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Sevoflurane exposure time and the neuromuscular blocking effect of vecuronium

Purpose: To determine the effect of sevoflurane exposure time on the duration of vecuronium neuromuscular blockade.

Methods: In 40 adult patients anesthesia was induced with $1.5\text{--}2\text{ mg}\cdot\text{kg}^{-1}$ propofol and $3\text{--}5\text{ }\mu\text{g}\cdot\text{kg}^{-1}$ fentanyl and the trachea was intubated without the aid of muscle relaxant. Patients were randomized into four groups of 10. In group 1, $0.05\text{ mg}\cdot\text{kg}^{-1}$ vecuronium was administered with N_2O and anesthesia was maintained by propofol infusion and fentanyl. Vecuronium was administered with sevoflurane 2% in 30 patients, commencing at the same time (group 2) and at 30, and 60 min after sevoflurane (groups 3, 4). Adductor pollicis force of contraction to train-of-four ulnar nerve stimulation was recorded. Times from vecuronium injection to 95%, maximal block, and recovery times to 25% recovery were recorded.

Results: There were no differences in times to 95% and maximal block in the four groups. Recovery times were longer in groups 3 and 4 than in groups 2 and 1 ($P < 0.01$). Times to 5% recovery were 15.0 ± 3.7 , 17.8 ± 4.8 , 28.2 ± 9.9 , and 29.5 ± 9.5 , and to 25% recovery were 22.3 ± 5.2 , 27.2 ± 6.4 , 42.3 ± 16.3 , and 50.5 ± 16.4 in groups 1, 2, 3, and 4 respectively. No differences were found between group 1 and group 2 nor between group 3 and group 4.

Conclusion: Sevoflurane produced time-dependent potentiation of vecuronium. After 30 min exposure, 25% recovery was prolonged by 89% and after 60 min by more than 100% compared with the control group.

Objectif : Déterminer l'effet du temps d'exposition au sévoflurane sur la durée du blocage neuromusculaire avec du vécuronium.

Méthode : On a induit l'anesthésie avec $1,5\text{--}2\text{ mg}\cdot\text{kg}^{-1}$ de propofol et $3\text{--}5\text{ }\mu\text{g}\cdot\text{kg}^{-1}$ de fentanyl chez 40 patients adultes et on a procédé à l'intubation endotrachéale sans myorelaxant. Les patients ont été répartis en quatre groupes de 10. Dans le groupe 1, on a administré $0,05\text{ mg}\cdot\text{kg}^{-1}$ de vécuronium avec N_2O et on a maintenu l'anesthésie avec une perfusion de propofol et de fentanyl. Chez 30 patients, le vécuronium a été administré avec le sévoflurane 2 %, en même temps aux patients du groupe 2, mais 30 et 60 min après le sévoflurane à ceux des groupes 3 et 4. La force de contraction de l'adducteur du pouce à la stimulation en train-de-quatre du nerf cubital a été notée. Le temps nécessaire pour que le vécuronium injecté produise 95 % du bloc, puis le bloc maximal, et le temps nécessaire pour atteindre une récupération de 25 %, ont été enregistrés.

Résultats : Il n'y a pas eu de différence de temps intergroupe pour produire 95 % du bloc, ni pour le bloc maximal. La récupération s'est prolongée dans les groupes 3 et 4 comparés aux groupes 2 et 1 ($P < 0,01$). Le temps nécessaire pour atteindre une récupération de 5 % ont été de $15,0 \pm 3,7$, $17,8 \pm 4,8$, $28,2 \pm 9,9$, et de $29,5 \pm 9,5$, et pour une récupération de 25 % ont été de $22,3 \pm 5,2$, $27,2 \pm 6,4$, $42,3 \pm 16,3$, et de $50,5 \pm 16,4$ dans les groupes 1, 2, 3, et 4 respectivement. Aucune différence n'a été rapportée entre les groupes 1 et 2, ni entre les groupes 3 et 4.

Conclusion : Le sévoflurane a produit une potentialisation du vécuronium dépendante du temps. Après 30 min d'exposition le temps nécessaire pour produire une récupération de 25 % s'est accru de 89 % et, après 60 min, de plus de 100 %, si on le compare au temps du groupe témoin.

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VOLATILE anesthetics potentiate the neuromuscular blocking effect of non-depolarizing muscle relaxants,¹⁻⁷ and this potentiation is dependent on the neuromuscular blocking agents,^{1,2} the specific inhalational anesthetic,³⁻⁵ and the concentration used.^{6,7} Recently, this potentiation has been suggested to be time dependent⁸⁻¹¹ but, in these studies, an infusion technique was used for relaxant administration,⁸⁻¹⁰ and inhalational anesthetics were initially administered at high concentration to achieve the desired end tidal anesthetic concentration quickly: none of which is common clinical practice. The maximum potentiating effect of inhalational anesthetics may not develop until the anesthetic has equilibrated with the muscle tissue, which may take one to two hours.¹² Sevoflurane is a new inhalational anesthetic with low muscle-gas partition coefficient of 3.13,¹³ suggesting that it may equilibrate rapidly with muscle tissue and that the maximum potentiating effect may be expected to be achieved quickly. This study was designed to demonstrate the effect of sevoflurane exposure time on the clinical duration of action of a single bolus dose of vecuronium.

Methods

The study protocol was approved by our department's ethical committee and informed consent was obtained from all patients. Forty adult patients ASA physical status 1-11 scheduled for elective surgical procedures requiring muscle relaxation were entered into the study. Patients with hepatic, renal or neuromuscular disease, or receiving drugs known to affect neuromuscular function were excluded. Patients with electrolyte imbalance or airway abnormality were also excluded. All patients were premedicated by 10 mg diazepam *po* and 1 mg atropine *im*, administered one hour before operation. Anesthesia was induced with 1.5-2 mg·kg⁻¹ propofol with 3-5 µg·kg⁻¹ fentanyl and the trachea was intubated without the aid of muscle relaxant. Anesthesia was maintained with intermittent doses of propofol and fentanyl as clinically indicated. The ECG, blood pressure, and oxygen saturation were monitored. Esophageal or rectal temperature was monitored and maintained above 36°C by covering any exposed part of the patient, using heating mattress, and adjustment of room temperature. Inspired and end tidal sevoflurane concentration and P_{ET}CO₂ were continuously monitored by multigas analyzer (Capnomac, Ultima, Datex). Ventilation was controlled to maintain P_{ET}CO₂ around 35 mmHg. Neuromuscular monitoring was done by measuring the adductor pollicis force of contraction in response to supramaximal TOF (train-of-four) stimulation of the ulnar nerve close to the wrist. The stimula-

tion was delivered at 2 Hz frequency every 12 sec. The first twitch in the train was considered as control twitch height, and a preload of 200-250 g was applied to the thumb. The resulting current was amplified and then recorded on a polygraph (8M36 Omnilite, NEC Sanei). A stable base line was maintained for at least 10 min before administration of vecuronium or sevoflurane. Patients were then randomized into four groups, 10 patients each. In group 1, anesthesia was maintained with a continuous infusion of propofol and a single bolus dose of 0.05 mg·kg⁻¹ vecuronium was administered together with nitrous oxide 50%. In group 2, patients received sevoflurane 2% inspired together with the same dose of vecuronium. In groups 3 and 4, patients received the same inspired concentration of sevoflurane as in group 2 but for 30 and 60 min, before administration of the same dose of vecuronium. Times to 95% block and onset time (time from vecuronium administration to maximum twitch depression), and recovery times up to T₂₅ (25% recovery of control twitch height, clinical duration of action) were recorded. All values are presented as mean ± SD. Statistical analysis of the data was performed using one-way ANOVA, followed by Bonferroni correction. A *P* value < 0.05 was considered significant.

Results

A difference was found between group 4 and group 1 with respect to age and weight but no differences were found between the other study groups (Table I). No differences were found regarding times to 95% and maximum block (Table II). Complete neuromuscular block was achieved in all patients. Times to 25% recov-

TABLE I Patients characteristics for the study groups

Patients characters	Group 1	Group 2	Group 3	Group 4
Age (yr)	44.5 ± 8.5	45.4 ± 11.3	50.5 ± 11.6	55.5 ± 8.7*
Gender m:f	3:7	2:8	4:6	6:4
Weight (kg)	49.2 ± 8.8	55.5 ± 9.6	59.2 ± 11.6	59.7 ± 7.1*

Mean ± SD. *P* * <0.05 compared with group 1.

TABLE II Onset and recovery data

Times	group 1	group 2	group 3	group 4
to 95% block	2.7 ± 0.5	2.5 ± 0.6	2.4 ± 0.7	2.9 ± 0.9
to max block	3.5 ± 0.7	3.0 ± 0.7	2.9 ± 0.6	3.5 ± 0.6
to 5% recovery	15.0 ± 3.7	17.8 ± 4.8	28.2 ± 9.9*†	29.5 ± 9.5*†
to 25% recovery	22.3 ± 5.2	27.2 ± 6.4	42.3 ± 16.3*†	50.5 ± 16.4*†

Mean ± SD.

* *P* < 0.05 compared with group 1, † compared with group 2.

ery were prolonged in the 30 and 60 min exposure groups, group 3 and 4, respectively, compared with group 1 and group 2 (Table II). In group 3, *P* values were .0009 and .0036, and in group 4 were <.0001 and .0002, respectively, compared with group 1 and 2. No differences were found between groups 1 and 2 or between groups 3 and 4. Although clinical duration (time to 25% recovery) was numerically longer in group 4 than in group 3, the difference was not statistically significant.

Discussion

The results of this study demonstrate that exposure to 30 min and 60 min sevoflurane anesthesia is sufficient to prolong the duration of vecuronium neuromuscular blocking effect. When sevoflurane was administered together with vecuronium, group 2, the duration of action was not prolonged compared with that in the propofol-fentanyl group, group 1, suggesting that the muscle concentration may not reach a sufficient level to produce a potentiating effect. However, 30 min of sevoflurane exposure (group 3) produced prolongation of the clinical duration of action by 89% and after 60 min exposure (group 4) the duration was more than double that in group 1. Clinical duration of action was chosen as it is believed to provide satisfactory relaxation for the majority of surgical procedures.¹⁴

Few studies have been done demonstrating the time course potentiation effect of inhalational anesthetics. Jalkanen and Meretoja, found that 10 min exposure to isoflurane was insufficient to affect mivacurium spontaneous recovery, but 30 min exposure prolonged recovery by 55-58%.¹¹ Meretoja *et al.*, found that potentiation of mivacurium by halothane and isoflurane was strongly time dependent and took at least 30 min before maximum potentiation was established.¹⁰ The infusion rate of mivacurium in subjects anesthetized with halothane and isoflurane was reduced maximally to 32% and 70% after 90 min of anesthetic inhalation. Withington *et al.* evaluated the time course of potentiation of atracurium by enflurane.⁹ They found a time-dependent reduction in the plasma concentration of atracurium needed to maintain 90% neuromuscular block. Exposure to 1 MAC enflurane was not associated with decreases in atracurium plasma concentration up to 30 min. However, at 45 min, atracurium plasma concentration was decreased by 33% and at two hours by 52%. They concluded that, the potentiating effect of atracurium by enflurane was negligible during procedures of less than 45 min. Stanski *et al.* found that when the plasma concentration of *d*-tubocurarine was kept constant, neuromuscular blockade was increased slowly by enflurane with time, at approximately 9% per hour.⁹

Muscle tissue equilibrates with the partial pressure of the volatile anesthetic in arterial blood within one-four hours,¹² and, as inhalational anesthetics differ in their muscle solubility,¹³ it is expected that each inhalational anesthetic has its own time course potentiation effect. In this study, the maximum time dependent potentiating effect of sevoflurane was reached at 30 min, and no difference was found at 60 min exposure time. While using enflurane, a more soluble anesthetic,¹² the potentiating effects of atracurium appear to increase even after a two hour exposure.⁹ Up to 90 min exposure to halothane and isoflurane was associated with decrease in mivacurium infusion rate.¹⁰

Sevoflurane is a new inhalational anesthetic with low muscle-gas partition coefficient of 3.13,¹³ its neuromuscular effect has not been characterized. However, Morita *et al.*¹⁵ and Kurahashi and Maruta¹⁶ compared the neuromuscular effect of sevoflurane with that of isoflurane and found no difference between them as regard their neuromuscular effects. Unfortunately, exposure time was not fixed in both studies, ranging between 8-27 min¹⁶ and > 40 min.¹⁵ To our knowledge, no study has been published to demonstrate the time dependent potentiating effect of sevoflurane. However, its low muscle-gas partition coefficient suggests that equilibration between muscle and blood may not take as long as with halothane, enflurane, and isoflurane and this may explain why 60 min exposure did not produce any greater difference than with 30 min exposure.

Unexpectedly, onset time did not differ among the four groups. Jalkanen and Meretoja found that 30 min isoflurane exposure produced shorter onset time than in the control group.¹¹ We do not have an exact explanation of this difference but isoflurane, in addition to its neuromuscular effect, produces marked vasodilatation of muscle blood vessels,¹⁷ which may result in delivery of relatively more relaxant to the motor end plate producing a more rapid effect.

Administration of sevoflurane together with vecuronium, a common clinical practice, did not prolong the clinical duration of vecuronium. Thus, there is no need to reduce the initial bolus dose even with the use of sevoflurane. However, 30 min sevoflurane exposure is associated with increased neuromuscular block and this should be taken into consideration in operations lasting more than 30 min.

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