reserved for emergency intubation or in instances where immediate securing of the airway is necessary . . . or for intramuscular use when a suitable vein is inaccessible.''# These changes in the package insert limit the clinician's ability to give succinylcholine intramuscular. Unfortunately, no other muscle relaxant has been demonstrated to have a sufficiently rapid onset, when given intramuscularly, to be considered a clinically acceptable alternative.

In the current study, we determined the clinical pharmacology of intramuscularly rocuronium in infants and children. In the first phase, we determined the optimal dose. As in most neuromuscular studies, we measured adductor pollicis twitch tension; however, adductor pollicis twitch depression provides limited information regarding conditions for tracheal intubation. Because a more appropriate predictor of intubating conditions is depression of the respiratory muscles,[3,4] we also used an indirect measure of depression of the diaphragm, *i.e.,* the effect of rocuronium on spontaneous minute ventilation.[5]

In the second phase, we administered the optimal doses determined in phase I and evaluated intubating conditions, to determine the optimal time at which the trachea can be intubated. In contrast to many intubation studies in which anesthetic conditions ensure good-to-excellent intubating conditions in most patients, we purposely selected a light plane of anesthesia, so that attempts at tracheal intubation would likely fail until paralysis occurred.

Methods

The study was conducted using Organon's Investigational New Drug Application, and the protocol was approved by our Committee on Human Research. After obtaining informed consent from parents, we studied 45 pediatric patients, ASA physical status 1 or 2, undergoing elective surgery. Patients were stratified by age into two groups: infants (3–12 months) and children (1–5 yr). No patient had a history of bleeding disorder, neuromuscular disease, or hepatic or renal insufficiency. Patients were excluded if they received anticonvulsants or aminoglycoside or polypeptide antibiotics perioperatively.

Phase I—Determination of Optimal Dose

Patients were not premedicated. Anesthesia was induced by inhalation of nitrous oxide (N_2O) and halothane, and tracheal intubation was accomplished without administration of muscle relaxants. Anesthesia was then maintained with 60% N_2O and halothane, 0.8–1.0 minimum alveolar concentration (MAC, end-tidal concentration) adjusted for age[6]; no opioids or other intravenous anesthetics were administered. Patients breathed spontaneously *via* a pediatric circle system (Marquest Medical Systems, Englewood, CO). When anesthetic conditions and baseline twitch and ventilation recordings were stable, 10 mg/ml rocuronium was injected *via* a 21-gauge needle 1–2 cm into a single quadriceps (n = 7) or deltoid (n = 18) muscle after negative aspiration for blood. The rocuronium dose for the first patient in each age group was 1,200 μg/kg. The dose for each subsequent patient was based on the adductor pollicis response of the previous patient in that age group during the first 5 min after injection[5]: if twitch tension decreased > 90%, the dose was decreased 100–200 μg/kg; if twitch tension decreased 75–90%, the dose was not changed; if twitch tension decreased <75%, the dose was increased by 100–300 μg/kg (to a maximum of 2,400 μg/kg). This ''up–down'' technique, similar to that used to determine MAC,[7] was designed to bracket the rocuronium dose that would depress twitch tension 75–90% during the 5 min after intramuscular administration. If ventilatory depression occurred (defined as spontaneous minute ventilation [$\dot{V}_e$] decreasing 50% from the control value, a 10-mmHg increase in end-tidal partial pressure of carbon dioxide, or arterial oxygen saturation < 90%[5]), mechanical ventilation was instituted. Anesthetic concentrations were not changed, and no supplemental anesthetic drugs were given after rocuronium administration until ventilation was controlled.

Phase II—Determination of Optimal Time for Tracheal Intubation

Patients were unpremedicated, and anesthesia was induced with nitrous oxide and halothane. After induction of anesthesia, nitrous oxide was discontinued, ventilation was controlled manually to maintain normocapnia, and the end-tidal halothane concentration was adjusted to 1.0% in children younger than 2.5 yr and 0.82% in children older than 2.5 yr. No opioids or intravenous anesthetics were administered. When end-tidal halothane concentrations and baseline twitch recordings were stable for >5 min, rocuronium (1,000 μg/kg for infants and 1,800 μg/kg for children; the

optimal doses determined in phase I) was injected into the deltoid muscle.

The time to attempted intubation for the first patient in each age group was 3.0 min. For each subsequent patient, the time to attempted intubation was based on the previous patient's intubating conditions: if intubating conditions were good–excellent (jaw relaxed, vocal cords immobile, minimal or no coughing), the time to attempted intubation was decreased by 0.5 min; if intubating conditions were adequate (jaw relaxed, vocal cords open, vigorous coughing), the time to attempted intubation remained unchanged; if intubating conditions were poor–inadequate (jaw not relaxed or vocal cords moving), the time to attempted intubation was increased by 0.5 min. No intubation was to be attempted before 1 min after rocuronium administration. This "up–down" technique was used to target the optimal time to intubation; however, time to intubation, rather than dose, was varied.

Observations, Measurement Techniques

Supramaximal square-wave train-of-four stimuli were administered at 2 Hz every 12 s to the ulnar nerve *via* needle electrodes at the wrist. Evoked tension of the adductor pollicis was measured using a Grass FT-03 force transducer while maintaining preload at 50–100 g. The force signal was amplified (DC Bridge Signal Conditioner, Gould Electronics, Valley View, OH), digitized (NB-MIO-16, National Instruments, Austin, TX) on a Macintosh computer (Apple, Hayward, CA), and displayed (LabView, National Instruments). The ratio of the first component of the train-of-four (T1) to its control value was determined. Each train-of-four also was recorded on a strip-chart (TA240, Gould).

Respiratory gas was sampled at the Y-connector, and partial pressure of carbon dioxide and anesthetic concentrations were determined by infrared analysis (Capnomac Ultima, Datex, Helsinki, Finland); end-tidal values during each 12-s epoch were determined using LabView. Arterial oxygen saturation was measured continuously (N200 Oximeter, Nellcor, Hayward, CA). In phase I, blood pressure and heart rate (Dinamap, Critikon, Tampa, FL) were measured before and every minute for 5 min after rocuronium administration. Minute ventilation was measured using a calibrated Fleisch pneumotachograph (Instrumentation Associates, New York) placed between the breathing circuit and the endotracheal tube. The flow signal was amplified (CD15 Carrier Demodulator, Validyne, Northridge, CA), digitized on a Macintosh computer, and the inspiratory signal (corrected for flow to the capnograph) integrated in 12-s epochs (LabView).

After injection of rocuronium, the injection site and the skin of the trunk and face were observed for erythema; signs consistent with histamine release were sought. At completion of surgery, if twitch tension had not recovered to the control value, 70 μg/kg neostigmine and 20 μg/kg atropine were given. The trachea was extubated after twitch tension recovered to >90% of the control value. In the operating room and the postanesthetic recovery room, patients were examined for signs of weakness, such as inability to sustain leg lift[8]; the injection site was examined for signs of tissue inflammation or damage.

Data Analysis

For phase I, magnitude of twitch depression at 5 min and peak depression of twitch tension (both expressed as a percentage decrease from the control value) and times to 10%, 50%, 90%, and peak twitch depression (onset) were determined. Spontaneous minute ventilation at 1 min after intramuscular injection (expressed as a percentage of the control value) and time to ventilatory depression were recorded. Values for blood pressure and heart rate were examined for changes exceeding 20% of the value before rocuronium. For phase II, magnitude of peak twitch depression, time to 10%, 50%, 90%, and peak twitch depression, and initial, 10%, 25% (clinical duration), and 90% (duration of action) spontaneous recovery of twitch tension were determined. Values are reported as median and range or as mean ± SD.

Results

Phase I

Infants aged 8 ± 2 months (n = 10) weighed 8 ± 1 kg. Children aged 3 ± 2 yr (n = 15) weighed 14 ± 4 kg.

Quadriceps Injections. The first infant and six children received their rocuronium injection in the quadriceps muscle. The infant developed rapid and complete twitch depression and a 50% decrease in $\dot{V}_e$ at 2.2 min (table 1). In 2 children, maximum twitch depression was <90%; in 5 children, time to peak twitch depression exceeded 10 min. Time to ventilatory depression was >11 min in 3 children. When surgical considerations prevented quadriceps injection in

Table 1. Magnitude and Onset of Twitch Depression and Onset of Ventilatory Depression in Patients Given Rocuronium Intramuscularly in the Quadriceps Muscle in Phase I

	Dose (μg/kg)	Twitch Depression at 5 min (%)	Peak Twitch Depression (%)	Time to Peak Twitch Depression (min)	Time to Ventilatory Depression (min)
Infants	1,200	98	98	5.2	2.2
Children	1,200	1	63	43	23
	1,500	0	99	23	12*
	1,800	71	98	12	4.2
	1,900	1	89	25	7.8
	2,200	77	99	7.6	4.4
	2,200	4	99	21	16

* Criterion for ventilatory depression was 10-mm increase in end-tidal P_{CO_2}. For other patients, criterion was 50% decrease in $\dot{V}_e$.

the subsequent child, that patient received rocuronium in the deltoid muscle. The magnitude and rapidity of response to deltoid injection in that patient led to all subsequent patients receiving rocuronium in the deltoid muscle. To obtain sufficient data on children given deltoid injections, the sample size for children was increased from a planned 10 to 15.

Deltoid Injections. For infants, rocuronium doses ranged from 800–1,100 μg/kg; for children, rocuronium doses ranged from 1,700–2,400 μg/kg (table 2).

Table 2. Magnitude and Onset of Twitch Depression and Onset of Ventilatory Depression in Patients Given Rocuronium Intramuscularly in the Deltoid Muscle in Phase I

	Infants	Children
n	9	9
Range of doses (μg/kg)	800–1,100	1,700–2,400
Time to 10% twitch depression (min)	2.6 (1.8–5.8)	2.2 (0.8–3.3)
Time to 50% twitch depression (min)	3.6 (2.4–8.2)	2.6 (0.8–4.4)
Time to 90% twitch depression (min)	4.8 (3.4–12.2)	3.4 (1.0–6.2)
Twitch depression at 5 min (%)	93 (2–98)	98 (44–100)
Maximum twitch depression (%)	100 (100–100)	100 (100–100)
Time to complete twitch depression (min)	6.6 (4.8–15.8)	4.0 (1.2–7.8)
Time to ventilatory depression (min)*	3.2 (2.0–9.2)	2.8 (1.6–4.4)†

Values are median (range).

* Defined at 50% decrease in $\dot{V}_e$, a 10-mmHg increase in end-tidal P_{CO_2}, or $Sp_{O_2} < 90\%$.

† n = 8.

All infants and children developed 100% twitch depression (example shown in fig. 1). Median time to 10% depression of twitch tension was 2.6 min in infants and 2.2 min in children. Median time to 50% twitch depression was 3.6 min in infants and 2.6 min in children. Median time to 90% twitch depression was 4.8 min in infants and 3.4 min in children. Median time to complete twitch depression was 6.6 min in infants and 4.0 min in children (fig. 2).

Ventilation (All Patients). Ventilation was controlled in 23 of 25 patients because of decreases in $\dot{V}_e$ to <50% of the control value and in 1 of 25 because of a 10-mm increase in partial pressure of carbon dioxide; in the remaining patient, $\dot{V}_e$ was not measured because of equipment failure. For patients given deltoid injections, median time to ventilatory depression was 3.2 min in infants and 2.8 min in children (fig. 3). In 4 of 10 infants and 6 of 15 children, $\dot{V}_e$ 1 min after injection of rocuronium exceeded 110% of the control value. For infants, median $\dot{V}_e$ at 1 min was 103% of the

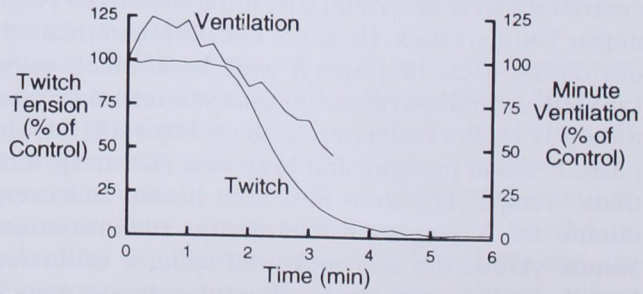

Fig. 1. Onset (min) of depression of adductor pollicis twitch tension and minute ventilation (% of control value) for a representative infant (infant #5 in figs. 2 and 3) given 1,100 μg/kg rocuronium intramuscularly in the deltoid muscle.

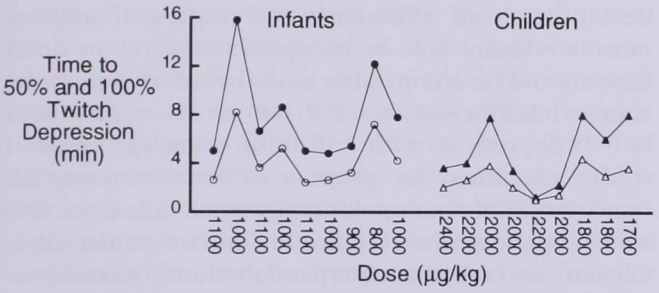

Fig. 2. Time (min) to 50% (open symbols) and 100% (closed symbols) twitch depression for infants and children given rocuronium intramuscularly in the deltoid muscle. The x-axis is the dose for each individual patient, displayed in the order in which the study was performed. An increase in dose indicated that the previous patient had <75% twitch depression within 5 min; a decrease indicated that the previous patient had >90% twitch depression within 5 min.

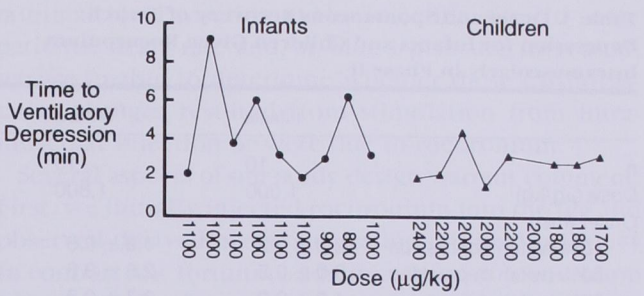

Fig. 3. Time (min) to ventilatory depression for infants and children given rocuronium intramuscularly in the deltoid muscle. The x-axis is the dose for each individual patient, displayed in the order in which the study was performed. An increase in dose indicated that the previous patient had <75% twitch depression within 5 min; a decrease indicated that the previous patient had >90% twitch depression within 5 min.

control value (range: 84–179%); for children, median $\dot{V}_e$ at 1 min was 105% of control (range: 82–158%).

Cardiovascular Effects. Six patients had a >20% increase in heart rate (range: 24–39%); none had a >20% decrease in heart rate. Ten patients had a >20% increase in systolic, diastolic, or mean blood pressure (range: 21–65%). Two patients had a >20% decrease in diastolic or mean pressure (range: 23–34%); none had a >20% decrease in systolic blood pressure.

Adverse Events. One patient developed mild erythema at the injection site that resolved spontaneously; none developed rashes or wheezing. Postoperatively, there was no evidence of tissue inflammation or damage at the injection site.

Phase II

Infants aged 8 ± 2 months (n = 10) weighed 8 ± 2 kg. Children aged 3 ± 1 yr (n = 10) weighed 12 ± 3 kg.

Injection of Rocuronium and Tracheal Intubation. Injection of rocuronium elicited vigorous movement (*e.g.*, extremity movement against gravity) in 50% of patients. In infants, intubation was attempted at 1.5–3.0 min (fig. 4). All four infants in whom intubation was attempted at ≥2.5 min had good–excellent intubating conditions. At 2 min, 2 of 4 infants had good–excellent intubating conditions; in the remaining 2, conditions were poor–inadequate. In children, intubation was attempted at 1.5–3.0 min (fig. 4). All children in whom intubation was attempted at 3.0 min had adequate or good–excellent intubating conditions. At 2.5 min, 2 of 3 children had adequate or good–excellent intubating conditions; 1 had poor–inadequate conditions.

Twitch Tension. Time to 10% twitch depression was 2.2 ± 0.2 min in infants and 1.6 ± 0.8 min in children (table 3). Time to 90% twitch depression was 4.3 ± 0.9 min in infants and 3.7 ± 0.8 min in children. All patients developed complete twitch depression, at 6.4 ± 1.6 min in infants and at 5.2 ± 0.8 min in children. Initial recovery of twitch tension occurred at 57 ± 13 min in infants and 70 ± 23 min in children; the longest values were 74 min in infants and 121 min in children. Clinical duration was 79 ± 11 min in infants and 89 ± 22 min in children; the longest values were 92 min in infants and 129 min in children. Duration of action was 104 ± 14 min in infants and 124 ± 42 min in children.

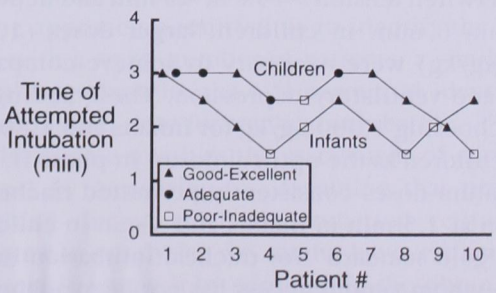

Fig. 4. Time (min) at which intubation was attempted is plotted for each infant and child. If intubating conditions were good–excellent (triangle), time of attempted intubation for the next patient was decreased 0.5 min. If intubating conditions were adequate (circle), time of attempted intubation for the next patient was not changed. If intubating conditions were poor–inadequate (open square), time of attempted intubation for the next patient was increased 0.5 min.

Table 3. Onset and Spontaneous Recovery of Twitch Depression for Infants and Children Given Rocuronium Intramuscularly in Phase II

	Infants	Children
n	10	10
Dose (μg/kg)	1,000	1,800
Onset (min)		
10% twitch depression	2.2 ± 0.2	1.6 ± 0.8
50% twitch depression	3.0 ± 0.5	2.5 ± 0.8
90% twitch depression	4.3 ± 0.9	3.7 ± 0.8
100% twitch depression	6.4 ± 1.6	5.2 ± 0.8
Spontaneous recovery (min)		
Initial recovery	57 ± 13 (n = 9)	70 ± 23
10% recovery	72 ± 13 (n = 8)	86 ± 27
25% recovery	79 ± 11 (n = 7)	89 ± 22 (n = 8)
90% recovery	104 ± 14 (n = 4)	124 ± 42 (n = 5)

Values are mean ± SD.

Adverse Events. Two infants experienced mild, transient erythema at the injection site; no other rashes or other signs of histamine release were observed. There was no evidence of inflammation at the injection site. No patients demonstrated clinical signs of weakness after tracheal extubation or during recovery.

Discussion

In the current study, we examined the clinical pharmacology of intramuscular rocuronium. Phase I was designed to determine the optimal dose. Deltoid injection of 900–1,100 μg/kg in infants typically depressed twitch tension >75% in <5 min and depressed $\dot{V}_e$ within 6 min. In children, larger doses (1,700–2,000 μg/kg) were necessary to achieve comparable twitch and ventilatory depression. These findings led to our choosing 1,000 μg/kg for infants and 1,800 μg/kg for children as the optimal doses. In phase II, these rocuronium doses consistently permitted tracheal intubation at 2.5 min in infants and 3 min in children.

The "gold standard" for tracheal intubation in children in whom venous access has not been achieved is intramuscular succinylcholine. However, concern about succinylcholine's adverse effects has encouraged development of alternative techniques. If another muscle relaxant is to be accepted clinically, its onset time should be comparable with that of intramuscular succinylcholine—4.0 ± 2.7 min to 90 ± 22% peak twitch depression with a dose of 4 mg/kg.** Several studies examined the response to nonintravenous administration of nondepolarizing muscle relaxants. Onset of intramuscular atracurium,[9] intramuscular mivacurium,[5] and subcutaneous pancuronium[10] is far slower than that of succinylcholine, suggesting limited clinical utility. Although differences in study design limit comparison, intramuscular rocuronium's time to 90% effect is similar to that of intramuscular succinylcholine. In addition, all patients given deltoid injections of rocuronium developed complete twitch depression; this contrasts with the variable peak effect with intramuscular succinylcholine, even with doses as large as 4 mg/kg.[11],** Therefore, our findings in phase I suggested that intramuscular rocuronium might be useful to facilitate tracheal intubation in infants and children.

One limitation of these studies, as of most studies of muscle relaxants, is the use of adductor pollicis response as a surrogate for intubating conditions. A more appropriate predictor of intubating conditions is onset time at the vocal cords or the diaphragm, both of which have a faster onset of paralysis than the adductor pollicis.[3,4] Only one study has examined the effects of intramuscular succinylcholine on these respiratory muscles. Mazze and Dunbar[12] reported that 2.2 mg/kg succinylcholine (a dose smaller than that typically recommended for intramuscular administration[13]) caused apnea in children at 3.5 ± 0.9 min. Although Mazze and Dunbar did not describe how onset of apnea was determined, nor did they evaluate intubating conditions, onset of apnea presumably parallels paralysis of the diaphragm and other respiratory muscles. Their value for onset of apnea is similar to our time to 50% depression of $\dot{V}_e$ with intramuscular rocuronium (phase I). This suggests that onset of intramuscular rocuronium at the diaphragm is comparable with that of 2.2 mg/kg intramuscular succinylcholine. We also demonstrate that administration of intramuscular rocuronium, 1,000 μg/kg in infants and 1,800 μg/kg in children, rapidly produces vocal cord immobility (phase II), thereby permitting tracheal intubation at 2.5 or 3 min.

To produce rapid onset of paralysis with intramuscular rocuronium, we gave doses larger than those typically given intravenously. These doses produced prolonged paralysis (time to initial recovery exceeded 1

** Sutherland GA, Bevan JC, Bevan DR: Neuromuscular blockade in infants following intramuscular succinylcholine in two or five per cent concentration. Can Anaesth Soc J 1983; 30:342–6.

h in most patients), a result of either the magnitude of the dose or delayed absorption. Without plasma concentration data, we cannot determine the rate or extent of absorption from the intramuscular depot. In addition, there are no published data on the duration of rocuronium doses >800 μg/kg intravenously in children. Whether residual paralysis can be adequately antagonized at the time of initial recovery of twitch has not been determined. For intravenous vecuronium (for which the spontaneous recovery profile in infants and children is similar to that for rocuronium), antagonism at 1% twitch tension permits rapid (<12 min) return to full neuromuscular function.[14] However, this finding might not apply to antagonism of intramuscular rocuronium because of differences in the routes of drug administration.†† Additional studies are needed to verify the earliest time after intramuscular administration of rocuronium at which antagonism will be effective.

Duration of intramuscular rocuronium markedly exceeds that of intramuscular succinylcholine. For example, Sutherland *et al.*** reported that time to complete recovery after 4 mg/kg intramuscular succinylcholine was 15.6 ± 4.0 min. This rapid recovery profile has probably encouraged use of intramuscular succinylcholine in brief (<20 min) procedures in infants and children. In contrast, the longer duration of intramuscular rocuronium suggests that its use should be limited to procedures exceeding 60 (or possibly 90) min. In addition, in certain instances, duration of action may exceed 2 h.

Before initiating this study, it was necessary to evaluate whether intramuscular injection of rocuronium would damage tissue. Studies in cats demonstrated no evidence of tissue damage (personal communication, H. Kenneth Spencer, Ph.D., Organon Inc., West Orange, NJ); similarly, we found no evidence of tissue toxicity in our patients. We were also concerned about potential adverse effects associated with large doses of rocuronium. We observed no systemic erythema or rash, and minimal local reaction at the injection site. In some patients, heart rate and/or blood pressure increased; we are unable to determine whether these cardiovascular changes resulted from stimulation from intramuscular injection or were due to rocuronium.

Several aspects of our study design warrant comment. First, we initially injected rocuronium into the leg and observed delayed onset, suggesting minimal utility.‡‡ In contrast, the fortuitous administration of rocuronium into the deltoid muscle resulted in rapid onset, presumably because of a more rapid absorption from that site. In support of this, Kirkpatrick *et al.*[15] reported that 10 min after intramuscular administration (the earliest time at which they obtained measurements), plasma morphine concentrations were greater with deltoid compared to gluteal injections. Our findings suggest that the deltoid is preferable for intramuscular injections.

Second, our study design differs from that used to determine dose requirements of muscle relaxants given intravenously. In most studies, each patient receives one of several doses, peak responses are plotted against doses, and the dose expected to depress twitch tension 90% (ED90) is determined by linear or nonlinear regression. In turn, the clinical dose is estimated as a multiple of the ED90. We chose not to use this traditional design; with intramuscular administration, dose and volume may influence absorption, thereby altering the plasma concentration *versus* time course. In addition, we were interested in estimating the rocuronium dose that would depress ventilation in a clinically relevant interval. This can only be estimated by administering relevant doses rather than by extrapolating based on the response to smaller doses. An "up–down" dosing approach permitted us to identify the optimal dose with a small number of patients; a similar "up–down" approach in phase II permitted identification of the optimal time for tracheal intubation.

A third issue involves the assessment of paralysis in phase I by measuring $\dot{V}_e$. Assuming that preventing coughing during tracheal intubation requires diaphragmatic paralysis, we might have estimated diaphragmatic strength by stimulating the phrenic nerve and measuring transdiaphragmatic pressure[16] or the electromyogram of the diaphragm.[3] Instead, we assumed that diaphragmatic paralysis would manifest as decreased $\dot{V}_e$ and that 50% depression of $\dot{V}_e$ would indicate onset—but not magnitude—of diaphragmatic paralysis. Spontaneous minute ventilation frequently

†† Compared with intravenous administration, continued absorption from the intramuscular depot might flatten the plasma concentration *versus* time curve during initial recovery; this slower decline in plasma concentration values might impair antagonism.

‡‡ With intramuscular mivacurium, no difference was observed in onset time and peak effect between quadriceps (n = 16) and deltoid (n = 4) injections.[5] However, because of the small sample size, additional studies with deltoid injection of mivacurium might be warranted.

increased 1 min after rocuronium administration; because intramuscular injection was the only change in noxious stimulation, we attributed this increase in $\dot{V}_e$ to pain from injection.

Another issue of study design involves our choice of anesthetic conditions for phase II. Yakaitis *et al.*[17] estimated that 1.12% end-tidal halothane would prevent movement during laryngoscopy in 50% of children aged 2–6 yr. Had we administered that halothane dose (adjusted to 1.02% at sea level), 50% of patients should have achieved good–excellent intubating conditions without any contribution from the muscle relaxant. Therefore, we selected a lighter plane of anesthesia, 0.82% end-tidal halothane in children older than 2.5 yr (80% of Yakaitis *et al.*'s value). Because halothane requirements decrease with age,[6] we selected a larger halothane concentration (1%) for younger children. In addition, to ensure that adequate intubating conditions would reflect the contribution of the muscle relaxant rather than that of the anesthetic alone, we gave no nitrous oxide, opioids, or intravenous anesthetics.§§ The response to intramuscular injection—frequent movement, including occasional extremity movement against gravity—confirms the light plane of anesthesia in our patients. Although we did not assess jaw opening at the time of intramuscular injection, we speculate that, in the absence of any rocuronium-induced paralysis, few (if any) patients could have been intubated successfully at this plane of anesthesia. This suggests that the successful intubating conditions we observed were facilitated by rocuronium.

It is likely that clinicians will maintain a deeper plane of anesthesia in children about to undergo tracheal intubation than we used in phase II. This might influence the response to intramuscular rocuronium. First, a larger halothane concentration should further potentiate the effect of rocuronium.[18] This greater magnitude of paralysis should provide better intubating conditions. Alternatively, greater potentiation might permit administration of a smaller dose of rocuronium, thereby decreasing duration of paralysis and increasing clinical utility. Second, because intubating conditions result from the combined contributions of anesthesia and paralysis,[19] a deeper plane of anesthesia might require a smaller contribution from the muscle relaxant; this might provide better intubating conditions at the optimal time or permit adequate conditions at an earlier time.

A final issue of study design involves our scoring system for intubating conditions. Several investigators assessed intubating conditions as good if the jaw was relaxed, vocal cords were immobile, and coughing was minimal or absent; conditions were scored as poor if vocal cords were mobile and coughing was vigorous. This system does not account for conditions we observed in many patients in which the vocal cords were immobile (thereby permitting tracheal intubation) but coughing was vigorous. To accommodate these conditions, we defined a new category, "adequate" intubating conditions. If the intent is to control the airway, and coughing is not of consequence, then the results of our study can guide clinical practice. However, if coughing might lead to dire consequences (*e.g.*, to a patient at risk for extrusion of vitreous), then larger doses of intramuscular rocuronium or a longer interval between drug administration and tracheal intubation might be needed. Finally, this study provides no insight into the potential for treatment of laryngospasm with intramuscular rocuronium.

In summary, deltoid (but not quadriceps) injection of 1,000 μg/kg rocuronium intramuscularly permits tracheal intubation in lightly anesthetized infants at 2.5 min; in children, 1,800 μg/kg rocuronium permits tracheal intubation at 3 min. Our results suggest that intramuscular rocuronium may facilitate elective tracheal intubation in infants and children in whom venous access has not been achieved. This permits clinicians to avoid both administration of intramuscular succinylcholine and potential adverse effects of a deep plane of inhalational anesthesia. However, the need for large intramuscular rocuronium doses to speed onset results in paralysis exceeding 1 h, possibly limiting its utility for brief procedures, particularly in children. Whether intramuscular rocuronium can be used to treat laryngospasm remains to be determined.

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§§ Scheller *et al.*[19] demonstrated that in the absence of a muscle relaxant, induction of anesthesia with propofol and alfentanil produces good-to-excellent intubating conditions.

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