Neuromuscular blocking effects of rocuronium during desflurane, isoflurane, and sevoflurane anaesthesia

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Purpose: To determine the magnitude of the potentiation of rocuronium by desflurane, isoflurane and sevoflurane 1.5 MAC anaesthesia.

Methods: In a prospective, randomised, study in 80 patients, the cumulative dose-effect curves for rocuronium were determined during anaesthesia with desflurane, sevoflurane and isoflurane (with N_2O 70%, 15 min steady state) or total intravenous anaesthesia (TIVA) using propofol/fentanyl. Neuromuscular block was assessed by acceleromyography (TOF-Guard®) after train-of-four (TOF) stimulation of the ulnar nerve (2Hz every 12sec, 200 μsec duration). Rocuronium was administered in increments of 100 $\mu g \cdot kg^{-1}$ until first twitch (T_1) depression > 95%.

Results: Rocuronium led to more pronounced T_1 depression with desflurane or sevoflurane anaesthesia than with TIVA. The ED_{50} and ED_{95} were lower during desflurane (95 ± 25 and 190 ± 80 $\mu g \cdot kg^{-1}$) and sevoflurane (120 ± 30 and 210 ± 40 $\mu g \cdot kg^{-1}$) than with TIVA (150 ± 40 and 310 ± 90 $\mu g \cdot kg^{-1}$) ($P < .01$), while the difference was not significant for isoflurane (130 ± 40 and 250 ± 90 $\mu g \cdot kg^{-1}$). Following equi-effective dosing ($T_1 > 95\%$) the duration to 25% T_1 recovery, recovery index (25/75), and $TOF_{0.70}$ was: 13.2 ± 1.8, 12.7 ± 3.4, and 26.9 ± 5.7 min during anaesthesia with desflurane; 15.5 ± 5.0, 11.4 ± 3.8, and 31.0 ± 6.0 min with sevoflurane; 13.9 ± 4.7, 10.7 ± 3.3, and 26.3 ± 8.9 min with isoflurane; and 13.9 ± 3.9, 11.3 ± 5.7, and 27.5 ± 8.2 min with TIVA anaesthesia (*P*: NS).

Conclusion: Interaction of rocuronium and volatile anaesthetics resulted in augmentation of the intensity of neuromuscular block but did not result in significant effects on duration of or recovery from the block.

Objectif : Déterminer l'importance de la potentialisation du rocuronium lors de l'anesthésie utilisant une CAM de 1,5 de desflurane, d'isoflurane et de sévoflurane.

Méthode : Dans une étude randomisée et prospective chez 80 patients, les courbes cumulatives de l'effet en fonction de la dose pour le rocuronium ont été déterminées pendant l'anesthésie avec du desflurane, du sévoflurane et de l'isoflurane (avec N_2O 70 %, à l'état d'équilibre après 15 min) ou pendant l'anesthésie exclusivement intraveineuse (AEI) utilisant du propofol et du fentanyl. La profondeur du bloc neuromusculaire a été mesurée à l'aide d'un accéléromyographe (TOF-Guard®) après une stimulation du nerf cubital en train de quatre (TDQ), (2 Hz toutes les 12 s, durée de 200 μs). Le rocuronium a été administré en accroissements de 100 $\mu g \cdot kg^{-1}$ jusqu'à ce que la première réponse (R_1) atteigne une réduction > 95 %.

Résultats : Le rocuronium provoque des dépressions de R_1 plus marquée lors de l'anesthésie avec le desflurane ou le sévoflurane que lors de l'AEI. Les ED_{50} et ED_{95} ont été plus faibles avec desflurane (95 ± 25 et 190 ± 80 $\mu g \cdot kg^{-1}$) et sévoflurane (120 ± 30 et 210 ± 40 $\mu g \cdot kg^{-1}$) qu'avec l'AEI (150 ± 40 et 310 ± 90 $\mu g \cdot kg^{-1}$) ($P < ,01$), tandis que la différence n'était pas significative avec isoflurane (130 ± 40 et 250 ± 90 $\mu g \cdot kg^{-1}$). A la suite d'un dosage à effet équivalent ($R_1 > 95\%$) la durée de la récupération à 25 % R_1, l'index de récupération (25/75) et le train de quatre$_{0,70}$ étaient : 13,2 ± 1,8; 12,7 ± 3,4 et 26,9 ± 5,7 min pendant l'anesthésie avec desflurane; 15,5 ±5,0; 11,4 ± 3,8 et 31,0 ± 6,0 min avec le sévoflurane; 13,9 ± 4,7; 10,7 ± 3,3 et 26,3 ± 8,9 min avec l'isoflurane; enfin, 13,9 ± 3,9; 11,3 ± 5,7 et 27,5 ± 8,2 min avec l'AEI (*P*: NS).

Conclusion : L'interaction du rocuronium et des anesthésiques volatils a provoqué l'augmentation de l'intensité du bloc neuromusculaire mais n'a pas eu d'effet significatif sur la durée du bloc ou sur la récupération qui a suivi.

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THE neuromuscular blocking effects of muscle relaxants are enhanced by volatile anaesthetics, a phenomenon called "potentiation".[1] The magnitude of this effect on the dose-response curve has not been investigated systematically for the recently introduced agent, rocuronium. Rocuronium is a non-depolarising steroidal muscle relaxant with a shorter onset of action than other available non-depolarising relaxants.[2] The new volatile agents, sevoflurane and desflurane, have a low blood-gas solubility resulting in rapid uptake and elimination.[3,4] Their physicochemical properties allow a fast recovery, thus making both agents suitable for day case surgery. Underestimation or ignoring of the enhancement of neuromuscular block by volatile anaesthetics during short procedures could result in inadvertent prolonged duration of relaxation. Therefore, the interaction of rocuronium with the new volatile anaesthetics, desflurane and sevoflurane, and with isoflurane was investigated and compared with the neuromuscular blocking effects of rocuronium during total intravenous anaesthesia (TIVA).

Methods

The investigation was planned in accordance with the recommendations outlined in "Good Clinical Research Practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents".[5]

Sample size estimation (power analysis) was based on the following previous results: The ED_{50} of rocuronium during halothane and enflurane anaesthesia is approximately 100 µg ± 10 µg (SD).[6] The time required for the first twitch (T_1) to recover to 75% after complete relaxation following continuous infusion of rocuronium was 30.2 ± 6.1 min during TIVA.[7] In another study recovery took 42 ± 9 min after complete relaxation following a single dose of 0.6 $mg \cdot kg^{-1}$ during anaesthesia with isoflurane.[8] Considering a difference of 20% in potency or recovery time to be of clinical importance and assuming a standard deviation of approximately 10-20% of the mean, the calculated sample size would have to be at least 11 (6-20) patients per group for single comparison ($\alpha = 0.05$; $ß = 0.2$). Since a comparison of several volatile anaesthetics with TIVA was planned and since some drop-outs were anticipated, a sample size of 20 patients per group was deemed appropriate.

Following ethics committee approval and written informed consent 80 consecutive Caucasian male or female adults (ASA 1 or 2) were included in this prospective randomised study. The patients were scheduled for minor elective ENT or ophthalmological surgery and were free from neuromuscular and endocrine diseases. Exclusion criteria were: body weight greater or less than 30% of the ideal, patients <18 yr or >59 yr, pregnancy or breast-feeding, history or laboratory signs of renal (creatinine > 100 $µmol \cdot l^{-1}$ (> 1.3 $mg \cdot dl^{-1}$)) or hepatic disease (γ-GT > 333 $nkat \cdot l^{-1}$ (> 20 $U \cdot l^{-1}$)), paresis, bedridden patients, intake of medication known to interact with non-depolarising muscle relaxants and allergic diathesis.

Cumulative dose-effect curves for rocuronium were determined during anaesthesia with 1.5 MAC (minimal alveolar concentration, desflurane (4.2 %), isoflurane (0.75 %), and sevoflurane (1.05 %) in nitrous oxide 70% /oxygen 30%, not age-adjusted) and compared with the potency determined in patients during TIVA with propofol/fentanyl. Premedication consisted of 20 mg dichlorazepat *po* on the evening prior to surgery. Anaesthesia was induced with 2-2.5 $mg \cdot kg^{-1}$ propofol and 0.1 mg fentanyl *iv* in the arm opposite to that connected to the neuromuscular monitoring equipment. The volatile anaesthetics were administered starting with 2.5-3 MAC inspiratory concentration. This was reduced within the next minutes to 1.5 MAC. Inspiratory and end-tidal concentrations of the anaesthetics were measured (Capnomac (Datex)). All study groups received O_2/N_2O 30/70%. End-tidal PCO_2 was adjusted to between 4.3 and 4.7 kPa (32 and 35 mmHg). Body temperature and skin temperature above the monitored muscle were measured and kept > 35C and 32C, respectively, by passive warming (wrapping of the patient and the arm in a cotton blanket). The blood pressure cuff was placed on the opposite arm. Light anaesthesia or moderate hypertension (> 120% of baseline) were treated initially with 0.1 mg fentanyl *iv* and, if necessary, by increasing by 20% the end-tidal concentration of the volatile anaesthetic or the propofol infusion rate, respectively. Hypotension (< 80% of baseline) was treated initially by infusion of fluids and then by decreasing by 20% the end-tidal concentration or the propofol infusion rate, respectively.

The left arm was attached to a special arm board (Armboard TOF-Guard®, Biometer Int., Odense DK) for assessment of neuromuscular block using acceleromyography (AMG).[9] The adductor pollicis muscle was monitored with the piezo-electric ceramic wafer placed at the distal interphalangeal joint of the thumb (TOF-Guard®, Biometer Int., Odense DK). Train of four (TOF) stimulation of the ulnar nerve via surface stimulating electrodes placed at the wrist was used (supra-maximal square wave impulses with 2Hz, applied every 12sec, 200 µsec duration).[5] All data were stored electronically and downloaded into a computer programme for further analysis (TOF-

Guard Card Reader 1.0 for Windows (Organon Teknika, Turnhout, Belgium)). Rocuronium was administered when neuromuscular response (stable control response in AMG for five minutes, a period that was demonstrated to be long enough for stabilization[10]) and equilibrium of inspiratory and end-tidal concentration of volatile anaesthetics appeared stable[11] (Capnomac (Datex)). Cumulative increments[12] of 100 $\mu g \cdot kg^{-1}$ rocuronium were administered repeatedly (injection time < 5 sec into a fast running *iv* line) until depression of the first twitch ≥ = 95% was achieved. Repeated doses were administered at least two minutes apart and only if three consecutive twitches (T_1) showed the same amplitude to document that a stable response was obtained between each dose. The time over which the doses were given was relatively short (four to eight minutes). In addition to the depression of the first twitch response, the following parameters of neuromuscular block were obtained during steady state anaesthesia: duration 25% (time after injection of the last cumulative dose until 25% recovery of T_1), recovery index: C time of recovery of T_1 from 25% to 75%), interval T_1 25% to a TOF ratio of 0.7 ($TOF_{0.7}$). Instead of TOF 0.8 (as suggested by the GCRP guidelines[5]) TOF ratio 0.7 was used since, in some patients, the concentration of the volatile anaesthetic had been reduced already approaching the end of operation.

In cases of baseline shift (failure of T_1 to recover to between 85% and 110% with a TOF ratio > 0.8), patients were excluded from further analysis. Individual dose-response curves were established by plotting the logarithm of the dose against the logit transform of the depression of T_1 relative to baseline (100% depression of T_1 was adjusted to 99%, 0% to 1% respectively) using linear least squares regression.[5,12] Study-group dose response curves were established and ED_{50} and ED_{95} of rocuronium were calculated.

Statistical analysis: Data are presented as mean ± SD. Statistical analysis was performed by one-way ANOVA (graph pad prism®, Kruskal-Wallis test and Dunn's post test for multiple comparison). α was set at 0.05, ß was set at 0.2.

Results

Patients in the study groups were similar in age, weight and sex distribution (Table I). Results from four patients were excluded from further analysis (drop-outs) because of deviation from the study protocol, baseline shift, and reduction of the concentration of the volatile anaesthetic < 1.2 MAC. In two patients in the isoflurane and in two patients in the sevoflurane group, the concentration of the volatile anaesthetic was reduced intermittently to 1.2 MAC during the study because of arterial hypotension. In one patient in each of the isoflurane and desflurane groups the concentration had to be increased to 1.8 MAC intermittently. The propofol infusion rate was decreased by 20% in two patients and increased by 20% in one patient intermittently.

Rocuronium, in cumulative doses up to 300 $\mu g \cdot kg^{-1}$, led to a more pronounced depression of T_1 when anaesthesia was maintained with desflurane or sevoflurane than with TIVA (Table II) ($P < 0.01$). Multiples of 2.2 ± 0.4, 2.6 ± 0.6 and 3.4 ± 0.7 of the dose of 100 µg were applied to obtain T1 < 5%. The ED_{50} and ED_{95} were lower during desflurane (95 ± 25 and 190 ± 80 $\mu g \cdot kg^{-1}$) and sevoflurane anaesthesia (120 ± 30 and 210 ± 70 $\mu g \cdot kg^{-1}$) than with TIVA (150 ± 40 and 310 ± 90 $\mu g \cdot kg^{-1}$) ($P < 0.01$)(Figure 1). Considering the correction for multiple comparison, the difference between the TIVA group and the isoflurane group (ED_{50} 130 ± 40; ED_{95} 250 ± 90 $\mu g \cdot kg^{-1}$) was not significant ($P = 0.08$). The degree of potentiation (ratio of ED_{50} during TIVA/ ED_{50} during volatile anaesthesia) was 1.6, 1.3, and 1.2 for desflurane, sevoflurane, and isoflurane respectively.

Following equi-effective dosing (depression of T1 to about 95%, that is: halogenated groups received less drug) the recovery data duration 25%, recovery index $_{25/75}$, and $TOF_{0.70}$ revealed no difference among the study groups (Table III).

Discussion

The mechanism by which volatile anaesthetic agents increase neuromuscular block is still under discussion.[13] Our goal was to determine the influence of the newer volatile anaesthetics, desflurane and sevoflurane, as well as isoflurane on the dose response relationship of rocuronium compared to a TIVA-control. In the present study the neuromuscular blocking effect of rocuronium was enhanced by desflurane and sevoflurane, whereas the effect of isoflurane was less pronounced. In contrast to some of the previous studies on the interaction of volatile anaesthetics and neuromuscular blocking drugs (NMBD), no effect on the duration and recovery could be demonstrated.

TABLE I Demographic data of the patients enrolled (mean ± SD)

	male/female	*Weight [kg]*	*height [cm]*	*age [y]*
Desflurane	8/10	73 ± 14	172 ± 11	44 ± 14
Isoflurane	13/6	80 ± 15	174 ± 9	47 ± 16
Sevoflurane	11/9	78 ± 15	175 ± 11	48 ± 14
TIVA	11/8	73 ± 12	171 ± 10	42 ± 15

TABLE II Neuromuscular blocking effects of rocuronium (ED_{50} and ED_{95})Depression of the first twitch (% of control) after 3 cumulative doses of 100 $\mu g \cdot kg^{-1}$ rocuronium during desflurane, isoflurane, sevoflurane and total intravenous anaesthesia (TIVA). ED_{50} and ED_{95} were calculated after logit transformation. $^*P < 0.05$

	Depression first twitch (% of control)				
	100 $\mu g \cdot kg^{-1}$	*200 $\mu g \cdot kg^{-1}$*	*300 $\mu g \cdot kg^{-1}$*	*ED_{50} $\mu g \cdot kg^{-1}$*	*ED_{95} $\mu g \cdot kg^{-1}$*
Desflurane	58 ±25*	95 ± 7*	100 ± 1*	95 ± 25*	190 ± 80*
Isoflurane	31 ± 24	78 ± 21	94 ± 8	130 ± 40	250 ± 90
Sevoflurane	45 ± 26*	90 ±13*	98 ± 5*	120 ± 30*	210 ± 40*
TIVA	14 ± 24	65 ± 22	90 ± 10	150 ± 40	310 ± 90

TABLE III Duration and recovery of neuromuscular block during desflurane, isoflurane, sevoflurane and total intravenous anaesthesia following equi-effective doses of rocuronium.

	ED_{95} $\mu g \cdot kg^{-1}$	*Dose Given*	*Duration 25% [min]*	*Recovery Index $_{25/75}$ [min]*	*$TOF_{0.70}$ [min]*
Desflurane	190 ± 80	224 ± 58	13.2 ± 1.8	12.7 ± 3.4	26.9 ± 5.7
Isoflurane	250 ± 90	287 ± 68	13.9 ± 4.7	10.7 ± 3.3	26.3 ± 8.9
Sevoflurane	210 ± 40	265 ± 49	15.5 ± 5.0	11.4 ± 3.8	31.0 ± 6.0
TIVA	310 ± 90	368 ± 46	13.9 ± 3.9	11.3 ± 5.7	27.5 ± 8.2

Potency (augmentation of the depression of T1)

Sevoflurane and desflurane augmented the neuromuscular block of rocuronium. Using a single-dose technique for rocuronium, Oris and coworker[6] reported a lower ED_{50} of 133 (ED_{90} of 230) $\mu g \cdot kg^{-1}$ during halothane anaesthesia and 118 (200) µg during enflurane anaesthesia compared with 167 (300) µg during total intravenous anaesthesia. Our data are in accordance with those of Muir *et al.* (enhancement by a factor of 1.25-1.4 compared with TIVA).[14] In theory, assuming that the neuromuscular block starts at 70-75% receptor occupancy and is half maximal at 87.5% receptor occupancy, the ratio ED_{95}/ED_{50} should be 1.95. Our results demonstrate that this is true for rocuronium under four different anaesthetic conditions (2.06, 2.0, 1.75, 1.92).

Data for interaction of sevoflurane and rocuronium are lacking. Isoflurane and sevoflurane 1.5 MAC augmented the neuromuscular block produced by vecuronium, pancuronium and atracurium to a similar degree[15] as did sevoflurane and halothane for the block produced by vecuronium in children.[16]

Interaction of rocuronium and volatile anaesthetics: duration and recovery

Usually, potentiation of NMBD by volatile anaesthetics results predominantly in prolongation of the duration and recovery of neuromuscular block.[17] These parameters were not prolonged significantly by volatile anaesthetics under the conditions of the present study. Saitoh *et al.* reported a minor prolongation of recovery from vecuronium-induced NMB during sevoflurane and enflurane by approximately 15%.[18] Duration and recovery time depend on the dose of the NMBD.[1,19] The most probable reason for the longer duration of action observed in some studies compared with our results is that rocuronium was given in high doses (e.g. 600-900 $\mu g \cdot kg^{-1}$),[11,20] while the administration of moderate doses (e.g. up to 300 $\mu g \cdot kg^{-1}$)[21] leads to results very similar to those in the present study. Could a difference have been missed because of a type I error (small sample size)? Indeed, the standard deviations of duration and recovery data were higher than the SD used for the sample size estimation (data from mechanomyography, see below). Nevertheless, post-hoc analysis shows that the chance of missing a prolongation of 25% or more was < 20%.

Advantages and disadvantages of the techniques used in the present study:

THE EFFECT OF CUMULATIVE DOSING

The cumulative dose technique may underestimate the potency of neuromuscular blocking. However, administration was standardised and the use of volatile anaesthetics or TIVA was randomised; thus the cumulative pattern of rocuronium administration would have similar effects in all groups. In addition, the aim of the current study was to determine anaesthesia-

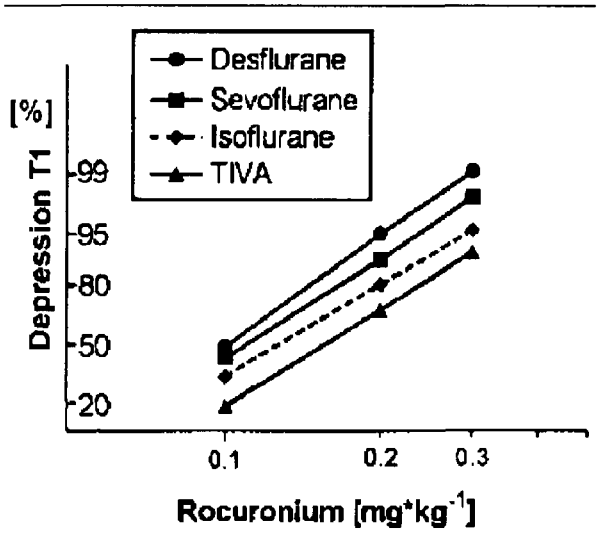

FIGURE 1 Log-probit plot comparing cumulative bolus dose-response curves for the neuromuscular block induced by rocuronium during desflurane, sevoflurane, isoflurane (1,5 MAC) and total intravenous anaesthesia (TIVA). (depression was set at 100%, if >95% was reached with 200 $\mu g \cdot kg^{-1}$ rocuronium already).

related effects of NMBD and not to provide absolute potency data. Nevertheless, the data presented by Oris *et al.*[6] are similar to the results of the present study using a cumulative dosing technique during desflurane and sevoflurane anaesthesia. Furthermore, in the present study the total dose was given in increments and, therefore, recovery from the first dose could have started while the last dose was being administered. This could result in an underestimation of duration of action, particularly during the TIVA technique.

We used repetitive incremental dosing until 95% depression of T_1 was obtained in an individual patient (equi- effective dose: identical end-point instead of identical doses). As a consequence, all halogenated groups received less drug. Using this approach of equi-effective dosing, enhancement of neuromuscular block could be demonstrated with regard to ED_{50} and ED_{95}, whereas recovery times were not different among the volatile anaesthetics and TIVA groups. In contrast, if NMBDs are given in identical fixed doses regardless of the individual effective dose, differences in duration of action and recovery will result.

THE INFLUENCE OF EQUILIBRATION TIME

We started our measurements at least 15 to 20 min following induction of anaesthesia, since accelerometric monitoring results in stable effects after equilibration of 10 min or less.[10] Inspiratory and end-tidal concentrations of volatile anaesthetics also indicated that steady state was approached, at least at the alveolar level. Diffusion of the inhaled anaesthetics into the muscle compartment is slow and requires about 30 - 45 min to approach equilibration. Therefore, in the present study, this process was probably incomplete. Enhancement of neuromuscular block might still increase after more than one hour of anaesthesia with volatile agents.[22-25] Studies beyond this time of final equilibrium are difficult to accomplish and bear little relevance to the routine clinical use of these agents.[17] Due to the difference in the physicochemical properties, the equilibration between the muscle compartment and the end-tidal concentration is reached faster for desflurane and sevoflurane than for isoflurane.[3,4,26] This phenomenon could explain the less pronounced effects of isoflurane in the present study. Nevertheless, our results are in agreement with those observed by Wright and colleagues in volunteers using a protocol with volatile anaesthetic administration for >60 min before NMBD administration.[26] They observed a 20% reduction in vecuronium requirement in the presence of 1.25 MAC desflurane compared with 1.25 MAC isoflurane. In contrast, Kumar *et al.* showed similar potentiation during desflurane and isoflurane anaesthesia after a stabilisation period of 10 min.[11] Both studies were performed without a TIVA control group.

Acceleromyography or mechanomyography?

Mechanomyography still is considered to be the "gold standard" of neuromuscular monitoring and should be used for phase I or II studies.[5] Acceleromyography and mechanomyography should not be used interchangeably,[9,27] but acceleromyography can be used to evaluate further neuromuscular blocking agents unless the established guidelines are adhered to.[5] Using acceleromyography there was good evidence of an interaction between volatile anaesthetics and rocuronium. The degree of augmentation of neuromuscular block was similar to the results of previous studies investigating rocuronium during anaesthesia with isoflurane using mechanomyography. Acceleromyography might have some limitations in regard to comparative measurements of duration and recovery, due to its greater drift and rather wide limits of agreement with mechanomyography.[27]

Conclusion

Under the conditions of the present study, the interaction of rocuronium and volatile anaesthetics results in an enhanced depression of the muscle twitch and a leftward shift in the dose response relationship in the first place. This should be taken into account when using rocuronium during desflurane or sevoflurane

anaesthesia. Prolongation in the duration of action of, or in the recovery from neuromuscular block did not show with the present study using potency-adjusted dosing and acceleromyographic monitoring.

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