

PHARMACOKINETICS AND PHARMACODYNAMICS OF ATRACURIUM WITH AND WITHOUT PREVIOUS SUXAMETHONIUM ADMINISTRATION

F. DONATI, S. S. GILL, D. R. BEVAN, J. DUCHARME, Y. THEORET AND F. VARIN

SUMMARY

Suxamethonium increases neuromuscular block produced by non-depolarizing agents administered subsequently. To determine if this effect has a pharmacokinetic or pharmacodynamic origin, 18 ASA physical status I or II adults received atracurium 0.2 mg kg⁻¹, with (n = 10) or without (n = 8) previous injection of suxamethonium 1 mg kg⁻¹, during a thiopentone-nitrous oxide-isoflurane (0.5% end-tidal) anaesthetic. Arterial blood samples were obtained and plasma atracurium concentration measured by HPLC. Train-of-four stimulation was applied to the ulnar nerve and the force of contraction of the adductor pollicis muscle was recorded. Mean (SEM) volume of distribution was slightly greater with previous suxamethonium (143 (13) ml kg⁻¹) than without (109 (5) ml kg⁻¹) (P < 0.04). Mean elimination half-life was unaffected (20.3 (0.8) min and 20.4 (1.6) min, respectively). Neuromuscular block was more intense and recovery was slower with previous administration of suxamethonium. Atracurium concentration at 50% block (C_P⁵⁰) was 305 (30) ng ml⁻¹ with and 454 (25) ng ml⁻¹ without previous suxamethonium (P < 0.01). It is concluded that suxamethonium may be associated with a slight increase in the volume of distribution of atracurium, but this effect is more than compensated by a decrease in atracurium concentration required for a given effect.

KEY WORDS

Drug interactions: atracurium, suxamethonium. Pharmacodynamics: atracurium. Pharmacokinetics: atracurium. Neuromuscular relaxants: atracurium, suxamethonium.

suxamethonium. A single dose of pancuronium [1, 2], vecuronium [2-5] or atracurium [6] has been reported to produce more intense block if given after suxamethonium. A shift to the right of the dose-response curve of vecuronium [3] has been described with previous administration of suxamethonium. The duration of this effect is at least 30 min [4] and possibly as long as 2 h or more [2].

Such a change in the relationship between dose and effect could be caused by a pharmacokinetic or pharmacodynamic alteration, or both. To determine quantitatively the role of each in the changes caused by suxamethonium, plasma concentrations should be measured and correlated with effect. Moreover, there are no comparative data on the pharmacokinetics of non-depolarizing blocking drugs with and without previous administration of suxamethonium.

The purpose of this study was to determine the pharmacokinetics of atracurium together with its pharmacodynamics (neuromuscular effect), with and without previous administration of suxamethonium.

PATIENTS AND METHODS

The study was approved by the Hospital Ethics Committee and informed consent was obtained

FRANÇOIS DONATI*, PH.D., M.D., F.R.C.P.(C.); SATWANT S. GILL, M.B., F.C.ANAES.; DAVID R. BEVAN, M.B., M.R.C.P., F.C.ANAES.; Departments of Anaesthesia, Royal Victoria Hospital and McGill University, Montreal (Quebec), Canada. JULIE DUCHARME, M.Sc.; FRANCE VARIN, PH.D.; Faculté de Pharmacie, Université de Montréal, Montreal (Quebec), Canada. YVES THEORET, PH.D., Département de Pharmacologie, Université de Montréal, Montreal (Quebec), Canada. Accepted for Publication: December 1, 1990.

*Address for correspondence: Department of Anaesthesia, Royal Victoria Hospital, 687 Pine Avenue West, Montreal (Quebec), Canada H3A 1A1.

The neuromuscular effect of non-depolarizing agents is affected by previous administration of

from each subject. We studied 18 ASA physical status I and II adult patients, aged 19–75 yr, undergoing elective surgery for which arterial cannulation was indicated. Patients with cardiovascular, pulmonary, neuromuscular, hepatic or renal disease were excluded. Other exclusion criteria included anaemia, a history of multiple allergies, and concurrent administration of drugs known or suspected to interfere with neuromuscular function. Patients who deviated from their ideal body weight by more than 20% were also excluded.

The patients were premedicated with diazepam 5–10 mg orally or a combination of pethidine 50–70 mg i.m. and atropine 0.4–0.6 mg i.m. On arrival of the patient in the operating room, ECG, haemoglobin oxygen saturation and arterial pressure were measured. Anaesthesia was induced with fentanyl 2–5 $\mu\text{g kg}^{-1}$ and thiopentone 4–7 mg kg^{-1} , and maintained with 70% nitrous oxide and 0.5% end-tidal isoflurane in oxygen, and fentanyl as required. In eight patients, the lungs were ventilated manually via a mask until atracurium had been given. Suxamethonium 1 mg kg^{-1} was given i.v. to the other 10 subjects, tracheal intubation was performed and mechanical ventilation of the lungs commenced. An arterial cannula was inserted into the left radial artery.

The left ulnar nerve was stimulated supra-maximally via silver–silver chloride electrodes applied to the skin at the elbow. The force of contraction of the adductor pollicis muscle was recorded using a Grass FT-10 force transducer. Train-of-four stimulation (2 Hz for 2 s) with impulses of 0.2 ms in duration was repeated every 12 s.

After a stable baseline had been obtained (or, in patients who received suxamethonium, after 100% T1 recovery from neuromuscular block), atracurium 0.2 mg kg^{-1} was given as a rapid i.v. bolus. In patients who did not receive suxamethonium, tracheal intubation was performed after injection of atracurium, when maximal twitch depression was observed. All patients underwent mechanical ventilation of the lungs. The end-tidal carbon dioxide was measured with a mass spectrometer (SARA) and maintained within normal limits. When first twitch height (T1) returned to 50% or more of control, surgical relaxation was continued with vecuronium.

Arterial blood samples (3 ml) were drawn into heparinized syringes at 0, 0.5, 1, 1.5, 2, 3, 5, 7, 10, 15, 20, 30, 45, 60, 90 and 120 min. The samples

were transferred immediately into glass tubes which were placed in ice for approximately 5 min. The samples were centrifuged, acidified to pH 4–5 with sulphuric acid 2 mol litre^{-1} and frozen.

Plasma concentrations of atracurium and laudanosine were measured by a specific HPLC assay with fluorimetric detection [7]. Plasma samples (250 μl) enriched with verapamil 250 ng (internal standard) were reacidified with 10 μl of sulphuric acid 0.5 mol litre^{-1} . The plasma proteins were precipitated with acetonitrile. After centrifugation, an aliquot of the supernatant was injected directly into the HPLC system. Atracurium and metabolites were separated with a Hichrom Spherisorb C_8 column (100 \times 4.6 mm i.d., 5- μm particle size; Reading, U.K.) using a linear gradient for the mobile phase (pH 5) at a flow rate of 1.7 ml min^{-1} . The mobile phase changed from 100% of 0.03-M phosphate buffer–methanol–acetonitrile (57.5:5:37.5) to 100% of 0.1-M phosphate buffer–methanol–acetonitrile (47.5:15:37.5) in 8 min. The Shimadzu fluorescence detector (Kyoto, Japan) excitation and emission wavelengths were set at 240 nm and 320 nm, respectively. The method was sensitive for concentrations greater than 20 ng ml^{-1} , the mean coefficient of variation was less than 5%, and linearity was present in the range 30–8000 ng ml^{-1} for both atracurium and laudanosine. Vecuronium did not interfere with the measurement of either atracurium or laudanosine.

The plasma concentration values of atracurium were fitted to a two-compartment mamillary model. Pharmacokinetic–pharmacodynamic correlations were also made by calculating a value for k_{eo} using a non-parametric link model [8]. A sigmoid E_{max} model was used to fit effect, measured as T1 depression, with effect compartment concentration, providing values for the concentration corresponding to 50% block ($C_{\text{P}50}$) and for the slope of the relationship (γ) [9]. Siphar software (SIMED, France) was used to fit these data.

TABLE I. Patient characteristics (mean (range or SEM))

	Suxamethonium	No suxamethonium
Number	10	8
Sex (M/F)	6/4	4/4
Age (yr)	52 (25–64)	56 (26–68)
Weight (kg)	61 (3)	65 (4)

TABLE II. Neuromuscular block (mean (SEM)). *P < 0.05 between groups

	Suxamethonium		No suxamethonium
Maximum block (%)	95.2 (2.0)	*	85.1 (3.8)
Time to max. block (min)	5.7 (0.6)	*	9.5 (0.8)
Time to 25 % recovery (min)	24.6 (2.9)	*	16.4 (2.1)
Time to 50 % recovery (min)	31.8 (3.0)	*	24.0 (1.6)

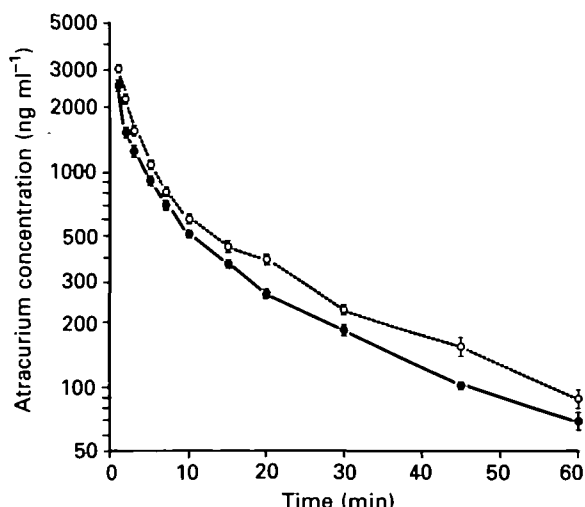


FIG. 1. Plasma concentrations of atracurium, after a bolus injection of 0.2 mg kg⁻¹ with (●) and without (○) previous administration of suxamethonium 1 mg kg⁻¹.

Unless specified otherwise, the results are presented as mean (SEM). Between-group comparisons were made using Student's *t* test. *P* ≤ 0.05 was considered significant.

RESULTS

Both groups were comparable in age, sex and weight (table I).

TABLE IV. Pharmacokinetic-pharmacodynamic relationships (mean (SEM)). *P < 0.05 between groups

	Suxamethonium		No suxamethonium
$C_{p^{ss}_{50}}$ (ng ml ⁻¹)	305 (30)	*	454 (25)
γ (logit log ⁻¹)	5.56 (0.54)		6.08 (0.68)
k_{eo} (min ⁻¹)	0.091 (0.012)		0.068 (0.007)

Maximum neuromuscular block was greater in patients who had received suxamethonium, and recovery times were longer (table II). Time to maximum block was the same in both groups.

At all times, the arterial plasma concentration of atracurium was slightly greater in patients who did not receive suxamethonium (fig. 1). There was no difference in mean residence time (MRT) or elimination half-lives. The volume of central compartment, volume of distribution at steady state and volume calculated according to the area under the curve (V^B) were greater (expressed per kg body weight) in patients who had received suxamethonium (table III). Clearance (*Cl*) was also slightly greater in patients who had received suxamethonium (table III).

Pharmacokinetic-pharmacodynamic modelling indicated that the concentration required for 50 % block ($C_{p^{ss}_{50}}$) was approximately 50 % greater in patients who did not receive suxamethonium (table IV). The slope of the effect-concentration

TABLE III. Pharmacokinetic variables (mean (SEM)). MRT = Mean residence time; V^B = volume of distribution calculated according to area under the curve; V^{ss} = volume of distribution at steady state; V_c = volume of central compartment; $T_{1/2}^a$, $T_{1/2}^b$ = half-lives; *Cl* = clearance. *P < 0.05 between groups

	Suxamethonium		No suxamethonium
MRT (min)	21.1 (0.8)		21.9 (1.6)
V^B (ml kg ⁻¹)	195 (16)	*	145 (8)
V^{ss} (ml kg ⁻¹)	143 (13)	*	109 (5)
V_c (ml kg ⁻¹)	63 (6)	*	41 (2)
$T_{1/2}^a$ (min)	2.59 (0.13)	*	2.01 (0.21)
$T_{1/2}^b$ (min)	20.3 (0.8)		20.4 (1.6)
<i>Cl</i> (ml kg ⁻¹ min ⁻¹)	6.6 (0.5)	*	5.0 (0.2)

relationship (γ) was similar in both groups and the rate constant (k_{eo}) for equilibrium with the neuromuscular junction was not statistically different between groups (table IV).

The sampling period was too short to carry out the pharmacokinetic analysis of laudanosine. Initial laudanosine concentrations were 3–10% of corresponding atracurium concentrations, suggesting that blood sampling was associated with little spontaneous degradation.

DISCUSSION

This study has demonstrated that the concentration corresponding to 50% atracurium block ($C_{P^{ss}_{50}}$) was decreased by previous administration of suxamethonium. In addition, the pharmacokinetics of atracurium were affected slightly by administration of suxamethonium. Elimination half-life of atracurium was not affected by suxamethonium administration, but the volume of central compartment and volume of distribution were increased by 20–30%. These pharmacokinetic changes were associated with smaller plasma concentrations, which tended to diminish the dynamic changes. The net result was a small but significant increase in neuromuscular block and time to 50% recovery.

In this study, atracurium concentrations were measured in arterial blood, not in peripheral venous blood as in most other studies [10–18]. This method is probably more accurate, as arterial blood is mixed and large differences may occur between venous concentrations, depending on the site of sampling [19]. This is especially true of early samples, when tissue uptake is most important. This may explain why the volume of distribution V^d obtained in this study in patients who did not receive suxamethonium (145 ml kg⁻¹) is at the lower end of the range reported previously (142–202 ml kg⁻¹) [10–18]. Similarly k_{eo} , or rate of transfer of drug into effect compartment, was less in the present (0.068 min⁻¹) than in previous studies (0.1 and 0.074 min⁻¹) [12, 17]. This again may be explained by the greater arterial concentrations in early samples. The distribution (2.01 min) and terminal (20.4 min) half-lives were similar to those reported previously (2–3 min and 17–21 min, respectively) [10–18].

The dose of 0.2 mg kg⁻¹ was chosen in this study because it approximates to ED₉₀–ED₉₅ [20]. Therefore, a large number of blood samples could be obtained during both onset and offset of

neuromuscular block, so that a better estimate of the kinetic–dynamic relationship could be obtained. In addition, small doses are associated with rapid recovery. Thus the sensitivity of the neuromuscular junction to atracurium was probably unchanged during recovery compared with onset. If such an alteration occurred, the present kinetic–dynamic analysis would be less reliable. However, the effects of suxamethonium on subsequent non-depolarizing block may last up to 2 h [2], much longer than the time to 50% recovery (31 min in this study). The problem associated with using a small dose was the relatively small plasma concentrations of atracurium, especially 2 h after injection. However, reliable measurements of plasma concentrations could be made until 90 min, or four to five times the terminal half-life.

The results of the kinetic–dynamic analysis suggest that, in the absence of previous administration of suxamethonium, the plasma concentration at steady state for a given degree of block may be increased by 50% compared with atracurium given after suxamethonium. In the present study, the $C_{P^{ss}_{50}}$ might have been reduced by administration of isoflurane, but both groups received the same concentration (0.5% end-tidal).

The present study suggests that administration of suxamethonium may be associated with small changes in atracurium kinetics. Distribution volume and clearance increased by 25–30% when suxamethonium had been given. Such alterations may be caused by suxamethonium-induced modification in the binding of atracurium to plasma proteins, red blood cells, or extravascular tissue. As suxamethonium may cause long-lasting dynamic changes at the neuromuscular junction, probably via an interaction with a receptor, a modification of other proteins is possible. The extent of binding of atracurium to plasma proteins is appreciable [17], and its affinity for extravascular tissue is not known. Suxamethonium, which produces hyperkalaemia, could also produce fluid shifts. It is not known if these changes last long enough to modify the distribution of drugs administered subsequently. Irrespective of the mechanism, these kinetic changes are small, and do not offset completely the dynamic changes. However, it is recommended that, for pharmacokinetic studies, administration of suxamethonium is standardized, because the use of this drug in some patients would be an unnecessary source of variation.

The main effect of administration of suxamethonium on subsequent atracurium block is a shift of the effect-concentration relationship to the left. In other words, smaller concentrations produce the same neuromuscular effect. The mechanism for this relatively long lasting potentiating effect is not known. However, this study suggests that this may be caused by an increase in end-plate sensitivity to atracurium. Clinically, less atracurium is required for an equivalent degree of block if suxamethonium has been used previously.

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