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A Comparison of the Intubation Conditions between Mivacurium and Rocuronium during Balanced Anesthesia

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Background: **Comparisons of the intubation conditions with mivacurium and rocuronium from previous reports are confounded by the use of varied induction regimens. The authors compared intubation conditions of mivacurium, rocuronium, and a placebo at 90 s and their recovery profiles during anesthesia with nitrous oxide, oxygen, and propofol.**

Methods: **After induction with midazolam, fentanyl, and propofol in a randomized blinded study, 100 patients received one of the following treatments: 0.25 mg/kg mivacurium in divided doses (0.15 mg/kg followed by 0.1 mg/kg 30 s later); 0.45, 0.6, 0.9, or 1.2 mg/kg rocuronium; or placebo. Evoked thumb adduction was measured throughout. Intubation was attempted 90 s after the initial dose of mivacurium and other treatment doses by a "blinded" physician. Intubating conditions were graded as excellent, good, poor, or not possible. Spontaneous recovery was studied until a 25% initial twitch height was reached. Mean arterial blood pressure and heart rate changes between groups were determined before induction through 6 min after administration of the study drugs.**

Results: **There were no important changes or intergroup differences in mean arterial blood pressure and heart rate. Intubation conditions were good or excellent for both mivacurium and rocuronium at the 0.9 mg/kg dose (93%) and at the 1.2 mg/kg dose (100%). Rocuronium at the 0.6 mg/kg dose was excellent in 27% of patients, whereas rocuronium at the 0.45 mg/kg dose had the least number of excellent conditions and the most poor or not possible assessments. Patients given placebo could not be intubated. Times to maximum blockade for 0.9 and 1.2 mg/kg rocuronium were the shortest. The times to 25% recovery for 0.6 mg/kg rocuronium (mean ± SD = 27 ± 8.6 min), 0.9 mg/kg (43.1 ± 10.8), and 1.2 mg/kg (62.3 ± 17.4 min) were significantly longer than were those for mivacurium (17.4 ± 6.2 min).**

Conclusions: **Mivacurium in a 0.25 mg/kg divided dose and rocuronium at 0.9 mg/kg and 1.2 mg/kg provide good or excellent intubation conditions at 90 s in most patients. Rocuronium was faster in onset at the higher doses (0.9 and 1.2 mg/kg) but had more prolonged recovery times to 25% single twitch height. (Key words: Neuromuscular blockers; spontaneous recovery; tracheal intubation.)**

MIVACURIUM chloride is a short-acting benzylisoquinolium diester neuromuscular blocking agent with an effective dose to 95% twitch suppression (ED_{95}) of 0.08 mg/kg that is hydrolyzed by plasma cholinesterase.[1,2] A mivacurium dose of 0.15 mg/kg produces good to excellent intubation conditions 2.5 min after administration.[2] When injected over 60 s, an increase in the mivacurium dose to 0.25 mg/kg shortens the intubation time to 2 min with minimal hemodynamic change.[2,3] Good to excellent intubation conditions at 90 s without histamine-related decreases in blood pressure[4] were reported using mivacurium in a divided dose of 0.15 mg/kg followed by 0.1 mg/kg 30 s later.[4]

Rocuronium bromide is an aminosteroid, intermediate-acting nondepolarizing muscle relaxant that is similar to vecuronium but with a faster onset.[5] The ED_{95} of rocuronium is 0.3 mg/kg.[6] Good to excellent intubation conditions with short onset times have been reported for rocuronium at 0.6 mg/kg,[5,7-11] 0.9 mg/kg,[5] and 1.2 mg/kg.[5]

Comparisons of the intubation conditions of rocuronium at different doses and between rocuronium and other muscle relaxants have been confounded by the use of multiple anesthetic induction regimens that have employed agents that may, in themselves, facilitate endotracheal intubation.[5,6,7-14] The present study was designed to examine the intubating conditions, hemody-

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namic changes, and recovery profiles to 25% single twitch height associated with mivacurium (0.25 mg/kg, divided dose), rocuronium (0.45, 0.6, 0.9, 1.2 mg/kg), and a placebo employing the same anesthetic induction-intubation sequence.

Materials and Methods

One hundred patients having surgery who were classified as American Society of Anesthesiologists physical status I and II and had normal upper airway anatomy gave institutional review board-approved written informed consent. They were 18-65 yr old and were within 30% of ideal body weight. Exclusion criteria were a history of malignant hyperthermia; abnormal plasma cholinesterase levels; neuromuscular, neurologic, hepatic, and renal conditions that might influence neuromuscular function; and use of drugs that might alter the response to neuromuscular blockade or affect histamine release.

Patients were assigned to groups of 15 each according to a computer-generated randomization sequence that was stratified by the expected length of surgery. Patients having procedures expected to last 1 h or less received either 0.25 mg/kg mivacurium in a divided dose (0.15 mg/kg followed 30 s later by 0.1 mg/kg), 0.45 mg/kg rocuronium, or 0.60 mg/kg rocuronium. For procedures >1 h, patients were given either 0.25 mg/kg mivacurium (divided dose), 0.9 mg/kg rocuronium, or 1.2 mg/kg rocuronium. Mivacurium was included for both long and short procedure groups for the purpose of blinding. A seventh group (n = 10) received a crystalloid placebo. The surgical procedures were generally gynecologic and lower extremity orthopedic operations.

Two minutes after the intravenous administration of 1-2 mg midazolam and 2 μg/kg fentanyl, anesthesia was induced with 2 mg/kg propofol followed by an infusion of 100-120 $\mu g \cdot kg^{-1} \cdot min^{-1}$. At the loss of the eyelash reflex, evoked thumb adduction was transduced (Grass FT-10 force transducer and a Grass Mark 7 polygraph, Quincy, MA) in response to supramaximal ulnar nerve stimulation (Fisher-Paykel model NS252J constant current stimulator, Auckland, New Zealand) *via* surface electrodes at the wrist using single twitch stimuli at 1.0 Hz (1 twitch/s) for 30 s to establish the supramaximal stimulus rapidly. This was followed by 0.1 Hz (one twitch every 10 s) for 3 min to obtain a stable control response before the study drug or placebo was given.

Table 1. Tracheal Intubation Scoring System

Grade	Description
1: Excellent	Easy passage of endotracheal tube without coughing; vocal cords relaxed and abducted
2: Good	Passage of endotracheal tube with slight coughing or bucking; vocal cords relaxed and abducted.
3: Poor	Passage of endotracheal tube with moderate coughing or bucking; vocal cords moderately abducted
4: Not possible	Unable to intubate

Noninvasive systolic, diastolic, and mean arterial blood pressures, heart rates, and electric activity of the heart were monitored before premedication, before and after propofol induction, and after each dose of the study relaxant or placebo every minute for 6 min thereafter. Tracheal intubation was attempted 90 s after the administration of the first dose of mivacurium, the rocuronium dose, or the crystalloid placebo regardless of twitch height. Tracheal intubation was performed and graded according to the criteria listed in table 1 by a blinded, experienced anesthesiologist who was not involved with the protocol. Blinding was accomplished by sequestering the intubator during the baseline phase of the study and the injection of the study drug by having him or her wait outside the operating room until immediately before the scheduled intubation attempts or positioning such that he or she could not see the patient or the mechanomyograph during induction of anesthesia and study drug administration. In the event of a failure to intubate on the first attempt, the intubator was asked to stop and resume mask ventilation until maximum twitch suppression was achieved to permit a second attempt. For patients in the placebo group, 1 mg/kg succinylcholine was given to facilitate tracheal intubation after the initial intubation proved impossible and the unblinded investigator revealed that the patient did not receive a study drug. For this group, the study was terminated at this point and anesthesia was conducted as determined by the anesthesiologist of record. Anesthesia was maintained for the mivacurium and rocuronium groups with nitrous oxide and oxygen, a 100-120 $\mu g \cdot kg^{-1} \cdot min^{-1}$ propofol infusion, and incremental doses of fentanyl as clinically indicated.

The times to 80% suppression of single twitch at 0.1 Hz and maximum block were measured. All patients

Table 2. Mean Arterial Blood Pressure at Baseline, after Induction, and after Administration of the Study Drug

Group	Baseline	1 min after Propofol	Time after Injection of Study Drug				
			0.5 min	1.5† min	2.5 min	4.5 min	7.5 min
Mivacurium 0.25 mg/kg*	76 ± 11 (56–104)	62 ± 10 (45–82)	72 ± 11 (53–95)	77 ± 15 (43–111)	90 ± 18 (59–127)	84 ± 15 (64–132)	74 ± 12 (55–112)
Rocuronium 0.45 mg/kg	76 ± 13 (46–93)	69 ± 11 (50–78)	71 ± 10 (51–81)	93 ± 23 (61–135)	90 ± 16 (66–117)	82 ± 12 (64–105)	75 ± 15 (50–116)
Rocuronium 0.6 mg/kg	76 ± 12 (58–95)	61 ± 11 (46–87)	75 ± 11 (60–92)	82 ± 18 (60–118)	99 ± 17 (72–123)	85 ± 18 (67–128)	77 ± 10 (63–93)
Rocuronium 0.9 mg/kg	74 ± 12 (56–96)	59 ± 11 (45–75)	77 ± 11 (64–98)	81 ± 13 (61–100)	101 ± 18 (76–143)	92 ± 21 (64–138)	76 ± 11 (59–104)
Rocuronium 1.2 mg/kg	76 ± 11 (62–97)	67 ± 10 (46–75)	78 ± 12 (63–100)	80 ± 13 (66–103)	104 ± 15 (81–130)	85 ± 11 (71–107)	79 ± 17 (60–126)

Values are mean ± SD (range) (mmHg).

* n = 30.

† Time of intubation.

recovered to 25% of control twitch height before supplemental doses of the relaxant were given if needed.

Fisher's exact test was used to compare intubation grades among mivacurium and each rocuronium group. Analysis of variance was used to determine hemodynamics and changes in onset and recovery times between the mivacurium and rocuronium groups. Significance at $P \leq 0.01$ was determined using a Bonferroni correction (denominator = 5) for multiple comparison tests between mivacurium and each rocuronium group.

Results

Data from 98 patients were used for analysis. Two patients were excluded from analysis because they were mistakenly entered in the study twice.

Tables 2 and 3 show the hemodynamic measurements before induction, after propofol administration, and after injection of the muscle relaxants before intubation and every minute for 6 min thereafter. There were no significant changes in mean arterial blood pressures and heart rates between the mivacurium and rocuronium groups from baseline, after propofol induction, and after study drug administration.

Table 4 shows intubation conditions. Excellent intubation conditions were found for mivacurium (63%), 0.9 mg/kg rocuronium (79%), and 1.2 mg/kg rocuronium (93%). Rocuronium at 0.6 mg/kg was rated as excellent in 29%. Only one patient who received 0.45 mg/kg rocuronium at 90 s (7%) was given an excellent score, whereas 47% scored poor and 13% were impossi-

Table 3. Heart Rate at Baseline, after Induction, and after Administration of the Study Drug

Group	Baseline	1 min after Propofol	Time after Injection of Study Drug				
			0.5 min	1.5† min	2.5 min	4.5 min	7.5 min
Mivacurium 0.25 mg/kg*	68 ± 11 (52–89)	64 ± 9 (44–99)	70 ± 12 (52–104)	76 ± 12 (49–103)	77 ± 11 (53–103)	74 ± 13 (51–110)	68 ± 10 (49–105)
Rocuronium 0.45 mg/kg	64 ± 12 (46–88)	57 ± 11 (45–68)	65 ± 14 (46–96)	73 ± 23 (46–127)	78 ± 18 (46–111)	75 ± 17 (50–111)	73 ± 14 (47–100)
Rocuronium 0.6 mg/kg	66 ± 10 (47–80)	59 ± 9 (53–68)	67 ± 11 (47–85)	75 ± 14 (48–94)	80 ± 15 (46–107)	76 ± 14 (45–96)	71 ± 12 (46–92)
Rocuronium 0.9 mg/kg	68 ± 12 (43–82)	60 ± 10 (39–76)	69 ± 13 (42–88)	74 ± 11 (53–93)	83 ± 17 (55–114)	86 ± 17 (58–114)	79 ± 16 (57–114)
Rocuronium 1.2 mg/kg	70 ± 12 (54–93)	60 ± 11 (43–74)	73 ± 11 (55–91)	80 ± 16 (51–104)	87 ± 11 (65–104)	85 ± 11 (61–103)	82 ± 9 (69–94)

Values are mean ± SD (range) (beats/min).

* n = 30.

† Time of intubation.

Table 4. Intubating Conditions 90 s after the First Bolus Dose of Mivacurium and after Rocuronium Doses

Group	N	Excellent	Good	Poor	Not Possible
Mivacurium 0.25 mg/kg	30	19 (63)	9 (30)	1 (7)	1 (7)
Rocuronium 0.45 mg/kg*	15	1 (7)	5 (33)	7 (47)	2 (13)
Rocuronium 0.6 mg/kg	14	4 (29)	6 (43)	4 (29)	0
Rocuronium 0.9 mg/kg	14	11 (79)	2 (14)	1 (7)	0
Rocuronium 1.2 mg/kg	15	14 (93)	1 (7)	0	0
Placebo*	10	0	0	0	10 (100)

Values are no. (%).

* Significant at $P \leq 0.01$ using Fisher's Exact Test compared with the distribution of mivacurium.

ble to intubate. The patients who could not be intubated at the first attempt were intubated on the second attempt, once maximal blockade was achieved. No patient in the placebo group could be intubated. The intubation conditions were not statistically different for 0.25 mg/kg mivacurium (divided dose), 0.6 mg/kg rocuronium ($P < 0.03$), 0.9 mg/kg rocuronium, and 1.2 mg/kg rocuronium.

The times to 80% and maximum suppression of the single twitch were significantly shorter for 0.9 and 1.2 mg/kg rocuronium compared with mivacurium (table 5). Mivacurium and rocuronium at the 0.45 mg/kg dose had the shortest recovery times to 25% (table 5).

Discussion

We have shown that 0.25 mg/kg mivacurium in a divided dose and the higher doses of rocuronium (at 0.9 and 1.2 mg/kg) provided good and excellent intubation conditions with hemodynamic stability after a midazolam, fentanyl, and propofol induction sequence. With the same induction protocol, intubation was not possible when a crystalloid control was used instead of the neuromuscular blocking drugs.

Transient increases in heart rate and decreases in mean arterial blood pressure have been associated with bolus doses of mivacurium[3] secondary to a histamine effect but were not seen when mivacurium was administered as a divided dose.[4] Rocuronium administration has been associated with increased heart rates with nitrous oxide, oxygen, and halothane anesthesia[15] but not during high-dose narcotic-based anesthesia for cardiac surgery.[16,17] In the present study, there were no relaxant-related hemodynamic changes after an anesthetic regimen that was designed for routine surgical procedures of relatively modest duration.

Successful intubation attempts have been reported without the use of muscle relaxants using various induction drugs at different concentrations. Investigators have induced general anesthesia with sodium thiopental (500–750 mg),[18] varied doses of alfentanil followed by propofol (2–2.5 mg/kg),[19,20] propofol (2.5 mg/kg) with intubation within 45 s after administration,[21] and immediately after administration but before mask venti-

Table 5. Onset and Recovery Times of Mivacurium and Rocuronium

Group	Time to 80% Suppression of Single Twitch	Time to Maximum Suppression of Single Twitch	Time to 25% Recovery of Single Twitch
Mivacurium 0.25 mg/kg*	2.6 ± 0.8 (1.6–5.2)	4.3 ± 1.7 (1.7–8.5)	17.4 ± 6.2 (10.2–23.2)
Rocuronium 0.45 mg/kg	2.9 ± 1.4 (1.0–5.0)	5.9 ± 2.4 (2.0–10.0)	22.3 ± 7.1 (11.8–33.0)
Rocuronium 0.6 mg/kg	2.6 ± 1.0 (1.2–4.5)	5.8 ± 1.8 (3.0–8.7)	27.0 ± 8.6 (12.7–45.8)‡
Rocuronium 0.9 mg/kg	1.1 ± 0.3 (0.7–1.7)†	2.3 ± 0.7 (1.5–4.0)†	43.1 ± 10.8 (26.8–62.7)‡
Rocuronium 1.2 mg/kg	1.1 ± 0.3 (0.7–1.7)†	1.8 ± 0.5 (1.0–3.0)†	62.3 ± 17.4 (39.5–109.0)‡

Values are mean ± SD (range).

* n = 30.

† Significance at $P \leq 0.01$ for shorter onset time *versus* mivacurium.

‡ Significance at $P \leq 0.01$ for longer recovery *versus* mivacurium.

lation.[22] Others used 2.5 mg/kg propofol with 1.5 mg/kg lidocaine[23] or 2.5 mg/kg propofol with 1 or 1.5 mg/kg lidocaine plus 20 or 30 μg/kg alfentanil.[24,25] Although it is difficult to compare intubation conditions using multiple techniques, the overall failure rate or intubation conditions that would be classified as poor in these reports varied from 7–78%.[18–25] We included the crystalloid control group to assure ourselves that the induction regimen did not facilitate intubation and alter the intubation scores.

Rocuronium at 1.5 × ED_{95} (0.45 mg/kg) was not adequate for intubation at 90 s in our study with similar times to maximum blockades as previously reported without evaluations of intubation. However, intubation at 60 s was reported as good or excellent after 0.5 mg/kg rocuronium after induction with 3–5 μg/kg fentanyl and 4–6 mg/kg sodium thiopental supplemented by additional doses of these induction drugs.[9]

Rocuronium at 0.6 mg/kg (2 × ED_{95}) provided combined good to excellent intubation conditions in 72% of patients in the present study. This dose was reported to provide 100% good or excellent intubation conditions in 90 s after induction with 1–3 μg/kg fentanyl and 4–6 mg/kg sodium thiopental with 5–7 min of maintenance with 1% isoflurane, nitrous oxide, and oxygen and incremental doses of fentanyl.[11] Other investigators found comparable intubation scores for succinylcholine and rocuronium.[12,13] In one study, muscle relaxants or placebo were given 4 min after induction with 1 mg alfentanil, 1.5–2.5 mg/kg propofol, and ventilation with 1% halothane, nitrous oxide, and oxygen. This latter regimen facilitated intubation because one half of the control patients who did not receive a muscle relaxant had intubation scores of good or excellent.[12] In addition, the intubators were not blinded because of succinylcholine-induced fasciculations.[12] Similar results at 60 s were reported for 0.6 mg/kg rocuronium 10 min after induction with 1–3 μg/kg fentanyl, 3–5 mg/kg sodium thiopental, and further incremental doses as needed.[13] Others found no difference between 0.6 mg/kg rocuronium and succinylcholine for tracheal intubation 1 min after induction with 25 μg/kg alfentanil, 2.5 mg/kg propofol followed by propofol, an alfentanil infusion, and nitrous oxide and oxygen.[9] Magorian *et al.*[5] reported excellent intubation conditions 60 s after 0.6 mg/kg rocuronium after a 5–10-min period of incremental thiopental injections. The latter authors believed that the thiopental dose and timing of rocuronium administration unlikely affected results, although others[14] have found that good and excellent intubation conditions with 0.6 mg/kg rocuronium were only feasible when sodium thiopental was increased from 4 to 6 mg/kg and the intubation time was increased from 60 to 90 s. Interestingly, their data revealed overall longer onset times with the lower dose of sodium thiopental.

Excellent scores at 90 s were reported for all patients receiving 0.6 mg/kg rocuronium compared with 52% excellent and 20% good for those given 0.2 mg/kg mivacurium after induction with 2 mg midazolam, 1.5 μg/kg fentanyl, and 4 mg/kg sodium thiopental.[8] However, a comparison of the latter findings with our data is not possible because the results were influenced by the dose of mivacurium and difference in the scoring system used. These investigators[8] used a score based only on jaw relaxation and the laryngoscopic view of the vocal cords before intubation. They did not report actual intubation conditions, such as coughing and bucking, as in our study.

The times to maximum block that we obtained are similar to those found by others[26] monitoring twitch response. The times to maximum block studied with train-of-four[5,26,27] correspond more to the times to 80% suppression of single twitch in the current study, possibly a reflection of the greater sensitivity of the train-of-four to detect the onset of neuromuscular block compared with the single twitch. As could be realized in this discussion, it has been difficult to compare our results with previous studies because of significant differences in the protocol designs and the multiple drugs used.

Although we found that 0.25 mg/kg mivacurium (in a divided dose) and 0.9 and 1.2 mg/kg rocuronium had similar intubation scores and the shortest times to 80% and maximum suppressions of the single twitch, we observed significant differences in their recovery times to 25% single twitch height. Our recovery times for rocuronium are comparable to those of previous reports for 0.6 mg/kg[26–28] and 0.9 and 1.2 mg/kg doses.[5] In the present study, rocuronium at 0.9 and 1.2 mg/kg, unlike mivacurium, had more prolonged times and wider ranges to 25% recovery. The more predictable recovery profile of mivacurium makes it more suitable than rocuronium for shorter procedures and cases of unpredictable length.

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