Neostigmine antagonism of rocuronium block during anesthesia with sevoflurane, isoflurane or propofol

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Purpose: To examine the influence of continuing administration of sevoflurane or isoflurane during reversal of rocuronium induced neuromuscular block with neostigmine.

Methods: One hundred and twenty patients, divided into three equal groups, were randomly allocated to maintenance of anesthesia with sevoflurane, isoflurane or propofol. Neuromuscular block was induced with rocuronium and monitored using train-of-four (TOF) stimulation of the ulnar nerve and recording the force of contraction of the adductor pollicis muscle. Neostigmine was administered when the first response in TOF had recovered to 25%. At this time the volatile agent administration was stopped or propofol dosage reduced in half the patients in each group (n = 20 in each group). The times to attain TOF ratio of 0.8, and the number of patients attaining this end point within 15 min were recorded.

Results: The times (mean ± SD) to recovery of the TOF ratio to 0.8 were 12.0 ± 5.5 and 6.8 ± 2.3 min in the sevoflurane continued and sevoflurane stopped groups, 9.0 ± 8.3 and 5.5 ± 3.0 min in the isoflurane continued and isoflurane stopped groups, and 5.2 ± 2.8 and 4.7 ±1.5 min in the propofol continued and propofol stopped groups ($P < 0.5$- 01). Only 9 and 15 patients in the sevoflurane and isoflurane continued groups respectively had attained a TOF ratio of 0.8 within 15 min ($P < 0.001$ for sevoflurane).

Conclusions: The continued administration of sevoflurane, and to a smaller extent isoflurane, results in delay in attaining adequate antagonism of rocuronium induced neuromuscular block.

Objectif : Examiner l'influence de l'administration continue de sévoflurane ou d'isoflurane pendant le renversement d'un bloc neuromusculaire induit avec du rocuronium et de la néostigmine.

Méthode : Cent vingt patients, répartis en trois groupes égaux, ont reçu au hasard du sévoflurane, de l'isoflurane ou du propofol pour le maintien de l'anesthésie. Le bloc neuromusculaire a été induit avec du rocuronium et placé sous monitorage d'une stimulation en train-de-quatre (TDQ) du nerf cubital et d'un enregistrement de la force de contraction du muscle adducteur du pouce. La néostigmine a été administrée au moment de la première réponse en TDQ d'une récupération à 25 %. À ce moment, l'administration de l'anesthésique volatil a été stoppée, ou le propofol réduit, chez la moitié des patients de chaque groupe (n = 20 dans chaque groupe). Le temps nécessaire pour atteindre un ratio de 0,8 du TDQ et le nombre de patients qui atteignent cette mesure cible en moins de 15 min ont été enregistrés.

Résultats : Le temps (moyenne ± écart type) de récupération du ratio de 0,8 du TDQ a été de 12,0 ± 5,5 et de 6,8 ± 2,3 min avec le sévoflurane continu et stoppé; 9,0 ± 8,3 et 5,5 ± 3,0 min avec l'isoflurane continu et stoppé; 5,2 ± 2,8 et 4,7 ± 1,5 min avec le propofol continu et stoppé ($P < 0,5$-01). Seulement 9 et 15 patients ayant reçu du sévoflurane et de l'isoflurane en administration continue ont atteint le ratio de 0,8 du TDQ en moins de 15 min ($P < 0,001$ pour le sévoflurane).

Conclusion : L'administration continue de sévoflurane et, dans une moindre mesure, d'isoflurane, a retardé le renversement d'un bloc neuromusculaire induit avec du rocuronium.

PREVIOUS studies have shown that antagonism of block with relaxants such as vecuronium is impeded in the presence of potent volatile agents such as sevoflurane and isoflurane.[1–3] It has also been shown that sevoflurane anesthesia potentiates the effect of rocuronium compared with isoflurane and propofol anesthesia.[4] Although there are reports of antagonism of rocuronium block with neostigmine, these have generally examined the influence of the dosage or the timing of administration of the anticholinesterase.[5–7] The aim of the present study was to examine the effect of the sevoflurane on the antagonism of rocuronium by neostigmine, and compare it with the effects of isoflurane, and intravenous anesthesia.

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Patients and methods

One hundred and twenty three ASA I or II patients (of whom three were replacement patients), aged between 18 and 65 yr, and scheduled to undergo elective body surface or orthopedic surgery lasting longer than 30 min were recruited into the study following their written informed consent and Research Ethics Committee approval. Patients whose body weight deviated by >30% of ideal, or who were receiving drugs known to interact with neuromuscular blocking agents were excluded from the study.

Patients were premedicated with 10-20 mg temazepam *po* 90 min preoperatively, if desired by them. Anesthesia was induced with 1-2 $\mu g \cdot kg^{-1}$ fentanyl and 1-3 $mg \cdot kg^{-1}$ propofol, and maintained with nitrous oxide 66% in oxygen, and sevoflurane, isoflurane, or propofol, as allocated by a computer generated randomization list. Ventilation was assisted to maintain the $P_{ET}CO_2$ between 35 and 45 mm Hg, and skin temperature over the adductor pollicis was maintained above 32°C by wrapping the arm in cotton wool. The end-tidal concentration of the volatile agents was monitored using a respiratory gas monitor and adjusted to 1.5 MAC adjusted for age and concomitant use of nitrous oxide (1.5-1.8% sevoflurane, 0.8-1.0% isoflurane) as described previously.[4] Patients whose anesthesia was maintained with *iv* propofol received a standard propofol infusion at 6-12 $mg \cdot kg^{-1} \cdot hr^{-1}$. Further doses of propofol or fentanyl were administered as required.

The ulnar nerve was stimulated transcutaneously at the wrist, with supramaximal stimuli of 0.2 msec duration in a train-of-four (TOF) mode at 2 Hz every 12 sec. The resulting force of contraction of the adductor pollicis muscle was measured and recorded using a force displacement transducer and a neuromuscular function analyser (Myograph 2000, Biometer, Denmark). Baseline neuromuscular responses were allowed to stabilize for about 10 min, during which time the end-tidal concentration of volatile anesthetics was also stabilized.

Patients received a bolus dose of 0.6 $mg \cdot kg^{-1}$ rocuronium as a single *iv* injection over five seconds, followed by increments if required when the T_1 had recovered to 25% of the control value. Tracheal intubation was carried out at the development of maximum block. At the end of surgery all patients had neuromuscular block antagonised with 50 $\mu g \cdot kg^{-1}$ neostigmine and 10 $\mu g \cdot kg^{-1}$ glycopyrrolate when T_1 (the first response in TOF) was 20-25%. Administration of sevoflurane, isoflurane or propofol was continued throughout the reversal in half the patients in each group (propofol-continued, sevoflurane-continued or isoflurane-continued groups), while the rest had the volatile agent discontinued or propofol infusion run at a lower (about 2 $mg \cdot kg^{-1} \cdot hr^{-1}$) rate (propofol-stopped, sevoflurane-stopped or isoflurane-stopped groups). Nitrous oxide 66% in oxygen was continued in all patients until completion of reversal.

The times to onset of effect of neostigmine (increase of 5% or more of T_1), attaining the TOF ratio of 0.8, and the recovery of T_1 from 25-75% were recorded. The number of patients who had not attained a TOF ratio of 0.8 by 15 min of neostigmine administration was also recorded. The end point of TOF ratio of 0.8 was chosen to represent adequate recovery according to recent guidelines compared with the previously used end point of 0.7.[8] The data of various time end points were subjected to analysis of variance, followed by post tests as indicated. The number of patients achieving reversal within the 15 min time period was subject to x^2 analysis. $P < 0.05$ was considered to represent a significant difference. Sixteen patients per group would have been required for the study for a power of 80% assuming a difference of 10 min between the fastest and the slowest reversing groups in the time taken to attain a TOF ratio of 0.8 we decided to include 20 subjects per group.

Results

Although 123 patients were recruited into this study, three of them replaced the three patients whose data had to be excluded, in two due to equipment malfunction and in the other due to a protocol violation. The results are therefore reported for 120 patients.

The groups were comparable in terms of age, weight, height, gender distribution and T_1 at reversal (Table I).

The main results are given in Table II. The times for onset of action of neostigmine (average of 0.6-0.7 min) did not differ among the six groups. The time to attaining a TOF ratio to 0.8 was longer ($P < 0.01$) in the sevoflurane-continued group being an average of 12.0 min. Although the time (mean of 9.0 min) was longer in the isoflurane-continued group also, the difference was not statistically significant when compared with the time in the isoflurane stopped group. The differences between the propofol groups and the groups where volatile agents were stopped at reversal were not different and averaged about five minutes. The data for four patients in the sevoflurane-continued and in one patient in the isoflurane-continued were not available as they had not attained the TOF ratio of 0.8 even after 30 min of neostigmine administration when, due to logistic reasons, their anesthe-

TABLE I Patient data

	Propofol Continued	*Propofol Stopped*	*Sevoflurane Continued*	*Sevoflurane Stopped*	*Isoflurane Continued*	*Isoflurane Stopped*
n	20	20	20	20	20	20
Age (yr)	37 ± 15.1	36 ± 13.0	38 ± 11.1	38 ± 11.9	34 ± 11.4	34 ± 12.5
[Range]	[19 – 61]	[23 – 57]	[20 – 57]	[19 – 57]	[19 – 58]	[19 - 57]
Weight (kg)	75 ± 12.7	77 ± 10.2	79 ± 13.9	74 ± 11.0	73 ± 17.5	71 ± 11.8
Height (cm)	171 ± 9.6	175 ± 10.2	175 ± 7.8	171 ± 9.7	171 ± 12.7	172 ± 9.8
Gender (M / F)	11 / 9	16 / 4	14 / 6	12 / 8	10 / 10	12 / 8
T_1 at reversal (%)	25 ± 1.6	24 ± 2.2	24 ± 2.2	24 ± 2.1	24 ± 2.2	24 ± 2.0

Data are mean ± SD, [range] or *n*

TABLE II Recovery parameters after neostigmine administration

	Propofol Continued	*Propofol Stopped*	*Sevoflurane Continued*	*Sevoflurane Stopped*	*Isoflurane Continued*	*Isoflurane Stopped*
Onset of action (min)	0.6 ± 0.2	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.2	0.7 ± 0.2
Time (min) to TOF ratio of 0.8	5.2 ± 2.8	4.7 ± 1.5	[a]12.0 ± 5.5†‡	6.8 ± 2.3	[b]9.0 ± 8.3*	5.5 ± 3.0
RI (min)	2.9 ± 0.8	2.4 ± 0.6	3.8 ± 3.6	2.3 ± 0.8	4.4 ± 3.6	2.7 ± 1.1
No of patients achieving TOF ratio of 0.8in < 15 min	20	20	9§	20	15	20

Data are mean ± SD or n; RI = recovery index

[a]n=16, [b]n=19;

§ $P < 0.001$

† $P < 0.01$ for sevoflurane continued *vs* propofol continued, propofol stopped and isoflurane stopped

‡ $P < 0.05$ for sevoflurane continued *vs* sevoflurane stopped

*$P < 0.05$ for isoflurane continued *vs* propofol stopped

sia had to be discontinued. All of them achieved the TOF ratio of 0.8 within a few minutes after discontinuation of the volatile agent. T_1 25-75% recovery indices although slightly longer in the groups where the volatile anesthetic administration was continued during reversal, were not significantly different.

Fewer patients (9 / 20) achieved a TOF ratio of 0.8 within 15 min in the sevoflurane-continued group ($P < 0.001$). Five patients in the isoflurane-continued group also did not attain this end point within 15 min.

Discussion

The results from the present study indicate that continuing administration of sevoflurane during reversal prolongs the time to adequate recovery. Indeed, in the sevoflurane-continued group, 11 of 20 patients failed to achieve a TOF ratio of 0.8 within 15 min after neostigmine administration, and four patients had not achieved this end point even by 30 min. Although recovery in some patients receiving isoflurane was also prolonged, the frequency was lower. The end-point of 15 min was selected arbitrarily, keeping in mind the logistics of the movement of patients on routine operating lists. Considering the fact that a TOF ratio of 0.8 was not attained even by 30 min in five patients in the groups continuing to receive the volatile agents during reversal, and whose data were excluded from analysis, the recovery could reasonably be expected to be even longer in these groups.

It has previously been shown that residual concentrations of isoflurane augment vecuronium induced neuromuscular block and that even after discontinuation of the volatile agent, impaired antagonism is not eliminated although there is some improvement.[1] In our study also, the reversal was slowed in the presence of sevoflurane, and to some extent isoflurane anesthesia, and in some patients the block had not reversed even by 30 min. However, when the volatile agent administration was discontinued at the time of neostigmine administration, the reversal times were not different from the propofol groups. This was the case with those patients also whose reversal was very slow in the presence of volatile agents but recovered on discontinuation of the volatile agent. Our study, therefore, shows that discontinuing administration of the volatile anesthetics improves the speed of reversal of block with neostigmine.

The continued administration of isoflurane during reversal of rocuronium-induced neuromuscular blockade, also tended to prolong the time to attaining the TOF ratio of 0.8 when compared with propofol anesthesia, a finding which has been reported by others.[9,10] The concurrent administration of enflurane has been shown to impair neostigmine antagonism of both pancuronium and vecuronium blocks,[11,12] and stopping administration of enflurane at the time of neostigmine administration decreases the potentiation of atracurium block produced by enflurane.[13] The recovery in the groups where the volatile agent administration was discontinued in the present study was fairly rapid and similar to that in the propofol groups. This would not be surprising given the rapid elimination of both sevoflurane and isoflurane due to their relatively low blood-gas solubilities. This was further evident in the cases where continued administration of sevoflurane and isoflurane resulted in slow and prolonged recovery which was accelerated once the volatile agent administration was discontinued.

Some previous studies have shown that the effects of isoflurane and sevoflurane are similar in prolonging the effects of muscle relaxants when the volatile agents have been administered for about 40 min before relaxant administration allowing enough time for equilibration of volatile agents between various compartments.[14–16] This may be the reason why in a recent study there was no marked prolongation in average reversal time of rapacuronium during sevoflurane compared to propofol anesthesia as the reversal was carried out within only about 15 min of relaxant and anesthetic administration.[17] These results are at variance with the findings of Lowry *et al.* who showed a more marked effect of sevoflurane on rocuronium block during spontaneous recovery even after shorter periods of volatile agent administration.[4] The greater effect of sevoflurane compared with isoflurane would, from the results of our study, appear to be present during the reversal of block as well indicating that sevoflurane may have inherently greater potentiating effect on muscle relaxants such as rocuronium. In our study, both sevoflurane and isoflurane were administered for similar average times (longer than those reported by others for equilibration between blood and muscle compartments), yet the reversal was slower in those receiving sevoflurane.

Although the T_1 25-75% recovery index also showed a tendency to be prolonged in the volatile agent continued groups, the difference was not statistically significant. This is in contrast to a previous study where the recovery index for rocuronium was prolonged during sevoflurane anesthesia.[4] However in that study recovery was taking place spontaneously and was considerably more prolonged.

Several reasons have been postulated as the cause of the potentiation of muscle relaxants by volatile agents. These include pre-junctional effects, increased blood flow to muscles during anesthesia, and a centrally mediated relaxation.[18–20] Whatever the mechanism, it appears that these effects are extended to the time of the reversal of the block as well. It would appear that sevoflurane potentiation of muscle relaxants is more marked than that of isoflurane. Any differences in muscle-gas solubility of the various volatile agents would not account for the effect of the volatile agents because when examining reversal, as in our study, enough time (approximately 40 min) would have elapsed to ensure equilibration between blood and muscle compartments.

In conclusion, the present study demonstrates the extent to which recovery from rocuronium induced neuromuscular block is slowed in the presence of potent volatile agents, and that this effect is more marked in patients receiving sevoflurane. It can also be seen that discontinuing administration of the volatile agents at reversal returns the time taken to adequate recovery to that in patients receiving an intravenous infusion of propofol. Thus it may be worthwhile considering earlier administration of reversal agents although it is not known if it facilitates early reversal, and it may also not be convenient. It is also important to monitor neuromuscular blockade routinely and correctly when using rocuronium with any of the volatile agents. However, if it is considered desirable to maintain administration of sevoflurane during rocuronium reversal by neostigmine, then slower attainment of adequate reversal should be anticipated.

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