

Quantitation of the Interaction Between Atracurium and Succinylcholine Using Closed-loop Feedback Control of Infusion of Atracurium

Klaus T. Olkkola, M.D.,* Helmut Schwilden, M.D., Ph.D.†

The authors used closed-loop feedback control of infusion of atracurium to study the effect of prior administration of succinylcholine on neuromuscular blockade induced by atracurium in patients undergoing otolaryngologic surgery. Anesthesia was maintained with nitrous oxide in oxygen, flunitrazepam, and fentanyl. Of 14 patients given atracurium, seven were given prior administration of succinylcholine and seven were not. Interaction between the two drugs was quantified by determining the asymptotic steady-state rate of infusion necessary to produce a constant 90% neuromuscular blockade. This was accomplished by applying nonlinear curve-fitting to data on the cumulative dose requirement during anesthesia. The neuromuscular blocking effect of atracurium was found to be greater after prior administration of succinylcholine. The asymptotic steady-state rate of infusion (\pm SD) for atracurium was $0.27 \pm 0.06 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for patients given succinylcholine and $0.38 \pm 0.10 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for those not given succinylcholine. The clinical implication of this study is that the clinician should be aware of the fact that an induction dose of 1 mg/kg of succinylcholine does reduce atracurium requirement for 90% neuromuscular blockade by approximately 30%. (Key words: Equipment: computers. Neuromuscular relaxants: atracurium; succinylcholine. Pharmacokinetic models.)

STUDIES REPORT that prior administration of succinylcholine augments the neuromuscular blocking effects of competitive neuromuscular blocking, *i.e.*, vecuronium, pancuronium, and *d*-tubocurarine.¹⁻⁴ Some reports have questioned this effect for the last two agents.^{5,6} No study has yet investigated the possible interaction between succinylcholine and atracurium-induced neuromuscular blockade, although one study has evaluated the effect of succinylcholine given during recovery from atracurium.⁷ To investigate this possible interaction, our study group used a closed-loop feedback control method of administering atracurium to produce and maintain a relatively constant neuromuscular blockade of 90%. Unlike the open-loop control system in which input to the system (*e.g.*, drug dosage) is independent of output (*e.g.*, degree of neuromuscular blockade), a closed-loop system deter-

mines what the input will be at any particular time by adjusting it to the previous output. Interaction between atracurium and succinylcholine was measured by determining the asymptotic steady-state rate of infusion necessary to produce 90% neuromuscular blockade with atracurium.

Materials and Methods

We obtained informed written consent and institutional approval to study eight male and six female patients undergoing otolaryngologic surgery. Patients considered to be poor anesthetic risks were excluded from study. Pre-anesthetic medication consisted of 1 mg of flunitrazepam and 0.5 mg of atropine im given 1 h before the start of anesthesia. After induction of anesthesia with thiopental (5 mg/kg) but before succinylcholine or atracurium for neuromuscular blockade, we used the Relaxograph® neuromuscular transmission monitor (Datex, Helsinki, Finland) to obtain control electromyographic values. Specifically, the train-of-four sequence was assessed (frequency of stimuli, 2 Hz; pulse width, 100 ms) by means of surface electrodes placed adjacent to the ulnar nerve at the wrist.⁸ The stimulus output is a rectangular wave with a current range of 0-70 mA, and the machine calibrates automatically by searching for the optimum signal levels before setting the supramaximal level.

Patients then were assigned randomly to one of two sequences: 1) bolus administration of succinylcholine (1 mg/kg), intubation, complete recovery from the depolarizing block, and intravenous bolus administration of atracurium (0.5 mg/kg); or 2) bolus administration of atracurium (0.5 mg/kg) and intubation but with no prior administration of succinylcholine.

The degree of neuromuscular blockade (assessed every 20 s with the Relaxograph®) was defined as the ratio of the measurement of first twitch in the train-of-four sequence (T1) to the corresponding control value. Anesthesia was maintained with 60% nitrous oxide in oxygen, flunitrazepam, and fentanyl. The end-tidal carbon dioxide tension was maintained at 4-5 kPa (30-38 mmHg).

Bolus administration of atracurium was followed by infusion of atracurium controlled by a model-driven, closed-loop feedback system (see Appendix). An infusion pump (Fresenius Infusomat CP®) and the Relaxograph®

* Alexander von Humboldt Research Fellow, Department of Clinical Pharmacology, University of Helsinki.

† Staff Anesthesiologist.

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Address reprint request to Dr. Olkkola: Department of Clinical Pharmacology, University of Helsinki, Paasikivenkatu 4, SF-00250 Helsinki, Finland.

were attached to a Toshiba® 1100+ computer by means of a serial RS232C interface. For safety reasons, the maximum rate of infusion was limited to 500 mg/h. The solution was administered through an indwelling catheter in a forearm vein.

For both groups, the desired level of neuromuscular block (*i.e.*, the set-point) was set to 90% (T1 = 10% from control). Controller performance was measured by calculating the mean offset from set-point and the mean SD from set-point during feedback infusion. During the closed-loop feedback infusion of atracurium, the measured values for effect and data on the rate of infusion were saved on the computer. To estimate the asymptotic steady-state rate of infusion (I_{ss}), we used nonlinear curve-fitting to fit the following formula to the curve representing the cumulative dose requirement of atracurium⁹:

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

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, and t = duration of atracurium administration.

The Mann-Whitney U test was used to compare the parameters between the groups.

Results

Table 1 shows the patient characteristics, average controller performance, and I_{ss} for the two groups. Figures 1 and 2 give an example of the time course of neuromuscular block and the cumulative dose requirements for atracurium in two representative patients, one from each group. Figure 3 shows the mean (\pm SE) cumulative dose requirements for atracurium for the two groups. Patient characteristics and controller performance did not differ significantly between the groups. The mean average rate of infusion of atracurium was 1.4 times higher for patients given no prior administration of succinylcholine than for

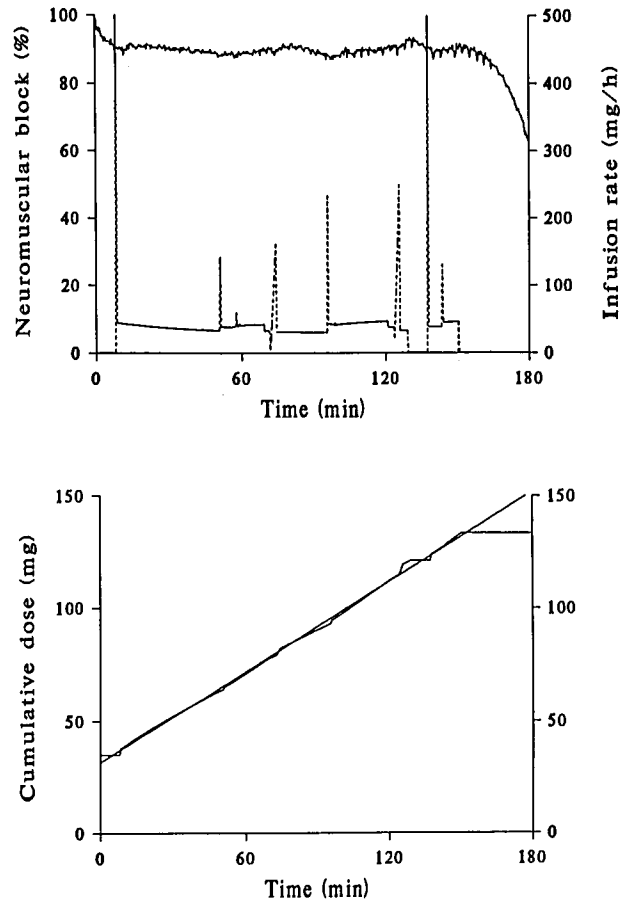


FIG. 1. Data for one representative patient in the group given no succinylcholine before neuromuscular blockade with atracurium. The top panel shows the rate of infusion (bottom trace) necessary to produce a constant 90% neuromuscular blockade (top trace) by closed-loop administration of atracurium. The bottom panel shows the cumulative atracurium dose and fitted cumulative dose (straight line) of atracurium for the same patient.

patients given succinylcholine for intubation ($P < 0.05$). The amount of fentanyl and flunitrazepam given during anesthesia did not differ between groups.

TABLE 1. Steady-State Infusion of Atracurium Controlled by a Feedback System, With and Without Prior Administration of Succinylcholine

Treatment	Patients				Controller Performance			Rate of Infusion of Atracurium* (mg · kg ⁻¹ · h ⁻¹)
	No. (M/F)	Age (yr)	Weight (kg)	Height (cm)	Length of Infusion (min)	Offset from Set-Point (%)	SD from Set-Point (%)	
ATR	7 (3/4)	54.8 ± 14.9	68 ± 15	166 ± 10	110 ± 39	-0.5 ± 0.8	1.6 ± 0.6	0.38 ± 0.10
SCh + ATR	7 (5/2)	45.0 ± 12.2	73 ± 15	172 ± 9	92 ± 82	-0.2 ± 1.1	2.3 ± 1.6	0.27 ± 0.06
P †		0.110	0.798	0.249	0.179	0.848	0.406	0.048

Values are mean \pm SD. ATR = atracurium; SCh = succinylcholine. * Asymptotic steady-state rate of infusion of atracurium.

† Determined by the Mann-Whitney U test.

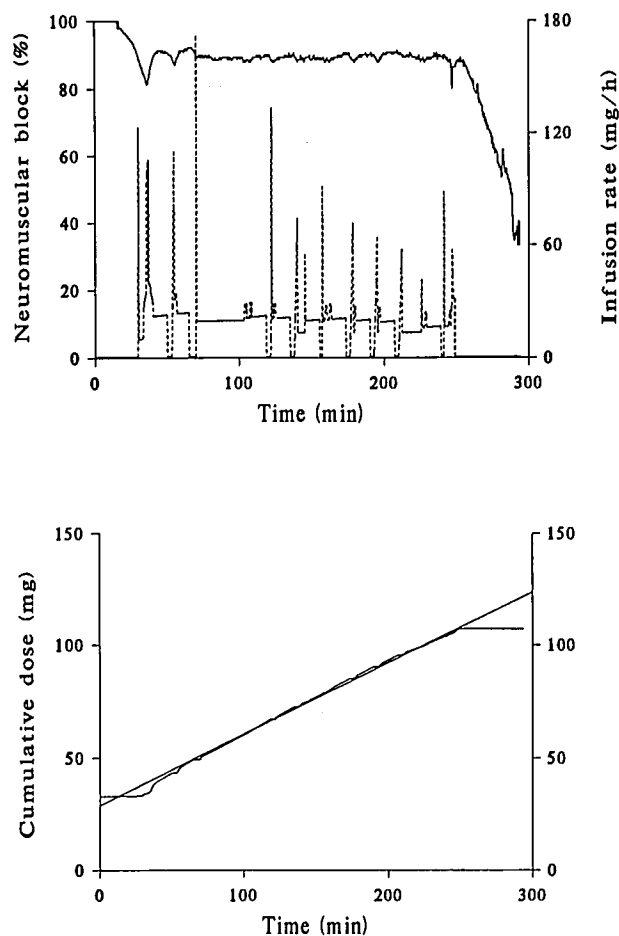


FIG. 2. Data for one representative patient in the group given succinylcholine before neuromuscular blockade with atracurium. The top panel shows the rate of infusion (bottom trace) necessary to produce a constant 90% neuromuscular blockade (top trace) by closed-loop administration of atracurium. The bottom panel shows the cumulative atracurium dose and fitted cumulative dose (straight line) of atracurium for the same patient.

Discussion

The model-driven, closed-loop feedback control of infusion of atracurium kept the desired degree of muscle relaxation at a reasonably constant level. Accordingly, by investigating the steady-state infusion requirements of atracurium, it was possible to draw conclusions about the possible interaction between the two neuromuscular blocking agents.

Fitting a straight line as asymptote to the data on the cumulative dose requirement of atracurium showed that prior administration of succinylcholine augmented neuromuscular block induced by atracurium. Although the longest infusions of atracurium following succinylcholine lasted over 3 h, augmentation of the nondepolarizing block did not seem to cease. This occurrence was unlike

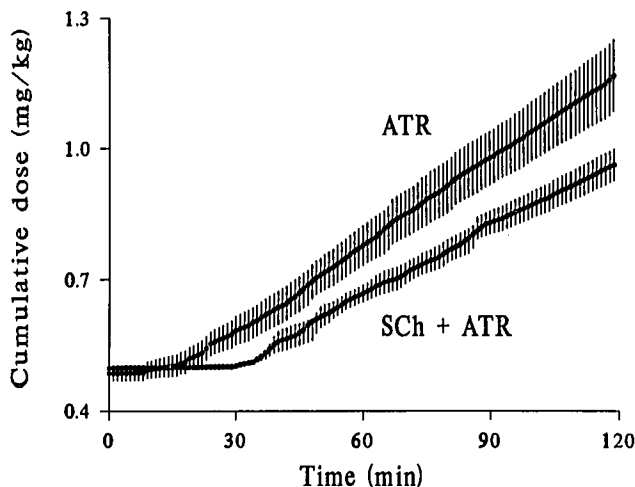


FIG. 3. The cumulative dose (\pm SE) calculated as milligrams of atracurium per body weight in the two groups given atracurium with (SCh + ATR) and without (ATR) prior administration of succinylcholine to produce a constant 90% neuromuscular blockade by closed-loop administration of atracurium.

that reported elsewhere for continuous infusion of vecuronium in which the effect of succinylcholine on vecuronium requirement did not last longer than 90 min.³

Because the elimination of atracurium occurs primarily through Hoffmann elimination, it is unlikely that its elimination could be affected by succinylcholine.^{10,11} This occurrence means in all probability that differences existed between the two groups regarding pharmacodynamics. Without measurement of concentrations, however, the source of these differences (c_0 vs. γ ; see Appendix for definitions) cannot be elucidated. Furthermore, our results do not justify any conclusions regarding the molecular mechanisms of the interaction.

The authors conclude that the neuromuscular blocking effect of atracurium is greater after prior administration of succinylcholine. Succinylcholine decreases the atracurium requirement by 30% at 90% neuromuscular block. Because the steepness of the response curve varies, one cannot necessarily assume that this reduction in dose requirement would occur at other levels of neuromuscular blockade, especially the lower levels. The clinical implication of this study is that the clinician should be aware of the fact that an induction dose of 1 mg/kg of succinylcholine does reduce atracurium requirement by approximately 30% at 90% neuromuscular blockade.

Appendix

MODEL-DRIVEN COMPUTERIZED INFUSION OF ATRACURIUM

A two-compartment, open mamillary model having a hypothetical effect compartment linked to the central compartment

was assumed to represent a valid model of the pharmacokinetics of atracurium.^{12,13} The integrated pharmacokinetic and pharmacodynamic model we used consists of two formulas (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, $c_e(t)$, *i.e.*,

$$c_e(t) = \int_0^t dt' G(t-t') I(t') \quad (1)$$

and one representing the relationship between concentration $c_e(t)$ and effect $E(t)$:¹⁴

$$E(t) = \frac{E_{\max} [c_e(t)]^\gamma}{c_0^\gamma + [c_e(t)]^\gamma} \quad (2)$$

The function $G(t)$ is given by the effect compartment concentration after bolus administration of a unit dose:¹⁵

$$G(t) = \left[\frac{A}{k_{eo} - \alpha} e^{-\alpha t} + \frac{B}{k_{eo} - \beta} e^{-\beta t} + \frac{A(\beta - k_{eo}) + B(\alpha - k_{eo})}{(\alpha - k_{eo})(\beta - k_{eo})} e^{-k_{eo} t} \right] k_{eo} \quad (3)$$

where A and B are the zero-time intercepts, and α and β are the exponential disposition rate constants describing the decay of plasma concentrations $c_p(t)$ after bolus administration of a unit dose [$c_p(t) = Ae^{-\alpha t} + Be^{-\beta t}$]. k_{eo} is the elimination rate constant for the effect compartment, E_{\max} is the maximum effect, and c_0 is the concentration at half-maximal effect. γ is a value describing the steepness of the concentration-response curve. The initial values used for the parameters were as follows: $A = 0.23 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{l}^{-1} \cdot \text{body weight (in kg)}$, $B = 0.059 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{l}^{-1} \cdot \text{body weight (in kg)}$, $\alpha = 0.231 \text{ min}^{-1}$, $\beta = 0.028 \text{ min}^{-1}$, $k_{eo} = 0.126 \text{ min}^{-1}$, $E_{\max} = 100\%$ (T1 0% from control), $c_0 = 0.7 \text{ mg/l}$, and $\gamma = 3.5$. A and B were normalized to 1 mg/kg of atracurium.¹¹

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 subsequently used for the calculation of the drug input function.¹⁶

For both groups, the desired level of neuromuscular block (*i.e.*, the set-point) was set to 90% (T1 = 10% from control). If the measured neuromuscular block was within 2% of the desired neuromuscular block, an infusion scheme was used to keep the effect of atracurium at its current level, as predicted by the pharmacokinetic-dynamic model (*i.e.*, equations 1 and 2). Otherwise, the difference between the measured and predicted neuromuscular block was used to correct the model parameters. 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 $(c_e, c_0) \rightarrow (\lambda c_e, \lambda c_0)$ for any number $\lambda \neq 0$. Consequently, the insertion of equation 1 to equation 2 does not depend on A , B , and c_0 but only on the ratios A/c_0 and B/c_0 , thus not allowing estimation of clearance or volume of distributions but only microconstants k_{e1} , k_{12} , k_{21} and the amount of drugs in diverse compartments. This is, however, sufficient for determining the drug input function. A complete adaptation would require the estimation of A/c_0 , B/c_0 , α , β , and k_{eo} . We chose to update only the parameters A/c_0 and B/c_0 during the feedback control. This allows the adaptation of the initial bolus to achieve a certain effect (short-term control) and the steady-state infusion rate to maintain the given effect (long-term control).

The effect E may be regarded as a function of A and B and the drug input $I(t)$:

$$E(t) = E(A, B, I(t)) \quad (4)$$

Denoting by $A + \delta A$ and $B + \delta B$ the true hybrid constants for an individual subject, the difference between measured and predicted effect (ΔE) can be expanded in a Taylor series as follows:

$$E = E(A + \delta A, B + \delta B, I(t)) - E(A, B, I(t)) \\ = (\partial E / \partial A) \delta A + (\partial E / \partial B) \delta B + \dots \quad (5)$$

In conjunction with the condition to minimize the expression $\delta A^2 + \delta B^2$, equation 5 was used to solve for δA and δB . A change in the range of $\pm 10\%$ of the previous values was allowed in each update. From the updated values, new microconstants were calculated that served to correct the drug input function. The adaptation algorithm has been published previously.¹⁷

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