General Anesthesia

Sevoflurane and isoflurane, but not propofol, decrease mivacurium requirements over time

[Le sévoflurane et l'isoflurane, mais pas le propofol, diminuent les besoins en mivacurium avec le temps]

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Purpose: Volatile anesthetic agents potentiate neuromuscular blockade, but the magnitude of potentiation appears to be time dependent. The time course of this interaction was studied by measuring mivacurium infusion rates during sevoflurane, isoflurane and propofol anesthesia.

Methods: After informed consent, anesthesia was induced in 48 ASA physical status I-II adults with propofol, fentanyl and mivacurium $0.25 \text{ mg}\cdot\text{kg}^{-1}$ and maintained with N_2O (60%) and one of the three agents chosen at random: sevoflurane 1.9%; isoflurane 1.2%; or propofol $100\text{--}150 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Train-of-four stimulation was applied every 15 sec to the ulnar nerve. Neuromuscular blockade was monitored with accelerometry. At 5% recovery of the first twitch (T1), a mivacurium infusion was started and adjusted every five minutes to maintain 90–95% T1 depression.

Results: The time to 5% T1 recovery after the initial dose was similar in all groups (13–15 min). Fifteen minutes after the start of the infusion mivacurium requirements were greater ($P < 0.05$) in the propofol group ($7.5 \pm 1.7 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; mean $\pm$ SD) than in either isoflurane ($4.7 \pm 1.6 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) or sevoflurane ($4.5 \pm 1.5 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) group. Then, the rate remained stable for propofol ($6.2 \pm 1.4 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ after 90 min of infusion) while it decreased with isoflurane to $2.9 \pm 1.6 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ at 90 min ($P < 0.05$ vs propofol) and to $1.4 \pm 1.0 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ in the sevoflurane group ($P < 0.05$ vs propofol and isoflurane).

Conclusion: Sevoflurane and isoflurane do not prolong the effect of a bolus dose of mivacurium, but potentiation increases with time from 30–105 min of exposure. This interaction is greater with sevoflurane than isoflurane.

Objectif: Les agents anesthésiques volatils potentialisent le bloc neuromusculaire, mais le degré de potentialisation semble dépendre du temps. Nous avons mesuré la vitesse de perfusion de mivacurium en fonction du temps pendant une anesthésie au sévoflurane, à l'isoflurane et au propofol.

Méthode : Chez 48 patients consentants, classifiés ASA I ou II, on a induit une anesthésie au propofol, fentanyl et $0.25 \text{ mg}\cdot\text{kg}^{-1}$, de mivacurium et on l'a entretenue à l'aide de N_2O (60 %) et un de trois agents choisis au hasard : sévoflurane à 1,9 %, isoflurane à 1,2 %, ou $100\text{--}150 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ de propofol. On a appliqué une stimulation de type train-de-quatre toutes les 15 sec au niveau du nerf cubital. Le bloc neuromusculaire était mesuré par accélérométrie. À 5 % de récupération du premier twitch (T1), on a amorcé une perfusion de mivacurium dont la vitesse était ajustée toutes les cinq minutes pour garder un bloc de 90–95 % du T1.

Résultats : Le temps de récupération jusqu'à 5 % de T1 après la première dose était la même dans les trois groupes (13–15 min). Quinze minutes après le début de la perfusion, sa vitesse était plus grande ($P < 0,05$) pour le groupe propofol ($7,5 \pm 1,7 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; moyenne $\pm$ écart) que pour le groupe isoflurane ($4,7 \pm 1,6 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) ou sévoflurane ($4,5 \pm 1,5 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Puis, la vitesse de perfusion est demeurée stable pour le propofol ($6,2 \pm 1,4 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ après 90 min de perfusion) tandis qu'elle diminuait encore pour l'isoflurane ($2,9 \pm 1,6 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ à 90 min ($P < 0,05$ comparé au propofol) et $1,4 \pm 1,0 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ pour le sévoflurane ($P < 0,05$ comparé au propofol et à l'isoflurane).

Conclusion : Le sévoflurane et l'isoflurane ne prolongent pas l'effet d'une dose unique de mivacurium, mais une potentialisation s'installe et augmente avec le temps entre 35 et 105 min d'exposition à l'halogéné. Cette interaction est plus prononcée avec le sévoflurane qu'avec l'isoflurane.

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NEUROMUSCULAR blocking agents are administered routinely in association with volatile or *iv* anesthetics. Studies reported that isoflurane decreased the effective dose for 50% or 95% blockade (ED_{50} or ED_{95}) or the plasma concentration for steady state blockade for d-tubocurarine,¹ pancuronium,² vecuronium,³ cisatracurium,⁴ and rocuronium.⁵ However, prolongation of the duration of action of neuromuscular blocking agents is not always found,^{6,7} and in certain settings the degree of potentiation is very modest.⁸ In one study, isoflurane did not alter mivacurium infusion rates compared with propofol.⁹ One possible explanation is that potentiation with volatile agents takes time to develop, because of the time taken for equilibrium of the agent with muscle tissue.¹⁰

Sevoflurane has been reported to potentiate blockade produced by mivacurium,¹¹ rocuronium,^{5,7} vecuronium,¹² and cisatracurium,⁴ but the effect is not always consistent. For example, only a slight decrease was found for the ED_{50} of mivacurium, and no change in its duration of action.⁸ As is the case for isoflurane, the degree of potentiation provided by sevoflurane might be time-dependent.¹²

The purpose of this study was to determine the time course of potentiation of neuromuscular blockade by isoflurane and sevoflurane in the clinical situation, when a bolus dose of neuromuscular blocking agent is administered at induction, followed by a maintenance dose when recovery started. Mivacurium was chosen because its two active isomers have a short half-life and infusion rate can be assumed to follow the changing requirements with time.

Patients and methods

The study was approved by the Institutional Ethics Committee and written informed consent was obtained from each patient. Forty-eight physical status ASA I–II patients aged 20–65 yr scheduled for elective surgery requiring general anesthesia with tracheal intubation were enrolled into the study. Those with a history of renal, hepatic or neuromuscular disease, or a history of abnormal plasma cholinesterase activity and those taking medication known to interfere with neuromuscular function were excluded, as were patients with electrolyte abnormality, diabetes or those with an anticipated difficult airway. Patients who deviated from their normal body weight by more than 30% did not take part in the study. Premedication was at the discretion of the anesthesiologist. When the patient arrived in the operating room surface electrodes connected to a TOF-GUARD accelerometer (Biometer International, Odense, Denmark) were applied over the ulnar nerve at the wrist with the

piezoelectric device placed on the corresponding thumb to assess neuromuscular blockade of the adductor pollicis muscle. After the insertion of an *iv* line, the electrocardiogram, pulse oximetry, and non-invasive blood pressure (contralateral to the site of accelerometry) were monitored. Preoxygenation was performed, and general anesthesia was induced with fentanyl 1.5–3 $\mu\text{g}\cdot\text{kg}^{-1}$, propofol 1.5–3 $\text{mg}\cdot\text{kg}^{-1}$. After loss of consciousness, the accelerometer was turned on and a constant supra-maximal (60 mA) train-of-four stimulation was applied every 15 sec. Mivacurium, 0.25 $\text{mg}\cdot\text{kg}^{-1}$, was then injected over at least 15 sec, and tracheal intubation was performed 2.5 min after the end of injection. The patient's lungs were ventilated mechanically with a mixture of 50% nitrous oxide and oxygen to maintain end-tidal CO_2 between 30 and 35 mmHg.

For maintenance of anesthesia, patients were randomized by a computer-generated assignment to receive sevoflurane (end-tidal concentration of 1.9%), isoflurane (1.2% end-tidal), or propofol, 100–150 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ intravenously. Hypotension was treated with ephedrine, 5–10 mg, and hypertension with fentanyl, 50–100 μg . In the propofol group, the infusion rate of propofol was adjusted according to changes in blood pressure. When first twitch (T1) recovered to 5% of pre-mivacurium control after the bolus dose, an infusion was started at a rate of 10 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, and adjusted manually every five minutes by 0.5–2 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ steps to maintain T1 between 5 and 10% (90–95% blockade). At the end of the procedure, the infusion was stopped, but the anesthetic was maintained stable until full recovery (> 95% T1) was observed. No reversal agent was given. During the whole procedure, skin temperature of the monitored thumb was maintained above 32°C.

Only the data obtained in patients who required an infusion of mivacurium for 90 min or more were retained for further analyses. For all these subjects, time from injection of the bolus dose of mivacurium and T1 recovery of 5% was noted. After the start of the infusion, the rate required to keep 90–95% T1 block was noted every five minutes for 90 min. The time to achieve 25%, 75% and 95% recovery of T1 after the infusion was stopped was noted.

For statistical analyses, Jandel Sigmapstat statistical software was used. One-way ANOVA and Kruskal Wallis one-way ANOVA on ranks was used to compare patient characteristics, dose of anesthetics, duration to 5% T1 recovery and recovery to 25%, 75% and 100% after the infusion was stopped. Two-way repeated measures of ANOVA with Fischer's least significant difference test for post-hoc analysis was used to com-

TABLE I PATIENT CHARACTERISTICS

	<i>Sevoflurane</i> <i>n</i> = 13	<i>Isoflurane</i> <i>n</i> = 12	<i>Propofol</i> <i>n</i> = 13	<i>Significance</i>
Age (yr) (mean $\pm$ SD)	42 $\pm$ 11	44 $\pm$ 12	41 $\pm$ 13	NS
Weight (kg) (mean $\pm$ SD)	62 $\pm$ 10	66 $\pm$ 10	64 $\pm$ 8	NS
Gender: male/female	4/9	4/8	5/8	NS
Propofol (mg) (mean $\pm$ SD)	190 $\pm$ 25	200 $\pm$ 40	190 $\pm$ 36	NS
Fentanyl (μ g) (mean $\pm$ SD)	160 $\pm$ 36	168 $\pm$ 40	160 $\pm$ 23	NS
Duration of anesthesia (min) (mean $\pm$ SD)	136 $\pm$ 10	139 $\pm$ 13	140 $\pm$ 17	NS
Duration of surgery (min) (mean $\pm$ SD)	102 $\pm$ 23	100 $\pm$ 22	105 $\pm$ 22	NS

TABLE II NEUROMUSCULAR CHARACTERISTICS

	<i>Sevoflurane</i> <i>n</i> = 13	<i>Isoflurane</i> <i>n</i> = 12	<i>Propofol</i> <i>n</i> = 13	<i>Significance</i>
Time from bolus dose to 5% recovery (min) (mean $\pm$ SD)	15 $\pm$ 3	14 $\pm$ 3	13 $\pm$ 5	NS
Time from end of infusion to 25% recovery (min) (mean $\pm$ SD)	9 $\pm$ 3	8 $\pm$ 3	6 $\pm$ 4	NS
Time from end of infusion to 75% recovery (min) (mean $\pm$ SD)	16 $\pm$ 5	15 $\pm$ 4	13 $\pm$ 6	NS
Time from end of infusion to 95% recovery (min) (mean $\pm$ SD)	19 $\pm$ 5	19 $\pm$ 4	16 $\pm$ 7	NS

pare data between groups for the infusion requirements. A *P* value less than 0.05 was considered to indicate statistically significant differences.

Results

Of the 48 patients who were recruited for the study, 38 had at least 90 min of infusion, and data were analyzed for these patients only. In the remaining ten patients, surgery was too short to allow for a 90-min infusion. The targeted value of 90–95% T1 blockade was maintained in all patients. Relatively large changes

in infusion rates had to be made for the first 15 min (1.5–2 μ g·kg⁻¹·min⁻¹ every five minutes). After 15 min, 0.5 μ g·kg⁻¹·min⁻¹ steps were sufficient.

No statistically significant differences were found between groups with respect to age, weight, gender distribution, dose of induction agents, and duration of anesthesia or surgery (Table I). The time from injection of mivacurium to 5% T1 recovery was similar in all three groups (Table II).

In the propofol group, the mean infusion rates decreased during the first 20–25 min after the start of

FIGURE Mivacurium infusion rates during sevoflurane, isoflurane, and propofol anesthesia vs time to keep 90–95% first twitch (T1) block. Values are mean $\pm$ SD. * $P < 0.0001$ sevoflurane group and isoflurane group vs propofol group; ** $P < 0.05$ isoflurane group vs sevoflurane group.

the infusion regimen, after which they remained stable at around $6 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. In the isoflurane and sevoflurane groups, the early decrease was even more accentuated, and a statistically significant difference was observed between sevoflurane and propofol by 15 min (Figure). Then, the mivacurium requirements decreased progressively in both volatile groups. At 90 min, the mivacurium infusion rate in patients given sevoflurane was only 25% that of subjects anesthetized with propofol. Patients receiving isoflurane needed 50% less than patients given propofol. The difference between isoflurane and sevoflurane was statistically significant ($P < 0.05$) towards the end of the infusion period. After stopping the infusion, time to 25%, 75% and 95% spontaneous recovery were not different between the groups (Table II).

Discussion

This study shows that mivacurium neuromuscular blockade is potentiated by sevoflurane and isoflurane in a time-dependent manner when compared with propofol. The duration of action of a bolus dose of mivacurium given at induction of anesthesia is not altered by the introduction of isoflurane or sevoflurane. However, potentiation becomes manifest as time progresses, and the time course of this interaction between mivacurium and the volatile agent is more important with sevoflurane than with isoflurane.

Mivacurium was chosen for this study because it is the non-depolarizing neuromuscular agent with the shortest half-life. The active isomers of the drug have an elimination half-life of one to two minutes.¹³ Thus, at any point in time, past history of drug administration has little influence on neuromuscular blockade and infusion rates can be thought of as indirect measures of concentration required at the neuromuscular junction. The design of the study paralleled the clinical situation. A bolus dose of mivacurium was given shortly after induction of anesthesia, before the introduction of the volatile agent, and stable muscle relaxation was maintained. The infusion regimen was preferred to the intermittent bolus method because it allowed neuromuscular blockade to be constant throughout surgery. The set minimum of 90 min for the duration of the infusion was somewhat arbitrary, but we wanted to consider all patients for the same duration to avoid swings in the mean infusion rates as either resistant or sensitive patients happen to drop out. Because the degree of potentiation of neuromuscular blockade depends on the concentration of volatile agent given,¹⁴ equipotent doses of isoflurane (1.2%) or sevoflurane (1.9%), equivalent to 1 MAC, were given. In addition, all groups received nitrous oxide.

The infusion rate of mivacurium required to maintain neuromuscular blockade decreased during the first 20–25 min after starting the infusion. The same phenomenon has been reported in other infusion studies with mivacurium,^{11,15} cisatracurium,¹⁶ rocuronium,¹⁶ atracurium¹⁷ and vecuronium.¹⁷ Infusion rates are relatively high when the patient recovers from a bolus dose, as occurred in all the above studies, because enough drug had to be provided not only to maintain blockade, but also to prevent recovery from the bolus dose.¹⁸ During stable infusion, only the drug to maintain blockade is needed. After this early phase, the mivacurium requirements during propofol- N_2O anesthesia remained stable with time, in accordance with previous studies,^{15,19} which suggests that the long acting cis-cis isomer of mivacurium has no clinically detectable effects.

Potentiation of muscle relaxants by volatile anesthetics has been investigated in many studies,^{1–12} and the results vary because the time of exposure to the volatile agent varied markedly from one study to the next. For example, Miller *et al.*¹ demonstrated that one hour of exposure to isoflurane reduced the requirement of d-tubocurarine by 70% compared with halothane anesthesia. Presumably, the difference would have been greater if the control group had received no volatile agent. Yet, a shorter (20–30 min) exposure to isoflurane had less impact on the ED_{90} of

rocuronium (a 30% decrease),²⁰ and the duration of action of atracurium and vecuronium administered was not modified by isoflurane introduced at the same time as the neuromuscular blocking agents.⁶

Although the data from the above studies suggest an increase in the isoflurane-induced potentiation of neuromuscular blockade, its exact time dependence remains unclear. Withington *et al.*¹⁰ found a significant reduction of plasma concentration of atracurium required to maintain 90% twitch depression under enflurane anesthesia after 45 min of exposure, and this concentration decreased for the next 75 min. This indicates that the process is not complete two hours after introduction of enflurane. A similar design has not been adopted for isoflurane or sevoflurane. Cannon *et al.*³ infused vecuronium during 1.2% isoflurane anesthesia, and found that steady state infusion rates were reduced by 67% and corresponding concentrations were decreased by 54%, after at least 1.5 hr of stable anesthesia.

With 1.7% sevoflurane the infusion rate and concentration of vecuronium was the same as with 1.2% isoflurane, after two hours of continuous administration.²¹ However, comparison with a non-volatile anesthetic was not made. The relationship between dose and response of rocuronium is affected only modestly by a ten-minute exposure to sevoflurane or isoflurane.⁷ The same applies to mivacurium, and in this case, only late indices of recovery, such as time taken for the return to a train-of-four ratio of 80% were prolonged by sevoflurane.⁸ The duration of action to 25% recovery of T1 was not affected.⁸ This is a finding analogous to ours, where duration of the intubating dose was not modified by the presence of the volatile anesthetic. Bevan *et al.*¹¹ compared mivacurium infusion requirements between patients given propofol or sevoflurane in adults and children, in a design very similar to ours. However, they did not analyze the changes in infusion rate with time, and their patients received mivacurium infusions for only 50 min, compared with 90 min in our study. Their mean infusion rates for mivacurium were $5.9 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ with propofol- N_2O anesthesia, and $2.9 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ with sevoflurane 1 MAC- N_2O . This is very similar to our findings at comparable infusion times. At 30 min, the mean infusion rates in the present study were similar: 6.3 and $4.0 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, for propofol and sevoflurane, respectively. Exposure to sevoflurane for an additional hour is associated with a marked decrease in mivacurium requirements ($1.4 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$).

Sevoflurane was given in this study at 1.9% end-tidal, approximately 1 MAC value at age 40 yr, which is evaluated to be between 1.7 and 2.05%.²² An

equipotent concentration of isoflurane (1.2%) was also administered. It is likely that the infusion rates required for both anesthetics would have converged to the same value if more time had been allowed. A previous study with vecuronium comparing isoflurane and sevoflurane²¹ reported similar infusion rates and concentrations after more than two hours of stable anesthetic. Thus, it appears that both isoflurane and sevoflurane can potentiate neuromuscular blockade to the same degree. The differences between isoflurane and sevoflurane found in the present study are probably the result of a faster equilibrium time with the neuromuscular junction. Sevoflurane is less lipid-soluble than isoflurane,²² but pharmacokinetic studies have failed to identify a faster time constant for access to muscle (approximately 60 min for both agents).²³ Nevertheless, the time constant is of the same magnitude as the time course of blockade in our study, suggesting that the site of action of potentiation is in muscle. The kinetic study²³ provided a huge variability on the estimation of the time constants, the standard deviation being approximately half the mean value. Thus, time constant of sevoflurane in muscle could be faster than that of isoflurane.

The present study suggests that a short exposure (30 min or less) to either sevoflurane or isoflurane does not potentiate mivacurium neuromuscular blockade to any significant extent. The same could be true of other short-to intermediate-acting neuromuscular blocking agents.

Potentiation between the volatile agents and neuromuscular blocking agents becomes apparent only after 45 min or so, and the intensity of the phenomenon increases for the next hour. This accentuation is greater with sevoflurane than isoflurane. Thus, these volatile agents can lead to a reduction of requirements for neuromuscular blocking agents only for relatively long procedures.

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