Continuous infusions of atracurium and vecuronium, compared with intermittent boluses of pancuronium: dose requirements and reversal

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This study was designed to determine the effect of prolonged infusion on the ease of reversal of atracurium and vecuronium, and whether factors which potentiate the block delayed reversal. In phase one, 40 patients were randomized (double blind) to determine the steady state conditions for atracurium and vecuronium. Fourteen atracurium patients and 17 vecuronium patients were evaluable. The unblinded second phase involved the steady state conditions using halothane or isoflurane and atracurium infusions. The infusion required for 95% twitch depression (TD_{95}) for atracurium was $7.6 \pm 1.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. The requirement for vecuronium changes with time: TD_{95} at 30 min was 1.01 ± 0.16 , at 60 min 0.89 ± 0.12 and after 90 min $0.85 \pm 0.17 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ($P < 0.05$). The mean TD_{95} was $0.94 \pm 0.23 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Multivariate regression analysis of the infusion data revealed a vecuronium model predicting TD_{95} by the duration of infusion ($P < 0.05$) and weight ($P = 0.05$). Atracurium TD_{95} was predicted by age ($P = 0.05$). The addition of an inhalation agent to atracurium reduced the infusion rate by $2.01 \pm 0.28 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ($P = 0.0001$) for each increase in MAC. The mean reversal times for atracurium with three different anaesthetics and for vecuronium were not different. Reversal of pancuronium blockade, from less profound twitch depression (86.4 vs 95%) took twice as long as for atracurium and vecuronium for which the following predictors were identified: age, weight, duration of infusion, level of blockade, and type of

anaesthetic, using a stepwise regression model. For vecuronium: age (coeff 2.84 ± 0.51 $P = 0.0001$) and duration of infusion (coeff 0.12 ± 0.02 $P = 0.0002$) were significant predictors. Age was the only predictor of the time to reverse block after atracurium blockade with all types of anaesthetic ($P = 0.05$).

Cette étude a pour but de déterminer l'effet et la réversibilité d'une perfusion prolongée d'atracurium ou de vécuronium, ainsi que les facteurs qui peuvent retarder la décuration. Dans la première étape de l'étude, 40 patients ont été désignés aléatoirement (méthode à double insu) pour déterminer les conditions d'équilibre de l'atracurium et du vécuronium. Quatorze patients furent conservés pour l'atracurium et 17 pour le vécuronium. La deuxième étape, à découvert, a étudié les conditions d'équilibre obtenues avec l'halothane ou l'isoflurane et des perfusions d'atracurium. La perfusion requise pour une dépression du twitch de 95% (TD_{95}) est de $7,6 \pm 1,1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ avec l'atracurium. Les besoins de vécuronium varient avec le temps: le TD_{95} à 30 minutes, de $1,01 \pm 0,16$; à 60 minutes de $0,89 \pm 0,12$ et après 90 minutes, de $0,85 \pm 0,17 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ($P < 0,05$). La valeur moyenne de TD_{95} est de $0,94 \pm 0,23 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. L'analyse par régression multivariée des doses de perfusion de vécuronium donnent une prédiction de la TD_{95} dépendant de la durée de la perfusion ($P < 0,05$) et du poids ($P = 0,05$). La TD_{95} de l'atracurium dépend de l'âge ($P = 0,05$). L'adjonction d'un agent d'inhalation à l'atracurium réduit la dose perfusée à $2,01 \pm 0,28 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ($P = 0,0001$) pour chaque augmentation du MAC. La durée moyenne de décuration pour l'atracurium avec trois agents anesthésiques différents et pour le vécuronium n'est pas différente. La réversibilité d'un bloc au pancuronium à partir d'une dépression du twitch moins profonde (86,4 vs 96%) est deux fois plus longue que celle de l'atracurium et du vécuronium. Les facteurs suivants doivent être considérés: l'âge, le poids, la durée de la perfusion, le degré du bloc et l'agent anesthésique étudiés avec un modèle de régres-

Key words

ANTAGONISTS, NEUROMUSCULAR RELAXANTS: atracurium, vecuronium, pancuronium.

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sion en palliers. Pour le vécuronium, l'âge (coeff. $2,84 \pm 0,51$, $P = 0,0001$) et la durée de perfusion (coeff. $0,12 \pm 0,2$, $P = 0,0002$) sont des prédicteurs significatifs. L'âge est le seul prédicteur de la durée de décurarisation après un bloc à l'atracurium avec tous les types d'agents anesthésiques ($P = 0,05$).

The introduction of muscle relaxants into clinical anaesthesia occurred concomitantly with an increase in anaesthetic complications.¹ Nineteen percent of anaesthetic deaths have been attributed to respiratory failure² from residual muscle relaxants. Complete return of muscular activity to preoperative levels is difficult to determine clinically.³ Patients can sustain ventilation with normal carbon dioxide levels but may not be able to maintain airway patency.^{4,5}

Two separate studies have shown that as many as 42% of patients may return to the recovery room with inadequate reversal of muscle relaxation.^{6,7} The use of atracurium and vecuronium reduces the incidence of incomplete reversal.^{8,9} With longer procedures the intermediate acting muscle relaxants require frequent boluses or a steady state infusion. Reversal of atracurium and vecuronium after steady state infusion has been previously studied.¹⁰ Using a balanced anaesthetic technique, neuromuscular function after both atracurium and vecuronium returned to 85% of control within 20 min. However, problems were encountered in reversing the block in elderly patients. Inhalational agents have been found to impair the reversal of pancuronium¹¹ but not of vecuronium.¹² While the inhalational agents are known to potentiate atracurium^{12,13} the effect has not been systematically studied with steady state infusions. The effect of inhalational agents on reversal after steady state infusion of atracurium has not been studied.

The present study was undertaken to define the factors which predict the timing of clinically acceptable reversal of muscle relaxants after steady state infusion. This was compared with the reversal of pancuronium given by intermittent boluses, as this is a frequent mode of muscle relaxation in longer lasting cases. We studied the doses of atracurium and vecuronium required for surgical relaxation (95% twitch depression) when given by steady state infusion, determined the potentiation of neuromuscular blockade with atracurium by isoflurane and halothane, and compared these with intermittent injections of pancuronium. Reversal of the blocks was then assessed and compared.

Methods

This study was approved by our institutional review board. American Society of Anesthesiology class I or II patients

scheduled for elective surgical procedures were eligible for study. Patients in whom average hourly blood loss was anticipated to exceed $200 \text{ ml} \cdot \text{hr}^{-1}$ were excluded, as were patients receiving drugs which are known to potentiate or antagonize neuromuscular blockade.

Anaesthetic

Patients received no premedication. An intravenous infusion of normal saline was established in the operating room. Diazepam $0.2 \text{ mg} \cdot \text{kg}^{-1}$ plus fentanyl ($10 \mu\text{g} \cdot \text{kg}^{-1}$) or sufentanil ($1 \mu\text{g} \cdot \text{kg}^{-1}$) was administered prior to induction of anaesthesia with thiopentone (up to $4 \text{ mg} \cdot \text{kg}^{-1}$) which was then maintained with oxygen (30%) and nitrous oxide (70%). The trachea was intubated without the aid of muscle relaxation. End-tidal carbon dioxide (PETCO_2) was measured with an on-line mass spectrometer (Sara System P.P.G. Industries, Lexana, Kansas) and maintained by adjusting minute ventilation between 36 and 44 mmHg. Patients in whom the PETCO_2 decreased outside these variables were excluded from analysis (one patient randomized to receive atracurium could not achieve a PETCO_2 above 31 mmHg despite repeated attempts at reducing ventilation and flow rates). Oesophageal or rectal temperature was monitored in all patients, and temperature was controlled with warming/cooling blankets, warmed intravenous fluids, and humidified gases. One patient was excluded from analysis due to hypothermia. Blood loss was recorded on an hourly basis. Seven patients (four atracurium and three vecuronium) were excluded after being randomized due to excessive blood loss (greater than $200 \text{ ml} \cdot \text{hr}^{-1}$).

Measurement of the effect of muscle relaxants

Using the Datex 221 NMT (Datex Instrumentarium Corp. Helsinki, Finland), a commercially available neuromuscular monitor, the EMG signal from the hypothenar eminence was monitored. A custom-designed hand splint, with foam backing, immobilized the hand. The hypothenar muscles are almost solely innervated by the ulnar nerve, have little motion when stimulated, and their activity correlates with respiratory functions.⁴ The arm was wrapped with a heated blanket to reduce heat loss. Monitoring was commenced after tracheal intubation and continued for ten minutes. The instrument was recalibrated prior to the administration of muscle relaxants, a procedure which has been found to minimize the drift that has been described with the NMT.

Patients were then paralysed with the appropriate drug bolus (atracurium $0.5 \text{ mg} \cdot \text{kg}^{-1}$ or vecuronium $0.1 \text{ mg} \cdot \text{kg}^{-1}$). At the return of a single twitch ($T_1/T_{1c} = 1\%$) the infusion was started. The initial infusion rate for atracurium was $8 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and for vecuronium was $1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. The level of blockade was assessed

every 20 sec using train-of-four stimulation. The infusion-rate (TD_{95}) which maintained a block of 95% twitch depression ($T_1/T_{1c} = 5\%$) was determined. The level of block, the infusion rate, $PETCO_2$, temperature, heart rate, and blood pressures were recorded every five minutes.

The time of reversal of neuromuscular blockade was defined as the time to achieve a T_4/T_1 ratio of 0.8. Previous studies⁴ have shown that an EMG T_4/T_1 ratio of 0.6 is associated with reduced hand grip and negative inspiratory pressure. Others have shown, in unanaesthetized subjects, reduced inspiratory pressure at a T_4/T_1 ratio of 0.6.⁵ A train-of-four ratio of 0.7 is the level of fade accepted as adequate reversal^{15,16} when mechanical force/contraction measurements are used. Levels less than 0.7 have shown some instances of ventilatory impairment.¹⁵ Kopman¹⁶ demonstrated that the mechanical train-of-four lags behind the EMG response using the Daxex NMT 221. Therefore the EMG train-of-four ratio must be > 0.7 to correspond with the 0.7 level of mechanical monitoring. We arbitrarily chose the level of 0.8.

Groups A1 (atracurium and narcotic) and V (vecuronium with narcotic) were studied in a blinded manner so that decisions about changes in dose would be unbiased. Both drugs were prepared in equal volumes (based on an atracurium/vecuronium potency ratio of 1/8). In determining this ratio we examined steady-state infusion data.¹⁷⁻²² The infusion rates for vecuronium ranged from $0.11 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ to $2.67 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ to maintain 90% twitch depression; a 24-fold variation. Atracurium steady-state infusions ranged from 3.7 to $14.3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, a 3.9-fold variation. Utilizing a latin square* we determined a potency ratio of 7.87:1 (approx 8:1). Since the comparisons were blinded the relative infusion rates reflect the true potency ratio in our population.

Five groups were studied after random allocation. Group A1 and V received a nitrous/narcotic anaesthetic and the muscle relaxant. Group A2 received a nitrous-narcotic anaesthetic and atracurium infusion, with isoflurane. In group A3 the inhalation agent was halothane. Group P received a nitrous/narcotic anaesthetic and pancuronium ($0.1 \text{ mg} \cdot \text{kg}^{-1}$ to facilitate intubation) and by intermittent bolus as appropriate to maintain 95% twitch depression. The concentration of inhalational agent was adjusted according to heart rate and blood pressure responses. The end-tidal concentrations of either isoflurane or halothane were recorded every five minutes. The infusion rate, level of block, and end-tidal agent were

unchanged for three consecutive measurements (15 min) before being analyzed.

Reversal of muscle relaxation

Neostigmine $50 \mu\text{g} \cdot \text{kg}^{-1}$ and glycopyrrolate $10 \mu\text{g} \cdot \text{kg}^{-1}$ were administered to antagonize neuromuscular blockade. Immediately after the neostigmine bolus the muscle relaxant infusion was stopped, and the inhalation agent was turned off. The rates of recovery of T_1/T_{1c} and T_4/T_1 were noted at control, one minute, two minutes and five minutes after the neostigmine bolus and every three minutes thereafter. Neuromuscular blockade was monitored until T_4/T_1 was > 0.8 .

Statistics

The demographic and infusion data, recovery times, and effect of inhalational agents were analyzed using one-way analysis of variance. If significant differences were encountered Student's *t* tests with Bonferroni correction were performed. In addition, factors affecting infusion rates and neuromuscular reversal were analyzed using a forward stepwise multiple regression model. Variables had to increase the predictive value by $P = 0.05$ before entering the model. In all statistics a *P* value of 0.05 or better was considered significant.

Results

Demographic data

The age, weight and duration of infusions were similar in all four infusion groups (Table I). Although the duration appears to be shorter for the vecuronium group this difference did not achieve statistical significance.

Neuromuscular doses

The infusion rate of atracurium at the time of reversal was $7.6 \pm 1.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in group A1. The mean dose of vecuronium at the time of reversal was $0.94 \pm 0.23 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. There appeared to be more variation in the vecuronium infusions. Using analysis of variance we compared the infusion rates in the two groups receiving nitrous narcotic anaesthesia (groups A1 and V) at 30, 60, and 90 min of infusion (Table II). Vecuronium infusion rates decreased with time ($1.01 \pm 0.16 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; 0.89 ± 0.12 ; and $0.85 \pm 0.17 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ respectively $P = 0.01$). We found no such decline with atracurium. Age, weight, duration of infusion and inhalation agents were entered into a forward stepwise multivariate regression to model predictors of dose. The results of this analysis are seen in Table III. Atracurium and vecuronium have different models for predicting dose. The significant predictors for atracurium include age (coeff = 0.28 ± 0.01 $P = 0.03$) and inhalational agent (coeff = -2.02 ± 0.29

*This method takes the mean value of the ratios obtained by dividing the high vecuronium level by the low atracurium level; the low vecuronium level by the high atracurium level; the low by the low and high by the high levels.

TABLE I Demographic mean $\pm$ SD

Study group	Number of patients	Age(yr)	Weight (kg)	Anaesthesia time (min)
Atracurium/narc	14	41.2 $\pm$ 24.0	65.0 $\pm$ 16.0	156.0 $\pm$ 18.0
Atracurium/isofl	14	37.3 $\pm$ 19.0	67.0 $\pm$ 12.0	163.0 $\pm$ 19.0
Atracurium/halo	14	43.0 $\pm$ 9.0	66.0 $\pm$ 18.0	148.0 $\pm$ 22.0
Vecuronium/narc	17	41.6 $\pm$ 21.0	63.0 $\pm$ 17.0	139.0 $\pm$ 19.0
Pancuronium/narc	16	44.1 $\pm$ 18.0	65.0 $\pm$ 21.0	147.0 $\pm$ 14.0

TABLE II Effect of duration on the infusion requirements (Effect of infusion time on the TD_{95} ; comparison of atracurium and vecuronium in patients receiving nitrous/narcotic anaesthesia (mean $\pm$ SD))

Agent	30 min	60 min	90 min	f	P value
ATR $n = 14^*$ $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{ml}^{-1}$	8.10 $\pm$ 0.21	7.90 $\pm$ 0.18	8.02 $\pm$ 0.17	0.5	0.2
VEC $n = 17^*$ $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{ml}^{-1}$	1.01 $\pm$ 0.16	0.89 $\pm$ 0.12	0.85 $\pm$ 0.17	3.82	0.03

*Six patients were excluded from atracurium analysis due to protocol violations; four for blood loss in excess of 200 ml $\cdot$ hr $^{-1}$; one for hypothermia; and one for hypocarbia. Three patients were excluded from vecuronium analysis all for blood loss in excess of 200 ml $\cdot$ hr $^{-1}$.

TABLE III Multivariate predictors of steady state TD_{95} for atracurium and vecuronium

	Variable	Coeff	P value
Atracurium	Age(yr)	0.28 $\pm$ 0.01	0.03
	Wt(kg)	0.004 $\pm$ 0.06	0.509
	MAC(age adjust)	-2.02 $\pm$ 0.29	0.0002
	Duration(min)	0.007 $\pm$ 0.11	0.923
Vecuronium	Age(yr)	0.007 $\pm$ 0.004	0.068
	Wt(kg)	0.006 $\pm$ 0.003	0.05
	Duration(min)	0.005 $\pm$ 0.002	0.03
	MAC*		

*Patients receiving vecuronium did not have inhalational agents at any time.

Regression equations for stepwise models are: Atracurium TD_{95} ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) = 8.36 - 2.02 (MAC) - 0.028(age) $f = 30.82$ $P = 0.0002$. Vecuronium TD_{95} ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) = 1.59 - 0.009 (duration) - 0.006 (Wt) $f = 4.32$ $P = 0.02$.

$P = 0.0002$). The regression equation for this model is:

$$TD_{95} \text{ atracurium infusion} = 8.36 - 2.02 (\text{MAC}) - 0.028 (\text{age}) \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \quad f = 30.82 \quad P = 0.0002.$$

The vecuronium model found duration of infusion (coeff = 0.005 $\pm$ 0.002 $P < 0.05$) and weight of the patient (coeff 0.006 $\pm$ 0.003 $P = 0.05$) to be predictors of the rate of infusion. The regression equation for this model is:

$$TD_{95} \text{ vecuronium infusion} = 1.59 - 0.005(\text{duration}) - 0.006 (\text{wt}) \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \quad f = 4.32 \quad P < 0.05.$$

The end-tidal halothane and isoflurane levels were con-

verted to their respective MAC equivalents using previously published values.^{23,24} We compared the halothane and isoflurane data separately with the multivariate model using the age-adjusted MAC level to normalize the inhalation agent values. The coefficient for isoflurane was -1.96 $\pm$ 0.34 and the corresponding coefficient for halothane was -2.12 $\pm$ 0.22 $P = 0.56$. We therefore treated the two groups as the same in our multivariate model. Thus atracurium infusion rates were reduced about two micrograms for each additional MAC added to the anaesthetic.

Reversal of neuromuscular blockade

Pancuronium blockade was reversed from less twitch depression (85.6%) than the other four groups (95.3; 96.5; 94.0; and 95.7% respectively, ANOVA $P = 0.01$). Despite lower twitch depression, the pancuronium reversal T_1/T_{1c} (25-75%) took a mean of 7.06 $\pm$ 0.27 min which was longer than groups A1: 4.8 $\pm$ 0.21; A2: 50 $\pm$ 0.17; A3: 4.3 $\pm$ 0.23; and V: 3.7 $\pm$ 0.18 min respectively (ANOVA $P = 0.05$). The time for neuromuscular function to return to T_4/T_1 (0.8) after pancuronium block was 23.24 $\pm$ 28.8 min. The mean reversal times for all other groups were less than half of this (A1: 11.9 $\pm$ 0.84; A2: 10.46 $\pm$ 0.21; A3: 12.1 $\pm$ 0.56; and V: 12.3 $\pm$ 0.81 min respectively, ANOVA $P = 0.001$) (Table IV).

Multivariate analysis using forward stepwise regression modelling considered five factors: age, weight, duration of infusion, inhalational agent and the T_1/T_{1c} at the time of reversal on the reversal time ($T_4/T_1 = 0.8$) (Table V). The only significant predictor of reversal after atracurium

TABLE IV Characteristics of reversal: mean $\pm$ SD (range)

Study group	T_1/T_{1c} (% at reversal)	T_1/T_{1c} (25–75%) min	T_4/T_1 (5–80%) min	TD_{95} at reversal ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)
A1	4.7 $\pm$ 3.6 (1–10)	4.8 $\pm$ 2.1 (2.6–7.1)	11.9 $\pm$ 8.4 (4.1–30.5)	7.6 $\pm$ 1.1 (6–10)
A2	3.5 $\pm$ 1.3 (1–6)	5.0 $\pm$ 1.7 (2.1–7.6)	10.5 $\pm$ 2.1 (4.1–15.6)	4.7 $\pm$ 1.1 (2.9–7.0)
A3	6.0 $\pm$ 3.5 (3–12)	4.3 $\pm$ 2.3 (4.2–6.8)	12.1 $\pm$ 5.6 (8.3–23.3)	6.1 $\pm$ 1.4 (3.9–8.0)
V	4.3 $\pm$ 2.0 (1–8)	3.7 $\pm$ 1.8 (1–8)	12.3 $\pm$ 8.1 (4.9–31)	0.94 $\pm$ 0.23 (0.57–1.6)
P	14.4 $\pm$ 13.0 (4–45)*	7.1 $\pm$ 2.7 (2.8–11.8)‡	23.4 $\pm$ 28.8 (4.0–102)†	

T_1 = the first twitch in a train-of-four; T_{1c} = the control value for the EMG; T_4 = the fourth twitch in the train-of-four; * P = 0.01; † P = 0.001 (P compared with all other groups); ‡ P = 0.05 (P compared with V only).

TABLE V Multivariate analysis of predictors of reversal (Usefulness of age, wt, duration of infusion, T_1/T_{1c} (at time of reversal), and the inhalational agent to predict the reversal time. Reversal time is defined as the time in minutes to achieve $T_4/T_1 = 0.8$)

	Variable	Coeff + SD	P value
Atracurium	Age(yr)	0.136 $\pm$ 0.049	0.050
	Wt(kg)	−0.007 $\pm$ 0.061	0.904
	Duration(min)	0.006 $\pm$ 0.011	0.594
	t_1/t_c (%)	0.256 $\pm$ 2.06	0.230
	MAC	−0.111 $\pm$ 0.159	0.421
Vecuronium	Age(yr)	2.840 $\pm$ 0.051	0.001
	Wt(kg)	−0.042 $\pm$ 0.060	0.413
	Duration(min)	0.120 $\pm$ 0.180	0.002
	t_1/t_c (%)	0.441 $\pm$ 0.260	0.238

Regression coefficients are computed using analysis of variance: the regression equations are derived using a forward stepwise model where each variable must add to the predictive value $P = 0.05$. The regression equations are: (a) atracurium reversal (min) = $7.87 + 0.136$ (age) $f = 2.87$ $P = 0.05$; (b) vecuronium reversal (min) = $-7.25 + 0.284$ (age) + 0.12 (duration) $f = 18.01$ $P = 0.0002$.

infusion was age (coeff. = 0.136 ± 0.05 $P = 0.05$). The regression equation for the model was:

$$\text{Atracurium reversal time (min)} = 7.87 \pm 0.136 (\text{age}); \\ f = 2.87; P = 0.05.$$

The vecuronium model predicting reversal shows that age (coeff = 2.84 ± 0.51 $P = 0.0002$) and the duration of infusion (coeff = 0.12 ± 0.01 $P = 0.0001$) are the only significant variables in the model. The regression equation for the model is:

$$\text{Vecuronium reversal time (min)} = -7.25 + 0.284 (\text{age}) \\ + 0.12(\text{duration}); f = 18.01; P = 0.0002.$$

This model predicts that vecuronium blockade would be reversed faster than atracurium in procedures lasting less than three hours or in younger patients. However, in cases

lasting more than three hours, and in the elderly, atracurium blockade would be reversed faster than vecuronium.

Discussion

This study has shown that in tightly controlled conditions there is considerable variation in the infusion rate required to maintain 95% twitch depression ($T_1/T_{1c} = 0.05$). We have found that the dose of vecuronium required to maintain 95% twitch depression varies with the duration of infusion and the weight of the patient. Atracurium infusions were found to vary with age.

The mean doses for both atracurium and vecuronium were similar to doses reported by other investigators.^{10,12,13,17–22} The large variation that we report can be explained on the basis of the differential effect of age and the duration of the infusions. The variation with age of both atracurium²⁶ and vecuronium²⁷ have been previously reported but it has not been reported previously that the duration of infusion affects the infusion rate for vecuronium. This phenomenon may be explained on the basis of accumulation of an active metabolite. Three desacetyl-vecuronium has been shown to be such a metabolite²⁸ which is cleared more slowly than the parent compound.²⁹ A second explanation for the changing infusion rates for vecuronium and not atracurium may be longer elimination half-life or a larger volume of distribution for vecuronium.^{30,31}

Isoflurane and halothane have similar effects on atracurium dose requirements. The dose of atracurium is reduced by approximately $2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for every increment of 1 MAC. A similar potentiation has been documented for atracurium infusions when used in paediatric patients^{32,33} and with bolus dosing in adults.³⁴ The effect of inhalation agents on vecuronium infusion requirements has been previously reported.¹³

The second stage of this study found that profound

neuromuscular blockade achieved with infusions of intermediate acting agents, under a variety of anaesthetic conditions, can be reversed nearly two times faster than that maintained by the use of intermittent pancuronium boluses. The mean reversal time of pancuronium was 23.24 ± 28.8 mins. With this large variation, one hour after reversal the block will not be adequately reversed in 10% of patients. We eliminated other factors which might have potentiated pancuronium blockade. There were no antibiotics or inhalation agents used to delay the reversal further. The reversal times for pancuronium in common clinical situations may be longer. Our measure of reversal time is more strict than others, but the use of less strict criteria may be associated with a decreased ability to protect the airway even though patients can maintain normocapnia. None of the 75 patients in this study had any clinical signs of residual paralysis.

Atracurium and vecuronium block is reversed in a similar time. After steady state 95% twitch depression the mean reversal time is approximately 12 min. The multivariate regression models predicting reversal time for atracurium and vecuronium are different. Atracurium reversal is predicted on the basis of age. Using the regression equation derived from this study, a 25-yr-old subject would require 11.2 min to reverse an atracurium blockade; an 80-yr-old would require 18.6 min. The vecuronium model uses age and the duration of the infusion to predict recovery time. The mythical 25-yr-old after a two-hour infusion would require 13 min to recover from vecuronium blockade; if the infusion time were increased to four hours the 25-yr-old requires 28 min to recover from the neuromuscular block. If we now consider the 80-yr-old with a two-hour infusion the model predicts a reversal time of 29 min.

A recent study indicated³⁵ that, after long and short infusions of these drugs, the spontaneous recovery of either was not significantly different. However, several differences in the study design are apparent; first the level of block was less (twitch depression was 90%); second, all patients were allowed to recover to some extent before reversal, and neuromuscular blockade was antagonised with edrophonium. Finally, the age of the subjects was not reported. The study we report was not designed to test kinetics or dynamics. The prediction models of reversal time are consistent with both the accumulation of an active metabolite or decreased organ clearance of the drug. Further, the accumulation of an active metabolite could explain the time-related decrease of infusion rates with time. Previous studies have indicated there may be potential difficulty reversing vecuronium in the elderly.¹⁰

The finding of prolonged recovery with prolonged infusions and in the elderly has clinical importance since

these patients are often those who manifest postoperative complications.³⁶

Conclusion

Infusions of atracurium and vecuronium can offer a stable degree of twitch depression for long surgical procedures. Atracurium reached a constant infusion rate quickly, whereas some patients having vecuronium infusions never maintained steady states for more than 15 min. Inhalation agents reduced the infusion requirements in a dose-dependent manner, but the addition of a potent inhalational agent did not affect the recovery times when compared to a nitrous/narcotic technique. The steady state infusions of atracurium and vecuronium were reversed in about half the time of intermittently administered pancuronium. A multivariate model predicting reversal of the former agents after infusion shows age to be important for both atracurium and vecuronium. The duration of vecuronium infusion also predicts reversal time.

Using the continuous infusion technique, twitch depression can be maintained, and then safely reversed in less than 20 min for most patients.

References

- 1 Beecher HI, Todd DP. A study of deaths associated with anesthesia and surgery based on a study of 599,548 anaesthetics in 10 institutions, 1948–1953 inclusive. *Ann Surg* 1954; 50: 2–34.
- 2 Lunn JN, Mushin WW. Mortality associated with anaesthesia. *Anaesthesia* 1982; 37: 856–9.
- 3 Viby-Mogensen J, Jensen NH, Engbaek J. Tactile and visual evaluation of the response to train-of-four nerve stimulation. *Anesthesiology* 1985; 63: 440–3.
- 4 Pavlin EG, Holle RH, Schoene RB. Recovery of airway protection compared with ventilation in humans after paralysis with curare. *Anesthesiology* 1989; 70: 381–5.
- 5 Sharpe MD, Lam AM, Nicholas JF, et al. Correlation between integrated evoked EMG and respiratory function following atracurium administration in unanaesthetized humans. *Can J Anaesth* 1990; 37: 307–12.
- 6 Viby-Mogensen J, Jorgensen BC, Ording H. Residual curarization in the recovery room. *Anesthesiology* 1979; 50: 539–41.
- 7 Bremer GH, Rosental P. Post operative neuromuscular function. *Anesth Intensive Care* 1986; 14: 41–5.
- 8 Bevan DR, Smith CE, Donati F. Postoperative neuromuscular blockade: A comparison between atracurium, vecuronium, and pancuronium. *Anesthesiology* 1988; 69: 272–6.
- 9 Brull SJ, Silverman DG, Ehrenwerth J. Problems of recovery and residual neuromuscular blockade: pancuronium vs. vecuronium. *Anesthesiology* 1988; 69: A473.

- 10 Kopman AF. Recovery times following edrophonium and neostigmine reversal of pancuronium, atracurium, and vecuronium steady-state infusions. *Anesthesiology* 1986; 65: 572–8.
- 11 Delisle S, Bevan DR. Impaired neostigmine antagonism of pancuronium during enflurane anaesthesia in man. *Br J Anaesthesia* 1982; 54: 441–5.
- 12 Dernovoi B, Agoston S, Barvais L, Baurain M, Lefebvre R, D'Hollander A. Neostigmism antagonism of vecuronium paralysis during fentanyl, halothane, and enflurane anaesthesia. *Anesthesiology* 1987; 66: 698–701.
- 13 Swen J, Gencarelli PJ, Koot HWJ. Vecuronium infusion dose requirements during fentanyl and halothane anaesthesia in humans. *Anesth Analg* 1985; 64: 411–4.
- 14 Cannon JE, Fahey MR, Castagnoli KP, *et al.* Continuous infusion of vecuronium: the effect of anaesthetic agent. *Anesthesiology* 1987; 67: 503–6.
- 15 Ali HH, Savarese JJ, Lebowitz PW, Ramsey FM. Twitch, tetanus, and train of four as indices of recovery from nondepolarizing neuromuscular blockade. *Anesthesiology* 1981; 54: 570–3.
- 16 Kopman AF. The relationship of evoked electromyographic and mechanical responses following atracurium in humans. *Anesthesiology* 1985; 63: 208–11.
- 17 Noeldge G, Hinsken H, Buzello W. Comparison between the continuous infusion of vecuronium and the intermittent administration of pancuronium and vecuronium. *Br J Anaesth* 1984; 56: 473–7.
- 18 Gramstad L, Lilleaasen P. Neuromuscular blocking effects of atracurium, vecuronium and pancuronium during bolus and infusion administration. *Br J Anaesth* 1985; 57: 1052–9.
- 19 Eager BM, Flynn P, Hughes R. Infusion of Atracurium for Long Surgical Procedures. *Br J Anaesthesia* 1984; 56: 447–51.
- 20 D'Hollander A, Czeruki R, DeVille A, Cuvelier F. Stable muscle relaxation during abdominal surgery using combined intravenous bolus and demand infusion: clinical appraisal of Org NC45. *Can Anaesth Soc J* 1982; 29: 136–41.
- 21 Fierro G, Trobbaini G, Sanfilippo M, Vilardi V, Favaro V, Menichetti A. Continuous infusion of vecuronium. *Acta Anaesthetica Italica* 1989; S1: 43–50.
- 22 Rowlands DE. Simple atracurium infusions. *Br J Anaesth* 1985; 51: 542.
- 23 Gregory GA, Eger EI, Munson LS. The relationship between age and halothane requirement in man. *Anesthesiology* 1969; 30: 488–91.
- 24 Stevens WC, Dolan WM, Gibbons RT, *et al.* Minimum alveolar concentrations (MAC) of isoflurane with and without nitrous oxide in patients of various ages. *Anesthesiology* 1975; 42: 197–200.
- 25 Donati F, Smith CE, Bevan DR. Dose-response relationships for edrophonium and neostigmine as antagonists of atracurium and vecuronium neuromuscular blockade. *Anesthesiology* 1989; 71: 37–43.
- 26 Beattie WS, Buckley DN, Deguzman C, Hewson JR, Forrest JB. The effect of age on the duration of block produced by bolus atracurium. *Can J Anaesth* 1988; 35: S118–9.
- 27 D'Hollander A, Massaux F, Nevelsteen M, Agoston S. Age-dependent dose-response relationship of ORG NC45 in anaesthetized patients. *Br J Anaesth* 1982; 54: 653–7.
- 28 Marshall IG, Gibb AJ, Durant NN. Neuromuscular and vagal blocking actions of pancuronium bromide, its metabolites, and vecuronium bromide (ORG NC 45) and its potential metabolites in the anaesthetized cat. *Br J Anaesth* 1983; 55: 703–14.
- 29 Segredo V, Matthay MA, Sharma ML, Gruenke LD, Caldwell JE, Miller RD. Prolonged neuromuscular blockade after long-term administration of vecuronium in two critically ill patients. *Anesthesiology* 1990; 72: 566–70.
- 30 Cronnelly R, Fisher D, Miller RD, Gencarelli P, Ngugen-Gruenka L, Catagnoli N. Pharmacokinetic and pharmacodynamics of vecuronium (ORG nc 45) and pancuronium in anesthetized humans. *Anesthesiology* 1983; 58: 405–8.
- 31 Ward S, Wright D. Combined pharmacodynamic and pharmacokinetic study of single bolus atracurium. *Br J Anaesth* 1983; 55: 35S–38S.
- 32 Brandom BW, Cook DR, Woelfel SK, Rudd GD, Fehr B, Lineberry CG. Atracurium infusion requirements in children during halothane, isoflurane, and narcotic anaesthesia. *Anesth Analg* 1985; 64: 471–6.
- 33 Goudsouzian E, Martyn J, Rudd GD, Liu LMP, Lineberry CG. Continuous infusion of atracurium in children. *Anaesthesiology* 1986; 64: 171–4.
- 34 Rupp S, Fahey A, Miller RD. Neuromuscular effects of atracurium during halothane nitrous oxide and enflurane nitrous oxide anaesthesia in humans. *Anesthesiology*, 1985; 63: 16–9.
- 35 Ratcliff A, LawMin JC, Donati F, Bevan DR. Neuromuscular recovery following short and long infusions of atracurium and vecuronium. *Can J Anaesth* 1990; 38: A128.
- 36 Forrest JB, Cahalan MK, Rehder K, *et al.* Multicenter Study of General Anaesthesia. II, Results. *Anesthesiology* 1990; 72: 262–8.