Assessment of the interaction between atracurium and suxamethonium at 50% neuromuscular block using closed-loop feedback control of infusion of atracurium

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SUMMARY
We have studied the effect of prior administration of suxamethonium on the infusion requirements of atracurium at 50% neuromuscular block in patients undergoing elective general surgery. Anaesthesia was maintained with nitrous oxide in oxygen, propofol and fentanyl. Of 20 patients given atracurium, only 10 were given prior administration of suxamethonium 1 mg kg$^{-1}$. At the beginning of the infusion, atracurium 0.3 mg kg$^{-1}$ was given by bolus administration. Interaction between the two drugs was assessed by determining the steady state rate of infusion necessary to produce a constant 50% neuromuscular block. This was accomplished by applying non-linear curve fitting to data on the cumulative dose requirements during anaesthesia. The neuromuscular blocking effect was found to be similar with or without prior administration of suxamethonium. The mean steady-state rate of infusion for atracurium was 0.19 (SD 0.03) mg kg$^{-1}$ h$^{-1}$ for patients given suxamethonium and 0.18 (0.09) mg kg$^{-1}$ h$^{-1}$ for those who were not given suxamethonium. Thus prior administration of suxamethonium did not affect the infusion requirements of atracurium at 50% neuromuscular block, unlike the situation at constant 90% neuromuscular block. (Br. J. Anaesth. 1994; 73: 199–203)

KEY WORDS

Prior administration of suxamethonium augments the neuromuscular block produced by bolus doses of the non-depolarizing neuromuscular blocking agents atracurium, pancuronium and vecuronium [1–5]. We have shown previously that prior administration of suxamethonium reduces, by 30%, the dose of atracurium needed to produce a constant 90% neuromuscular block [6]. We suggested that this was probably caused by a pharmacodynamic interaction with suxamethonium and that the dose reduction of atracurium would not necessarily occur at other levels of neuromuscular block because the steepness of the response curve varies. Donati and colleagues [2] have studied the interaction between atracurium and suxamethonium using an integrated pharmacokinetic–pharmacodynamic model. Their analysis showed that in contrast with our views, prior administration of suxamethonium altered both the pharmacokinetics and pharmacodynamics of atracurium. By using the mean pharmacokinetic and pharmacodynamic variables of Donati and colleagues, it can be calculated that at constant 90% neuromuscular block induced by continuous infusion, the reduction in atracurium requirements produced by suxamethonium should be approximately 8% and at 50% neuromuscular block approximately 11% (for derivation of the equations, see Appendix 1). Because there was an obvious discrepancy between our previous study and the predictions based on the mean pharmacokinetic and pharmacodynamic variables of Donati and colleagues, we decided to investigate the effect of suxamethonium on the infusion requirements of atracurium at 50% neuromuscular block. We used a closed-loop feedback control method of administering atracurium to produce and maintain a relatively constant neuromuscular block of 50%. Interaction between atracurium and suxamethonium was measured by determining the asymptotic steady state rate of infusion necessary to produce 50% neuromuscular block with atracurium.

PATIENTS AND METHODS
With approval of the local Medical Ethics Committee and after obtaining informed written consent, we studied 20 male or female patients, ASA physical status I or II, aged 18–70 yr, scheduled for general surgery. Patients were excluded if they had muscular dystrophies, myopathy or cerebral palsy, significant renal, hepatic or cardiac dysfunction, marked ventilatory impairment caused by underlying respiratory disease, raised intracranial pressure or were receiving concomitant medication known to affect neuromuscular transmission. We also decided to exclude patients if peroperative blood loss exceeded 15 ml kg$^{-1}$, but no patient was in this category.

Premedication consisted of oxycodone 0.14 mg kg$^{-1}$ and promethazine 12.5–25 mg i.m., 1 h before the start of anaesthesia. A standard dose of i.v.
glycopyrronium 0.2 mg was given to all patients before induction of anaesthesia with propofol 2–2.5 mg kg\(^{-1}\). Before administration of suxamethonium or atracurium, we used a Relaxograph neuromuscular transmission monitor (Datex, Helsinki, Finland) to obtain control electromyographic values. Train-of-four sequence was assessed (frequency of stimuli, 2 Hz; pulse width, 100 μs) using stimulating surface electrodes placed adjacent to the ulnar nerve at the wrist. Recording electrodes were placed on the first dorsal interosseous muscle and second finger [7]. The stimulus output was a rectangular wave with a current range of 0-70 mA and the machine was calibrated automatically by searching for the optimum signal levels before setting the supramaximal level. We waited for a stable baseline calibration signal before administration of suxamethonium or atracurium.

Patients were allocated randomly to one of two sequences: (1) bolus administration of suxamethonium 1 mg kg\(^{-1}\), tracheal intubation, complete recovery from the depolarizing block, assessed by electromyography, and i.v. bolus administration of atracurium 0.3 mg kg\(^{-1}\); or (2) bolus administration of atracurium 0.3 mg kg\(^{-1}\) and intubation, but without prior administration of suxamethonium.

The degree of neuromuscular block, assessed every 20 s with the Relaxograph, was defined as the ratio of the measured first response (T1) in the train-of-four sequence to the corresponding control value. Anaesthesia was maintained with a continuous infusion of propofol 6–8 mg kg\(^{-1}\) h\(^{-1}\), fentanyl and 70% nitrous oxide in oxygen. Additional fentanyl was given if anaesthesia was thought to be inadequate, as assessed by motor responses, excessive salivation, lachrymation and changes in cardiovascular variables (more than 30% increase in systolic arterial pressure). Cardiorespiratory variables were measured according to our routine which included non-invasive measurement of arterial pressure, heart rate, continuous ECG, minute ventilation, ventilatory frequency, end-tidal carbon dioxide and inspiratory oxygen concentrations, airway pressure and \(\text{SpO}_2\). Palmar skin temperature was measured and maintained above 32°C. End-tidal carbon dioxide partial pressure was maintained at 4–5 kPa.

Bolus administration of atracurium was followed by infusion of atracurium controlled by a model-driven closed-loop feedback system (see Appendix 2). An infusion pump (Fresenius Infusomat CP-1S, Fresenius AG, Bad Homburg, Germany) and the Relaxograph were attached to a Compaq Portable
atracurium per body weight in the two groups given atracurium and suxamethonium to produce a constant 50% neuromuscular block with (Sux. + Atr.) and without (Atr.) prior administration of suxamethonium. The cumulative dose calculated as milligrams of atracurium for the two groups. Patient characteristics, average controller performance and the asymptotic steady state rate of infusion of atracurium did not differ significantly between the groups. The amount of fentanyl given during anaesthesia did not differ between the groups. The model-driven computerized infusion of atracurium maintained the desired degree of neuromuscular block at a reasonably constant level and the controller performance appeared to be similar in the two groups, which allowed quantitation of the possible interaction between atracurium and suxamethonium. Offset from set-point was similar to the offset in our previous report on the interaction between suxamethonium and atracurium [6] but the SD from set-point appeared to be about 50%, greater, which is not surprising because of the sigmoid shape of the concentration–response curve [9]. However, from a clinical point of view, neuromuscular block was maintained constant and the minor fluctuation did not hamper quantitation of the interaction.

Unlike previous observations at 90% neuromuscular block [6], prior administration of suxamethonium did not affect the infusion requirements of atracurium to maintain the neuromuscular block constant at 50%. In terms of an integrated pharmacokinetic–pharmacodynamic model, this implies that the concentration at half-maximal effect (see Appendix 1) is changed, if suxamethonium does not change the pharmacokinetics of atracurium. However, the previous study by Donati and colleagues showed that suxamethonium changed both the pharmacokinetics and pharmacodynamics of atracurium [2]. Based on their experience, it can be predicted that suxamethonium would decrease atracurium requirements by 11% at 50% neuromuscular block. Compared with the present study, there appears to be no major difference because as a result of large interindividual variation, such a difference between the theoretical values and measured values is plausible. However, there is a larger difference between the study of Donati and colleagues [2] and our previous study at 90% neuromuscular block [6]. In that study anaesthesia was induced with thiopentone and maintained with nitrous oxide in oxygen, fentanyl and flunitrazepam. Volatile anaesthetics were not used. In the present study, anaesthesia was induced with propofol and maintained with nitrous oxide in oxygen, fentanyl and propofol. Based on theory, prior administration of suxamethonium should reduce atracurium requirements by less than 8% at 90% neuromuscular block but we observed a reduction of 30%. In the study of Donati and colleagues [2], anaesthesia was induced with thiopentone and fentanyl and maintained with nitrous oxide and 0.5% end-tidal isoflurane in oxygen, with fentanyl as required. Unlike the present study where electromyography was used, they used mechanomyography. However, when used correctly these two methods appear to be in good agreement [10]. Because volatile anaesthetics, including isoflurane, potentiate the neuromuscular blocking action of non-depolarizing neuromuscular blocking agents, the use of isoflurane may explain their differences [11]. Our results show that highly biased conclusions are possible if models are extrapolated beyond the data upon which they are derived. Thus it cannot be concluded with
certainty from the study of Donati and colleagues [2] that suxamethonium would change the pharmacokinetics and pharmacodynamics of atracurium to the same extent unless the patient is anaesthetized with the same technique. All conclusions are further biased by the fact that the potentiation of non-polarizing neuromuscular blocking agents is a time-dependent phenomenon [12]. In order to describe quantitatively an interaction between a neuromuscular blocking agent and a volatile anaesthetic, it is crucial to document the duration of administration of the volatile agent. Because volatile anaesthetics are known to affect the pharmacokinetics and pharmacodynamics of drugs [13] it would be optimal to study the interaction of, for example suxamethonium with atracurium, during anaesthesia without volatile anaesthetics. It has been shown previously that infusion regimens designed from prior pharmacokinetic studies may not perform well during time periods not sampled in the original research [14]. Thus prediction of the effect of suxamethonium on infusion requirements of atracurium is further hampered by the fact that the pharmacokinetic and pharmacodynamic variables were obtained after bolus administration of atracurium. It should also be kept in mind that unlike tubocurarine, for example, atracurium is a mixture of 10 stereoisomers. It is doubtful therefore if predictions derived from integrated pharmacokinetic-pharmacodynamic models in general are applicable.

**APPENDIX 1**

The relationship between the concentration of atracurium at the site of action $C_{s}(t)$ and effect $E(t)$ is given by the following equation [15]:

$$E(t) = \frac{E_{\text{max}} \left[C(t)_{E}^{(0)}(t)^{y}\right]}{\left[C(t)_{E}^{(0)}(t)^{y} + \left[C(t)_{r}^{(0)}(t)^{y}\right]\right]}$$  \(1\)

where $E_{\text{max}}$ = maximum effect, $C_{s}(t) = C_{r}(t)$, and $y$ is a value describing the steepness of the concentration-response curve. For neuromuscular blocking agents, we can denote $E_{\text{max}} = 1$. Thus, equation (1) may be written:

$$E(t) = \frac{\left[C(t)_{E}^{(0)}(t)^{y}\right]}{\left[C(t)_{E}^{(0)}(t)^{y} + \left[C(t)_{r}^{(0)}(t)^{y}\right]\right]}$$  \(2\)

Because at steady-state the rate of infusion $(I(t))$ necessary to maintain the neuromuscular block constant at the level $E(t)$ is given by $I(t) = CI \cdot C_{s}(t)$ equation (2) is transformed into:

$$E(t) = \frac{\left[I(t)\right]^{y}}{\left[C(t)_{E}^{(0)}(t)^{y} + \left[I(t)\right]^{y}\right]}$$  \(3\)

where $CI$ = plasma clearance of atracurium.

This equation may be used to solve $I(t)$:

$$I(t) = CI \cdot C_{s}(t) \left(1 - \frac{E(t)}{E_{\text{max}}}\right)^{1/y}$$  \(4\)

By inserting the pharmacokinetic and pharmacodynamic variables of Donati and colleagues [2] we can calculate that at constant 90% neuromuscular block induced by continuous infusion, the reduction in atracurium requirements by suxa-methonium should be approximately 8% and at 50% neuromuscular block 11%.

**APPENDIX 2**

**MODEL-DRIVEN COMPUTERIZED INFUSION OF ATRACURIUM**

A two-compartment, open mammillary model having a hypothetical effect compartment linked to the central compartment was assumed to represent a valid model of the pharmacokinetics of atracurium [16, 17]. The integrated pharmacokinetic and pharmacodynamic model we used consists of two formulae (both given as a function of time, $t$), one representing the relationship between the function for drug input, $I(t)$, and the concentration of the drug in the effect compartment, $C_{e}(t)$.

$$C_{e}(t) = \int_{0}^{t} G(t-r) I(r) \, dr$$  \(1\)

and one representing the relationship between concentration $C_{e}(t)$ and effect $E(t)$ [18]

$$E(t) = \frac{E_{\text{max}} \left[C(t)_{E}^{(0)}(t)^{y}\right]}{\left[C(t)_{E}^{(0)}(t)^{y} + \left[C(t)_{r}^{(0)}(t)^{y}\right]\right]}$$  \(2\)

The function $G(t)$ is given by the effect compartment concentration after bolus administration of a unit dose [13]:

$$G(t) = C_{s} e^{-\lambda_{1} t} + C_{r} e^{-\lambda_{2} t} + \frac{C_{e}(\lambda_{3} - \lambda_{2}) + C_{r}(\lambda_{3} - \lambda_{2}) - e^{-\lambda_{2} t}}{(\lambda_{1} - \lambda_{2}) (\lambda_{3} - \lambda_{2})}$$  \(3\)

$C_{s}$ and $C_{r}$ are zero-time intercepts; $\lambda_{1}$ and $\lambda_{2}$ are exponential disposition rate constant describing the decay of plasma concentrations, $C_{e}(t)$, after bolus administration of a unit dose ($G(t)$ = $C_{e} e^{-\lambda_{1} t}$ + $C_{r} e^{-\lambda_{2} t}$); $\lambda_{3}$ = elimination rate constant for the effect compartment; $E_{\text{max}}$ = maximum effect; $C_{r} = $ concentration at half-maximal effect; and $y$ is a value describing the steepness of the concentration-response curve. The initial values used for the parameters are as follows: $C_{s} = 0.23 \text{ mg kg}^{-1} \text{ litre}^{-1}$ body weight (in kg), $C_{r} = 0.059 \text{ mg kg}^{-1} \text{ litre}^{-1}$ body weight (in kg), $\lambda_{1} = 0.231 \text{ min}^{-1}$, $\lambda_{2} = 0.023 \text{ min}^{-1}$, $\lambda_{3} = 0.126 \text{ min}^{-1}$, $E_{\text{max}} = 100\%$ (Ti 0\% from control), $C_{r} = 0.7 \text{ mg litre}^{-1}$; $y = 3.5$. $C_{s}$ and $C_{r}$ were normalized to atracurium 1 mg kg$^{-1}$ [19].

By applying the superposition principle, it is possible to calculate the concentration of atracurium in effect compartment at any moment and during any drug administration scheme. Equations (1-3) give a full description of the drug input-effect relationship. Given a set-point, equation (2) may be solved for the necessary concentration in effect compartment. The pharmacokinetic model (equation 1) may be used subsequently for calculation of the drug input function [20].

If the measured neuromuscular block was within 2\% of the desired neuromuscular block, an infusion scheme was used to maintain the effect of atracurium at its current level, as predicted by the pharmacokinetic-dynamic model (that is equations 1 and 2). Otherwise, the difference between the measured and predicted neuromuscular block was used to correct the model variables. The updated values were then used to calculate the new infusion scheme for achieving and maintaining the desired level of neuromuscular block. This cycle was performed every 20 s. Adjustment of the parameters of the pharmacokinetic-dynamic model was begun 2 min after activation of the closed-loop system.

**Adaptation algorithm**

One observes that equation (2) is scale invariant with respect to the transformation $(C_{r} C_{s}) \rightarrow (C_{r} C_{s})$ for any number $\lambda \neq 0$. Consequently, the insertion of equation (1) to equation (2) does not depend on $C_{s}$, $C_{r}$ and $C_{s}$ but only on the ratios $C_{r} C_{s}$ and $C_{r} C_{s}$ thus not allowing estimation of clearance or volume of distributions but only microconstants $\lambda_{1}$, $\lambda_{2}$, $\lambda_{3}$, and the amount of drugs in diverse compartments. This is, however, sufficient for determining the drug input function. A complete adaptation would require estimation of $C_{r} C_{s}$, $C_{r} C_{s}$, $\lambda_{1}$, $\lambda_{2}$ and $\lambda_{3}$. We chose to update during the feedback control only variables.
Controller performance

Controller performance was measured by calculating the mean offset from set-point and mean SD from set-point during feedback infusion. Feedback infusion is said to begin when block returns from overshoot to the set-point of 90% after the initial bolus. Mean offset was calculated by:

\[
\text{Mean offset} = \frac{1}{n} \sum_{t=1}^{n} (s_b - b_t)
\]

where \( s_b \) = set-point, \( b_t \) = neuromuscular block measured every 20 s during feedback infusion, \( n \) = number of measurements.

Mean SD from set-point was SD for mean offset defined above.

REFERENCES