Intubating conditions and blockade after mivacurium, rocuronium and their combination in young and elderly adults

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Purpose: Mivacurium-rocuronium combinations have been demonstrated to be more potent than either drug given alone. Combinations were compared with mivacurium and rocuronium, with respect to onset, intubating conditions, and duration of action in young and elderly adults.

Methods: Fentanyl-propofol-N_2O-isoflurane anesthesia was given to ASA I and II adults aged 18-65 yr (45 patients) and over 66 yr (45 patients). In this blinded randomized study, we compared accelerographic adductor pollicis response and visual assessment of response to facial nerve stimulation after 0.25 $mg \cdot kg^{-1}$ mivacurium, 0.6 $mg \cdot kg^{-1}$ rocuronium, and a combination of 0.08 $mg \cdot kg^{-1}$ mivacurium plus 0.2 $mg \cdot kg^{-1}$ rocuronium. Intubating conditions at 2.5 min were rated as excellent, good, fair or poor.

Results: Onset times were similar for all drugs regimens and for both age groups (204-276 sec at the thumb; 142-196 sec at the eye) ($P < 0.05$ between muscles). Intubating conditions were similar in all groups, and rated good or excellent, except in two subjects. In young patients duration to 25% recovery was longer ($P < 0.05$) for rocuronium (mean ± SD) (39 ± 11 min) than for either mivacurium (23 ± 6 min), or the combination (27 ± 7 min). Duration was prolonged in the elderly for rocuronium (54 ± 17 min), and the combination (35 ± 11 min), but not for mivacurium (24 ± 6 min).

Conclusions: Mivacurium-rocuronium combinations yield onset times and intubating conditions similar to either parent agent with only two thirds as much total drug. Duration for such a mixture is similar to that of mivacurium in young adults and slightly prolonged in the elderly.

Objectif : Le mélange de rocuronium et de mivacurium est plus puissant que l'un ou l'autre de ses composants donné seul. On a comparé ce mélange au mivacurium et au rocuronium quant au délai d'installation, aux conditions d'intubation et à la durée d'action chez des adultes jeunes et âgés.

Méthode : Une anesthésie au fentanyl, propofol, N_2O et isoflurane a été administrée à 45 patients de 18 à 65 ans et à 45 sujets de plus de 65 ans. De façon randomisée et aveugle, on a comparé la réponse accélérographique de l'adducteur du pouce et l'évaluation visuelle de la réponse à la stimulation du nerf facial après 0,25 $mg \cdot kg^{-1}$ de mivacurium, 0,6 $mg \cdot kg^{-1}$ de rocuronium ou un mélange de 0,08 $mg \cdot kg^{-1}$ de mivacurium et 0,2 $mg \cdot kg^{-1}$ de rocuronium. Les conditions d'intubation à 2,5 min ont été classifiées comme excellentes, bonnes, passables ou inadéquates.

Résultats : Les délais d'installation étaient semblables pour tous les myorelaxants et pour les deux groupes d'âge (204-276 sec au pouce, 142-196 sec près de l'œil ($P < 0,05$ entre les muscles). Les conditions d'intubation étaient semblables dans tous les groupes et cotées bonnes ou excellentes, excepté chez deux sujets. Chez les jeunes, la durée d'action jusqu'à 25 % de récupération était plus longue ($P < 0,05$) pour le rocuronium (moyenne ± ET) (39 ± 11 min) que pour le mivacurium (23 ± 6 min), ou le mélange (27 ± 7 min). Chez les sujets âgés, la durée était prolongée pour le rocuronium (54 ± 17 min) et le mélange (35 ± 11 min), mais pas pour le mivacurium (24 ± 6 min).

Conclusion : Le mélange de mivacurium et de rocuronium produit des délais d'installation et des conditions d'intubation semblables à ceux de l'un ou l'autre myorelaxant avec une quantité totale réduite au deux tiers. La durée du mélange est semblable à celle du mivacurium chez les jeunes, mais un peu plus longue chez les sujets âgés.

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MIXTURES of two nondepolarizing blocking drugs are additive when the effect is the sum of equipotent doses of either drug given alone, for example, the combination of d-tubocurarine with gallamine,[1] pancuronium and gallamine,[1] pipecuronium and vecuronium,[2] pancuronium and vecuronium,[3] rocuronium with other steroidal muscle relaxants,[4] and atracurium with cistracurium.[5] When the effect of the mixture is greater than the equipotent dose of either drug, synergism is observed. This has been reported in the case of pancuronium-metocurine,[6] pancuronium with d-tubocurarine,[6] gallamine-metocurine,[1] d-tubocurarine-vecuronium,[7] mivacurium with rocuronium,[8] and cistracurium with rocuronium,[5,9] mivacurium,[9] or vecuronium.[9]

The main advantages of synergistic mixtures are the decreased likelihood of side effects of either drug and decreased overall cost, provided that equipotent doses of both drugs have comparable price. For mivacurium-rocuronium combinations, there could be an additional advantage. Onset has been reported to be as rapid as that of rocuronium and duration as short as for mivacurium.[7] In other words, the mixture keeps the desirable features of each agent.[7]

However, it is difficult to extrapolate results from an onset and duration study performed during steady-state anesthesia to clinical practice. The adductor pollicis response depends on the stabilization time. Onset is shorter if stimulation has been applied for 15-20 min, than for one minute,[10,11] as is the case in clinical practice. Furthermore, the response of the adductor pollicis is a poor predictor of intubating conditions. In this respect, visual inspection of the loss of response of muscles surrounding the eye is a better guide.[12] In addition, onset and duration data might be different in the elderly[13,14] who constitute a growing part of anesthetic practice.

Therefore, the aim of the study was to compare intubating doses of mivacurium, rocuronium, and their combinations on adductor pollicis response measured by accelerometry, on the response to facial nerve stimulation observed visually, and on intubating conditions, both in young and elderly adults.

Patients and methods

The study was approved by the hospital Ethics Committee and written informed consent was obtained from each patient. Ninety patients of both sexes scheduled for elective surgery requiring tracheal intubation were enrolled into the study. They were divided into two groups of 45 individuals each according to age: patients aged 18-65 yr (young group), and those aged 66-90 yr (elderly group). Patients with a history of renal, hepatic, or neuromuscular disease were excluded, as those with diabetes or an anticipated difficult airway. Premedication was at the discretion of the anesthesiologist.

After the patient arrived in the operating room, an intravenous line was inserted. Standard monitoring was applied and consisted of ECG, pulse oximetry and non-invasive arterial pressure. Neuromuscular function was measured at the adductor pollicis by a TOF-GUARD accelerometer (Biometer International, Odense Denmark). Two surface electrodes were applied over the ulnar nerve at the wrist and a piezoelectric device measuring acceleration was placed on the corresponding thumb. Another set of two surface electrodes was applied over the temporal branch of the facial nerve and connected to the stimulator unit of another TOF-GUARD accelerometer, without using the probe. Anesthesia was induced with 1.5-3 $\mu g \cdot kg^{-1}$ fentanyl and 1.5-3 $mg \cdot kg^{-1}$ propofol, titrated to loss of consciousness and loss of eyelash reflex. Then, supramaximal train-of-four stimulation (2 Hz, 2 sec) was applied every 15 sec to both the ulnar nerve at the wrist (60 mA), and to the temporal branch of the facial nerve lateral and posterior to the eye (30 mA). The lungs were ventilated manually with oxygen 100% via a face mask.

Patients in the young and elderly groups were further randomized into three subgroups. They were assigned to receive, in a random fashion, 0.25 $mg \cdot kg^{-1}$ mivacurium, 0.6 $mg \cdot kg^{-1}$ rocuronium, or a combination of 0.08 $mg \cdot kg^{-1}$ mivacurium, plus 0.2 $mg \cdot kg^{-1}$ rocuronium, iv over 10 sec, as soon as both stimulators were functioning. Laryngoscopy and tracheal intubation were performed 2.5 min after injection of the neuromuscular blocking agent. Intubating conditions were assessed by an observer who was unaware of which drug or combination had been given. They were rated as excellent, good, fair or poor (Table I). After intubation, the lungs were ventilated mechanically with N_2O 60% in O_2 and isoflurane 1.0-1.5 % (inspired). Ventilation was adjusted to keep $P_{ET}CO_2$ in the range 32-38

TABLE I Assessment of intubating conditions

Intubating conditions	Laryngoscopy
1= excellent	vocal cords open, no coughing, easy laryngoscopy
2= good	vocal cords moving, coughing with diaphragm, fair laryngoscopy
3= poor	vocal cords closing, clear coughing, difficult laryngoscopy
4= inadequate	vocal cords closed, severe coughing, laryngoscopy impossible

TABLE II Patient characteristics, (young group), (mean ± SD)

	Mivacurium (n=14)	*Combination (n=18)*	*Rocuronium (n=13)*
Age (yr)	44 ±14	41 ±15	47 ± 15
Sex: male/female	7/7	12/6	8/5
Weight (kg)	67± 8	70 ± 12	63 ± 16
Height (cm)	171 ± 5	172 ± 8	172 ± 8
Propofol (mg)	203 ± 20	209 ± 35	192 ± 18
Fentanyl (μg)	175 ± 35	177± 33	173 ± 37

No statistically significant difference was found among subgroups.

TABLE III Patient characteristics, (elderly group), (mean ± SD)

	Mivacurium (n=15)	*Combination (n=15)*	*Rocuronium (n=15)*
Age (yr)	74 ± 10	77 ±13	75 ±10
Sex: male/female	7/8	11/4	6/9
Weight (kg)	69 ± 12	72 ± 15	64 ± 11
Height (cm)	169 ± 6	170 ± 4	169 ± 7
Propofol (mg)	162 ± 28	158 ± 35	149 ± 26
Fentanyl (μg)	140 ± 45	126 ± 45	131 ± 39

No statistically significant difference was found among subgroups.

TABLE IV Onset, duration and intubating conditions

Young patients	*Mivacurium (n=15)*	*Combination (n=15)*	*Rocuronium (n=15)*
Onset 95% thumb (sec; mean ± SD)	180 ± 120	210 ± 165	160 ± 100
Onset of maximum blockade thumb (sec; mean ± SD)	271 ± 103	276 ± 102	253 ± 132
Onset eye (seconds; mean ± SD)	142 ± 54	151 ± 49	158 ± 67
Duration 25 % (min; mean ± SD)	23 ± 6	25 ± 7	39 ± 11*
Intubating conditions (1/2/3/4)	7/6/2/0	8/7/0/0	10/5/0/0
Elderly patients	*Mivacurium (n=15)*	*Combination (n=15)*	*Rocuronium (n=15)*
Onset 95% thumb (sec; mean ± SD)	176 ± 78	213 ± 71	152 ± 52
Onset of maximum blockade thumb (sec; mean ± SD)	223 ± 108	273 ± 88	204 ± 102
Onset eye (sec; mean ± SD)	147 ± 66	174 ± 62	196 ± 93
Duration 25% (min; mean ± SD)	23 ± 6	35 ± 11*†	54 ± 17*§†
Intubating conditions (1/2/3/4)	11/4/0/0	11/4/0/0	13/2/0/0

* $P < 0.05$ compared with mivacurium;
§ $P < 0.05$ compared with combination
† $P < 0.05$ compared with young group

mmHg. Isoflurane concentration was kept at 0.8-1% end-tidal and fentanyl (50-100 μg *iv*) was given to increase the depth of anesthesia if required.

Onset time at the adductor pollicis was defined as the interval between injection and maximum blockade of first twitch (T1) in a train-of-four as measured by accelerometry. Onset time at the eye was defined as the time from injection until total disappearance of muscular activity around the eye. Duration of action was defined as the time from injection of the neuromuscular blocking agent until 25% T1 recovery as measured by accelerometry at the adductor pollicis. The presence or absence of cutaneous reaction (rash) was noted after injection of the neuromuscular blocking drug.

Comparisons were made among drug regimens within the same age group, and for the same drug regimen between the young and elderly. Results of continuous variables are presented as mean ± SD. For statistical analysis, a Jandel Sigmastat statistical software was used. The sample size was determined to detect a minimum difference of 60 sec in the onset times with an expected standard deviation of 50 sec and a desired power of 0.8. A P value less than 0.05 was considered to indicate a statistically significant difference. To compare patients characteristics, dose of anesthetics, onset, duration one way ANOVA or Kruskall Wallis ANOVA on ranks was used. To compare gender distribution and intubation conditions, Chi Square test or Fisher exact test was used.

Results

Within each age group, each subgroup was comparable with respect to age, weight, height, sex distribution and dose of induction anesthetics (Tables II, III). The elderly received less fentanyl and less propofol than young patients. All subjects had at least 95% blockade at the adductor pollicis. Six patients did not achieve 100% blockade at the adductor pollicis. Seven others did not demonstrate complete abolition of response following facial nerve stimulation, in which case onset time was set arbitrarily at five minutes.

For each drug or drug combination given, onset time was similar in young and elderly subjects (Table IV). Within each age group, there were no differences in onset time among mivacurium, rocuronium, and the combination (Table IV). Onset of neuromuscular blockade was shorter at the orbicularis oculi than at the adductor pollicis ($P < 0.05$; Table IV). Intubating conditions were all excellent or good, except for two

patients in the mivacurium subgroup (young patients), who had poor conditions. The type of relaxant used did not influence intubating conditions (Table IV). Excellent intubating conditions were observed in 25/45 patients in the young group, compared with 35/45 in the elderly (N.S.).

In young patients, duration of action of the combination was similar to that of mivacurium, approximately 15 min shorter than that of rocuronium ($P < 0.05$ when compared with mivacurium or the combination) (Table IV). In the elderly, the duration of action of the combination and of rocuronium was prolonged compared with that in young adults (Table IV). Thus, in the elderly, the duration of action of the combination was longer than that of mivacurium, but still shorter to that of rocuronium (Table IV).

Cutaneous rash was seen only in the mivacurium group. It was observed in 6/15 young patients and 6/15 elderly subjects. No bronchospasm was observed.

Discussion

This study shows that, in adults aged 18-65 yr, a mixture of 0.08 mg·kg^{-1} mivacurium, and 0.2 mg·kg^{-1} rocuronium, provides onset characteristics and intubating conditions comparable to those associated with either mivacurium or rocuronium given alone. The combination contains the equivalent of two thirds as much drug as either parent drug administered alone. In adults younger than 65 yr, the duration of action of the mixture is similar to that of the shorter-acting drug, mivacurium. In the elderly (>66 yr), the duration of action of the mivacurium-rocuronium combination was prolonged and became slightly longer than that of mivacurium. Duration of action of rocuronium alone was also prolonged in the elderly. Giving the combination offers two advantages: only two thirds as much drug is given so that costs are reduced, and the incidence of cutaneous side effects is less. Under the conditions of this study, onset time and intubating conditions were similar for mivacurium, rocuronium, and their combination.

A previous study described the interaction between mivacurium and rocuronium.[8] Dose response relationships were first established. The ED_{50}s for mivacurium and rocuronium administered alone were 38.8 and 125 μg·kg^{-1}, respectively. The ED_{50} for the combination was 11.4 μg·kg^{-1} mivacurium plus 38.8 μg·kg^{-1} rocuronium, that is 62 % as much drug (in equipotent doses) was required to produce the same effect. In the same study, onset and duration for the combination were measured and compared with 2 × ED_{95} doses of the parent drugs (0.15 mg·kg^{-1} mivacurium or 0.6 mg·kg^{-1}rocuronium). For the combination of 0.0375 mg·kg^{-1} mivacurium plus 0.15 mg·kg^{-1} rocuronium, which represents one ED_{95} in terms of total drug amount, but 1.58 × ED_{95} in terms of potency, onset time was only slightly longer than for 0.6 mg·kg^{-1} rocuronium, (114 *vs* 99 sec) and duration was approximately equal to that of 0.15 mg·kg^{-1} mivacurium, (14.7 *vs* 14.5 min). Giving twice as much of the combination, namely 2 × ED_{95} in drug amount, or 3.16 × ED_{95} in drug potency, yielded a short onset of action (69 sec) but a longer duration (34 min), comparable to that of 0.6 mg·kg^{-1} rocuronium (36 min). The doses had to be modified for the purpose of the present study. First, mivacurium, 0.15 mg·kg^{-1} has been shown to yield poor intubating conditions.[15] Better results are obtained with 0.2-0.25 mg·kg^{-1}, without producing a large increase in duration of action.[15,16] Thus a dose of 0.25 mg·kg^{-1} was chosen, in an attempt to obtain the best possible effect from mivacurium. It is likely that smaller doses would have produced longer onset times and poorer intubating conditions. For rocuronium, the lowest dose reported to be consistent with acceptable intubating conditions, or 0.6 mg·kg^{-1},[17–19] was used, because larger doses are associated with a prolonged duration of action.[18] The combination dose was based on the reported value of 62% for the synergism between both drugs, that is 31% of each drug given together produces an effect equivalent to 100% of either drug given alone.[8] This figure was rounded off to 2/3 (1/3 for each drug) for practical reasons.

In the present study, onset times at the adductor pollicis for mivacurium and especially rocuronium (3.5 - 4.5 min) were longer than usually reported for these drugs. This might be explained by the short stabilization time, which tends to increase measured onset times. For example, onset time after 0.16 mg·kg^{-1} mivacurium was reported to be 198 sec if stabilization time was one minute, and only 106 sec if stabilization time was 20 min.[10] For 0.6 mg·kg^{-1} rocuronium, the differences appear even greater: 150 and 46 sec after one and 20 min respectively.[11] In the present study, onset times for mivacurium and rocuronium were not statistically different. This finding is usually present when neuromuscular monitoring is applied immediately after induction. For example, Pino *et al.*[17] reported an onset time of 5.8 min for 0.6 mg·kg^{-1} rocuronium, not very different from the 4.3 min obtained for 0.25 mg·kg^{-1} mivacurium. Similarly, Audibert *et al.*[18] report values of 5.0 and 5.25 min for 0.6 mg·kg^{-1} rocuronium and for 0.2 mg·kg^{-1} mivacurium, respectively. In both these studies, neuromuscular monitoring was started immediately after

induction. To obtain a fast onset, one could increase the dose of rocuronium to 0.9 mg·kg^{-1}, but the duration of action would be increased considerably.[19,20]

Intubating conditions were assessed at 2.5 min in the present study. The time chosen for this procedure appears rather arbitrary, as intervals varying between one minute and three minutes have been chosen by various investigators.[15,17,19–23] It is expected that intubating conditions would have been less optimal if a shorter interval had been used. Conditions reported here might appear worse than in most published studies. This is probably because, in the present investigation, any movement meant that conditions were not excellent. There were only two patients (of 90) with poor intubating conditions. Time to disappearance of response to facial nerve stimulation was shorter in all groups, when compared with the adductor pollicis. A more rapid onset at the orbicularis oculi was observed before with vecuronium,[24] atracurium,[12,25] and mivacurium.[26,27]

The response of the orbicularis oculi was recommended as a guide to intubating conditions because disappearance of response, as evaluated visually, was found to correlate with maximum blockade of laryngeal muscles.[12] Other evidence includes the fast onset and short duration of both the mechanical responses at the larynx and the EMG data recorded near the eyebrow after the same doses of vecuronium in two separate studies.[24,28] However, a more recent study reported late recovery of accelerographic response of the orbicularis oculi measured over the eyelid after vecuronium, atracurium and mivacurium, similar to that of the adductor pollicis.[29] This suggests that muscles supplied by the facial nerve have different sensitivities to neuromuscular blocking drugs. The palpebral part of the orbicularis oculi, located on the eyelid, is sensitive, whereas the muscles located near the eyebrow, such as the corrugator supercilii, is resistant.[30] Visual inspection detects movement of the latter.

The elderly group was studied because the pharmacodynamics of rocuronium are altered[14] and mivacurium has been reported to have a slightly increased duration in this age group.[31] This increased duration of mivacurium is small and was not found in the present study probably because of the small number of patients. The duration of rocuronium blockade was longer in the elderly (54 *vs* 39 min), which corresponds to earlier observations.[14] The mivacurium-rocuronium combination also has an increased duration of action in the elderly, according to the present study. It was expected that the onset at the adductor pollicis and the orbicularis oculi would be longer in the elderly patient, because of longer circulation time. This was not the case. It is possible that our selection of patients (ASA I and II) might have excluded most subjects with decreased circulation time, or that younger adults had a greater decrease in circulation time because they received a larger dose of induction agent.

The mechanisms accounting for synergism between two neuromuscular blocking drugs are unclear. However, this phenomenon occurs more frequently with two drugs having different chemical structures, for example metocurine-pancuronium,[6] d-tubocurarine-pancuronium,[6] d-tubocurarine-vecuronium,[7] cistracurium-rocuronium,[5,9] and mivacurium and rocuronium.[8,21] Drug combinations have been proposed to decrease the incidence of side effects and cost. In the present study minor cutaneous rash was seen only in the mivacurium group. When cost is considered, using a mixture of drugs is advantageous if both agents are within the same price range. If one drug is considerably cheaper than the other, then it is more economical to use only the less expensive drug. Mid-1999 prices (in Canadian dollars) at our institution were $0.26 and $0.55 per milligram for rocuronium ($13.00 for 50 mg) and mivacurium ($10.75 for 20 mg), respectively. The cost of the intubating doses given in the present study to a 70-kg patient would be $10.92, $9.62 and $6.72. The cost advantage of the combination must be balanced against the greater possibility of wastage as two vials are open. Nevertheless, the main advantage of using two drugs with different onset times and duration of action, such as mivacurium and rocuronium, appears to be, from this study and others,[8,21] that a judicious combination can be chosen for its neuromuscular properties, that is to obtain onset of one drug with the duration of an other.

In summary, combinations of mivacurium and rocuronium can be used to obtain acceptable onset times with duration of action similar to that of mivacurium, at least in adults younger than 65 yr. This is achieved by using 1/3 less drug and cutaneous side effects of mivacurium are likely to be avoided. Such a combination might be considered especially when the anticipated duration of the anesthetic is 20-30 min.

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