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A comparison of the infusion pharmacokinetics and pharmacodynamics of cisatracurium, the 1R-*cis* 1′R-*cis* isomer of atracurium, with atracurium besylate in healthy patients

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Summary

We have compared the pharmacokinetics of cisatracurium with atracurium when given by bolus dose followed by continuous infusion. Twenty healthy patients were anaesthetised with thiopentone, midazolam, fentanyl and 70% nitrous oxide in oxygen. Ten patients (Group C) were randomly allocated to receive cisatracurium 0.1 mg.kg^{-1} and 10 patients (Group A) were given atracurium 0.5 mg.kg^{-1}. Neuromuscular block was monitored using a mechanomyograph. When the first twitch of the train-of-four had recovered to 5% of control, an infusion of cisatracurium 3 μg.kg^{-1}.min^{-1} was started in Group C and an infusion of atracurium 10 μg.kg^{-1}.min^{-1} was started in Group A. The infusion rates were adjusted to maintain the first twitch of the train-of-four at 5% of control. The times to 90% and maximum depression of the first twitch of the train-of-four were significantly longer after cisatracurium than atracurium (2.2 and 3.4 min compared with 1.3 and 1.8 min, respectively; $p < 0.01$ in each instance). No significant differences were found in recovery parameters between the two groups. Blood samples were taken at regular intervals following the bolus, during the infusion and for 8 h thereafter. The plasma samples were analysed using high-performance liquid chromatography for cisatracurium and atracurium (using a method which distinguishes between the three geometric isomer groups), laudanosine and monoquaternary alcohol. The results were analysed using the Non-linear Mixed Effects Model program. A two-compartment model was fitted to the data. The different isomer groups of atracurium have different pharmacokinetics, the *trans–trans* group having the highest clearance (1440 ml.min^{-1}) and the *cis–cis* group the lowest (499 ml.min^{-1}). The clearance of cisatracurium (425 ml.min^{-1}) is less than that of *cis–cis* atracurium and its elimination half-life is longer (34.9 min and 21.9 min, respectively). The plasma concentration of laudanosine after cisatracurium was one-fifth of that after atracurium.

Keywords *Neuromuscular relaxants*; cisatracurium, atracurium. *Pharmacokinetics. Pharmacodynamics. Metabolism.*

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The neuromuscular blocking agent atracurium besylate consists of three groups of geometric isomers: three *cis–cis*, four *cis–trans* and three *trans–trans* [1]. The properties of each of the isomers have been studied to determine whether any possess fewer side-effects than the parent drug. One of the *cis–cis* isomers, cisatracurium (51W89: 1R-*cis* 1′R-*cis* atracurium) makes up 15% of atracurium [2]. This isomer was found to stimulate less histamine release in cats than atracurium [2]. It is also more selective for the postjunctional nicotinic receptor and thus has less autonomic effect [2]. Cisatracurium is about five times as potent as atracurium (effective dose producing 95% twitch depression (ED_{95}) = 0.05 mg.kg^{-1} [3] and 0.22 mg.kg^{-1} [4], respectively, during neuroleptanaesthesia) and thus a

lower dose is required to produce neuromuscular block. Its use might be expected to produce lower plasma metabolite levels, including laudanosine, a product of Hofmann degradation which is epileptogenic in animals [5].

The purpose of this study was to determine the pharmacokinetics of cisatracurium in healthy patients in comparison with the three isomer groups of atracurium and to study the resulting plasma metabolite concentrations, particularly laudanosine and the product of ester hydrolysis, monoquaternary alcohol. The study also compares the pharmacodynamics of the two neuromuscular blocking agents when given by bolus dose followed by continuous infusion.

Methods

This randomised study was approved by the Committee of Safety of Medicines and the Ethics Committee of the Royal Liverpool University Hospital. Written informed consent was obtained from 20 healthy patients scheduled for elective operations in the following disciplines: general surgery, ophthalmology and major otorhinolaryngology. The patients were over 18 years of age. Females in whom pregnancy could not be excluded or who were breast feeding were not studied. Other exclusion criteria included a personal or family history of malignant hyperthermia, hypersensitivity to neuromuscular blocking agents, alcoholism or drug addiction, psychiatric, neuromuscular, cardiovascular, renal or hepatic impairment and asthma. In addition, patients were not studied if they were receiving or had recently taken any antibiotics (except the penicillins, cephalosporins and tetracyclines), lignocaine, quinidine, procainamide, antidepressants (except selective serotonin re-uptake inhibitors), phenytoin, carbamazepine or antihistamines.

A clinical history and examination were conducted on each patient and a blood sample was taken for haemoglobin, platelet count, white cell count, serum creatinine, alkaline phosphatase and alanine aminotransferase. The weight and height of each patient was recorded.

Anaesthesia

Each patient was premedicated with diazepam 5–10 mg orally 2 h before anaesthesia. Anaesthesia was induced with midazolam 50–100 $\mu g.kg^{-1}$, fentanyl 2–8 $\mu g.kg^{-1}$ and thiopentone 4–8 $mg.kg^{-1}$ and was maintained with further increments of these drugs and 70% nitrous oxide in oxygen. Monitoring included noninvasive blood pressure measurement, ECG, pulse oximetry, capnography and inspired nitrous oxide and oxygen concentrations.

Neuromuscular monitoring

This was instituted using a mechanomyograph (Myograph, Biometer). The skin over the ulnar nerve near the wrist was cleaned with alcohol and two stimulating electrodes were applied. The position of the thumb connected to the force transducer was adjusted to obtain a stable trace. A continuous recording of the force of contraction of adductor pollicis in response to supramaximal train-of-four (TOF) stimulation, applied to the ulnar nerve every 12 s, was obtained over at least 3 min to establish baseline values. The monitored arm was wrapped in cotton wool to keep it warm.

The neuromuscular blocking drug to be given was selected, in order of patient presentation, from a predetermined randomised sequence. The study was not blinded. The drug was injected into a freely running intravenous infusion in the opposite arm from that used for neuromuscular monitoring. Patients in Group C received cisatracurium 0.1 $mg.kg^{-1}$ ($2 \times ED_{95}$) and those in Group A received atracurium besylate 0.5 $mg.kg^{-1}$. On the return of the first twitch of the TOF (T_1) to 5% of control (i.e. $T_1/T_0 = 5\%$), an infusion of neuromuscular blocking agent was started; cisatracurium 3 $\mu g.kg^{-1}.min^{-1}$ in the patients in Group C and atracurium 10 $\mu g.kg^{-1}.min^{-1}$ in Group A. The infusion rates were adjusted at 3-min intervals to maintain T_1/T_0 between 1 and 9%. At the end of surgery, spontaneous recovery was allowed to occur. No anticholinesterase was given. Neuromuscular monitoring was continued until at least 80% recovery of T_1/T_0.

The trace was analysed to determine times to 90%, 95% and maximum depression of T_1/T_0 and the maximum depression attained. The times to 5% recovery of T_1/T_0 following the bolus dose of neuromuscular blocking agent and, following the cessation of the infusion, the times to 25% recovery of T_1/T_0, the recovery index (the time from 25% to 75% recovery of T_1/T_0) and the time to recovery of the TOF ratio (the ratio of the fourth to the first twitch of the train-of-four) to 0.7 were noted. The pharmacodynamic variables for cisatracurium were compared to those for atracurium using the Mann–Whitney *U*-test.

Blood sampling

A baseline blood sample (5 ml) was taken from a cannula inserted into a vein in the monitored arm before the bolus dose of neuromuscular blocking agent was given. Blood samples were then taken at predetermined intervals (2, 4, 6, 10, 20, 30, 45 and 60 min) or until the return of T_1/T_0 to 5%.

Once T_1/T_0 had reached 5%, a pre-infusion blood sample was taken. Blood samples were then taken every 15 min during the infusion. At the end of surgery, a blood sample was taken and the infusion was stopped. Spontaneous recovery was allowed to occur. Further blood samples were taken at predetermined intervals following the termination of the infusion (2, 5, 10, 20, 30, 45, 60, 90, 120, 150, 180, 240, 360 and 480 min).

Each 5-ml blood sample was immediately added to a lithium heparin tube and centrifuged at 20 000*g* for 30 s. Plasma (2 ml) was transferred to a plain polypropylene tube containing 8 ml of 0.015 M sulphuric acid. The sample was deep frozen within 30 min of the blood sample being taken.

The plasma samples were analysed using high-performance liquid chromatography (HPLC) with fluorescence detection [6]. All the samples were analysed for atracurium using an assay which separates the three geometric isomer groups: *cis–cis*, *cis–trans* and *trans–trans*. Thus samples from patients in Group C were analysed for cisatracurium and samples from patients in Group A were analysed for the three isomer groups. In addition, all samples were analysed for laudanosine and monoquaternary alcohol. The coefficient of variation of the interassay estimates for cisatracurium was 5.8% for atracurium: *cis–cis* 3.9%, *cis–trans* 3.3% and *trans–trans* 10.3%, for laudanosine 4.5% and for monoquaternary alcohol 8.7%. There was very little difference in the coefficients of variation for each drug across the assay range, e.g. at cisatracurium concentrations of 20, 200 and 2000 ng.ml^{-1}. The lower limit of quantification of each method was 10 ng.ml^{-1}. The concentration of the administered cisatracurium was 109.9% of that stated on the vial (2 mg.ml^{-1}). For atracurium, the isomer group proportions were *cis–cis* 57.0%, *cis–trans* 36.7% and *trans–trans* 6.3%.

The patients were interviewed on the day after surgery. They were questioned about any postoperative problems and were examined clinically. A further blood sample was taken to repeat all the tests performed pre-operatively. The demographic data on the patients in the two groups were compared using the Mann–Whitney *U*-test.

Pharmacokinetic analysis

A two-compartment model was fitted to the plasma concentration data (for the parent drug) using the Nonlinear Mixed Effects Model (NONMEM) program [7]. This program analyses the data from all the patients and estimates the population mean for each pharmacokinetic variable and also its random variability within the population. The influence of factors such as weight and age is assessed by the contribution they make to the fit of the model to the data. All model fitting was conducted using standard open models; no attempt was made to take account of the destruction of atracurium outside the central compartment. Pharmacokinetic model selection is guided by the NONMEM objective function which is a measure of the extent to which the model fits the data. In this respect, it is analogous to the sum of squares in ordinary least squares regression. It is defined as minus twice the logarithm of the likelihood of the data, conditional upon the fitted model. The maximum likelihood criterion finds a model which maximises the likelihood of obtaining the data which was actually obtained. Inclusion of a parameter in the model is statistically justified at the $p < 0.005$ level if its inclusion results in a fall in the objective function of 7.9 or greater.

For the majority of the analyses, the two-compartment model was parameterised in terms of the clearance, the central (V_1) and peripheral (V_2) volumes of distribution and the intercompartmental clearance (Q), where $Q = V_1.k_{12} = V_2.k_{21}$. To determine the distribution and elimination half-lives, additional NONMEM runs were performed with the model parameterised in terms of V_1, the redistribution half-life ($t_{½\alpha}$), elimination half-life ($t_{½\beta}$) and the ratio of the intercepts of the distribution and elimination phases (A/B).

Table 1 Physical characteristics of the two groups of patients. Values are given as mean (SD) [range]. No statistically significant differences were found between the two groups.

	Group C Cisatracurium	Group A Atracurium
Sex; M: F	4: 6	5: 5
Age; years	50 (11) [27–64]	39 (15) [21–65]
Weight; kg	66 (8) [55–77]	77 (14) [60–108]
Height; cm	167 (7) [155–175]	173 (9) [157–188]

Results

The physical characteristics of the 20 patients are given in Table 1. There were no significant differences between the two groups. The results of all the pre- and postoperative blood tests were within the normal range. The mean (range) total infusion dose of cisatracurium was 7.9 mg (3.75–14.5 mg) and of atracurium was 21.5 mg (7.5–48.1 mg). The mean (range) duration of the infusion in Group C was 79.2 min (48–150 min) and in Group A was 92.4 min (48–204 min). The mean (range) number of infusion changes in Group C was 2.4 (1–4) and in Group A was 2.4 (1–8).

Pharmacodynamics

Table 2 shows the pharmacodynamic variables for the two groups of patients. Time to 90% and 95% depression of T_1/T_0 was significantly longer after cisatracurium than after atracurium (2.3 vs. 1.3 min and 2.4 vs. 1.5 min, respectively: $p < 0.01$) as was the time to maximum depression (3.6 vs. 1.8 min: $p < 0.01$). The maximum depression of T_1/T_0 achieved in all the patients was 100%. There was no significant difference in the time to 5% recovery of T_1/T_0 following the bolus dose of neuromuscular blocking agent (Group C: 37.1 min, Group A:

Table 2 Mean onset and recovery variables for the two groups of patients. Values are given as mean (SD) [range].

	Group C Cisatracurium	Group A Atracurium
Onset		
Time to 90% depression of T_1/T_0; min	2.3 (0.4) [1.7–2.7]	1.3 (0.2) [0.8–1.6]*
Time to 95% depression of T_1/T_0; min	2.4 (0.4) [1.7–2.9]	1.5 (0.3) [0.8–1.8]*
Time to maximum depression of T_1/T_0; min	3.6 (0.9) [2.1–5.0]	1.8 (0.4) [1.0–2.3]*
Maximum depression of T_1/T_0; %	100	100
Recovery after bolus		
Time to 5% recovery of T_1/T_0; min	37.1 (5.9) [29.7–44.0]	41.6 (5.9) [36.0–52.0]
During infusion		
Minimum depression of T_1/T_0; %	90 (4.0) [85–96]	85 (8.0) [67–93]
Maximum depression of T_1/T_0; %	98 (1.0) [96–100]	97 (2.0) [94–100]
Recovery after infusion		
Time to 25% recovery of T_1/T_0; min	16.3 (10.1) [6.5–42.5]	14.2 (11.0) [0.0–37.2]
Recovery index: (25–75%); min	15.9 (5.2) [10.0–25.7]	17.3 (6.9) [11.6–43.9]
Time to TOF ratio = 0.7; min	40.7 (14.1) [27.8–76.4]	40.0 (17.0) [23.1–79.2]

* $p < 0.01$.

41.6 min). The mean (SD) T_1/T_0 on starting the infusion was 5.8 (2.8)% in Group C and 6.5 (1.7)% in Group A. The mean depression of T_1/T_0 during the infusion was 95.4% in Group C and 92.5% in Group A. Following the termination of the infusion, there were no differences between Groups C and A in the time to 25% recovery of T_1/T_0 (16.3 min vs. 14.2 min), the recovery index (15.9 min vs. 17.3 min) or the time for the TOF ratio to reach 0.7 (40.7 min vs. 40.0 min).

Plasma levels

Figures 1 and 2 show the decay in mean plasma cisatracurium levels compared with the concentrations of the three groups of isomers of atracurium on stopping the infusion.

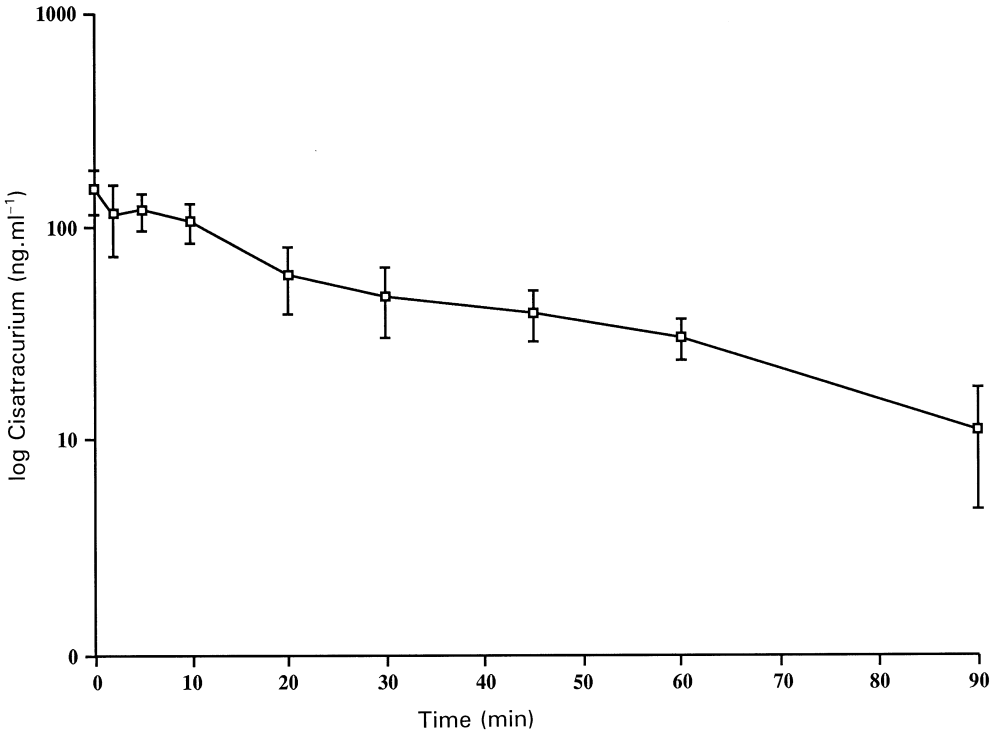

Figure 1 Mean plasma cisatracurium concentrations after stopping the infusion at time zero. Error bars indicate 95% confidence intervals.

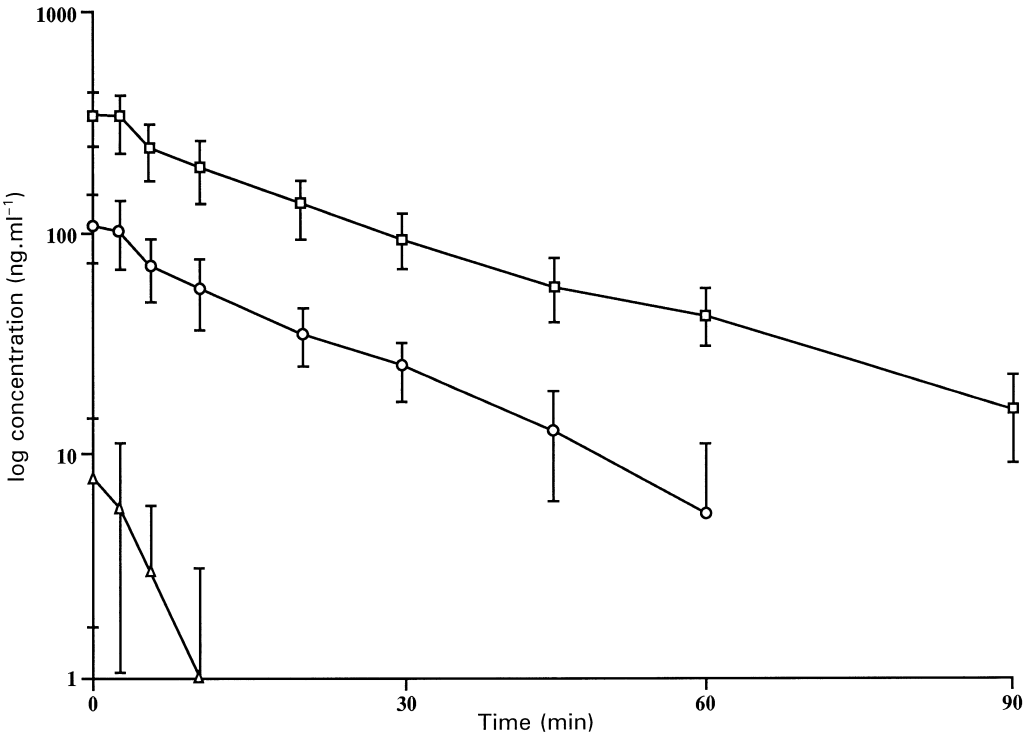

Figure 2 Mean plasma concentrations of the *cis–cis* (□), *cis–trans* (○) and *trans–trans* (△) isomer groups of atracurium after stopping the infusion at time zero. The last data point for the *cis–cis* isomer is from eight patients and the last data point for *cis–trans* atracurium is from seven patients. Error bars indicate 95% confidence intervals.

The plasma concentrations of cisatracurium were consistently lower than those of the *cis–cis* isomer group of atracurium and higher than the *cis–trans* and *trans–trans* groups. Cisatracurium was detectable in plasma for up to 150 min after stopping the infusion and the *cis–cis* group of isomers of atracurium was detectable for up to 120 min.

Figures 3 and 4 show the mean plasma concentrations of laudanosine and monoquaternary alcohol in Groups C and A on stopping the infusion of neuromuscular blocking drug. The plasma levels of each metabolite are up to five times higher after atracurium than after cisatracurium. The mean plasma laudanosine level 8 h after infusion was only 5 ng.ml^{-1} after cisatracurium compared with 70 ng.ml^{-1} after atracurium.

Pharmacokinetic analysis

A two-compartment model was preferred to a one-compartment model for all data sets as shown by a large reduction in the objective function with the two-compartment as opposed to the one-compartment model (cisatracurium improved by 383, *trans–trans* atracurium improved by 81.5, *cis–trans* atracurium improved by 221, *cis–cis* atracurium improved by 215). Normalisation of volume terms according to weight worsened the fit of the two-compartment model to the data in patients given cisatracurium (the objective function was worsened by 16) and produced minor changes in the model for the three isomer groups in Group A (*trans–trans* improved by 4.7, *cis–trans* by 6.2 and *cis–cis* worsened by 0.5). For this reason, and in keeping with previous work, we did not adjust the volume terms for body weight

The calculated pharmacokinetic parameters are shown in Table 3. The clearance of cisatracurium was similar to that of the *cis–cis* atracurium isomer group but very much less than that of the other two isomer groups. Other parameters were similar between cisatracurium and the *cis–cis* atracurium group, except that the elimination half-life ($t_{½\beta}$) for cisatracurium (34.9 min) was longer than that of any of the isomer groups of atracurium.

The effect of age on each parameter was tested. For cisatracurium, the incorporation of a parameter to account for the effect of age on clearance produced a reduction in the objective function of 35 ($p < 0.005$). The effect of age on the mean clearance (SEM) of cisatracurium may be expressed:

$$\text{Clearance} = 702\ (37)\ \text{ml.min}^{-1} - 5.33\ (0.57)\ \text{ml.min}^{-1}.\ \text{year}^{-1}.$$

No effect of age was found on any of the pharmacokinetic parameters for any of the isomer groups in the

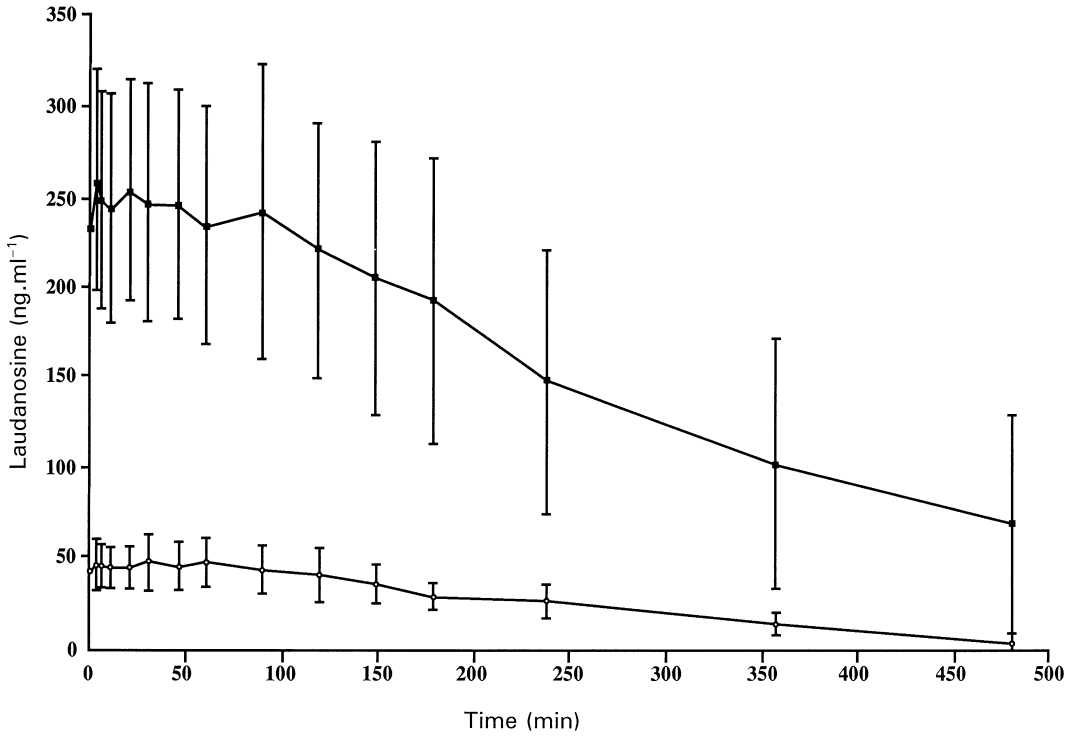

Figure 3 Mean plasma laudanosine concentrations in Groups C (cisatracurium) (○) and A (atracurium) (■) after stopping the infusion at time zero. Error bars indicate 95% confidence intervals.

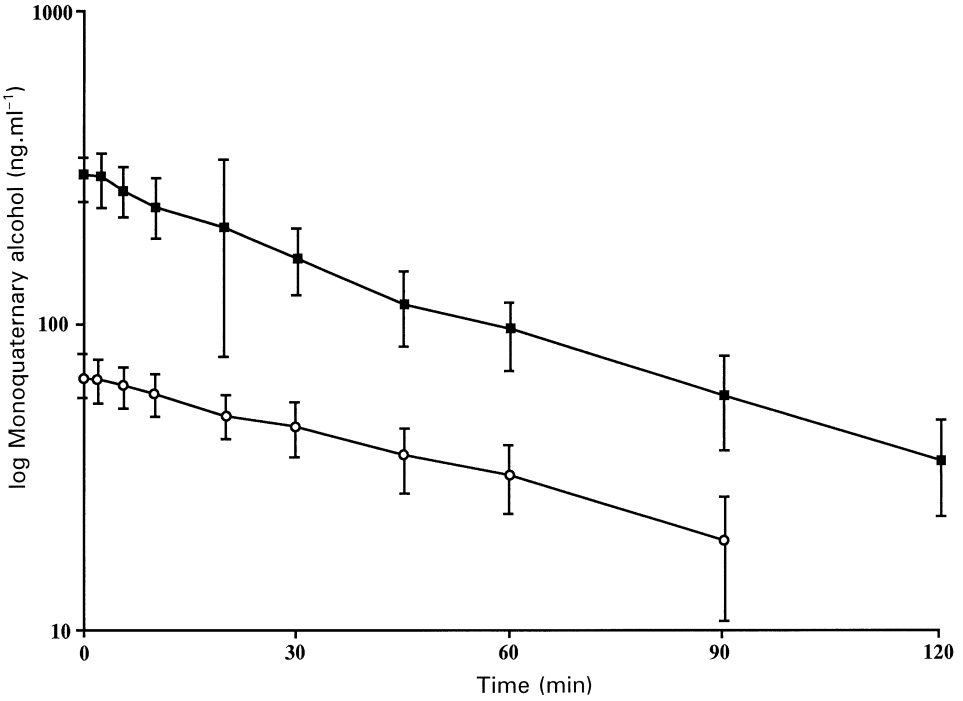

Figure 4 Mean plasma monoquaternary alcohol concentrations in Group C (cisatracurium) (○) and A (atracurium) (■) on stopping the infusion of each neuromuscular blocking drug. Error bars indicate 95% confidence intervals.

Table 3 Pharmacokinetic variables for cisatracurium (Group C) and for the three groups of geometric isomers of atracurium (Group A). Values given are mean (SEM).

	Group C	Group A: Atracurium		
	Cisatracurium	*cis–cis*	*cis–trans*	*trans–trans*
Clearance; ml.min^{-1}	425 (17.9)	499 (35.1)	996 (88)	1440 (112)
V_1; ml	7220 (292)	7190 (994)	9330 (1310)	8410 (1090)
V_2; ml	6450 (433)	4400 (752)	8480 (698)	9020 (1270)
Q; ml.min^{-1}	234 (27.5)	277 (105)	737 (107)	771 (92.1)
$t_{½\alpha}$; min	6.4 (0.5)	4.3 (1.2)	2.5 (0.2)	1.9 (0.2)
$t_{½\beta}$; min	34.9 (1.3)	21.9 (1.1)	18.1 (0.7)	15.0 (2.3)

V_1 Central volume of distribution; V_2 Peripheral volume of distribution; Q Intercompartmental clearance; $t_{½\alpha}$ Redistribution half-life; $t_{½\beta}$ Elimination half-life.

patients who received atracurium (Group A), nor was sex found to affect any of the pharmacokinetic parameters in either group.

Discussion

The introduction of atracurium in 1982 was a major advance in anaesthesia. For the first time, a nondepolarising neuromuscular blocking agent which did not depend on renal or hepatic function for its disposition was available. However, atracurium is known to cause histamine release, especially if a large dose is given rapidly [8]. In addition, its use by continuous infusion in critically ill patients on an intensive care unit can lead to the accumulation of the epileptogenic product of Hofmann elimination, laudanosine [9]. Attention therefore focused on the properties of the 10 isomers of atracurium, to determine if any had advantages over commercially available atracurium. The *cis–cis* isomers are thought to release less histamine than the *trans–trans* isomers and to have a longer duration of action [2]. The 1R-*cis* 1′R-*cis* isomer, cisatracurium (51W89), was selected for clinical study.

Cisatracurium is up to five times as potent as atracurium so a smaller dose of the drug is used. After $2 \times ED_{95}$ (0.1 mg.kg^{-1}), its onset time is significantly longer than after atracurium 0.4 mg.kg^{-1} (time to maximum depression of $T_1 = 7.7$ min vs. 6.2 min, respectively) [10]. This difference may be related to the greater potency of the new agent. It has been suggested that drugs of lower potency, given in a larger dose, will have a more rapid onset of effect [11]. In contrast, recovery times for cisatracurium and atracurium were similar in this study, although Boyd *et al.* reported significantly longer recovery times after a bolus dose of cisatracurium 0.1 mg.kg^{-1} compared with atracurium 0.4 mg.kg^{-1} [10]. In addition, the postinfusion recovery variables after cisatracurium were shorter than those reported in a potency study after a single bolus dose of cisatracurium 0.1 mg.kg^{-1} [12]; neuroleptanaesthesia was used in both investigations. This is strong evidence of lack of any cumulative property of this drug.

This study calculated pharmacokinetic variables for the three geometric isomer groups of atracurium. To our knowledge, only one paper has provided pharmacokinetic information on the *cis–cis* and *cis–trans* isomer groups of atracurium in healthy subjects (data on the *trans–trans* groups was not included due to the rapid elimination of this isomer *in vivo* as demonstrated in Fig. 2 [13]). The pharmacokinetic results for the *cis–cis* and *cis–trans* groups in these two studies were comparable.

The present study demonstrates that the clearance of cisatracurium is similar to that of the three *cis–cis* isomers of atracurium but much less than the values for the *cis–trans* or *trans–trans* groups (Table 3). The central volume of distribution (V_1) and intercompartmental clearance (Q) were similar for cisatracurium and the *cis–cis* isomer group of atracurium but less than those for the other isomer groups. The elimination half-life ($t_{½\beta}$) of cisatracurium was, however, significantly longer than that of any of the isomer groups (34.9 min vs. 21.9, 18.1 and 15.0 min for *cis–cis*, *cis–trans* and *trans–trans* atracurium, respectively). It is also markedly longer than that reported for atracurium in healthy patients (20.1 min) [14]. Despite the dynamic findings of this study, it may be expected that recovery would be longer after cisatracurium than after atracurium. Nevertheless, as with atracurium, Hofmann elimination of this new drug may still be expected to occur. Indeed, *in vitro* work on human plasma suggests that ester hydrolysis is relatively less important for cisatracurium than for atracurium [6, 15]. Conversely, therefore, Hofmann degradation may be the predominant route for elimination of cisatracurium.

In this study the mean values for the volume of the peripheral compartment (V_2) for cisatracurium, *cis–cis* and *cis–trans* atracurium were smaller than the values for the central compartment (V_1). In contrast, in our previous pharmacokinetic study of a bolus dose of cisatracurium 0.1 mg.kg^{-1}, the value for V_2 was, as usual with neuromuscular blocking drugs, somewhat higher than V_1 [16]. We cannot explain this discrepancy. Unlike some pharmacokinetic studies of atracurium [17], we did not take

account of the peripheral destruction of cisatracurium as we believe that this cannot be estimated satisfactorily, even if additional measurements are made [18]. As a result, if anything, we have underestimated V_2.

The higher clearance of cisatracurium reported in this study (425 ml.min^{-1}) compared with our previous report (293 ml.min^{-1}) [16] is also difficult to explain. It is unlikely to be due to a real variation in patient groups. The surgical operations did vary between these two studies but the ranges of age, weight and sex distribution were similar. In addition, a similar anaesthetic technique (neurolept-anaesthesia) was used in both studies. All the plasma samples were prepared and stored in an identical manner to that used in our previous kinetic studies of atracurium and cisatracurium and all the assays reported in this study were performed in the same laboratory. The only salient difference between the two studies is the design of the dose regime. In the earlier study, a bolus dose of cisatracurium was given, in the later one a bolus followed by an infusion was used. This should not affect the results, as the model fitting process takes account of the dosage regime in each individual. However, the relationship between parameter values and measured concentrations is not linear; there is a risk of bias in the regression estimates. Interestingly, limited series of simulated data arising from the model under two dosage regimens, allowing 50% random variability in each parameter and a 10% random measurement error, produced lower clearance values in the bolus study. This may not be the explanation for the discrepancy but is certainly a matter for further study. As dose-independent kinetics have already been demonstrated for both atracurium [19] and cisatracurium [20], we would be reluctant to suggest, as an explanation of these findings, that the kinetics of cisatracurium were nonlinear. Although different from the values we reported previously, our estimates of clearance are comparable with those noted more recently after a bolus of $2 \times ED_{95}$ of cisatracurium [20].

After the termination of the infusion of cisatracurium, the plasma concentrations of monoquaternary alcohol which, with monoquaternary acid, is a product of ester hydrolysis of atracurium, were between 3 and 4.5 times lower than following the termination of the atracurium infusion (Fig. 4). This finding would substantiate the *in vitro* results [6]. Monoquaternay alcohol is not known to have any toxic effects. More interestingly, the mean plasma level of laudanosine at the point of termination of the infusions is five times lower following cisatracurium than after atracurium. This difference could be due to the lower mass of drug given but there may be other explanations. Laudanosine is formed both from atracurium and other metabolites. It is thus generated from substrates whose total concentration varies in a complex way over time. Furthermore, the parent drug, laudanosine and the intermediate metabolites of ester hydrolysis, which also break down to form laudanosine, are all subject to redistribution. The time course of the plasma concentration of laudanosine is therefore very complicated. Detailed explanation of any differences in the time course of plasma laudanosine between atracurium and cisatracurium awaits further investigation.

The lower plasma levels of laudanosine indicate a potential advantage for the use of cisatracurium over atracurium, especially if the drug is needed by constant infusion in the critically ill patient. It must not, however, be forgotten that the onset time of the newer drug may be slightly longer than atracurium and its elimination half-life is somewhat greater.

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