Desflurane reduces the effective therapeutic infusion rate (ETI) of cisatracurium more than isoflurane, sevoflurane, or propofol

[Le desflurane, comparé à l'isoflurane, au sévoflurane ou au propofol, réduit davantage la vitesse de perfusion thérapeutique utile (PTU) du cisatracurium]

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Purpose: The present study investigated the interaction between the cumulative dose requirements of cisatracurium and anesthesia with isoflurane, sevoflurane, desflurane or propofol using closed-loop feedback control.

Methods: Fifty-six patients (18–85 yr, vitrectomies of more than one hour) were studied. In the volatile anesthetics groups, anesthesia was maintained by 1.3 MAC of isoflurane, sevoflurane or desflurane; in the propofol group, anesthesia was maintained by a continuous infusion of 6–8 $mg \cdot kg^{-1} \cdot hr^{-1}$ propofol. After bolus application of 0.1 $mg \cdot kg^{-1}$ cisatracurium, a T1%-level of 10% of control level (train-of-four stimulation every 20 sec) was maintained using closed-loop feedback controlled infusion of cisatracurium. The effective therapeutic infusion rate (ETI) was estimated from the asymptotic steady-state infusion rate I_{ss}. The I_{ss} was derived from fitting an asymptotic line to the measured cumulative dose requirement curve. The ETI of the different groups was compared using Kruskal-Wallis- test, followed by rank sum test, corrected for the number of comparisons, $P < 0.05$ was regarded as showing significant difference.

Results: ETI in the isoflurane group was 35.6 ± 8.6 $\mu g \cdot m^{-2} \cdot min^{-1}$, in the sevoflurane group 36.4-± 11.9 $\mu g\ m^{-2} \cdot min^{-1}$, in the desflurane group 23.8 ± 6.3 $\mu g \cdot m^{-2} \cdot min^{-1}$. The ETI of the volatile anesthetic groups were all significantly lower than the ETI in the propofol group at 61.7 ± 25.3 $\mu g \cdot m^{-2} \cdot min^{-1}$ ($P < 0.002$). The ETI in the desflurane group was significantly lower than in all other groups ($P < 0.02$).

Conclusion: In comparison to propofol, isoflurane, sevoflurane and desflurane reduce the cumulative dose requirements of cisatracurium to maintain a 90% neuromuscular blockade by 42%, 41% and 60%, respectively.

Objectif : Rechercher l'interaction entre la dose cumulative nécessaire de cisatracurium et l'anesthésie avec de l'isoflurane, du sévoflurane, du desflurane ou du propofol, en utilisant un système de rétroaction en boucle fermée.

Méthode : L'étude a porté sur 56 patients (18–85 ans, vitrectomie de plus d'une heure). Chez les patients qui ont reçu un anesthésique volatil, l'anesthésie a été entretenue avec 1,3 CAM d'isoflurane, de sévoflurane ou de desflurane; chez ceux qui ont eu du propofol, on a administré une perfusion continue de 6–8 $mg \cdot kg^{-1} \cdot h^{-1}$ de propofol. Après l'administration d'un bolus de 0,1 $mg \cdot kg^{-1}$ de cisatracurium, une première réponse T1à 10 % (d'une stimulation en train-de-quatre répétée toutes les 20 s) a été maintenue au moyen d'une perfusion de cisatracurium contrôlée par un système de rétroaction en boucle fermée. La vitesse de perfusion thérapeutique utile (PTU) a été évaluée à partir de la vitesse de perfusion asymptotique à l'équilibre P_e. La P_e a été dérivée de l'ajustement d'une ligne asymptotique à la courbe de la dose cumulative nécessaire. La PTU des différents groupes a été comparée à l'aide du test de Kruskal-Wallis, suivi du test de la somme des rangs, ajusté en fonction du nombre de comparaisons, $P < 0,05$ a été considéré comme une différence significative.

Résultats : La PTU associée à l'isoflurane a été de 35,6 ± 8,6 $mg \cdot m^{-2} \cdot min^{-1}$; au sévoflurane, 36,4 ± 11,9 mg $m^{-2} \cdot min^{-1}$ et au desflurane, 23,8 ± 6,3 $mg \cdot m^{-2} \cdot min^{-1}$. La PTU associée aux anesthésiques volatils a été significativement plus basse que celle qui est associée au propofol, 61,7 ± 25,3 $mg \cdot m^{-2} \cdot min^{-1}$ ($P < 0,002$). La PTU associée au desflurane a été significativement plus basse que celles qui concernent tous les autres anesthésiques ($P < 0,02$).

Conclusion : Comparés au propofol, l'isoflurane, le sévoflurane et le desflurane réduisent de 42 %, 41 % et 60 %, respectivement,

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la dose cumulative nécessaire de cisatracurium pour maintenir un blocage neuromusculaire à 90 %.

CISATRACURIUM is the 1-R-cis-1'R-cis isomer of atracurium; in comparison to atracurium, it has a slower onset time[1] and less propensity to liberate histamine.[2,3] The reduction of the cumulative dose requirements of atracurium by volatile anesthetics has been shown in several studies.[4,5] The cumulative dose requirements of cisatracurium have not yet been determined nor has the effect of desflurane on any non-depolarizing neuromuscular blocking drug.

A recent study[6] has shown that volatile anesthetics lower ED_{50} and ED_{95} of cisatracurium significantly in comparison to propofol. However, data about the influence of volatile anesthetics on the clinical duration of the neuromuscular blockade after cisatracurium were inconclusive. During surgery requesting a high and steady level of neuromuscular blockade (e.g., eye surgery) the non-depolarizing muscle relaxant can easily be applied via continuous infusion and the effect repetitively controlled.

We used a closed-loop feedback control model-driven system to administer cisatracurium to maintain a neuromuscular blockade of 90% in patients undergoing vitrectomy; the effect of desflurane, isoflurane, sevoflurane, or propofol on the infusion requirements of cisatracurium was measured by calculating the effective therapeutic infusion rate (ETI) to maintain a level of neuromuscular blockade at 90% of control twitch height of the first twitch amplitude (T1).

Materials and methods

After obtaining approval by the local Ethics Committee and written informed consent, 56 patients (ASA I–III) undergoing vitrectomy of an anticipated duration of more than one hour were studied. Patients with neuromuscular disorders or patients on medication known to interact with neuromuscular blockade were excluded from the study. Ten milligrams of chlorazepatedipotassium was given orally at 22:00 hr on the evening before the operation and one hour prior to the start of anesthesia. Anesthesia was induced with 0.3 $mg \cdot kg^{-1}$ etomidate and 10 $\mu g \cdot kg^{-1}$ alfentanil. The Relaxograph® (Datex Instrumentarium, Helsinki, Finland) was used to measure the train-of-four (TOF) response from the adductor pollicis muscle over the thenar area via surface skin electrodes. After induction of anesthesia the Relaxograph® was automatically calibrated by setting optimum signal levels at supramaximal stimulation (TOF stimulation for five minutes in all patients before application of cisatracurium). The TOF sequence was assessed every 20 sec; the degree of neuromuscular blockade was defined as the ratio of the first twitch in the TOF-ratio compared to the corresponding control value (T1%).

Neuromuscular blockade then was induced by injecting 0.1 $mg \cdot kg^{-1}$ cisatracurium (2 x ED_{95}) intravenously. After complete neuromuscular blockade (T1% <5%), endotracheal intubation was performed. Body temperature was monitored at the hand and kept above 35.6C using a heating blanket (Bair Hugger, MN, USA).

Patients were randomly assigned to one of the four groups: in the isoflurane, sevoflurane, desflurane groups (groups I, S, D), general anesthesia was maintained by end-tidal 1.3 MAC of each volatile anesthetic in oxygen/air (30% oxygen). In the propofol group (group P), anesthesia was maintained by a continuous infusion of 6–8 $mg \cdot kg^{-1} \cdot hr^{-1}$ of propofol; as breathing gas an oxygen/air mixture (30% oxygen) was used. Alfentanil was given at the discretion of the anesthesiologist (not more than 1 mg $alfentanil \cdot hr^{-1}$ of surgery). Patients were kept in normoventilation with an end-tidal carbon dioxide of 30–40 mmHg.

After the bolus administration, cisatracurium was infused intravenously according to a model-driven, closed-loop feedback system. The Infusomat CP® (Fresenius, Bad Homburg, Germany) and the Relaxograph® were connected to a Toshiba® T 1850C laptop via a serial RS 232 C interface. The set point of neuromuscular blockade was defined as T1%=10%; the controller performance was calculated as the mean offset of the measured T1% from the set point during feedback control.

Statistical analysis

Difference of means and standard deviation of I_{ss} (4,5) was used to determine group size for a power of more than 0.9 (beta error=10%). The ETI ($\mu g \times m^{-2}$ body surface area $\times min^{-1}$) maintaining 90% of neuromuscular blockade was estimated from the asymptotic steady-state infusion rate I_{ss}. I_{ss} was calculated by fitting an asymptotic line to the measured cumulative dose requirement curve using least square fitting (see appendix).

Parameters were compared using Kruskal-Wallis-test, followed by rank sum test, corrected for the number of comparisons, $P < 0.05$ was regarded as showing statistical significance. Correlation between anthropometric data and ETI for each group was tested by Spearman's test ($P < 0.05$).

Results

The anthropometric data, the duration of feedback control and the controller performance for each group

TABLE Patient data, feedback, control period and controller performance (mean offset from set-point: 90% blockade of control value)

Groups	*ASA I, II, III*	*Sex (m/f)*	*Age (y)*	*Weight (kg)*	*Body surface area (m^2)*	*Feedback control*	*Mean offset from set point*
I	2,5,7	9/5	56 (19)	83 (15)	1.93 (0.19)	118 (41)	3.19 (1.78)
S	2,5,7	6/8	61 (17)	72 (13)	1.81 (0.21)	83 (22)	2.06 (1.56)
D	4,5,5	8/6	61/20	74 (9)	1.86 (0.12)	97 (35)	2.00 (1.51)
P	2,4,8	8/6	51 (18)	81 (14)	1.93 (0.21)	88 (20)	2.49 (1.65)

Values are mean ± SD.

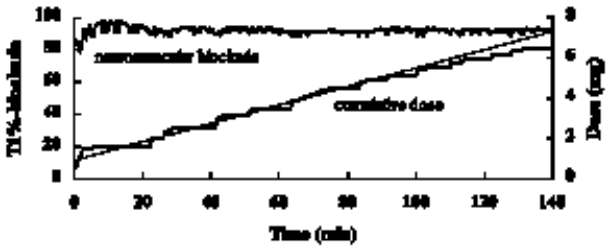

FIGURE 1 Data for one representative patient; the figure shows the time course of the neuromuscular blockade and the cumulative dose requirements; I_{ss} is calculated by non-linear curve fitting (least square fitting, dotted straight line). ETI: 32 $\mu g \cdot m^{-2} \cdot min^{-1}$, isoflurane group.

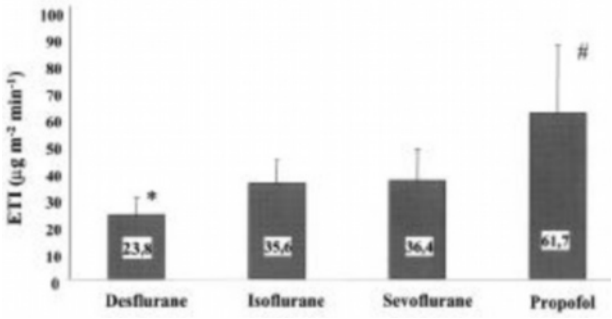

FIGURE 2 Shows the ETI for all groups. #P <0.002: ETI (propofol) *vs* ETI (volatile anesthetics); *P <0.02: ETI (desflurane) *vs* ETI (propofol, sevoflurane, isoflurane).

are shown in the Table. There were no significant differences in sex distribution, age, and weight or ASA classification between the groups. The controller performance was not different between the groups. All patients completed the study according to the protocol, there were no technical problems with the closed loop delivery system. The mean duration between cisatracurium bolus application and start of the closed loop control was 22 ± 5 min. The mean duration of cisatracurium-infusion was longest in the isoflurane group (118 min) without being statistically significantly different from the other groups. The neuromuscular blockade after bolus administration of 0.1 $mg \cdot kg^{-1}$ cisatracurium achieved levels of more than 95% blockade of T1% in all patients at a mean of 210 ± 55 sec, thus providing good conditions for intubation.

Figure 1 demonstrates an example of the time course of neuromuscular blockade and the cumulative dose requirements for one representative patient. Figure 2 shows the ETI to maintain the desired level of neuromuscular blockade for each group. The ETI was lowest in group D at 23.8 ± 6.3 $\mu g\ m^{-2} \cdot min^{-1}$ (P <0.02), and highest at 61.7 ± 25.3 $\mu g \cdot m^{-2} \cdot min^{-1}$ in group P (P <0.002). The ETI in groups I and S did not differ statistically. There was no correlation between the age and weight of patients and the ETI.

Discussion

Isoflurane, sevoflurane and desflurane at 1.3 MAC reduce the cumulative dose requirements of cisatracurium by 42%, 41% and 60% in comparison to propofol at 6–8 $mg \cdot kg^{-1} \cdot hr^{-1}$. Desflurane significantly reduced the cumulative dose requirements of cisatracurium in comparison to sevoflurane and isoflurane.

Cisatracurium has widely replaced atracurium because of the absence of histamine liberation.[2,3] Using 0.1 $mg \cdot kg^{-1}$ cisatracurium for intubation followed by a closed-loop feedback controlled infusion, no sign of histamine liberation such as skin rash or changes in hemodynamics were noticed. The onset time of the bolus application of 0.1 $mg \cdot kg^{-1}$ cisatracurium at the adductor pollicis muscle was between three to five minutes, comparable to results in other studies.[7–9]

The controller performance was regarded as sufficient at an average difference from 2.0% (group D) to 3.2% (group I) between the set point of T1%=10% and the measured degree of neuromuscular blockade. The controller performance for cisatracurium was different

from those found for other non-depolarizing muscle relaxants such as vecuronium,[10,11] atracurium[12,13] or rocuronium.[14] In the latter study, Olkkola *et al.* investigated the interaction of rocuronium with several *iv* anesthetics or isoflurane; the best controller performance values were achieved at 0.2% to 0.8% average offset from set point. The controller performance found in our study could have been anticipated because cisatracurium shows a more marked hysteresis and slower onset time than the other three non-depolarizing muscle relaxants. Wulf *et al.*[6] recently showed a significant decrease of ED_{50} and ED_{95} of cisatracurium during anesthesia with 1.5 MAC (in a mixture of 70% nitrous oxide/30% oxygen) of desflurane, sevoflurane or isoflurane in comparison to propofol. It is interesting to note that the time to reach 25% of control level of

TOF stimulation was not statistically different between the groups, but recovery index and time to reach a TOF ratio of 0.7 were significantly prolonged during anesthesia with desflurane and sevoflurane in comparison to propofol, but not so for isoflurane. There are, however, several limitations to that study. The cumulative dose technique might underestimate the potency of the neuromuscular blocking drugs. Diffusion of the inhaled anesthetic requires more than 30 min to reach equilibrium and this time span is different for the volatile anesthetic tested. Hendricks *et al.*[15] showed that uptake for desflurane and isoflurane might even take up to an hour. These findings limit at least the interpretation of the degree of ED_{50} or ED_{95} reductions. Wulf *et al.* admit themselves that the application of the total dose in increments could have underestimated the effect of the duration of action of cisatracurium during continuous infusion of propofol. Finally, in contrast to the current study, which used the algorithm presented by Mapleson[16] to calculate the age-related adaptation of MAC value for each patient, the Vol % equalling MAC was not adjusted to age. However, 1 MAC of desflurane in 100% oxygen for a 40-yr-old patient would be 6.6 Vol % in comparison to 5.1 Vol % for an 80-yr-old patient, a difference of 25%.

In contrast to the present study, most studies have compared cumulative dose requirements of volatile anesthetics in breathing gas mixtures including nitrous oxide. A recent study,[17] however, shows by calculating isoboles for desflurane and cumulative doses of nitrous oxide, that the decrease of the required desflurane concentrations by the administration of nitrous oxide might be less than expected from their MAC values. This could mean that for different volatile anesthetics, the additive effect of nitrous oxide might be different, limiting the comparability of the studies. In the current study, all volatile anesthetics were compared in a breathing gas mixture consisting of air/oxygen (30% oxygen).

It could be assumed that the significant 20% reduction of the cumulative cisatracurium dose requirement of desflurane in comparison to isoflurane and sevoflurane is due to a different depth of anesthesia achieved by 1.3 MAC of desflurane. Kansanaho *et al.*[13] studied the influence of several doses of enflurane on the cumulative dose requirements of atracurium to maintain a constant 90% neuromuscular block; this study showed that enflurane decreased the atracurium requirements in a dose-dependant manner: 0.5 MAC of enflurane reduced the atracurium requirements by 20%, 1 MAC by 25% and 1.3 MAC reduced the I_{ss} of atracurium by 28%. The assumption that 1 MAC of desflurane might create a different depth of anesthesia than 1 MAC of sevoflurane or isoflurane cannot, however, be supported by a recent study by Rehberg *et al.*[18] In a study of pharmacodynamic modelling of the EEG slowing effect of isoflurane, sevoflurane and desflurane, these authors have shown that MAC and MAC multiples are valid representations of the concentration response curve for the anesthetic suppression of the 95th percentile of the power spectrum with no significant difference of the EC_{50} values.

The effect of desflurane on cumulative dose requirements using closed loop feedback systems had not been studied previously. Several studies, however, have determined the effect of desflurane on the recovery of neuromuscular blockade of vecuronium,[19] mivacurium[20] and rapacuronium.[21] Desflurane prolonged the recovery of neuromuscular blockade of those non-depolarizing blocking drugs in a degree similar to sevoflurane or isoflurane.

One reason for the significantly higher ETI reduction by desflurane in comparison to sevoflurane or isoflurane might be the need for a much higher partial pressure to achieve the same MAC multiples because of its weaker anesthetic potency.

In our study, isoflurane, sevoflurane and desflurane at 1.3 MAC reduced the cumulative dose requirements of cisatracurium by 42%, 41% and 60% in comparison to propofol at 6–8 $mg \cdot kg^{-1} \cdot hr^{-1}$. Our findings did not differ from other investigators who - in contrast to animal studies -[22,23] could not show any interaction between *iv* anesthetic agents such as midazolam, etomidate, thiopental or fentanyl and muscle relaxants.[14] Propofol seems to show an interaction similar to these other agents.

The clinical implication of this study is that the dose of cisatracurium required to maintain a given degree of neuromuscular blockade is influenced by volatile anesthetics as much as for other muscle relax-

ants such as vecuronium, rocuronium or atracurium and needs to be adjusted accordingly. It is noteworthy that desflurane reduced the ETI of cisatracurium in comparison to sevoflurane or isoflurane by a further 20%; this might have economic implications in surgeries such as neurosurgical procedures where a high degree of neuromuscular blockade must be maintained for a long period of time but short awakening times are desirable. Large interindividual differences, however, and the absence of any correlation between patient characteristics, such as age, weight or even body surface area, and the ETI to maintain the desired level of neuromuscular blockade make monitoring of the neuromuscular function mandatory. When monitoring neuromuscular blockade at the adductor pollicis muscle, one should remember the shorter onset, faster recovery and less intense block at the orbicularis oculi muscle[24] for appropriate site-related relaxation.

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Appendix

Estimating the Effective Therapeutic Infusion rate (ETI)

Given a drug disposition function of the form

$$G(t) = Ae^{-\ t} + Be^{-ß\,t} + Ce^{-\gamma t} \ldots.$$

the cumulative drug requirement D(t) to maintain a given plasma concentration c_0 is given by

$$D(t)=V_c c_0 \left(1+k_{el}t+\frac{k_{12}}{k_{21}}(1\ \ e^{\ k_{21}t})+\frac{k_{13}}{k_{31}}(1\ \ e^{\ k_{31}t})+\ldots.\right.$$

whereby V_c denotes the central volume of distribution and k_{ij} the transfer micro-constants associated with the hybrid constants A, , B, ß, C, γ...

The asymptote A(t) to the cumulative drug requirement is a straight line.

$$A(t) = D_0 + I_{as}t,$$

the slope Ias of which defines an infusion rate. If D(t) is measured at constant drug effect, than Ias denotes the infusion rate which is effective to maintain that effect at steady-state (I_{ss}). If the effect was chosen within the therapeutic window, I_{as} defines an effective therapeutic infusion (ETI).

This infusion rate can be estimated by least square fitting the above formula for D (t) to the measured cumulative drug requirement as identified by the closed loop system.