Different priming techniques, including mivacurium, accelerate the onset of rocuronium

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Different priming sequences of equipotent doses of rocuronium and mivacurium on the onset of maximum neuromuscular block and intubating conditions were compared with those obtained after succinylcholine. During thiopentone-fentanyl-nitrous oxide anaesthesia, 70 patients were randomly assigned into seven groups. Group I received mivacurium 0.15 mg · kg^{-1} as a single bolus dose. Group II received a priming dose of mivacurium 0.015 mg · kg^{-1} followed three minutes later by mivacurium 0.135 mg · kg^{-1}. Group III received rocuronium 0.6 mg · kg^{-1} as a single bolus dose, and Group IV received an initial dose of rocuronium 0.06 mg · kg^{-1} followed by rocuronium 0.54 mg · kg^{-1}. Group V received a priming dose of mivacurium 0.015 mg · kg^{-1} followed by rocuronium 0.54 mg · kg^{-1}. Group VI received an initial dose of rocuronium 0.06 mg · kg^{-1} followed by mivacurium 0.135 mg · kg^{-1}. Group VII received succinylcholine 1.0 mg · kg^{-1}. Groups I, III, and VII received a placebo injection before the administration of the neuromuscular blocking drug. Additional thiopentone 2 mg · kg^{-1} iv was given 30 sec before intubation. Onset times (mean (95% confidence interval)) after priming a rocuronium block with either rocuronium (73 (57–90) sec) or mivacurium (58 (47–69) sec) were similar to those after succinylcholine (54 (40–68) sec), and were shorter ($P < 0.01$) than that observed in other groups. Intubating conditions were not different between the groups. The duration of neuromuscular block was shortest with succinylcholine. It is concluded that priming a rocuronium block with either mivacurium or rocuronium resulted in a neuromuscular block comparable to that of succinylcholine in both the onset of action and intubating conditions.

Cette étude compare l'influence de différentes séquences d'amorçage avec des doses d'égale puissance de rocuronium et de mivacurium sur le début du bloc neuromusculaire complet et les conditions d'intubation avec celles de la succinylcholine. Pendant une anesthésie au thiopentone-fentanyl-protoxyde d'azote, 70 patients sont assignés au hasard entre sept groupes. Le groupe I reçoit un seul bolus de mivacurium 0,15 mg · kg^{-1}. Le groupe II reçoit une dose d'amorce de mivacurium 0,015 mg · kg^{-1} suivie trois minutes plus tard de mivacurium 0,135 mg · kg^{-1}. Le groupe III reçoit un seul bolus de rocuronium 0,6 mg · kg^{-1}. Le groupe IV reçoit une dose initiale de 0,06 mg · kg^{-1} de rocuronium suivie de rocuronium 0,54 mg · kg^{-1}. Le groupe V reçoit une dose initiale de mivacurium 0,015 mg · kg^{-1} suivie de rocuronium 0,54 mg · kg^{-1}. Le groupe VI reçoit une dose initiale de rocuronium 0,06 mg · kg^{-1} suivie par mivacurium 0,135 mg · kg^{-1}. Le groupe VII reçoit succinylcholine 1,0 mg · kg^{-1}. Les groupes I, III et VII reçoivent un placébo en injection avant le myorelaxant. Un supplément de thiopentone 2 mg · kg^{-1} iv est administré 30 sec avant l'intubation. Le début d'action (moyenne (intervalle de confiance 95%)) après l'amorçage du bloc au rocuronium (73 (57–90) sec) ou au mivacurium (58 (47–69) sec) est identique à celui qui suit la succinylcholine (54 (40–68) sec) et est plus court ($P < 0,01$) que celui qui est observé dans les autres groupes. Les conditions d'intubation ne diffèrent pas entre les groupes. Le bloc neuromusculaire le plus court est obtenu avec la succinylcholine. En conclusion, l'amorçage du bloc neuromusculaire avec soit le mivacurium soit le rocuronium produit un bloc comparable à celui de la succinylcholine tant pour le début d'action que pour les conditions d'intubation.

Key words

INTERACTIONS: mivacurium, rocuronium (ORG 9426);
MONITORING: train-of-four;
NEUROMUSCULAR RELAXANTS: mivacurium, rocuronium, succinylcholine;
PHARMACODYNAMICS: priming principle.

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Succinylcholine continues to be the relaxant of choice where there is a need for rapid tracheal intubation as it consistently provides muscle relaxation within 60 to 90 sec. When succinylcholine is considered undesirable or contra-indicated, the onset of nondepolarizing neuromuscular blocking drugs can be accelerated by the use of high doses of an individual agent[1,2] or combinations

of relaxants[3] or by preceding the intubating dose with a priming dose of relaxant.[4-6] The high-dose regimens of nondepolarizing neuromuscular blocking drugs, however, have not consistently achieved the rapid onset of succinylcholine and were associated with considerable prolongation of the duration of action.[1,2] Although some combinations of mivacurium and rocuronium can achieve rapid onset without undue prolongation of action and without undesirable effects,[7] combination therapy was not reliable in achieving rapid onset consistently.[3] Priming, on the other hand, can accelerate the onset of neuromuscular blockade but, after priming, intubating conditions do not match those after succinylcholine.[8]

Intubating conditions depend on many factors, the most important of which are the degree of relaxation of the muscle groups involved, the depth of anaesthesia, the anatomy of the upper airways and the skill of the anaesthetist. The superior intubating conditions associated with succinylcholine may lie not as much in its rapid onset but may because it has a greater potency at the laryngeal muscles than nondepolarizing neuromuscular blocking drugs.[9] Further, Naguib *et al.*[10] have demonstrated that the priming technique can be made to provide better conditions for tracheal intubation in <90 sec. They noted that administration of 2 $mg \cdot kg^{-1}$ thiopentone before injection of the intubating dose resulted in improvement of intubating conditions, probably due to the increase in the depth of anaesthesia.[10]

Rocuronium bromide and mivacurium chloride are nondepolarizing neuromuscular blocking agents that have recently been introduced to clinical practice.[11,12] Mivacurium has a considerably shorter duration of action than any other currently used nondepolarizing agent.[11] Rocuronium, on the other hand, has a brief onset but an intermediate duration of action.[12] Because the onset of action of rocuronium is more rapid than that of other nondepolarizing muscle relaxants it may prove to be the muscle relaxant of choice with the priming technique. However, we are not aware of any study that has evaluated different priming techniques with rocuronium.

The purpose of this study was to compare the onset time of neuromuscular blockade, tracheal intubating conditions, and neuromuscular recovery following different priming techniques with equipotent doses of rocuronium and mivacurium, with that produced by succinylcholine.

Methods

After obtaining institutional approval and informed consent, 70 ASA physical status I or II patients were studied. All patients were undergoing elective procedures, had no neuromuscular, hepatic or renal disease, were not suspected of presenting difficulty with tracheal intubation, and were not taking any drug known or suspected to interfere with neuromuscular function.

No premedication was administered. An infusion of lactated Ringer's solution was given *iv* before induction of anaesthesia. Pulse oximetry, ECG, and arterial blood pressure were monitored. Temperature was monitored by a nasopharyngeal thermistor and maintained at 36.5 ± 0.5°C.

Anaesthesia was induced with midazolam 0.03 $mg \cdot kg^{-1}$ *iv* followed two to three minutes later by thiopentone 5–7 $mg \cdot kg^{-1}$ and was maintained with N_2O and O_2 (70:30) and incremental doses of fentanyl. Following loss of consciousness, the ulnar nerve was stimulated supramaximally at the wrist with square pulses of 0.2 msec duration, delivered in a train-of-four (TOF) sequence at 2 Hz every 12 sec, using a Myotest peripheral nerve stimulator (Biometer International, Odense, Denmark). The resultant contraction of the adductor pollicis muscle was recorded using 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 (T_1) of the TOF was considered the twitch height.

Once a steady state twitch was established, patients were assigned randomly to one of seven groups (n = ten in each). Patients in Group I received mivacurium 0.15 $mg \cdot kg^{-1}$ as a single bolus dose, whereas those in Group II received an initial (priming) dose of mivacurium 0.015 $mg \cdot kg^{-1}$ followed three minutes later by mivacurium 0.135 $mg \cdot kg^{-1}$. Group III received rocuronium 0.6 $mg \cdot kg^{-1}$ as a single bolus dose, and Group IV received an initial dose of rocuronium 0.06 $mg \cdot kg^{-1}$ followed three minutes later by rocuronium 0.54 $mg \cdot kg^{-1}$. Patients in Group V received an initial dose of mivacurium 0.015 $mg \cdot kg^{-1}$ followed three minutes later by rocuronium 0.54 $mg \cdot kg^{-1}$. Group VI received an initial dose of rocuronium 0.06 $mg \cdot kg^{-1}$ followed three minutes later by mivacurium 0.135 $mg \cdot kg^{-1}$. Group VII (controls) received succinylcholine 1.0 $mg \cdot kg^{-1}$. Patients in Groups I, III, and VII received a saline placebo injection three minutes before the administration of the neuromuscular blocking drug. The priming interval (three minutes) and the priming dose (10% of the total dose) were chosen based on the results of previous studies.[5,6,13,14]

Additional thiopentone 2 $mg \cdot kg^{-1}$ *iv* was given approximately 30 sec before intubation. Tracheal intubation was performed after complete neuromuscular block by an experienced anaesthetist who was not involved in the study and was not aware of the muscle relaxant used. Intubating conditions were scored as "excellent" if the jaw was relaxed, the vocal cords were immobile, and there was no diaphragmatic movement; and "good" if all the

TABLE I Demographic data

Group	*Priming dose* $mg \cdot kg^{-1}$	*Intubating dose* $mg \cdot kg^{-1}$	*n*	*Sex M/F*	*Age (yr)*	*Weight (kg)*
I	-	Mivacurium 0.15	10	6/4	31.5 (8.2)	72.7 (9.5)
II	Mivacurium 0.015	Mivacurium 0.135	10	5/5	35.7 (10.7)	61.3 (10.6)
III	-	Rocuronium 0.6	10	3/7	31.5 (9.5)	66.6 (10.2)
IV	Rocuronium 0.06	Rocuronium 0.54	10	6/4	30.4 (10.5)	72 (12.3)
V	Mivacurium 0.015	Rocuronium 0.54	10	7/3	28.4 (9.9)	72.7 (7.9)
VI	Rocuronium 0.06	Mivacurium 0.135	10	6/4	33.2 (11.7)	62.9 (11.5)
VII	-	Succinylcholine 1.0	10	7/3	35.5 (11.1)	70.1 (11.1)

Values are presented as means (SD).

TABLE II Priming sequence, onset time, intubating conditions and recovery of twitch height (T_1) to 10% of control tensions

Group	*Priming dose* $mg \cdot kg^{-1}$	*Intubating dose* $mg \cdot kg^{-1}$	*Onset time (sec)*	*Intubating conditions*				*10% recovery of T_1 (min)*
				Excellent	*Good*	*Poor*	*Inadequate*	
I	-	Mivacurium 0.15	164 (141-186)†	6	3	1	0	15.3 (13.4-17.2)
II	Mivacurium 0.015	Mivacurium 0.135	103 (60-111)	5	5	0	0	17.1 (14.8-19.3)
III	-	Rocuronium 0.6	90 (71-109)	7	3	0	0	37.5 (31.3-43.8)†
IV	Rocuronium 0.06	Rocuronium 0.54	73 (57-90)*	6	4	0	0	39 (32.2-45.8)†
V	Mivacurium 0.015	Rocuronium 0.54	58 (47-69)*	6	4	0	0	36.8 (29.6-43.9)†
VI	Rocuronium 0.06	Mivacurium 0.135	106 (87-125)	4	6	0	0	18.2 (14.7-21.8)
VII	-	Succinylcholine 1.0	54 (40-68)*	8	2	0	0	8.4 (7.6-9.3)*

Values are presented as means and 95% confidence intervals.
Onset time is the time from administration of the intubating dose to the development of maximum depression of T_1.
*Significantly ($P < 0.01$) shorter from all others.
†Significantly ($P < 0.01$) longer from all others.

above criteria were met except for diaphragmatic movement. Conditions were scored as "poor" if the vocal cords were moving and if there was coughing or bucking; and "inadequate" if, in addition to the above criteria, the jaw clinically was not relaxed. Following intubation, anaesthesia was maintained with 70% nitrous oxide and 0.5-1% isoflurane and ventilation was adjusted to maintain normocapnia ($P_{ET}CO_2$ 35-40 mmHg). End-tidal concentrations of CO_2 and isoflurane were measured with a multiple-gas analyzer (Capnomac, Datex Instrumentarium Corporation, Helsinki, Finland).

Onset time (time from administration of the intubating dose to the development of maximum depression of T_1) and the time from injection to 10% recovery of T_1 were determined. These times were compared with a one-way analysis of variance (ANOVA) and the Student-Newman-Keuls multiple range test. Differences yielding critical values corresponding to $P < 0.05$ were considered statistically significant. Intubating conditions were analyzed by Kruskall-Wallis test after assigning a numeric value to each intubation score. All statistical analyses were carried out using BMDP statistical package, release 7.01 (University of California Press, Berkeley, California, 1994). Unless otherwise specified, the results were expressed as means and 95% confidence intervals.

Results

Demographic data are shown in Table I. The study groups did not differ in age, sex distribution or weight. The intubating doses resulted in 100% depression of twitch tension in all, but three patients in Group I. The maximum twitch depression observed in those patients were 96, 97 and 98% of the control tension. Onset times and times to 10% recovery of T_1 are summarized in Table II. Onset times in Group IV (priming dose 0.06 $mg \cdot kg^{-1}$ rocuronium, intubating dose rocuronium 0.54 $mg \cdot kg^{-1}$) and Group V (priming dose 0.015 $mg \cdot kg^{-1}$ mivacurium, intubating dose 0.54 $mg \cdot kg^{-1}$ rocuronium) did not differ from those of succinylcholine 1.0 $mg \cdot kg^{-1}$ (Table II; Figure). Onset times following administration of rocuronium 0.6 $mg \cdot kg^{-1}$ as a single bolus dose (Group III) or mivacurium in priming sequence (Groups II and VI) were longer than that observed in the aforementioned groups. The onset time of in Group I (who received mivacurium

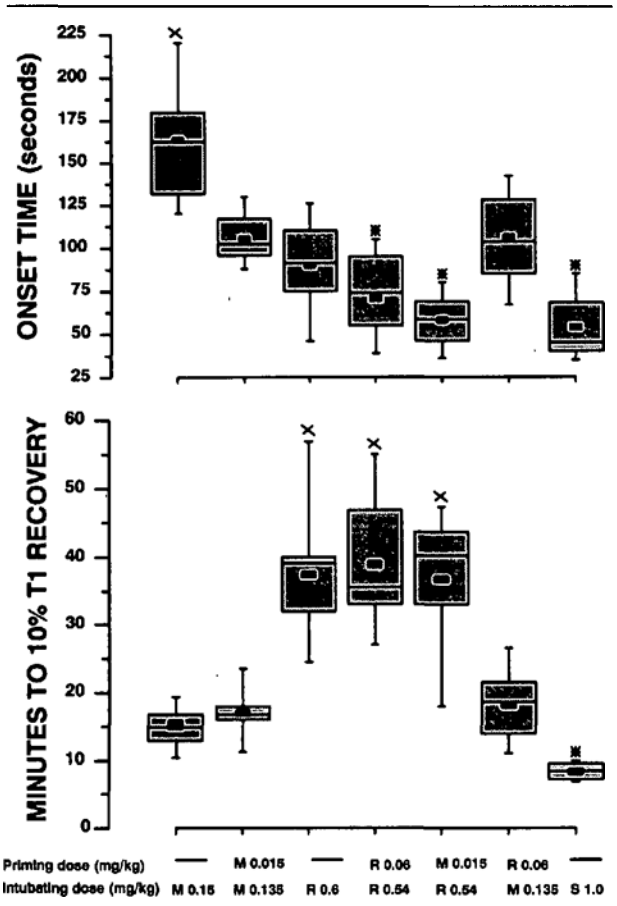

FIGURE Onset time in seconds (upper box chart) and time to 10% recovery of T_1 in min (lower box chart). The 25th to 75th percentiles are represented by the shaded areas. Medians are shown as horizontal lines within the shaded areas and mark the 50th percentiles. The rectangular symbols in the shaded areas mark the means. Ranges are represented by thet extended bars. M = Mivacurium. R = Rocuronium. S = Succinylcholine. *Significantly ($P < 0.01$) shorter from all others. ˣSignificantly ($P < 0.01$) longer from all others.

0.15 mg · kg^{-1} as a single bolus dose) was longer ($P < 0.01$) than that in each of the other study groups.

Intubating conditions did not differ in the seven groups (Table II). Times to 10% recovery of T_1 were shortest ($P < 0.01$) in the succinylcholine group, and longest ($P < 0.01$) in Groups III, IV and V (Table II; Figure). Priming a mivacurium block with mivacurium or rocuronium, or priming a rocuronium block with rocuronium or mivacurium did not affect the duration of action of mivacurium or rocuronium, respectively.

Discussion

The results of this study indicate that administration of a priming dose of rocuronium 0.06 mg · kg^{-1} or of mivacurium 0.015 mg · kg^{-1} followed three minutes later by an intubating dose of rocuronium 0.54 mg · kg^{-1} results in a neuromuscular block that resembles succinylcholine 1.0 mg · kg^{-1} in both the onset of action and intubating conditions. In this study we used the standard intubating doses of all drugs studied. It should be noted, however, that the dose of succinylcholine used in this study (1.0 mg · kg^{-1}, 3 × ED_{95})[15] is larger than that of rocuronium (0.6 mg · kg^{-1}, 2 × ED_{95})[7,16] or mivacurium (0.15 mg · kg^{-1}, 2 × ED_{95}).[7,17] The total doses administered to Groups I–VI were equipotent.

In the analysis of the onset time of rocuronium and mivacurium with and without priming, it is important to make comparisons with those of succinylcholine. Despite its rapid onset of action,[12] we noted in this study that the mean time to maximum block of 90 sec following administration of a single bolus dose rocuronium 0.6 mg · kg^{-1} was longer ($P < 0.01$) than a mean time of 54 sec with succinylcholine 1.0 mg · kg^{-1}. Our results agree with those of others.[2,18] Cooper *et al.*[18] reported onset times of 60.4 (22.4) and 88.9 (36.9) sec (mean (SD)), respectively, after succinylcholine 1.0 mg · kg^{-1} and rocuronium 0.6 mg · kg^{-1} in patients anaesthetized with thiopentone, fentanyl and nitrous oxide in oxygen. Similarly, Magorian *et al.*[2] reported onset times of 50 (17) and 89 (33) sec (mean (SD)) after succinylcholine 1.0 mg · kg^{-1} and rocuronium 0.6 mg · kg^{-1}, respectively.

In this study, we demonstrated that the priming technique can accelerate the onset time of rocuronium further and makes it comparable with that of succinylcholine (Table II; Figure). Using the priming technique with rocuronium in anaesthetized rats, Foldes *et al.*[19] reported that the onset time of 1.15 × ED_{90} of rocuronium, 16.3 (3.2) (mean (SEM)), decreased to 10 (0.8) and 9.6 (1.0) sec ($P < 0.01$) respectively, when rocuronium was administered one minute after priming with 0.25 × ED_{90} d-tubocurarine or vecuronium, 0.85 × ED_{90}. The same group, however, reported that administration of a 0.1 mg · kg^{-1} priming dose of rocuronium followed by an 0.5 mg · kg^{-1} intubating dose four minutes later in man did not result in any acceleration in the onset time.[20] This difference in results could be attributed to the difference in the size of the priming doses (0.1 mg · kg^{-1} vs 0.06 mg · kg^{-1} in this study) and priming intervals (four vs three minutes in this study). A priming interval of four minutes may be too long for a rapid-acting drug like rocuronium.

We have demonstrated that mixtures of rocuronium and mivacurium are synergistic in humans.[7] The calculated ED_{50} of rocuronium and mivacurium mixture was only 62% of the predicted value assuming a purely additive interaction.[7] In this study, priming a rocuronium with rocuronium (Group IV) shortens the onset time by approximately 20% (from 90 to 73 sec; Table II; Figure), whereas in Group V, priming with mivacurium produced

a greater reduction (approximately 35%) in the onset time (from 90 sec to 58 sec). The results of this study also indicate that using the priming technique with mivacurium (Groups II and VI) does shorten the onset time by approximately 40% (from 164 to slightly over 100 sec; Table II; Figure). Nevertheless, the acceleration in the onset time was not of sufficient magnitude to approximate that of succinylcholine (Table II; Figure). In agreement with our results, Molbegott and Baker[21] reported that the onset time of a bolus dose of mivacurium 0.15 $mg \cdot kg^{-1}$ was reduced from 169.9 (7.8) sec to 99.6 (6.7) sec (mean (SEM)) following a priming sequence (priming dose of 0.015 $mg \cdot kg^{-1}$ followed five minutes later by an intubating dose of 0.135 $mg \cdot kg^{-1}$). They also noted that, only by increasing the intubating dose of mivacurium to 0.2 $mg \cdot kg^{-1}$ (a total dose of 0.21 $mg \cdot kg^{-1}$), did the onset time of mivacurium approximate that of succinylcholine 1.0 $mg \cdot kg^{-1}$ (81.9 (2.7) sec and 82.9 (3.5) sec, respectively).[21]

As reviewed in the introduction, intubating conditions depend on many factors, and depth of anaesthesia is a fundamental component contributing to the adequacy of the intubating conditions. In this study, a supplemental dose of thiopentone 2 $mg \cdot kg^{-1}$ was administered before the injection of the intubating dose. We noted earlier that such a technique can result in better conditions for tracheal intubation.[10] That the intubating conditions did not differ among the seven groups studied (Table II) emphasizes the importance of this technique. The results of this study also indicate that, after priming, rocuronium resembles succinylcholine in producing good-to-excellent intubating conditions in approximately 60 sec. The intubating conditions of rocuronium and succinylcholine described in this study were similar to those reported by others.[2,18] Cooper *et al.*[18] found that the intubating conditions after rocuronium 0.6 $mg \cdot kg^{-1}$ to be clinically acceptable (good or excellent) in 95% of patients at 60 sec and in all patients at 90 sec and in all patients at both times after succinylcholine 1.0 $mg \cdot kg^{-1}$. As reported in their study,[18] the degree of neuromuscular block at the time of tracheal intubation with rocuronium was 89 (SD 15.5)% at 60 sec and 98 (3.0)% at 90 sec. Magorian *et al.*,[2] using a different protocol, reported excellent intubating conditions in 100% of their patients after rocuronium 0.6 $mg \cdot kg^{-1}$.

Differences in neuromuscular blocking potency and in the rate of block development between the skeletal muscle and the vocal cords with other muscle relaxants have been reported both in animal and humans.[9,22-24] Donati *et al.*[22] were able to demonstrate with vecuronium more rapid onset of block on the vocal cords than on the adductor pollicis muscle in anaesthetized patients. In another study,[23] they reported that rocuronium had a faster onset at both muscles than vecuronium. The reason for this rapid onset could be attributed to potency[25] and/or different buffering[26] (i.e., the repetitive binding of relaxant molecules) of muscle relaxants.

In the current study, times to 10% recovery of T_1 for the same total dose of mivacurium or rocuronium were not influenced by priming with the equipotent doses of either drug (Table II). This observation is in agreement with the results of other studies.[5,10,13]

In conclusion, this study demonstrates that priming with rocuronium 0.06 $mg \cdot kg^{-1}$ or mivacurium 0.015 $mg \cdot kg^{-1}$ followed three minutes later by rocuronium 0.54 $mg \cdot kg^{-1}$ resulted in a neuromuscular block which was similar to that of succinylcholine 1.0 $mg \cdot kg^{-1}$ in both the onset of action and intubating conditions. This study also illustrates that the priming technique can reduce the onset time of both mivacurium (by approximately 40%) and rocuronium (by approximately 20–35%). Priming with alternative drug does not seem to offer advantages.

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