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Evaluation of Neuromuscular and Cardiovascular Effects of Two Doses of Rapacuronium (ORG 9487) versus *Mivacurium and Succinylcholine*

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Background: **This study compares the neuromuscular blocking and cardiovascular effects of rapacuronium (ORG 9487), a new aminosteroid nondepolarizing muscle relaxant, to recommended intubating doses of succinylcholine and mivacurium.**

Methods: **Adult patients were randomized in an open-label fashion to receive 1–5 μg/kg fentanyl before 1.5 mg/kg propofol induction followed by 1.5 or 2.5 mg/kg rapacuronium, 1.0 mg/kg succinylcholine, or 0.25 mg/kg mivacurium (*i.e.*, 0.15 mg/kg followed by 0.1 mg/kg 30 s later).**

Results: **Patient neuromuscular blockade status was monitored by measuring the train-of-four response to a supramaximal stimulus at the ulnar nerve every 12 s. Percentage of the first twitch of the train-of-four (T_1) at 60 s was similar in patients receiving 1.5 mg/kg rapacuronium, 2.5 mg/kg rapacuronium, and succinylcholine and was significantly less than in patients in the mivacurium group (26, 16, and 18%, respectively, *vs.* 48%; $P < 0.01$). Times to 80% T_1 depression were also similar among patients in the 1.5 mg/kg rapacuronium, 2.5 mg/kg rapacuronium, and succinylcholine groups and significantly longer in the mivacurium group (62, 54, and 54 s, respectively, *vs.* 112 s; $P < 0.01$). Clinical duration was longer in all groups compared with the succinylcholine group; however, clinical duration in the 1.5 mg/kg rapacuronium group was shorter compared with the mivacurium group (15 *vs.* 21 min, respectively; $P < 0.01$). Heart rate changes were mild in the 1.5 mg/kg rapacuronium, succinylcholine, and mivacurium groups. The patients in the 2.5mg/kg rapacuronium group had significantly higher heart rates compared with patients in the mivacurium group. No differences were found in blood pressure changes among patients in the four groups.**

Conclusions: **Rapacuronium, 1.5 and 2.5 mg/kg, produced neuromuscular blockade as rapidly as succinylcholine and significantly faster than mivacurium. Although succinylcholine continued to show the shortest duration, 1.5 mg/kg rapacuronium used a rapid onset and a relatively short duration and may be considered an alternative to succinylcholine. (Key words: Monitoring; neuromuscular blockade; neuromuscular relaxant.)**

THE search for a nondepolarizing muscle relaxant as an acceptable substitute for succinylcholine has been ongoing. The desire to achieve a rapid onset similar to that of succinylcholine, with an agent devoid of its undesirable side effects (hyperkalemia, myalgia, malignant hyperthermia trigger, among others), led to various neuromuscular blocking dosing regimens. Priming techniques, timing principles, and high-dose techniques have all been used but are fraught with inherent dangers and often are accompanied by an undesirable prolongation of effect. The development of a rapid-onset, short-duration nondepolarizing relaxant would be a welcome addition to the muscle relaxant armamentarium.

Rapacuronium (ORG 9487) is an aminosteroid neuromuscular blocker that has been undergoing clinical trials in humans and has shown a rapid onset with a relatively short duration of action.[1–5] The purpose of this multicenter trial was to evaluate doses of rapacuronium at 1.5 and 2.5 mg/kg and compare onset, duration, and cardiovascular effects to recommended intubating regimens of mivacurium and succinylcholine in adult patients receiving a balanced anesthetic.

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Methods and Materials

Institutional approval for the study protocol was obtained, and all patients gave informed, written consent. Adult patients classified as American Society of Anesthesiologists physical status I, II, or III were eligible to participate in the study. Patient recruitment was conducted to ensure that approximately 25% of study patients would be older than 65 yr of age. Patients were excluded from study participation if they were pregnant, as determined by history and physical examination or a positive urine or serum human chorionic gonadotropin test. Other exclusion criteria included presence of significant cardiovascular, renal, or hepatic dysfunction, neuromuscular disorders, or family history of malignant hyperthermia. Patients were also excluded if a rapid-sequence intubation was envisioned, if they were receiving antihistamines, anticonvulsants, or aminoglycoside or polypeptide antibiotics long-term. Obese patients, those exceeding ideal body weight by 30% or more, were excluded. Ideal body weight was calculated by the following formulae: male ideal body weight = 110 lb + 5 lb/inch above or −5 lb/inch below 5 ft of height; female ideal body weight = 100 lb + 5 lb/inch above or −5 lb/inch below 5 ft of height.

All patients were premedicated with 1 or 2 mg intravenous midazolam. All standard monitors were used, and the noninvasive blood pressure cuff was placed on the side contralateral to the neuromuscular monitoring. Anesthesia was induced with 1–5 μg/kg intravenous fentanyl followed by 1.5 mg/kg intravenous propofol and maintained with $N_20{:}0_2$ in a 60:40 mix. Halogenated agents were not used throughout the study. Intravenous increments of fentanyl 1 or 2 μg/kg were given, as dictated by patient condition intraoperatively. The lungs were mechanically ventilated, and ventilation was adjusted to maintain end-tidal carbon dioxide (ET_{CO_2}) pressure between 35 and 40 mmHg. After the patients lost consciousness, before the administration of muscle relaxants, baseline train-of-four readings were obtained. Surface electrodes were placed at the wrist to stimulate the ulnar nerve. The four sites used three different types of neuromuscular transmission monitoring. Three investigators (R.M, H.N., F.F.F.) used a force-displacement transducer (Myotrace model APM-6; Professional Instruments, Houston, TX); two (T.W., R.B.) used a Digi-Stim II Peripheral Nerve Stimulator (Neurotechnology, Houston, TX); and two (R.F., C.S.) used a Datex Relaxograph (Datex-Ohmeda, Helsinki, Finland) to record the electromyographic responses of the adductor pollicis to train-of-four stimulation. Supramaximal square-wave impulses with a duration of 0.2 ms were administered at 2 Hz, lasting 1.5 s. A constant-current stimulator was used to deliver a train-of-four impulse every 12 s, and the results were continuously recorded on paper using a polygraph. After obtaining baseline readings for at least 60 s to ensure satisfactory electrical stimulator and recording function, patients received study medications.

In an open-label manner, patients were randomized to receive 1.5 or 2.5 mg/kg intravenous rapacuronium (1.5R and 2.5R groups, respectively), 1 mg/kg succinylcholine (S group), or 0.25 mg/kg mivacurium (M group). Doses of rapacuronium and succinylcholine were administered over 5-s periods; mivacurium was administered using a divided-dose paradigm (*i.e.*, 0.15 mg/kg intravenous followed by 0.1 mg/kg 30 s later). In all groups, the study medications were administered over 5 s. All muscle relaxants were injected into the injection port most proximal to the insertion site of a rapidly flowing intravenous line, and all timed measurements were determined from the end of injection. In the patients in the M group, the measurements were taken from the end of subsequent fractionation of the dose.

Baseline heart rate and blood pressures were measured before the administration of fentanyl, every minute for the first 5 min, and 10 min after muscle relaxant dosing. Percent changes from baseline were summarized by treatment group and time point. Tracheas were intubated 5 min after muscle relaxant administration.

The following neuromuscular blockade parameters were recorded: percentage of the first twitch of the train-of-four (T_1) at 60 s; onset time (defined as time to 80% T_1 depression); time to peak effect (or maximum block), defined as the first T_1 that shows no further decrease over three consecutive trains-of-four after study drug administration; time to spontaneous 25% T_1 recovery (REC_{25}, clinical duration), time to 70% $T_4{:}T_1$ ratio recovery (REC_{70}), time to 80% $T_4{:}T_1$ ratio recovery (REC_{80}), and time to 90% T_1 recovery (REC_{90}).

Patients were observed postoperatively throughout the stay in the postanesthesia care unit. They were questioned regarding the presence of muscle pain, nausea, and vomiting. All other reported side effects were recorded. Patients were no longer observed after discharge from the postanesthesia care unit.

A sample-size calculation was performed based on the ability to detect a 5-min difference in clinical duration at 80% power and at the 0.05 significance level. Data were analyzed using two-factor analysis of variance for comparing the patients in the two rapacuronium groups to

Table 1. Patient Demographics

	1.5 mg/kg Rapacuronium (n = 35)	2.5 mg/kg Rapacuronium (n = 31)	1 mg/kg Succinylcholine (n = 31)	0.25 mg/kg Mivacurium (n = 32)
Age (yr ± SD)	45 ± 18	43 ± 14	46 ± 18	48 ± 19
Weight (kg ± SD)	73 ± 16	68 ± 14	69 ± 14	72 ± 14
Gender (m:f)	21/12	8/21	17/14	15/17
ASA class				
I	16	12	16	12
II	15	15	14	17
III	2	2	1	3

Age and weight expressed as mean ± standard deviation (SD). Gender and ASA expressed as numbers of patients.

* $P \leq 0.05$ *versus* the other groups.

those of the succinylcholine and mivacurium groups, using the treatment group and site as the two factors. The analysis was performed on untransformed data (parametric approach) and rank-transformed data (nonparametric approach). Pairwise comparisons in each of the two rapacuronium groups to the succinylcholine and mivacurium groups with respect to the cardiovascular assessments 1–5 min after drug administration were carried out using repeated-measures analysis on rank-transformed (nonparametric) and untransformed (parametric) data. Differences among treatment groups were considered statistically significant $P \leq 0.05$.

Results

Demographics

A total of 129 patients were enrolled in the study and 125 received study medication (35 patients in group 1.5R, 31 in group 2.5R, 31 in group S, and 32 in group M). Four patients were enrolled but were not studied for the following reasons: one patient because of surgeon request, one because of mechanical problems with the mechanomyograph, one because of cancellation of surgery, and one because of inability to obtain preoperative laboratory analyses. Demographics were similar among the patients in the four groups, except for a greater percentage of women in the 2.5R group (table 1).

Neuromuscular Data

The results for onset of relaxation are reported in table 2. Percentage of T_1 at 60 s was similar in the patients in groups 1.5R, 2.5R, and S and significantly lower than in the patients in the M group ($P \leq 0.01$). Times to 80% T_1 depression were also similar among the patients in groups 1.5R, 2.5R, and S and were significantly shorter in duration in the patients receiving rapacuronium at both doses compared with group M ($P \leq 0.01$). Time to peak effect was similar between groups 2.5R and S, longer in group 1.5R compared with patients in group S ($P < 0.01$), and significantly longer in patients in group M compared with those in both the rapacuronium groups (1.5R, $P \leq 0.05$, and 2.5R, $P \leq 0.01$).

The data of recovery profiles of the patients in the four

Table 2. Onset of Relaxation Data

	1.5 mg/kg Rapacuronium	2.5 mg/kg Rapacuronium	1 mg/kg Succinylcholine	0.25 mg/kg Mivacurium
Percent T1 at 60 s [median: range]	26 ± 30 [15: 0–94]	16 ± 26 [1: 0–95]	18 ± 31 [0.5: 0–100]	48 ± 31* [50: 4–100]
Time to 80% T1 depression (seconds) [median: range]	56 ± 19 [51: 23–96]	48 ± 18 [50: 11–80]	48 ± 18 [44: 25–80]	77 ± 30* [73: 28–169]
Time to peak effect (s) [median: range]	98 ± 46 [86: 35–219]	68 ± 25† [63: 30–115]	67 ± 27† [59: 31–138]	127 ± 50* [116: 64–261]

Values are mean ± standard deviation, unless otherwise noted and are based on muscle relaxant end of administration time (or end of the second fractionated dose in the case of the patients in the mivacurium group).

* $P \leq 0.01$ *versus* the patients in the other groups. For percent T1 at 60 s, nonparametric analyses were used based on the analysis of variance for the rank-transformed data.

† $P < 0.01$ *versus* patients in the 1.5 rapacuronium and mivacurium groups.

Table 3. Recovery Data

	1.5 mg/kg Rapacuronium	2.5 mg/kg Rapacuronium	1 mg/kg Succinylcholine	0.25 mg/kg Mivacurium
Clinical duration (min)	15.4 ± 6*	25 ± 10†	9 ± 3‡	21 ± 5
Recovery rate (min)	8.3 ± 5	13 ± 9	2.1 ± 1‡	8.8 ± 5
Time to 90% T1 recovery (min)	27.4 ± 12	41.6 ± 12	11.5 ± 3‡	31.9 ± 10
Time to 70% T4:T1 recovery (min)	38.2 ± 21	62.8 ± 21*	—	31.9 ± 7
Time to 80% T4:T1 recovery (min)	37.9 ± 13	73.1 ± 25*	—	33.7 ± 8

Values are mean ± standard deviation (SD). Data for 70% and 80% T4:T1 ratio were not collected for the patients in the succinylcholine group.

Clinical duration = time to spontaneous 25% recovery of T1; Recovery rate = time to recover from 25% to 75% T1.

* $P < 0.01$ *versus* mivacurium group.

† $P = 0.05$ compared to group M.

‡ $P < 0.01$ *versus* other groups.

groups are presented in table 3. *Clinical duration,* defined as time to spontaneous 25% T_1 recovery (REC_{25}) was significantly longer in all groups ($P < 0.01$), compared with the patients in group S. Although patients in group 1.5R had significantly shorter clinical duration times compared with mivacurium-treated patients ($P \leq 0.01$), patients in the 2.5R group had a longer time than the patients in the M group. Times to spontaneous REC_{90} were shorter in patients in group S, compared with all other groups ($P < 0.01$). No differences were found in the times to REC_{90} recovery between the patients receiving rapacuronium and mivacurium. *Recovery rate index,* defined as the time for T_1 to recover spontaneously from 25% to 75%, was shorter in patients in group S compared with all other groups ($P < 0.01$). No differences in recovery rate index were found if the patients receiving rapacuronium were compared with the mivacurium-treated patients. Times to 70% and 80% T_4:T_1 were similar among the patients in groups 1.5R and M; the patients in group 2.5R showed a longer time to this recovery compared with the patients in group M.

Cardiovascular Data

The effects on heart rate are depicted in figure 1. The patients in all groups showed similar baseline heart rates. The mean percent change in heart rate from baseline in the first 5 min did not exceed 9% in groups 1.5R, S, and M. Heart rate change in the patients in group 2.5R ranged from a mean increase of 5–14%. Mivacurium-treated patients consistently had lower heart rates, with differences reaching statistical significance compared with the patients in both rapacuronium-treated patient groups ($P < 0.01$). Significant changes (*i.e.*, greater than 30% from baseline) in heart rate occurred most com-

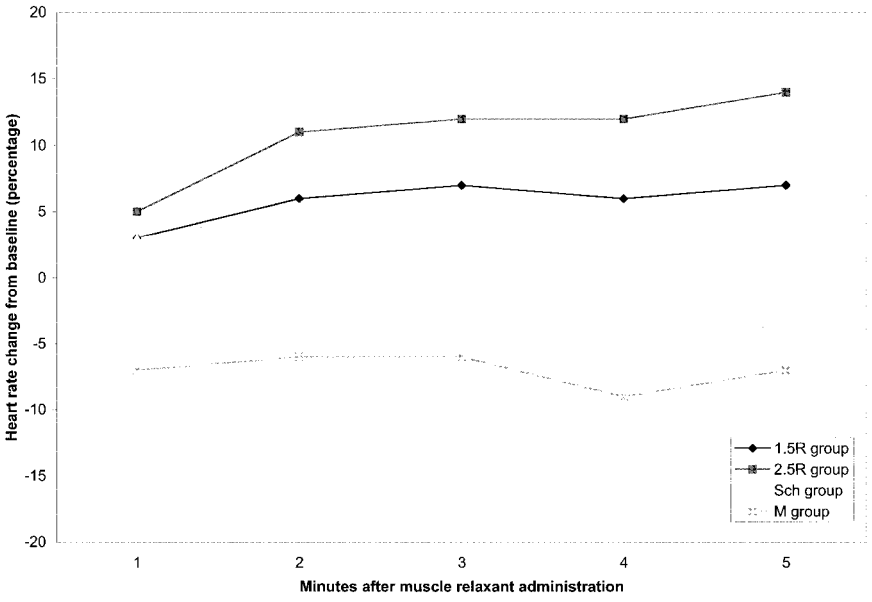

Fig. 1. Heart rate change after muscle relaxant administration, expressed as mean in minutes. No statistically significant differences were seen among the patients in the four groups.

monly in the patients in group 2.5R. Nine patients in group 2.5R had significant increases in heart rate compared with two, three, and two in groups 1.5R, S, and M, respectively.

Systolic, diastolic, and mean blood pressure changes are presented in table 4 and figure 2. The mean percentage changes in either systolic or diastolic blood pressure in the four groups during the 5 min after muscle relaxant administration were similar, and the differences were not statistically significant. Mild changes in blood pressure commonly were seen in all groups, and mean systolic and diastolic pressures decreased from 5–15% and 5–18%, respectively. Significant changes in mean arterial pressure occurred less commonly in the patients in group 1.5R, compared with patients in the other groups.

Adverse Events

Three instances of truncal erythema were seen, all in the patients receiving mivacurium, and two episodes of intraoperative bronchospasm were seen, one each in the two rapacuronium groups. Four patients had serious postoperative adverse events. These consisted of urinary retention, ileus, atrial fibrillation, and intracerebral hemorrhage with respiratory failure. None of the serious adverse events were thought by the investigators to be related to the study medications. No patients were excluded from the study because of adverse events. The patients in groups S and M reported nausea and vomiting more frequently than the patients in the rapacuronium groups ($P < 0.05$). Two patients in group 1.5R, two in group 2.5R, three in group S, and five in group M complained of nausea while in the postanesthesia care unit. One patient in group 1.5R, none in group 2.5R, two in group S, and three in group M vomited during their postanesthesia care unit stays. Myalgia was reported in one patient in group 2.5R and in three of the patients in group S.

Discussion

In this report, data are presented regarding the neuromuscular and cardiovascular characteristics of rapacuronium, a new aminosteroid nondepolarizing muscle relaxant not available for clinical use. The study was conducted in a randomized open-label fashion, but this was not thought to be a significant drawback. All data contributing to the primary goals of the study (*e.g.*, neuromuscular twitch results, heart rate and blood pressure readings) were objective measurements not likely

Table 4. Systolic/Diastolic Blood Pressure Data

	Baseline	1 min	2 min	3 min	4 min	5 min	10 min
1.5 mg/kg rapacuronium	111 ± 22/64 ± 12	−8 ± 10/−9 ± 15	−11 ± 12/−8 ± 18	−9 ± 20/−8 ± 21	−8 ± 17/−7 ± 16	−5 ± 17/−5 ± 17	16 ± 25/22 ± 38
2.5 mg/kg rapacuronium	105 ± 17/60 ± 12	−8 ± 12/−11 ± 17	−13 ± 14/−18 ± 15	−10 ± 15/−17 ± 15	−14 ± 16/−18 ± 19	−11 ± 15/−15 ± 19	7 ± 25/5 ± 27
1 mg/kg succinylcholine	111 ± 25/64 ± 14	−9 ± 13/−8 ± 17	−8 ± 12/−6 ± 18	−7 ± 13/−5 ± 17	−6 ± 15/−7 ± 17	−4 ± 17/−7 ± 16	2 ± 17/7 ± 23
0.25 mg/kg mivacurium	114 ± 23/67 ± 14	−11 ± 16/−13 ± 17	−15 ± 16/−18 ± 15	−12 ± 20/−13 ± 21	−13 ± 20/−16 ± 20	−11 ± 23/−11 ± 22	8 ± 27/3 ± 24

Data are mean ± standard deviation (SD). Baseline blood pressure expressed as mmHg mean ± standard deviation and changes (1–10 min) recorded as percent change from baseline ± standard deviation.

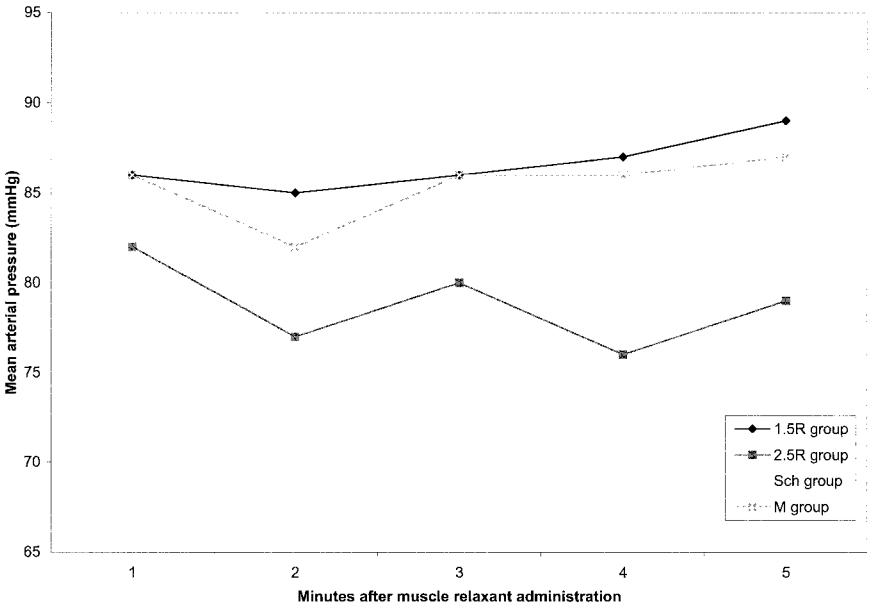

Fig. 2. Mean arterial pressure change after muscle relaxant administration, expressed as mean in millimeters of mercury. No statistically significant differences were seen among the patients in the four groups.

to be influenced by investigator bias. Because the primary aim of this study was to determine the neuromuscular and cardiovascular effects of rapacuronium and compare them with those of succinylcholine and mivacurium, subjective assessments, such as intubation scores, were not included in this review.

No potent volatile agents were used in our study to prevent potentiation of neuromuscular block; however, nitrous oxide was used during the maintenance of anesthesia. Although nitrous oxide has been described to potentiate succinylcholine-induced blockade,[6] it is generally accepted that its potentiation of a nondepolarizing block is weak and would not be expected to affect the results.

The results of the current study support the rapid onset time described in previous studies.[1–5] For example, Kahwaji *et al.*[5] investigated five dosages of rapacuronium (0.5, 1.0, 1.5, 2.0, and 2.5 mg/kg) in a nitrous oxide–oxygen–propofol anesthetic. They found a mean of 43% T_1 at 60 s, with 81% of patients demonstrating good to excellent intubating conditions at 60 s after administration of 1.5 mg/kg rapacuronium. Although the 2.5-mg/kg dose evaluated in our study yielded a mean of 16% T_1 at 60 s, 1.5 mg/kg provided T_1 depression to 26% of control. Although not evaluated in our study, it is reasonable to assume that in an anesthetized patient these degrees of twitch depression would be expected to provide satisfactory intubating conditions. This may be particularly true with rapacuronium because it has been found to possess a faster onset at laryngeal muscles than at the adductor pollicis longus.[1] Faster laryngeal onset times also have been described for succinylcholine,[7] rocuronium,[8] mivacurium,[9] and atracurium.[10] Although the faster onset at the larynx is probably caused by increased blood flow compared with the blood flow of the adductor pollicis muscle, the faster onset *per se* may be related to its lower potency.[11] In drugs of low potency, large numbers of molecules need to be administered, thereby producing a large gradient between plasma and site of action. Other explanations may be the relatively higher lipophilic profile of rapacuronium[12] (octanol/Krebs:water partition coefficient = 1.05) as compared with other neuromuscular blocking agents (*i.e.*, rocuronium, 0.163, and vecuronium, 0.165), which allow it to traverse cell membranes rapidly, producing more rapid equilibration between plasma and site of action or its calcium channel blocking action, increasing capillary blood flow and decreasing contractility.[13]

Patients in both rapacuronium groups showed onset times comparable to succinylcholine and a significantly faster onset time than mivacurium. This is even more impressive if one considers the finding that neuromuscular twitch measurements were determined at the end of injection, in the case of mivacurium after subsequent fractionation of the dose, a technique that would bias the results in favor of a shorter onset time with mivacurium.

The clinical durations (REC_{25}) of both doses of rapacuronium were significantly longer ($P < 0.01$) than the duration of succinylcholine (15.4, 25.0, 9.0, and 21.1

min for groups 1.5R, 2.5R, S, and M, respectively). This is consistent with findings by other investigators.[2] Patients receiving 1.5 mg/kg rapacuronium showed a significantly shorter clinical duration than mivacurium-treated patients (15.4 *vs.* 21.1 min, $P \leq 0.01$); the patients treated with 2.5 mg/kg showed a longer duration compared with mivacurium (25 *vs.* 21.1 min; $P = 0.05$). To reduce clinical duration, Wierda *et al.*[2] administered 40 μg/kg neostigmine 2 min after administration of 1.5 mg/kg rapacuronium. Patients receiving the rapacuronium–neostigmine sequence recovered neuromuscular function more rapidly than the succinylcholine-treated patients (*e.g.*, $REC_{25} = 5.7$ *vs.* 8 min; $P < 0.05$). With early reversal, Wierda *et al.*[2] also found rapid recovery of the T_4:T_1 ratio to 20% (6.6 min) in patients receiving 1.5 mg/kg rapacuronium. This may indicate a relative margin of safety. In another study that evaluated atracurium, diaphragmatic function was reasonably restored at this level of train-of-four recovery.[14]

The effect on heart rate on the patients in this study was minimal. Mean heart rate changes for the patients in groups 1.5R, S, and M were within 10% of baseline, which was measured before intubation. Because heart rate and blood pressure recordings were taken during the first 5 min after study drug administration and because laryngoscopy was performed at that time, endotracheal intubation would not be expected to influence those results. Laryngoscopy and intubation could have influenced the results at 10 min. Patients in group 2.5R were found to have heart rates statistically significantly higher than the patients in group M; the former increased from baseline and the latter decreased from baseline. These findings are consistent with those of other investigators[15] who found little difference in heart rate after comparing five doses of rapacuronium (0.5, 1, 1.5, 2, and 2.5 mg/kg) with placebo in a nitrous oxide–barbiturate–fentanyl anesthetic.

As seen in this study, both doses of rapacuronium produced neuromuscular blockade as rapidly as succinylcholine and significantly faster than mivacurium. Duration was shortest in succinylcholine-treated patients, although 1.5 mg/kg rapacuronium had a shorter duration of action than mivacurium, and 2.5 mg/kg rapacuronium had a longer duration than mivacurium. Rapacuronium at a dose of 1.5 mg/kg appears to be a suitable alternative to succinylcholine. Higher doses appear to decrease onset time further at the expense of a longer duration.

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