Quantifying the effect of enflurane on atracurium infusion requirements

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The present study was designed to evaluate the interaction between atracurium and enflurane in 40 adult surgical patients using closed-loop feedback control of infusions of atracurium. Anaesthesia was induced with thiopentone and fentanyl and intubation was facilitated with atracurium $0.5 \text{ mg} \cdot \text{kg}^{-1}$ lean body mass. During the first 90 min, anaesthesia was maintained with nitrous oxide in oxygen (2:1) and fentanyl. For the following 90 min the patients were randomly assigned to receive enflurane at different end-tidal concentrations: Group I, control, fentanyl-nitrous oxide anaesthesia; Group II, enflurane 0.3%-nitrous oxide; Group III, enflurane 0.6%-nitrous oxide; Group IV, enflurane 0.9%-nitrous oxide. The possible interaction of atracurium with enflurane was quantified by determining the asymptotic steady-state rate of infusion (I_{ss}) of atracurium necessary to produce a constant 90% neuromuscular block. This was accomplished by applying nonlinear curve fitting to data on the cumulative dose requirements. Every patient served as his/her own control and the changes in the infusion rates were determined individually. Patient characteristics and controller performance, i.e., the ability of the controller to maintain the neuromuscular blockade constant at the setpoint, did not differ among groups. In Group II I_{ss} decreased from 0.33 ± 0.12 to $0.26 \pm 0.08 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ ($P < 0.01$), in Group III from 0.32 ± 0.12 to $0.24 \pm 0.08 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ ($P < 0.001$) and in Group IV from 0.29 ± 0.09 to $0.21 \pm 0.09 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$

($P < 0.001$). In the control group atracurium requirements remained unchanged throughout the study. Enflurane reduces atracurium requirements in a dose-dependent manner. During enflurane anaesthesia the rate of atracurium infusion should be reduced but because of interindividual differences the monitoring of the neuromuscular function is important to ensure the appropriate level of neuromuscular block.

Cette étude vise à évaluer avec un contrôle de feed-back fermé des perfusions d'atracurium l'interaction de l'atracurium avec l'enflurane chez 40 opérés adultes. L'anesthésie est induite au thiopentone et au fentanyl et l'intubation est réalisée sous atracurium $0,5 \text{ mg} \cdot \text{kg}^{-1}$ de masse corporelle maigre. Pendant les premières 90 min, l'anesthésie est entretenue avec du protoxyde d'azote en oxygène (2:1) et du fentanyl. Pendant les 90 min suivantes, les patients sont assignés au hasard pour recevoir de l'enflurane à différentes concentrations téléexpiratoires: groupe I, contrôle, anesthésie au fentanyl-protoxyde d'azote; groupe II, enflurane 0,3%-protoxyde d'azote; groupe III, enflurane 0,6%-protoxyde d'azote, groupe IV, enflurane 0,9%-protoxyde d'azote. L'interaction éventuelle de l'atracurium avec l'enflurane est quantifiée à l'état d'équilibre par la détermination de la vitesse de perfusion asymptotique (I_{ss}) d'atracurium nécessaire pour produire un bloc neuromusculaire à 90%. Ceci est réalisé en appliquant le lissage non linéaire à la courbe des données des besoins cumulatifs. Chaque patient est son propre contrôle et les modifications apportées à la perfusion sont déterminées individuellement. Les caractéristiques du patient et la performance du contrôleur, c'est-à-dire l'habileté du contrôleur à maintenir la constance du bloc neuromusculaire au niveau prédéterminé, ne diffère pas entre les groupes. Dans le groupe II, I_{ss} diminue de $0,33 \pm 0,12$ à $0,26 \pm 0,08 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ ($P < 0,01$), dans le groupe III de $0,32 \pm 0,12$ à $0,24 \pm 0,08 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ ($P < 0,001$) et dans le groupe IV de $0,29 \pm 0,09$ à $0,21 \pm 0,09 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ ($P < 0,001$). Dans le groupe contrôle, les besoins en atracurium demeurent inchangés pendant toute l'étude. L'enflurane diminue les besoins d'atracurium proportionnellement à la dose. Pendant l'anesthésie à l'enflurane la dose d'atracurium devrait être diminuée mais à cause des différences entre individus, le monitoring de la fonction neuromusculaire est important pour assurer un degré de bloc adéquat.

Key words

ANAESTHETICS, VOLATILE: enflurane;
NEUROMUSCULAR RELAXANTS: atracurium;
PHARMACODYNAMICS: interaction.

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Atracurium is a nondepolarizing neuromuscular blocking drug with an intermediate duration of action and a relatively short elimination half-life. Therefore, if it is used during long anaesthetics, it is likely to be administered as a continuous infusion.^{1,2} The interaction of muscle relaxants and volatile anaesthetics depends both on the neuromuscular blocking drug and inhalational anaesthetic. The intermediate-acting relaxants appear to be potentiated less by volatile anaesthetics than are the older long-acting drugs.¹ Although there is some information about the interaction of inhalational anaesthetics and atracurium given by continuous infusion,³⁻⁶ the information of different concentrations of volatile anaesthetics on atracurium infusion requirements is lacking.

This study was designed to quantify the effect of clinically relevant concentrations of enflurane on atracurium infusion requirements and to investigate the possible time dependence of this interaction. We used the technique of closed-loop feedback control of atracurium infusion to maintain a steady neuromuscular blockade of 90%. The effect of enflurane on the atracurium infusion requirements was quantified by determining the asymptotic steady-state infusion rates necessary to produce 90% neuromuscular blockade at different levels of enflurane anaesthesia.

Methods

With approval of the local Medical Ethics Committee and after obtaining informed consent, 40 adult general surgical patients, ASA physical status 1-3, aged 23-68 yr, were studied. Patients with hepatic or renal dysfunction, neuromuscular disease or patients receiving concomitant medication known to affect neuromuscular transmission were excluded from the study.

For premedication patients received oxycodone hydrochloride 0.14 mg · kg⁻¹ and 12.5-25 mg promethazine hydrochloride *im* one hour before the start of anaesthesia. A standard dose of glycopyrrolate 0.2 mg *iv* was given to all patients prior to induction of anaesthesia. Anaesthesia was induced with thiopentone 3-6 mg · kg⁻¹ and fentanyl 0.1-0.2 mg. During the first 90 min, anaesthesia was maintained with nitrous oxide in oxygen (2:1). Additional fentanyl (0.05-0.2 mg) or thiopentone (50-100 mg) bolus doses were given when anaesthesia was thought to be inadequate as judged by motor responses, lacrimation or changes in the cardiovascular variables (>15% increase in systolic blood pressure).

After 90 min the patients were randomly assigned to one of the four study groups. In the control group (Group I) anaesthesia was continued with fentanyl-nitrous oxide. In the other groups we administered enflurane at different end-tidal concentrations: 0.3% (Group II), 0.6% (Group III) and 0.9% (Group IV). Together with 67% nitrous

oxide the administration of enflurane resulted in MAC values of 0.8, 1.0 and 1.2 in Groups II-IV, respectively. The second study period lasted also 90 min. After the 180-min study period anaesthesia was continued according to clinical needs. The monitoring included noninvasive or invasive blood pressure, continuous ECG, minute ventilation, ventilatory rate, capnography, inspiratory O₂ concentration, volatile anaesthetic end-tidal concentration, airway pressure and pulse oximetry. Palmar skin temperature was measured and kept >32°C. End-tidal CO₂ tension was maintained at 4.5-5 kPa.

The degree of neuromuscular blockade was assessed electromyographically every 20 sec with a Relaxograph® (Datex, Helsinki, Finland) neuromuscular transmission monitor. Surface electrodes were placed over the ulnar nerve on the wrist to stimulate the nerve supramaximally with a train-of-four sequence (frequency of stimuli, 2 Hz; pulse width 100 µs) and over the first interosseus muscle of the hand and on the base of the index finger to record the compound electromyogram. The stimulus output was a rectangular wave with a current range of 0-70 mA and the machine calibrated automatically by searching for the optimum signal levels before setting the supramaximal level. The degree of neuromuscular blockade was defined as the ratio of the measurement of the first twitch in the train-of-four sequence (T₁) to the corresponding control value. The first calibration of the neuromuscular monitoring device was carried out immediately after the induction of anaesthesia. Then, a stable calibration signal was awaited before the second calibration. The interval between the two calibrations was 5-10 min.

After the second calibration, all patients received atracurium 0.5 mg calculated per lean body mass⁷ and their tracheas were intubated. The initial bolus dose was followed by a continuous infusion of atracurium through an indwelling venous catheter in a forearm vein. The infusion rate was controlled by a model-driven closed-loop feedback system as described previously.⁸ An infusion pump (Fresenius infusomat CP-IS®, Fresenius AG, Bad Homburg, Germany) and the Relaxograph® were attached to a Compaq® Portable 386 Computer (Compaq Computer Corporation, Houston, TX, USA) by means of a serial RS232 interface. The desired neuromuscular blockade was set to 90% (T₁ = 10% from control). Controller performance was measured by calculating the mean offset and the mean standard deviation from the set-point during feedback infusion.⁹ During the close-loop feedback infusion of atracurium, the measured values for effect and the infusion rates were saved on computer. To estimate the asymptotic steady-state rate of infusion (I_{ss}), we used nonlinear curve fitting for both of the 90-min study periods.¹⁰

TABLE I Patient characteristics

Group	No (M/F)	ASA physical status (1/2/3)	Age (yr)	Weight (kg)	Height (cm)
N ₂ O/O ₂ (2:1)	10 (6/4)	7/3/0	42 ± 15	66 ± 14	169 ± 7
+0.3% enflurane	10 (5/5)	5/4/1	47 ± 14	73 ± 12	174 ± 9
+0.6% enflurane	10 (4/6)	3/6/1	47 ± 14	73 ± 16	170 ± 8
+0.9% enflurane	10 (6/4)	0/8/2	50 ± 12	71 ± 15	167 ± 7
<i>P</i>	0.776†	0.074†	0.613*	0.646*	0.294*

Values are mean ± SD.

*Determined by one-way ANOVA.

†Determined by Chi-Square test.

FIGURE 1 Data for one representative patient in the group anaesthetized with fentanyl-nitrous oxide for the initial period of 90 min and then with enflurane (0.9% end-tidal concentration)-nitrous oxide.

$$\text{Cumulative dose of atracurium} = D(1 - e^{-kt}) + I_{ss}t$$

where D = amount of atracurium contained in its apparent distribution volume, k = relative rate of distribution of atracurium, I_{ss} = asymptotic steady-state rate of infusion of atracurium, t = duration of atracurium administration.

In this study every patient served as his/her own control and the changes in the atracurium infusion rates from the first (I_{ss1}) to the second (I_{ss2}) 90-min study period were determined individually by determining the I_{ss2}/I_{ss1} ratio. To investigate the possible time-dependence of the interaction of atracurium and enflurane, we also compared the cumulative dose requirements of atracurium at 30-min intervals during the second 90-min study period.

For statistical analysis we used analysis of variance and Chi-square test to compare the variables among

groups. Following analysis of variance, *a posteriori* testing was done with Fisher's least significant difference test. Linear regression analysis was used for the analysis of possible linear correlation between end-tidal enflurane concentration and atracurium infusion requirements. Student's *t*-test for paired samples was used to compare I_{ss1} and I_{ss2} values and the values for the palmar skin temperature at the end of the first and second study period in each group. $P < 0.05$ was considered to indicate statistically significant differences. All results are given as mean ± SD.

Results

The patient characteristics are shown in Table I. The study groups did not differ with regard to age, weight, height or ASA physical status. Figure 1 shows an example of the time course of neuromuscular blockade and the cumulative dose requirements of atracurium for one patient belonging to Group IV. Table II shows the average controller performance, I_{ss} for both of the 90 min study periods and the cumulative infusion requirements of atracurium at 30 min intervals during the second study period for the four groups. Controller performance, peripheral skin temperature and end-tidal carbon dioxide tension were similar in all groups.

During the first 90-min study period when no volatile anaesthetic was given, the I_{ss} values were at the same level. During the second study period, when enflurane was added, the I_{ss} values decreased. In Group II (enflurane 0.3%) the I_{ss} decreased from 0.33 ± 0.12 to $0.26 \pm 0.08 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ (Student's *t* test; $P < 0.01$), in group III (enflurane 0.6%) from 0.32 ± 0.12 to $0.24 \pm 0.08 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ ($P < 0.001$) and in Group IV (enflurane 0.9%) from 0.29 ± 0.09 to $0.21 \pm 0.09 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ ($P < 0.001$). In the control group the atracurium infusion requirements remained at the same

TABLE II Controller performance, cumulative atracurium requirements during the 2nd 90-min study period and steady-state rate of infusion of atracurium during fentanyl-nitrous oxide and different levels of enflurane-nitrous oxide anaesthesia

Group	Controller performance				Rate of infusion of atracurium* ($\text{mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$)			Cumulative atracurium requirements during the 2nd 90 min study period (mg)		
	Offset from the set-point (%)		SD from set-point (%)		1st 90 min (I_{ss1})	2nd 90 min (I_{ss2})	I_{ss2}/I_{ss1} ratio	0-30 min	30-60 min	60-90 min
	1st 90 min	2nd 90 min	1st 90 min	2nd 90 min						
$\text{N}_2\text{O}/\text{O}_2$ (2:1)	0.5 ± 2.1	0.2 ± 1.9	3.6 ± 2.1	1.8 ± 1.9	0.34 ± 0.08	0.34 ± 0.07	1.01 ± 0.09	11.0 ± 3.0	11.2 ± 4.5	10.9 ± 4.2
+0.3% enflurane	0.6 ± 1.5	0.6 ± 0.8	3.2 ± 1.5	1.7 ± 0.8	0.33 ± 0.12	0.26 ± 0.08	0.80 ± 0.12	9.9 ± 4.9	10.2 ± 4.7	9.5 ± 2.7
+0.6% enflurane	0.9 ± 1.0	0.7 ± 0.6	3.2 ± 1.0	1.6 ± 0.6	0.32 ± 0.12	0.24 ± 0.08	0.77 ± 0.09	9.1 ± 3.2	8.6 ± 2.9	8.3 ± 3.0
+0.9% enflurane	0.8 ± 0.9	1.0 ± 0.7	2.9 ± 0.9	1.7 ± 0.7	0.29 ± 0.09	0.21 ± 0.09	0.71 ± 0.11	7.3 ± 2.6	6.7 ± 2.7	7.2 ± 2.1
$P^\dagger$	0.782	0.083	0.720	0.959	0.726	0.007	<0.001	0.140	0.062	0.060

Values are mean $\pm$ SD.

*Asymptotic steady-state rate of infusion of atracurium calculated per body weight.

† Determined by one way ANOVA.

FIGURE 2 Ratio of the steady-state rate of infusion of atracurium during the 90-min period of enflurane-nitrous oxide anaesthesia (I_{ss2}) to the corresponding rate of infusion (I_{ss1}) during 90 min control period when the same patients were anaesthetized with fentanyl-nitrous oxide. Enflurane was administered at end-tidal concentrations of 0, 0.3, 0.6 and 0.9%.

level for the whole 180-min study period. Linear regression analysis revealed a linear relationship between the end-tidal enflurane concentration and the I_{ss2}/I_{ss1} -ratio (Figure 2). The I_{ss2}/I_{ss1} -ratio of the control group differed significantly from all the other groups and Group II differed from Group IV. According to analysis of variance, the cumulative atracurium dose requirements calculated at 30-min intervals during the second 90-min study period were similar in all groups.

Discussion

The steady-state infusion rate of atracurium was found

to decrease linearly when end-tidal enflurane concentration was increased, although the differences in atracurium infusion requirements among the groups receiving 0.3%, 0.6% or 0.9% end-tidal enflurane were very small and statistically significant only between Groups II and IV. Adding 0.3% end-tidal enflurane decreased the infusion rate by 20%, 0.6% enflurane by 23%, and 0.9% enflurane by 29%. In the control group the atracurium infusion requirements remained unchanged during both of the 90-min study periods. However, the interindividual differences were large. For example, in Group IV there were patients in whom enflurane decreased the infusion rate over 40% and patients in whom there was almost no change.

Compared with our previous study with vecuronium,¹¹ atracurium infusion requirements are less affected by enflurane. For example, 0.9% enflurane decreased the infusion rate of vecuronium by 54% but that of atracurium by only 29%. Vecuronium, but not atracurium, infusion rate was found to decrease also in the control group during the second 90-min study period. These findings appear to be related to the pharmacokinetic differences of these relaxants. The elimination half-life of vecuronium is considerably longer (approximately 70 min) than that of atracurium (approximately 20 min). Therefore steady-state will be achieved earlier during atracurium than during vecuronium infusion.² It has been demonstrated that long-acting neuromuscular blocking drugs are potentiated more by volatile anaesthetics than are the intermediate-acting relaxants.¹ During long infusions the interaction between enflurane and vecuronium is obviously very similar to the interactions observed between enflurane and long-acting drugs with long elimination

half-lives, e.g., pancuronium or d-tubocurarine. Thus, the magnitude and nature of the interaction between vecuronium and enflurane may be related to the pharmacokinetic and not to the pharmacodynamic properties of vecuronium.

The computer-controlled infusion of atracurium kept the desired degree of neuromuscular blockade at a reasonably constant level. There were only minor differences of less than 1% in the mean offset from the set-point values among the groups. This allowed quantification of the interaction between atracurium and enflurane. Neuromuscular blockade was measured by EMG, although it has been criticized because it does not measure events taking place beyond the endplate and because of the sometimes incomplete recovery of T_1 . However, previous investigations have demonstrated that regardless of whether EMG or mechanomyography has been used to measure neuromuscular blockade, they have yielded similar results.^{4,6,12,13} In the present study the feedback signal from the Relaxograph® remained stable throughout the three-hour study period as could be seen in the infusion requirements of atracurium in the control group; atracurium requirements did not change during the study period.

The extent of the interaction of muscle relaxants and inhalation anaesthetics depends both on the neuromuscular blocking drug and the volatile anaesthetic.¹ Several studies have compared the potency of atracurium under different anaesthetic conditions. Sokoll *et al.*¹⁴ found that 1.25 MAC of isoflurane-nitrous oxide anaesthesia decreased the ED_{50} for atracurium by 40% compared with fentanyl-nitrous oxide anaesthesia. Rupp *et al.*^{15,16} compared by ED_{50} -values of atracurium under fentanyl-nitrous oxide and 1.25 MAC of halothane-, enflurane- and isoflurane-nitrous oxide anaesthesia. The potency of atracurium was no more than 20% lower with enflurane or isoflurane than with fentanyl-nitrous oxide anaesthesia. Halothane did not change the potency of atracurium. These findings are in good agreement with the present study, in which 0.8–1.2 MAC of enflurane-nitrous oxide anaesthesia decreased atracurium infusion requirements by 20–29%.

O'Hara *et al.*⁴ studied the effects of enflurane, isoflurane, halothane and morphine-nitrous oxide anaesthesia on atracurium infusion requirements. During morphine-nitrous oxide anaesthesia, the mean infusion rate of atracurium to maintain the neuromuscular blockade at 90% was $5.7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. One MAC of halothane, enflurane and isoflurane reduced the requirements to 4.9, 3.5 and $4.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ respectively. Thus, 1 MAC of enflurane reduced atracurium requirements by almost 40% which appears to fit well with the results of the present study where the end-tidal enflurane concentrations

were considerably lower than 1 MAC of enflurane. Similar results have been obtained by Goudsouzian *et al.*⁵ who found that 2% enflurane inspired concentration, decreased the infusion requirements of atracurium by almost 50% compared with halothane-nitrous oxide or morphine-nitrous oxide anaesthesia in children.

It has been shown that the interaction between volatile anaesthetics and muscle relaxants is a time-dependent phenomenon.^{6,12,17,18} Withington *et al.*⁶ showed that the interaction of atracurium and enflurane is negligible during procedures of less than 45 min, but the degree of potentiation increased between 45 and 120 min after administration of enflurane. We studied the interaction of atracurium and enflurane for 90 min, but were not able to repeat this finding. In the study of Withington *et al.* the infusion rate of atracurium needed to maintain 90% neuromuscular blockade was found to decrease immediately after the administration of 1 MAC of enflurane was started and was then maintained constant at 50–60% of the control level for the remainder of the 120-min study time. This finding is similar to our study. During the second 90-min study period when enflurane was administered, the cumulative dose requirements of atracurium calculated at 30-min intervals did not decrease in any of the study groups after the initial 30-min period. Another interesting finding in the study of Withington *et al.* was that despite the stable infusion rate of atracurium, the concentration needed to produce 90% neuromuscular blockade during enflurane anaesthesia decreased throughout the study time. This could indicate that enflurane increased the clearance of atracurium; indeed, Parker *et al.*¹⁹ have observed that isoflurane anaesthesia increases the clearance of atracurium. If the effect of enflurane on the pharmacokinetics of atracurium is similar to that of isoflurane, it would explain the apparent discrepancy in the study of Withington *et al.* If enflurane increased the clearance of atracurium, this would indicate that the concentrations of atracurium necessary for constant 90% neuromuscular blockade would be lower and thus the atracurium-enflurane interaction is greater than can be predicted from the calculated steady-state infusion rates. For quantifying the interaction of volatile anaesthetics with neuromuscular blocking agents, our methodology assumes that the clearance of atracurium is independent of enflurane administration.

To our knowledge, the effect of different levels of enflurane anaesthesia on the infusion requirements of atracurium has not been studied previously. The previous studies which have quantified the potentiation of muscle relaxants by different concentrations of volatile anaesthetics were done by comparing the ED_{50} -doses. Miller *et al.*²⁰ found that the degree of neuromuscular blockade produced by pancuronium and d-tubocurarine was directly

related to alveolar concentrations of halothane and isoflurane. Rupp *et al.*²¹ quantified the effect of enflurane, isoflurane and halothane on the neuromuscular blockade produced by vecuronium. Increasing the concentration of the inhalation anaesthetic from 1.2 to 2.2 MAC decreased the ED₅₀ of vecuronium 51% for enflurane, 33% for isoflurane and 18% for halothane. The present study demonstrates that during continuous infusion of atracurium the potentiation of atracurium by enflurane is also linearly dependent on the end-tidal enflurane concentration.

The interaction between volatile anaesthetics and muscle relaxants is clinically important. This study shows that enflurane potentiates atracurium in a dose-dependent manner and the infusion rate of atracurium must be decreased when used together with enflurane. The potentiation seems to be less than with vecuronium or long-acting relaxants and the interindividual differences in the extent of the interaction are large.

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