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Neuromuscular Effects of Rocuronium Bromide and Mivacurium Chloride Administered Alone and in Combination

*Mohamed Naguib, M.B., B.Ch., M.Sc., F.F.A.R.C.S.I., M.D.**

Background: **Rocuronium is a new nondepolarizing neuromuscular blocking agent with a rapid onset but with intermediate duration of action. Mivacurium, on the other hand, is a new short-acting nondepolarizing neuromuscular relaxant, but of slower onset of action. The current study was undertaken to characterize the interaction between rocuronium and mivacurium.**

Methods: **In the first study, the dose–response relations of rocuronium, mivacurium, and their combination were studied in ASA physical status 1 or 2 patients during thiopental–fentanyl–N_2O anesthesia. One hundred ten patients, randomly assigned to 1 of 11 groups of 10 patients each, received mivacurium 30, 50, or 70 $\mu g \cdot kg^{-1}$; rocuronium 100, 200, 250, or 300 $\mu g \cdot kg^{-1}$; or an equieffective combination of both drugs (1 ED_{50} rocuronium + 1 ED_{50} mivacurium; ½ ED_{50} rocuronium + ½ ED_{50} mivacurium; ¼ ED_{50} rocuronium + ¼ ED_{50} mivacurium; or ⅛ ED_{50} rocuronium + ⅛ ED_{50} mivacurium, where ED_{50} is the dose producing 50% depression of the first twitch height). In the second study, 50 patients, ASA physical status 1 or 2, anesthetized with thiopental–fentanyl–N_2O, were randomly allocated to 5 groups of 10 patients each to receive one of the following neuromuscular blocking drugs or drug combination: rocuronium 600 $\mu g \cdot kg^{-1}$ (group 1), mivacurium 150 $\mu g \cdot kg^{-1}$ (group 2) rocuronium 150 $\mu g \cdot kg^{-1}$ + mivacurium 37.5 $\mu g \cdot kg^{-1}$ (group 3), rocuronium 300 $\mu g \cdot kg^{-1}$ + mivacurium 75 $\mu g \cdot kg^{-1}$ ((group 4), or rocuronium 600 $\mu g \cdot kg^{-1}$ + mivacurium 150 $\mu g \cdot kg^{-1}$ (group 5).**

Results: **The calculated ED_{50} values and their 95% confidence intervals were 125 (122–129) and 37 (36–38) $\mu g \cdot kg^{-1}$ for the rocuronium and mivacurium groups, respectively. The interaction between rocuronium and mivacurium was found to be synergistic. The measured ED_{50} of the mixture was only 62% of the predicted value assuming a purely additive interaction. In the second study, rocuronium 600 $\mu g \cdot kg^{-1}$ group and group 3 had similar onset times (99 [74–123] and 114 [100–128] s, respectively), which were significantly shorter than that observed in the mivacurium 150 $\mu g \cdot kg^{-1}$ group (178 [149–206] s). Onset times in groups 4 and 5 were significantly shorter than that in each of the other study groups (69 [63–76] and 73 [65–80] s, respectively). Clinical duration of action (recovery of T1 to 25% of baseline twitch height) was significantly greater in group 5 (55 [51–60] min) than with all other doses and agents, and briefest ($P < 0.01$) with mivacurium 150 $\mu g \cdot kg^{-1}$ (14.5 [12.6–16.5] min) and group 3 (14.7 [13.4–16] min).**

Conclusions: **The interaction between rocuronium and mivacurium was found to be synergistic. (Key words: Interactions (drug): isobolographic analysis; mivacurium chloride; rocuronium bromide (ORG 9426). Monitoring: train-of-four. Neuromuscular relaxants: mivacurium chloride; rocuronium bromide. Potency: ED_{50}.)**

ROCURONIUM bromide (ORG 9426, Organon Teknika, Belgium) and mivacurium chloride are nondepolarizing neuromuscular blocking agents recently introduced to clinical practice.[1,2] Mivacurium has a considerably shorter duration of action than any other currently used nondepolarizing agent.[2] Rocuronium, on the other hand, has a brief onset but an intermediate duration of action.[1] These differences in the pharmacodynamic characteristics might confer some advantage in combining the two drugs in clinical practice.

It has been shown that concomitant administration of some mixtures of nondepolarizing neuromuscular blocking compounds (*d*-tubocurarine and gallamine[3]; pancuronium and gallamine[3]; or pipecuronium and vecuronium[4]) does result in additive effect. Other combinations of nondepolarizing neuromuscular blocking agents (pancuronium and metocurine[3,5]; gallamine and metocurine[3]; or *d*-tubocurarine and pancuronium[3,5]) clearly demonstrate synergistic effects. Although Waud and Waud[6] have suggested that potentiation can be entirely of postsynaptic origin, others have attributed synergism to both presynaptic and motor end-plate effects.[5]

The current study was undertaken to characterize the interaction of rocuronium and mivacurium in humans by the isobolographic method and to compare the onset and duration of neuromuscular blockade produced by

* Associate Professor.

Received from the Department of Anaesthesia and the Intensive Care Unit, King Saud University, Faculty of Medicine at King Khalid University Hospital, Riyadh, Saudi Arabia. Accepted for publication April 18, 1994.

Address reprint requests to Dr. Naguib: Department of Anaesthesia, King Khalid University Hospital, P.O. Box 7805, Riyadh 11472, Saudi Arabia.

rocuronium and mivacurium in combination with that produced by each drug alone.

Materials and Methods

Interaction Studies

After obtaining institutional approval and informed consent, we studied 110 ASA physical status 1 or 2 patients of both sexes, aged 18–54 (mean 31.7 [SD 8.55]) yr and weighing 45–86 (mean 66.5 [SD 9.5] kg. All patients were undergoing elective procedures, had no neuromuscular, hepatic or renal disease, and were not taking any drug known or suspected to interfere with neuromuscular function.

All patients received 2 mg oral lorazepam 90 min before operation. An infusion of lactated Ringer's solution was given intravenously before induction of anesthesia. The electrocardiogram, hemoglobin O_2 saturation by pulse oximetry, and arterial blood pressure were monitored. Temperature was monitored by a nasopharyngeal thermistor and maintained at 36.5 ± 0.5°C.

Anesthesia was induced with thiopental 5 $mg \cdot kg^{-1}$, and was maintained with N_2O and O_2 (70:30) supplemented with fentanyl 4–5 $\mu g \cdot kg^{-1}$. The trachea was sprayed with 4 ml of 4% lidocaine and was intubated without the use of neuromuscular relaxants. After intubation, the concentrations of the N_2O, O_2, and CO_2 were determined continuously by a multiple-gas analyzer (Capnomac, Datex Instrumentarium Corporation, Helsinki, Finland). Ventilation was adjusted to maintain normocapnia (end-tidal CO_2 pressure 35–40 mmHg).

The ulnar nerve was stimulated supramaximally at the wrist with square pulses of 0.2-ms duration delivered in a train-of-four (TOF) sequence at 2 Hz every 12 s by g a Myotest peripheral nerve stimulator (Biometer International, Odense, Denmark). The resultant contraction of the adductor pollicis muscle was recorded with a force-displacement transducer and neuromuscular function analyzer (Myograph 2000, Biometer International, Odense, Denmark). Preload tension on the thumb was maintained at 300 g throughout the investigation. The first twitch (T1) of the TOF was considered the twitch height.

The following predetermined doses of drugs were administered: mivacurium 30, 50, or 70 $\mu g \cdot kg^{-1}$ or rocuronium 100, 200, 250, or 300 $\mu g \cdot kg^{-1}$. Studies of the single-drug groups were concluded first, so that doses of combination could be planned. From the dose–response curves of the neuromuscular agents administered alone, the respective effective doses resulting in a 50% reduction of T1 (ED_{50}) were determined. Subsequently, a dose–response curve was obtained by the administration of the two drugs in a constant dose ratio based on the ED_{50} values of the single agent. The following dosage combinations were administered (1 ED_{50} rocuronium + 1 ED_{50} mivacurium; ½ ED_{50} rocuronium + ½ ED_{50} mivacurium; ¼ ED_{50} rocuronium + ¼ ED_{50} mivacurium, and ⅛ ED_{50} rocuronium + ⅛ ED_{50} mivacurium). From the dose–response curve of the combined drugs, the ED_{50} value of the total dose of the mixture was calculated, and, based on the known dose ratio, the single doses of the agents in the combination were obtained for plotting on the isobologram. All drugs were administered randomly to subgroups of ten patients, and were injected in 5 s into a rapidly flowing intravenous infusion. In the combination group, drugs were injected simultaneously into two separate intravenous catheters inserted in one arm. The neuromuscular response was recorded as the maximum depression of T1, expressed as a percentage of the control value. Once the maximum effect of the selected dose was reached (that is, when no further decrease in evoked response to three consecutive stimuli occurred), the study was terminated and anesthesia continued as appropriate for surgery.

The percentage values for T1 depression in each group were transformed to probits and plotted against the logarithm of the dose with PCNONLIN version 4.2A (ClinTrials, Lexington, KY).[7] Regression lines were compared by analysis of covariance. First, we tested the lines to determine if they deviated from parallelism. If they did not, an F test was applied to determine if the elevations were different. If so, a *t* test was applied to determine which line differed in elevation[8] (BMDP statistical package, release 7.0, University of California Press, Berkeley, CA, 1993). The ED_{50} and ED_{95} values (doses causing 50% and 95% depression of twitch tension, respectively) were calculated from the log-probit regression lines for each group. Using analysis of variance, we compared age, body weight, between the different groups. Unless otherwise specified, the results were expressed as means and 95% confidence intervals (CI), and were considered significant when $P < 0.01$.

Isobolographic[9,10] and algebraic (fractional)[11] analyses were used (ED_{50} level) to define the type of interaction between rocuronium and mivacurium. Isobolographic analysis for drug–drug interaction was conducted according to the procedure of Tallarida *et*

al.[9] This analysis has the advantage of being independent of the slopes of the dose–response curves; *i.e.*, parallelism does not have to be established. The isobologram was constructed by plotting single-drug ED_{50} points on the dose coordinates of the isobologram, and a combined ED_{50} point in the dose field. A straight line joining the single-drug ED_{50} points is termed the "additive line." If the ED_{50} of a combination falls on the theoretical additive line, the effect of the drug mixture is additive (zero-interactive). Points to the left of the theoretical additive line would be consistent with a synergistic interaction, whereas points to the right of the line would indicate an antagonistic interaction. CIs for each point were calculated from the variances of each component alone. The CIs were evaluated for statistical significance with a Student's *t* test.

The algebraic (fractional) analysis was used to describe the magnitude of the interaction. It was based on the expression of the component doses of the two agents of the combination as fractions of the doses that produce the same effect when given separately. The sum of the fractional doses, as expressed by the following equation, indicates the type of interaction:

$$d_r/(ED_{50})_r + d_m/(ED_{50})_m$$

where $(ED_{50})_r$ and $(ED_{50})_m$ = the ED_{50} values of rocuronium and mivacurium, respectively, given alone, and d_r and d_m = the doses of rocuronium and mivacurium, respectively, that when combined are equipotent with $(ED_{50})_r$ or $(ED_{50})_m$. Values near 1 indicate additive interaction, values greater than 1 imply an antagonistic interaction and values less than 1 indicate a synergistic interaction.

Clinical Studies

After obtaining institutional approval and informed consent, 50 ASA physical status 1 or 2 patients of both sexes, aged 21–58 (mean 36 [SD 8.7]) yr and weighing 44–83 (mean 63.4 [SD 9.4] kg were studied. Premedication and intraoperative monitoring were similar to that described in the isobolographic study. Anesthesia was induced with midazolam 0.03 $mg \cdot kg^{-1}$, fentanyl 4–5 $\mu g \cdot kg^{-1}$, followed by a small dose of thiopental 1–2 $mg \cdot kg^{-1}$, and maintained with N_2O and O_2 (70:30) supplemented with incremental doses of thiopental to permit baseline TOF monitoring without patient discomfort. Patients were randomly allocated to five groups of 10 each to receive one of the following neuromuscular blocking drug or drug combination: rocuronium 600 $\mu g \cdot kg^{-1}$ (approximately 2 ED_{95}) (group 1), mivacurium 150 $\mu g \cdot kg^{-1}$ (approximately 2 ED_{95}) (group 2), rocuronium 150 $\mu g \cdot kg^{-1}$ + mivacurium 37.5 $\mu g \cdot kg^{-1}$ (group 3), rocuronium 300 $\mu g \cdot kg^{-1}$ + mivacurium 75 $\mu g \cdot kg^{-1}$ (group 4), or rocuronium 600 $\mu g \cdot kg^{-1}$ + mivacurium 150 $\mu g \cdot kg^{-1}$ (group 5). All drugs were injected in 5 s into a rapidly flowing intravenous infusion. In the combination group, drugs were injected simultaneously into two separate intravenous catheters inserted in one arm. Tracheal intubation was performed at the maximal block. Anesthesia was maintained with N_2O and O_2 (70:30) supplemented with incremental doses of fentanyl and/or thiopental. Additional maintenance doses of mivacurium 100 $\mu g \cdot kg^{-1}$ and mixture of rocuronium 150 $\mu g \cdot kg^{-1}$ + mivacurium 37.5 $\mu g \cdot kg^{-1}$ were administered to all patients in the mivacurium group (group 2) and group 3, respectively. In both groups, the first maintenance dose was administered at T1 = 75% of control. If additional doses were required the second maintenance dose was administered whenever T1 had recovered to 25% of the control. Patients in whom the TOF ratio was less than 0.75 at the completion of the study received neostigmine 30 $\mu g \cdot kg^{-1}$ with atropine 15 $\mu g \cdot kg^{-1}$ for antagonism of residual neuromuscular blockade.

The times from the injection of neuromuscular blocking drug or drug combination to complete ablation of T1 (onset time), from injection to recovery of T1 to 25% of baseline twitch height (T25) (clinical duration of action), and from recovery of T25 to 75% of baseline twitch height (T75) (recovery index) were recorded. These times were compared with a one-way analysis of variance and the Student-Newman-Keuls multiple-range test. Differences yielding critical values corresponding to $P < 0.01$ were considered statistically significant.

Results

Interaction Studies

The dose–response curves are displayed in figure 1. The slopes for the rocuronium–mivacurium combination, rocuronium and mivacurium groups were 4.01, 4.86 and 6.17, respectively. The regression lines for rocuronium–mivacurium combination and rocuronium groups did not deviate from parallelism, but differed significantly in position. Calculated ED_{50} and ED_{95} (and 95% CI) values for rocuronium group were 125 (122–129) and 273 (263–284) $\mu g \cdot kg^{-1}$, respectively. Corresponding values for mivacurium group were 37 (36–

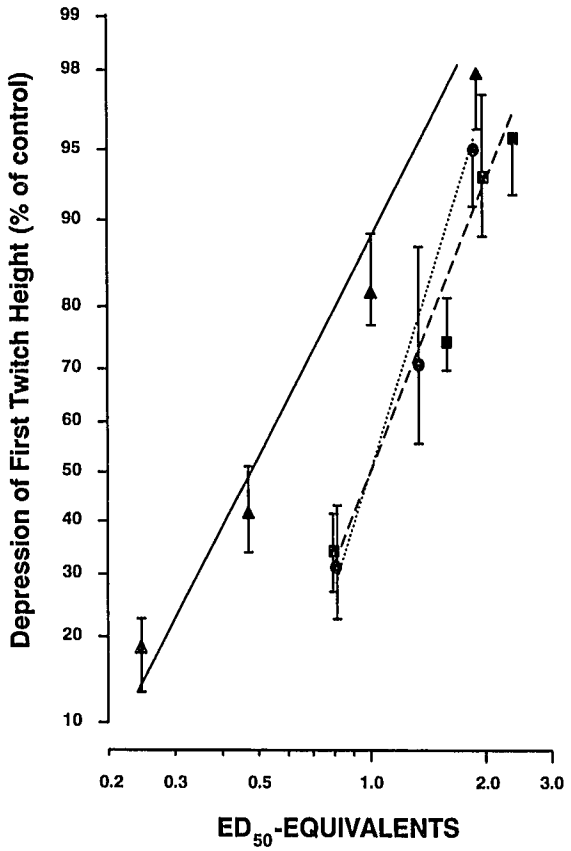

Fig. 1. Log dose-probit plot for first-twitch depression for rocuronium (squares), mivacurium (circles), and their combination (triangles). Individual points = mean T1 depression (percentage of control) with each dose; bars = 95% confidence intervals. Drug doses are represented as ED_{50}-equivalents.

38) and 69 (66–71) $\mu g \cdot kg^{-1}$, respectively. The times for the development of the maximal effect of the smallest dose (mivacurium 30 $\mu g \cdot kg^{-1}$ and rocuronium 100 $\mu g \cdot kg^{-1}$) and largest dose (mivacurium 70 $\mu g \cdot kg^{-1}$ and rocuronium 300 $\mu g \cdot kg^{-1}$) were, respectively, 345 (279–393) and 307 (275–339) s for mivacurium and 240 (188–292) and 210 (161–259) s for rocuronium. Corresponding values for their combinations (⅛ ED_{50} rocuronium + ⅛ ED_{50} mivacurium and 1 ED_{50} rocuronium + 1 ED_{50} mivacurium) were 220 (211–269) and 135 (101–169) s, respectively.

The isobolographic analysis demonstrated a synergistic interaction with respect to the neuromuscular blocking activity of rocuronium and mivacurium combination. Figure 2 represents ED_{50} isobologram for the rocuronium–mivacurium interaction. The experimentally determined ED_{50} (and 95% CI) for the combination was 39 (37–41) $\mu g \cdot kg^{-1}$ for rocuronium and 11.5 (11–12) $\mu g \cdot kg^{-1}$ for mivacurium. The theoretical additive ED_{50} (and 95% CI) was calculated to be 63 (61–65) $\mu g \cdot kg^{-1}$ for rocuronium and 18.5 (18–19) $\mu g \cdot kg^{-1}$ for mivacurium. The CIs of these points do not overlap, and the results of a Student's t test for potency ratio were significant ($P < 0.0001$) indicating synergism. The fractional (algebraic) analysis of this interaction also demonstrated synergism (table 1).

Clinical Studies

Onset times, clinical duration of action, and recovery indices for all groups are summarized in figure 3 and table 2. Complete neuromuscular blockade developed in all, but 3 patients in group 3 (rocuronium 150 $\mu g \cdot kg^{-1}$ + mivacurium 37.5 $\mu g \cdot kg^{-1}$), in whom the maximum blockade observed was 99% depression of T1. Patients in group 1 (rocuronium 600 $\mu g \cdot kg^{-1}$) and

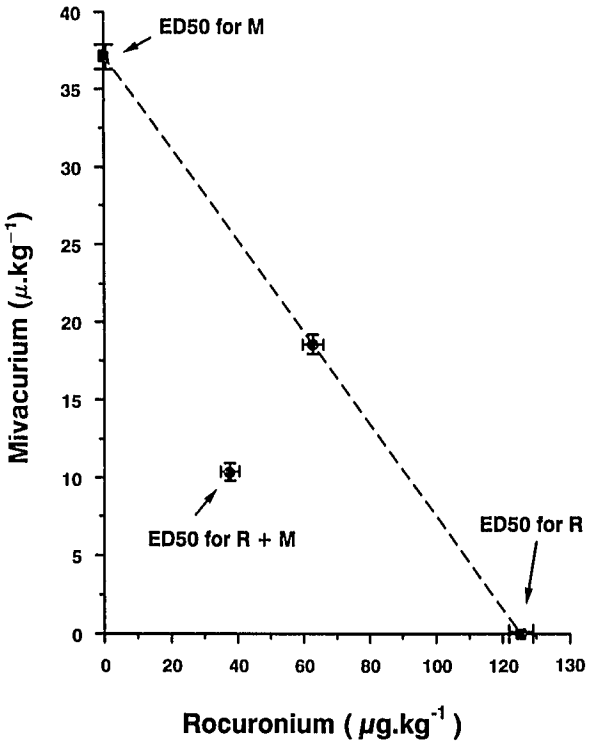

Fig. 2. First-twitch ED_{50} isobologram for the interaction of rocuronium and mivacurium. Dashed line connecting the single drug ED_{50} points = theoretical additive line; point on line = theoretical additive ED_{50} point (95% confidence interval). The experimentally determined ED_{50} dose (95% confidence interval) of the rocuronium–mivacurium combination fell significantly ($P < 0.0001$) below the corresponding theoretical additive point, indicating synergistic interaction.

Table 1. Rocuronium-Mivacurium Interaction: Equi-effective Doses of Rocuronium-Mivacurium Combination

Group	Rocuronium Component		Mivacurium Component		Sum of Fractions
	Fraction of ED_{50}	Dose ($\mu g \cdot kg^{-1}$)	Fraction of ED_{50}	Dose ($\mu g \cdot kg^{-1}$)	
Rocuronium	1	125	—	—	1
Mivacurium	—	—	1	37	1
Combination	0.31	38.8	0.31	11.4	0.62

ED_{50} = equi-effective dose.

group 3 (rocuronium 150 $\mu g \cdot kg^{-1}$ + mivacurium 37.5 $\mu g \cdot kg^{-1}$) had similar onset times, which were significantly shorter ($P < 0.01$) than that observed in group 2 (mivacurium 150 $\mu g \cdot kg^{-1}$). In groups 4 and 5, onset times were significantly shorter than that in each of the other study groups. Clinical duration of action (recovery to T25) was significantly longer with group 5 than with all other doses and agents, and briefest ($P < 0.01$) with mivacurium 150 $\mu g \cdot kg^{-1}$ (group 2) and group 3 (rocuronium 150 $\mu g \cdot kg^{-1}$ + mivacurium 37.5 $\mu g \cdot kg^{-1}$). The recovery index (recovery from T25 to T75) was significantly less for the mivacurium 150 $\mu g \cdot kg^{-1}$ group (group 2), group 3 (rocuronium 150 $\mu g \cdot kg^{-1}$ + mivacurium 37.5 $\mu g \cdot kg^{-1}$) and group 4 (rocuronium 300 $\mu g \cdot kg^{-1}$ + mivacurium 75 $\mu g \cdot kg^{-1}$) than that observed with rocuronium group (group 1) and group 5 (rocuronium 600 $\mu g \cdot kg^{-1}$ + mivacurium 150 $\mu g \cdot kg^{-1}$) (fig. 3 and table 2).

The onset times and the clinical duration of action of the first and the second maintenance doses administered to patients in groups 2 and 3 are presented in table 3.

Discussion

In the current study, isobolographic analysis demonstrated that rocuronium–mivacurium combinations exert a greater effect than that seen with an equipotent dose (in terms of ED_{50} multiples) of either agent administered alone. The magnitude of this interaction can be appreciated by the examination of the fractional dose scores (table 1). The measured ED_{50} of the mixture was only 62% of the predicted value assuming a purely additive interaction. The results of this study are consistent with the observation that combinations of structurally dissimilar neuromuscular blocking drugs (pancuronium and *d*-tubocurarine or pancuronium and metocurine) produce a potentiating response.[5] The chemical structure of rocuronium bromide (monoquaternary aminosteroid) is different from that of mivacurium chloride (bis-benzylisoquinolinium compound). On the other hand, a zero (additive) interaction has been demonstrated after administration of chemically related agents such as pipecuronium and vecuronium,[4] or pancuronium and vecuronium.[12]

The results of this study also demonstrate that combinations of rocuronium and mivacurium produce a shorter onset time and a longer duration of neuromuscular blockade than would be expected from simple additivity. It is interesting to note that the combination administered to the patients in group 3 (rocuronium 150 $\mu g \cdot kg^{-1}$ + mivacurium 37.5 $\mu g \cdot kg^{-1}$) produced a neuromuscular blockade characterized by rapid onset

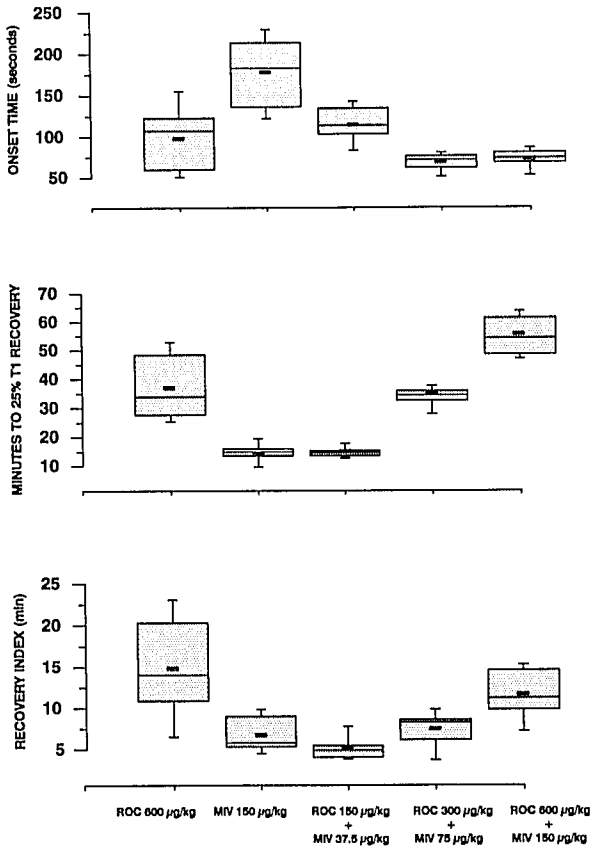

Fig. 3. Comparison of the onset time (*top*), duration of action (*middle*), and recovery index (*bottom*) in the different groups. ROC = rocuronium; MIV = mivacurium. Shaded areas = 25th to 75th percentiles; horizontal lines within shaded areas = medians, marking 50th percentiles; rectangular symbols in shaded areas = means; extended bars = ranges.

Table 2. Onset and Recovery Data

	600 $\mu g \cdot kg^{-1}$ Rocuronium (Group 1)	150 $\mu g \cdot kg^{-1}$ Mivacurium (Group 2)	150 $\mu g \cdot kg^{-1}$ Rocuronium + 37.5 $\mu g \cdot kg^{-1}$ Mivacurium (Group 3)	300 $\mu g \cdot kg^{-1}$ Rocuronium + 75 $\mu g \cdot kg^{-1}$ Mivacurium (Group 4)	600 $\mu g \cdot kg^{-1}$ Rocuronium + 150 $\mu g \cdot kg^{-1}$ Mivacurium (Group 5)
Onset time (s)	99 (73.7–123)*	178 (149–206)	114 (100–128)*	69 (62.9–75.7)†	73 (65.1–80.1)†
Duration (min)	36 (28.9–43.5)‡	14.5 (12.6–16.5)†	14.7 (13.4–16)†	34 (32–36)‡	55 (50.6–59.8)
Recovery index (min)	14.8 (10.9–18.9)†	6.8 (5.4–8.2)	5.2 (4.3–6)	7.5 (6.1–8.8)	11.7 (9.8–13.7)†

Data are presented as means (95% confidence intervals).

Onset time = the interval between the completion of injection of the neuromusclar blocking drug or drug combination and time to maximal depression T1; Duration = the interval between the completion of injection of the neuromuscular blocking drug or drug combination and time to T1 recovery to 25% of control; recovery index = the time from T25 to T75 percentage of recovery.

* $P < 0.01$ *versus* 150 $\mu g \cdot kg^{-1}$ mivacurium group (group 2).

† $P < 0.01$ *versus* other groups.

‡ $P < 0.01$ *versus* 600 $\mu g \cdot kg^{-1}$ rocuronium + 150 $\mu g \cdot kg^{-1}$ mivacurium combination group (group 5).

(114 s)—similar to that produced by rocuronium 600 $\mu g \cdot kg^{-1}$ (group 1)—and short duration (14.7 min)—similar to that produced by mivacurium 150 $\mu g \cdot kg^{-1}$ (group 2). Further, combination of rocuronium 300 $\mu g \cdot kg^{-1}$ + mivacurium 75 $\mu g \cdot kg^{-1}$ (group 4) produced a 30% shorter onset time ($P < 0.01$) than that produced by rocuronium 600 $\mu g \cdot kg^{-1}$ (69 *vs.* 99 s, respectively). The duration of action produced by the latter combination was identical to that produced by rocuronium 600 $\mu g \cdot kg^{-1}$ (34 *vs.* 36.2 min, respectively). Increasing the size of the dose further as in group 5 (rocuronium 600 $\mu g \cdot kg^{-1}$ + mivacurium 150 $\mu g \cdot kg^{-1}$) did not produce a significantly faster onset time but significantly prolonged the duration of action (fig. 3 and table 2). A 34% prolongation ($P < 0.01$) of the clinical duration of the latter group was noted when compared with that produced by rocuronium 600 $\mu g \cdot kg^{-1}$ (55.2 *vs.* 36.2 min, respectively).

Several investigators have shown that increasing the dose of nondepolarizing neuromuscular drugs is associated with a reduction in onset time.[13,14] However, concerns regarding the use of high-dose nondepolarizing neuromuscular relaxants have focused on their prolonged duration of action.[14,15] Magorian *et al.*[14] noted that doubling the dose of rocuronium from 600 to 1,200 $\mu g \cdot kg^{-1}$ was associated not only with 38% reduction ($P < 0.05$) in onset time (89 *vs.* 55 s), but also with 49% prolongation ($P < 0.05$) in the clinical

Table 3. Onset Times and Clinical Duration of Maintenance Doses

	Maintenance Doses					
	First*			Second†		
Group		Onset Time (s)	Clinical Duration (min)		Onset Time (s)	Clincial Duration (min)
150 $\mu g \cdot kg^{-1}$ Mivacurium (group 2)	100 $\mu g \cdot kg^{-1}$ Mivacurium	120 (104–137)	12.6 (10.1–15.1)	100 $\mu g \cdot kg^{-1}$ Mivacurium	64.5 (49.5–79.5)	13.1 (10.8–15.5)
150 $\mu g \cdot kg^{-1}$ Rocuronium + 37.5 $\mu g \cdot kg^{-1}$ mivacurium (group 3)	150 $\mu g \cdot kg^{-1}$ Rocuronium + 37.5 $\mu g \cdot kg^{-1}$ mivacurium	50 (44.3–55.5)	19.6 (17.3–21.9)	150 $\mu g \cdot kg^{-1}$ Rocuronium + 37.5 $\mu g \cdot kg^{-1}$ mivacurium	41 (35.1–46.3)	20.4 (18.3–22.5)

Data are presented as means (95% confidence intervals).

Onset time = the time interval between the completion of injection of the neuromuscular blocking drug or drug combination and time to maximal depression T1; Clinical duration = the time interval between the completion of injection of the neuromuscular blocking drug or drug combination and time to T1 recovery to 25% of control.

* First maintenance dose was administered at T1 = 75% of control.

† Second maintenace dose was administered at T1 = 25% of control.

duration of action (37 *vs.* 73 min). Similarly, Tullock *et al.*[15] reported that the average onset time was reduced from 164 (SEM 27) s to 88 (17) s by increasing the dose of vecuronium from 100 to 300 $\mu g \cdot kg^{-1}$. This was accompanied with an increase in the clinical duration (time to T25 recovery) from 42 (5) to 111 (19) min.[15] The same group also noted that increasing the dose of vecuronium further, to 400 $\mu g \cdot kg^{-1}$, did not produce a further acceleration in the onset time.[15]

The clinical implication of our finding is that by using different combinations of rocuronium and mivacurium, the anesthesiologist can have different mixtures with different characteristics. For example, one mixture (rocuronium 150 $\mu g \cdot kg^{-1}$ + mivacurium 37.5 $\mu g \cdot kg^{-1}$) is characterized by rapid onset (114 s) and short duration of action (14.7 min), and another mixture (rocuronium 300 $\mu g \cdot kg^{-1}$ + mivacurium 75 $\mu g \cdot kg^{-1}$) is characterized by a briefer onset time (69 s), but with an intermediate duration (34 min). Therefore, in situations where rapid tracheal intubation is required but succinylcholine is contraindicated, the anesthesiologist can choose between a large dose of a single nondepolarizing neuromuscular blocking agent (with or without a priming dose)[14-16] or, as shown in this study, a combination of smaller doses of rocuronium and mivacurium. An ideal combination for tracheal intubation would reliably reduce the onset time (60 s range), but would not prolong the duration of action. Our results indicate that this can be achieved with the use of rocuronium 300 $\mu g \cdot kg^{-1}$ + mivacurium 75 $\mu g \cdot kg^{-1}$ combination regimen.

The apparent onset of neuromuscular blockade in the adductor pollicis muscle depends on the pattern and duration of stimulation.[17] Curran *et al.*[17] postulated that TOF (as compared with single-twitch) stimulation at 0.08 Hz hastens onset time by increasing local muscle blood flow. TOF stimulation every 12 s was used in the current study. A similar stimulus pattern (TOF every 10–15 s) was used by other investigators for determination of the dose–response relations of mivacurium.[18,19] Because the same pattern of stimulation was used for all patients, the relative potencies of mivacurium and rocuronium determined in this study are likely to be accurate.

The ED_{50} value of 37 (95% CI 36–38) $\mu g \cdot kg^{-1}$ for mivacurium calculated in the current study is in close agreement with (39 and 41 $\mu g \cdot kg^{-1}$) that reported by Caldwell *et al.*[18] and Weber *et al.*,[19] respectively, who used TOF mode of stimulation and mechanomyography during thiopental–fentanyl–N_2O anesthesia. In this study, the calculated first-twitch ED_{50} (and 95% CI) value for rocuronium during thiopental–fentanyl–N_2O anesthesia was 125 (122–129) $\mu g \cdot kg^{-1}$. Similar ED_{50} values were reported by Cooper *et al.*[20] (147 (95% CI 130–165) $\mu g \cdot kg^{-1}$) who used single-twitch mode of stimulation and mechanomyography.

The isobolographic method is a generally valid procedure for analyzing interactions between agents irrespective of their mechanisms of action or their dose–response relations.[9,10] In addition, in isobolographic analysis, it is unnecessary to have complete dose–response curves of all of the agents in a combination to detect and categorize an interaction.[10] Chou and Talalay[21] indicated, however, that this method of analysis can be used to demonstrate synergism when the effect of drugs are "mutually exclusive"—that is, when they act at (or are bound by) the same receptor or enzyme site.

Although the precise mechanisms underlying synergistic interaction are not known, hypotheses that have been put forward include (1) the existence of multiple binding sites at the neuromuscular junction (pre- and postsynaptic receptors)[5,22,23]; (2) nonequivalence of binding sites in the regions of the α-chain responsible for ligand recognition, resulting from the asymmetric azimuthal orientation of the five subunits in the acetylcholine pentamer that determines different contacts for the α_1 and α_2 chains[6,24,25]; and (3) alteration of the pharmacokinetic behavior of one drug by the other, a hypothesis disputed by Martyn *et al.*[26]

In conclusion, both isobolographic and clinical studies demonstrated that the interaction of rocuronium and mivacurium combination is the result of synergistic action at the neuromuscular junction. Different combinations yielded different clinical profiles. One mixture (rocuronium 150 $\mu g \cdot kg^{-1}$ + mivacurium 37.5 $\mu g \cdot kg^{-1}$) was characterized by rapid onset (114 s) and short duration of action (14.7 min), and another (rocuronium 300 $\mu g \cdot kg^{-1}$ + mivacurium 75 $\mu g \cdot kg^{-1}$) was characterized by a briefer onset time (69 s), but with an intermediate clinical duration (34 min). Increasing the size of the dose in the mixture to (rocuronium 600 $\mu g \cdot kg^{-1}$ + mivacurium 150 $\mu g \cdot kg^{-1}$) did not affect onset time significantly but resulted in a significant prolongation of the duration of action.

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