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Potency and time course of mivacurium block during sevoflurane, isoflurane and intravenous anesthesia

Purpose: To determine the potency and time course of action of mivacurium neuromuscular block under routine clinical conditions during sevoflurane, isoflurane and intravenous anesthesia.

Method: Patients were anesthetized with nitrous oxide 66% in oxygen and 1.5 MAC sevoflurane or isoflurane or a propofol infusion, neuromuscular block being monitored using mechanomyography. Potency was determined using administration of single doses of mivacurium of 40-100 $\mu\text{g}\cdot\text{kg}^{-1}$ and construction of dose-response curves ($n = 72$). The onset and duration of action were determined following a bolus dose of 0.2 $\text{mg}\cdot\text{kg}^{-1}$ of mivacurium ($n = 30$).

Results: The ED_{50} and ED_{95} (with 95% confidence limits) were estimated to be 42 (35-51) and 86 (74-98) $\mu\text{g}\cdot\text{kg}^{-1}$, 52 (45-60) and 89 (72-110) $\mu\text{g}\cdot\text{kg}^{-1}$, and 53 (45-62) and 95 (81-112) $\mu\text{g}\cdot\text{kg}^{-1}$ during sevoflurane, isoflurane and propofol anesthesia respectively ($P < 0.05$ between sevoflurane and propofol). Following administration of the 0.2 $\text{mg}\cdot\text{kg}^{-1}$ dose, neither the times (mean $\pm$ SD) to maximum block (1.6 ± 0.31 , 1.7 ± 0.21 and 1.6 ± 0.45 min, respectively) nor the times to 25 and 90% recovery of T_1 (20 ± 4.5 and 33 ± 8.8 min, 21 ± 3.8 and 33 ± 6.5 min, and 18 ± 4.1 and 28 ± 5.8 min respectively) were different among groups. The times to recovery of TOF ratio to 0.8 were 40 ± 10.0 , 36 ± 8.5 and 29 ± 5.5 min in the sevoflurane, isoflurane and propofol groups respectively ($P = 0.017$ between the sevoflurane and propofol groups).

Conclusions: Under usual conditions of clinical anesthesia the potency of mivacurium was slightly enhanced during sevoflurane compared with intravenous anesthesia but the duration of action was only minimally prolonged during sevoflurane and isoflurane anesthesia.

Objectif : Déterminer la puissance et l'évolution d'un blocage neuromusculaire avec du mivacurium appliqué selon des conditions cliniques de routine pendant une anesthésie avec du sévoflurane ou de l'isoflurane ou un agent intraveineux.

Méthode : L'anesthésie a été réalisée avec un mélange d'oxygène et de protoxyde d'azote à 66 % et 1,5 CAM de sévoflurane ou d'isoflurane ou une perfusion de propofol. Le monitoring du blocage neuromusculaire était assuré par la mécanomyographie. Pour déterminer l'efficacité, on a administré des doses uniques de 40-100 $\mu\text{g}\cdot\text{kg}^{-1}$ de mivacurium et on a élaboré des courbes dose-réponse ($n = 72$). Le début et la durée de l'action ont été définis à la suite d'une dose en bolus de 0,2 $\text{mg}\cdot\text{kg}^{-1}$ de mivacurium ($n = 30$).

Résultats : La ED_{50} et la ED_{95} (avec un intervalle de confiance de 95 %) ont été estimées à 42 (35-51) et à 86 (74-98) $\mu\text{g}\cdot\text{kg}^{-1}$, à 52 (45-60) et à 89 (72-110) $\mu\text{g}\cdot\text{kg}^{-1}$, à 53 (45-62) et à 95 (81-112) $\mu\text{g}\cdot\text{kg}^{-1}$ pendant l'anesthésie avec sévoflurane, isoflurane ou propofol respectivement ($P < 0,05$ entre le sévoflurane et le propofol). Après l'administration de la dose de 0,2 $\text{mg}\cdot\text{kg}^{-1}$, ni le temps requis (moyenne $\pm$ écart-type) pour atteindre le blocage maximal ($1,6 \pm 0,31$, $1,7 \pm 0,21$ et $1,6 \pm 0,45$ min, respectivement) ni le temps de parvenir à une récupération de 25 et 90 % de T_1 ($20 \pm 4,5$ et $33 \pm 8,8$ min; $21 \pm 3,8$ et $33 \pm 6,5$ min; $18 \pm 4,1$ et $28 \pm 5,8$ min respectivement) n'ont été différents d'un groupe à l'autre. Le temps nécessaire à la récupération selon un ratio de TDQ à 0,8 a été de $40 \pm 10,0$, $36 \pm 8,5$ et $29 \pm 5,5$ min pour le sévoflurane, l'isoflurane et le propofol respectivement ($P = 0,017$ entre le sévoflurane et le propofol).

Conclusion : Dans les conditions cliniques habituelles de l'anesthésie, l'efficacité du mivacurium a été légèrement accentuée pendant l'utilisation de sévoflurane comparée à celle du propofol intraveineux, mais la durée d'action n'a été prolongée que de peu avec l'anesthésie au sévoflurane ou à l'isoflurane.

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This study was supported by a grant from Abbott Laboratories UK. Dr. D.W. Lowry was in receipt of a DHSS Clinical Research Fellowship.

Accepted for publication October 22, 1998

SEVOFLURANE, like other volatile anesthetic agents, tends to potentiate the effects of non-depolarising neuromuscular blocking agents.¹⁻³ Little is known, however, about the interaction of sevoflurane with the short acting muscle relaxant, mivacurium, except for one report in children.⁴ The present study was undertaken to estimate the potency and the time course of action of mivacurium during sevoflurane anesthesia and compare the results with groups anesthetised with isoflurane or intravenous anesthesia with propofol.

Methods

One hundred and two adult patients aged 18-60 yr and scheduled to undergo elective surgery were included in the study with their written informed consent and approval of the Research Ethics Committee. Patients whose weight was 30% above or below the ideal for their height, or who were receiving medication (such as corticosteroids or diuretics) known to interact with neuromuscular blocking drugs were not included.

Anesthesia was induced with 1-2 $\mu\text{g}\cdot\text{kg}^{-1}$ fentanyl and 1-3 $\text{mg}\cdot\text{kg}^{-1}$ propofol, and maintained with nitrous oxide 66% in oxygen and sevoflurane, isoflurane or propofol, as allocated by a computer-generated randomisation scheme. Ventilation was assisted to maintain normocapnia (35 - 45 mm Hg) and the skin temperature over the adductor pollicis was maintained $> 32^\circ\text{C}$ by wrapping the arm in cotton wool. The end-tidal concentration of volatile agent was monitored using a calibrated Ohmeda 5250 respiratory gas monitor and stabilised at 1.5 MAC (adjusted for age and concomitant use of nitrous oxide, the actual concentrations being 1.8 and 1.5% sevoflurane for 18-35 yr and 36-58 yr olds respectively,^{1,5} and 0.84 and 0.75% isoflurane for 18-30 yr and 31-58 yr olds respectively⁶). Patients allocated to the *iv* anesthesia group received a standard propofol infusion regimen of 6-10 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$. Further doses of propofol or fentanyl were administered if indicated. Tracheal intubation was carried out after development of maximum block.

The ulnar nerve was stimulated at the wrist using surface electrodes with supramaximal stimuli of 0.2 msec duration in a single twitch mode at 0.1 Hz for the potency estimation and in a train-of-four (TOF) mode at 2 Hz every 12 sec for the onset and duration of action part of the study. The resultant force of contraction of the adductor pollicis muscle was recorded using a force displacement transducer and neuromuscular function analyser (Myograph 2000, Biometer Ltd., Denmark). Baseline neuromuscular responses were allowed to stabilise over about ten minutes in all patients including

those receiving propofol anesthesia. At the same time, the end-tidal concentration of the volatile agent was also being stabilised. A time of ten minutes was chosen to represent normal clinical practice.

Seventy two patients were included in the potency estimation part of the investigation. The single dose technique, as used in previous studies for relaxants of shorter duration of action was used for potency estimation.^{7,8} Six patients each, in each of the three groups were allocated at random to receive mivacurium 40, 60, 80 or 100 $\mu\text{g}\cdot\text{kg}^{-1}$. The maximum block attained in each patient with each dose was recorded. The study was terminated at this stage and anesthesia maintained as appropriate for surgical needs. The twitch height data were subjected to arc-sine transformation.⁹ Dose-response curves were constructed following least-squares regression analysis and subjected to analysis of covariance, and the ED_{50} and ED_{95} (doses required to produce 50 and 95% block respectively) estimated.

Thirty patients (ten each in the sevoflurane, isoflurane and propofol groups) were studied for assessing the onset and duration of action. They were anesthetised and stabilized as above and received a single dose of 200 $\mu\text{g}\cdot\text{kg}^{-1}$ of mivacurium. The variables

FIGURE Dose-responses for mivacurium during anesthesia with sevoflurane (■ - - ■), isoflurane (● — ●) and propofol (○...○). Individual points represent mean and the bars standard deviation.

TABLE I Patient details.

	<i>Propofol</i>	<i>Sevoflurane</i>	<i>Isoflurane</i>
<i>Potency estimation</i>			
Age (yr)	32 ± 10.6 [18 - 58]	31 ± 10.3 [18 - 47]	31 ± 10.8 [19 - 55]
Weight (kg)	72 ± 11.1	72 ± 13.5	72 ± 11.6
Height (cm)	172 ± 9.0	171 ± 10.0	172 ± 9.1
Male / Female	15 / 9	14 / 10	14 / 10
<i>Time course of action</i>			
Age (yr)	36 ± 10.7 [24 - 54]	30 ± 6.8 [20 - 41]	28 ± 5.9 [19 - 38]
Weight (kg)	74 ± 14.0	78 ± 13.9	75 ± 14.6
Height (cm)	172 ± 11.1	176 ± 10.7	176 ± 10.8
Male / Female	7 / 3	8 / 2	7 / 3

Values are mean ± SD [range] where appropriate

TABLE II Maximum block attained with different doses of mivacurium.

<i>Mivacurium dose (µg·kg⁻¹)</i>	<i>Propofol</i>	<i>Sevoflurane</i>	<i>Isoflurane</i>
40	26 ± 22.4	51 ± 18.0	28 ± 17.8
60	65 ± 27.7	65 ± 26.4	55 ± 19.5
80	80 ± 14.1	88 ± 13.1	87 ± 13.5
100	96 ± 2.6*	99 ± 0.5	99 ± 0.9

Mean ± SD

* $P < 0.05$ compared with sevoflurane and isoflurane

recorded were the onset time (time from drug administration to maximum effect), the times to recovery of T_1 (the first twitch in the train-of-four) to 25, 75 and 90% of control, and the time to spontaneous recovery of the TOF ratio to 0.8. The results of this part of the study were analysed using ANOVA followed by post-tests as appropriate. Statistical significance was assumed at $P < 0.05$. The sample sizes for both parts of the study were based on an earlier study with rocuronium which showed a difference of about 30 % in the potency and duration of action between propofol and sevoflurane.^{10,11}

Results

The respective groups in each part of the study were comparable with regard to age, weight, height and sex distribution (Table I). The average maximum block following each dose is given in Table II and, as expected, the effects were dose related. The degree of maximum block following the 100 µg·kg⁻¹ dose was lower in the group anesthetised with propofol ($P < 0.05$).

The dose-response curves (Figure) showed separation between the sevoflurane and propofol groups ($P < 0.05$) but they did not differ in their slopes showing

TABLE III ED₅₀ and ED₉₅ values (95% confidence intervals) for mivacurium.

	<i>ED₅₀ (µg·kg⁻¹)</i>	<i>ED₉₅ (µg·kg⁻¹)</i>
Propofol	53 (45 - 62)	95 (81 - 112)
Sevoflurane	42 (35 - 51)*	86 (74 - 98)*
Isoflurane	52 (45 - 60)	89 (72 - 110)

* $P < 0.05$ compared with propofol group

TABLE IV Onset and duration of block (min) after mivacurium 0.2 mg·kg⁻¹

	<i>Propofol</i>	<i>Sevoflurane</i>	<i>Isoflurane</i>
Time to maximum block	1.6 ± 0.45	1.6 ± 0.31	1.7 ± 0.21
Time to recovery of			
T_1 to 25%	18 ± 4.1	20 ± 4.5	21 ± 3.8
T_1 to 90%	28 ± 5.8	33 ± 8.8	33 ± 6.5
TOF ratio of 0.8	29 ± 5.5	40 ± 10.0*	36 ± 8.5
Recovery index			
(T_1 25-75%)	7 ± 1.9	9 ± 3.1	8 ± 2.4

mean ± SD.

* $P < 0.05$ compared with propofol

enhanced potency for mivacurium during sevoflurane compared with propofol anesthesia. The actual ED₅₀ and ED₉₅ values are given in Table III and were 42 and 86 µg·kg⁻¹ during anesthesia with sevoflurane, 53 and 95 µg·kg⁻¹ during anesthesia with propofol and 52 and 89 µg·kg⁻¹ during anesthesia with isoflurane.

The results for the onset and duration of action are given in Table IV. Onset times were between 1.6 and 1.7 min and did not differ among the groups. The times to 25% recovery of T_1 were 20, 21 and 18 min; to recovery of T_1 to 90% 33, 33 and 28 min; and to a TOF ratio of 0.8 40, 36 and 29 min, respectively, in the sevoflurane, isoflurane and propofol groups. The 25-75% recovery indices ranged between 7 and 9 min. The only variable that was different was the time taken to recover to a TOF ratio of 0.8 between the sevoflurane and the propofol groups ($P = 0.017$).

There was no clinical evidence of histamine liberation such as cutaneous erythema or bronchospasm nor were there any clinically important changes in heart rate or arterial pressure in any of the groups.

Discussion

The present study has shown that the estimated potency of mivacurium is greater during sevoflurane than during propofol anesthesia although the actual difference in ED₉₅ is only about ten per cent. Similarly, the recovery after a bolus dose of 0.2 mg·kg⁻¹ is only slightly prolonged. The differences between the isoflurane and propofol groups were minimal.

The estimated ED₉₅ of mivacurium under isoflurane anesthesia was 89 µg·kg⁻¹ in the present study which is almost identical to the value of 88 µg·kg⁻¹ reported by Kumar *et al.*¹² Similarly, the ED₉₅ of mivacurium during intravenous anesthesia as estimated in the present study differs only marginally from the values obtained under balanced anesthesia by other workers.^{13,14} In contrast, the apparent potency is slightly increased during sevoflurane anesthesia.

Some previous studies have shown increases in potency of a somewhat similar magnitude with relaxants such as rocuronium and vecuronium during sevoflurane and isoflurane anesthesia.^{1,3} In the present study, however, the effects during isoflurane anesthesia were not different from those during propofol anesthesia. This is most likely to be due to the patients receiving the volatile anesthetics for about 40 min in previous studies compared with only about ten minutes in the present study. The effects of sevoflurane, but not those of isoflurane, become apparent much earlier due to its lower muscle-gas solubility coefficient (2.38 compared with 4.40 for isoflurane)¹⁵ resulting in its earlier delivery into the muscle compartment. It is likely that the effects of isoflurane would have been similar had we administered it for a longer time before mivacurium administration.

The onset times for 0.2 mg·kg⁻¹ mivacurium were similar in the three groups in the present study, being around 1.6 min. This is similar to the times reported in other studies during balanced anesthesia and using TOF stimulation,^{12,16,17} but faster than the time of 2.5 min reported by Savarese *et al.* using single twitch stimulation.¹⁸ It has been shown previously that onset time for intermediate onset neuromuscular blocking drugs is faster using a TOF mode of stimulation.¹⁹ The mode of stimulation may have a greater impact within the first few minutes rather than the administration of the volatile agents which take longer to equilibrate and would explain the similar onset times in the groups in the present study.

The recovery times for mivacurium in the present study were only marginally longer in the volatile anesthetic groups than in the intravenous anesthesia group. The absence of any large influence of even sevoflurane on the duration of action of mivacurium in our study compared with intermediate acting relaxants such as rocuronium and vecuronium is probably due to the inherently shorter duration of action of mivacurium due to its rapid metabolism by plasma cholinesterase, even in the absence of volatile anesthetic agents.^{17,18} The studies which have shown an influence of volatile agents have generally used mivacurium by infusion or over a longer period of time.^{20,21} In general, potentiation of action of muscle relaxants

by volatile agents is more likely during prolonged exposure or longer stabilisation times. The latter, however, bears little relevance to routine clinical practice compared to the period of ten minutes used in the present study.

In conclusion, the results from the present study show that the effects of mivacurium are only slightly enhanced during sevoflurane compared with those during isoflurane or intravenous anesthesia.

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