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Pharmacokinetics and Neuromuscular Blocking Effects of Atracurium Besylate and Two of Its Metabolites in Patients with Normal and Impaired Renal Function

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Summary

The pharmacokinetics of atracurium, laudanosine and the quaternary alcohol were studied in patients with normal and impaired renal function following intravenous administration of atracurium. Anaesthesia consisted of thiopental, fentanyl, halothane and nitrous oxide in oxygen. Plasma and urine concentrations of the parent compound and its degradation products were measured by high performance liquid chromatography. Renal failure was defined as a creatinine clearance of less than 5 ml/min; it caused no significant differences in the pharmacokinetics of atracurium but did result in a different pharmacokinetic profile of laudanosine, with a 3-fold increase in the mean (± SD) terminal half-life (176 ± 84 and 516 ± 262 minutes for patients with normal and impaired renal function, respectively). Moreover, the half-life of the quaternary alcohol increased from 27.1 ± 8.3 minutes in patients with normal renal function to 42.5 ± 8.3 minutes in those with impaired renal function (mean ± SD). Renal elimination of unchanged atracurium accounted for 11% of the administered dose and at least 27% of the total degradation of atracurium occurred via ester hydrolysis.

The neuromuscular function was monitored by measuring the twitch tension of the adductor pollicis muscle elicited by stimulation of the ulnar nerve at 0.1Hz. The total duration of neuromuscular blockade (51.8 ± 11.5 minutes) and the recovery index (9.6 ± 2.0 minutes) are shortened in patients with impaired renal function, compared with those with normal renal function (64.1 ± 7.2 and 16.7 ± 4.1 minutes, respectively), indicating that sensitivity to the neuromuscular blocking action of atracurium may be altered by renal failure.

Atracurium is a nondepolarising, neuromuscular blocking agent with an intermediate mode of action. As vecuronium, atracurium shows only minimal dependence on the kidneys for their elimination. In the case of atracurium this phenomenon is explained by the unique degradation pattern (Stenlake et al. 1983), consisting of a chemical- and enzyme-mediated ester hydrolysis by which the quaternary alcohol and acid are formed, in combination with a spontaneous temperature- and pH-dependent degradation pathway called Hofmann elimination, yielding laudanosine and an acrylate moiety (fig. 1). Consequently, 4 primary metabolites are formed from atracurium *in vivo* and a

number of secondary ones by degradation of the primary metabolites.

The pharmacokinetic profile of atracurium has been described in several studies in healthy anaesthetised subjects (De Bros et al. 1986; Fahey et al. 1984; Ward & Weatherley 1986), in patients with renal failure (De Bros et al. 1986; Fahey et al. 1984; Ward & Weatherley 1986), or in patients with combined renal and hepatic disease (Ward & Neill 1983). Fahey et al. (1984) were the first to report the plasma concentrations of laudanosine in patients treated with atracurium. The present article is the first in which the neuromuscular blocking effects of atracurium and the pharmacokinetic profiles and renal excretion of atracurium, laudanosine and the quaternary alcohol were prospectively studied in patients with normal and impaired renal function in a uniform fashion: that is, in this study identical anaesthetic agents were administered to all patients, and the methodological, analytical and statistical techniques were exactly the same for both patient groups.

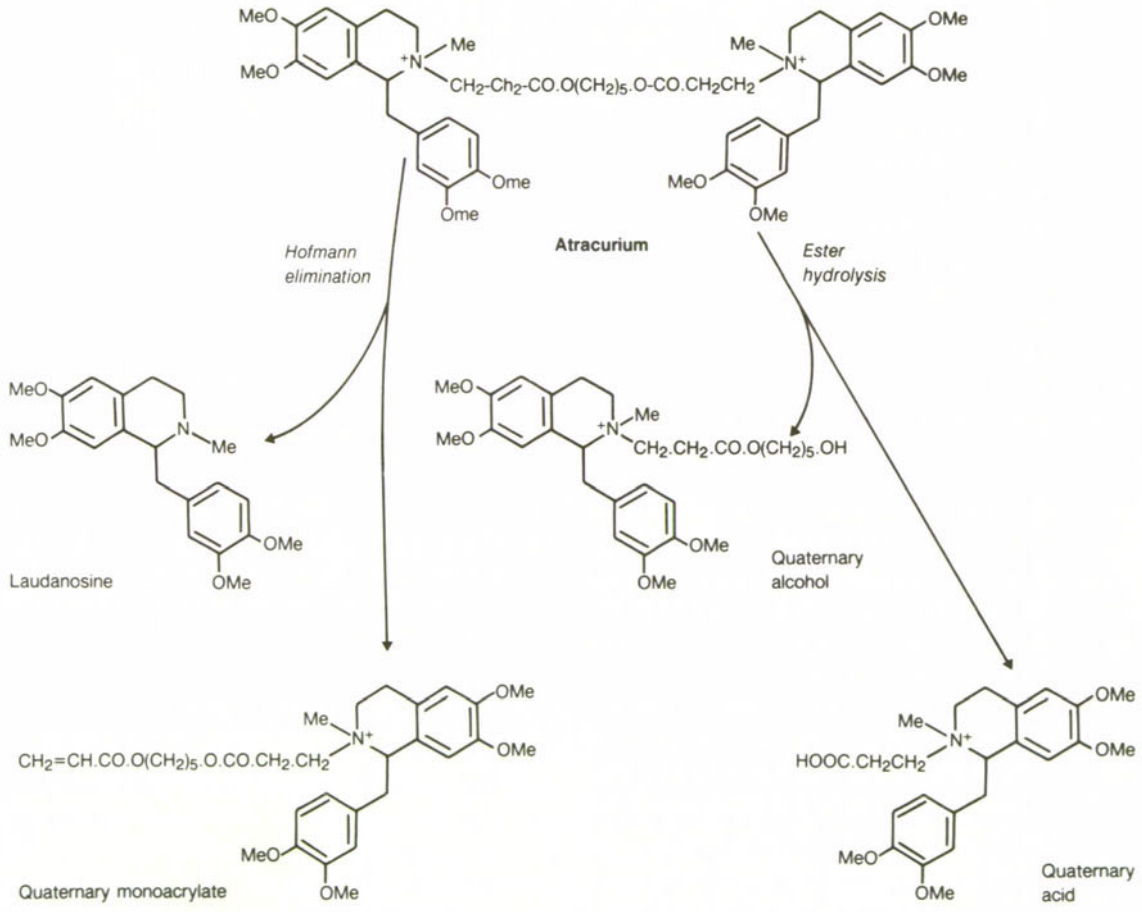

Fig. 1. Routes of breakdown of atracurium.

Patients and Methods

This study was approved by the ethical committee of the University Hospital of Groningen; 23 patients gave informed consent to participation. The mean (± SD) age of the 17 patients with normal renal function was 33.7 ± 9.8 years; that of the 6 patients with impaired renal function was 49.3 ± 13.7 years. The bodyweights were 66.1 ± 10.2 and 77.7 ± 15.9kg for patients with normal and impaired renal function, respectively. Obese patients were excluded from the study in order to avoid adjustments of the dose of atracurium to obtain comparable pharmacodynamic parameters. Renal failure was defined as a creatinine clearance of less than 5 ml/min, and all patients with renal failure were totally anuric and had been dialysed during the 24-hour period preceding anaesthesia. None of the 23 patients suffered from cardiovascular, hepatic or neuromuscular disease.

The patients were premedicated with oral diazepam 0.15 mg/kg 1.5 hours before induction of anaesthesia; if required, night sedation with oral nitrazepam 5mg was provided. Anaesthesia was induced with intravenous thiopental 4 to 6 mg/kg and fentanyl 5 to 7 μg/kg followed by inhalation of 66% nitrous oxide in oxygen. Atracurium 500 μg/kg (402.1 nmol/kg) was administered by bolus injection over 10 seconds, and tracheal intubation was performed. Anaesthesia was maintained with halothane 0.5 to 1% and repeated doses of fentanyl. Ventilation was controlled and the end-expiratory pCO_2 was maintained between 4.0 and 4.6 kPa (30 to 35mm Hg). A central venous catheter with its tip positioned at the right atrium was inserted via an antecubital vein. Central body temperature was measured continuously pending the experiment and was maintained at between 35.5 and 37.5°C.

Blood samples were collected from the central venous catheter. One blank sample was collected prior to, and the remainder after, the administration of atracurium (at 3, 6, 9, 12, 15, 20, 30, 45, 60, 75, 90, 120, 180, 240, 300, 360 and 420 minutes). Additional samples were collected at 10, 25, 50, 75 and 90% recovery of the single twitch height. The samples were immediately centrifuged for 30 seconds. Plasma samples of 2ml were acidified with 100μl of sulphuric acid 1 mol/L, frozen and stored at −20°C.

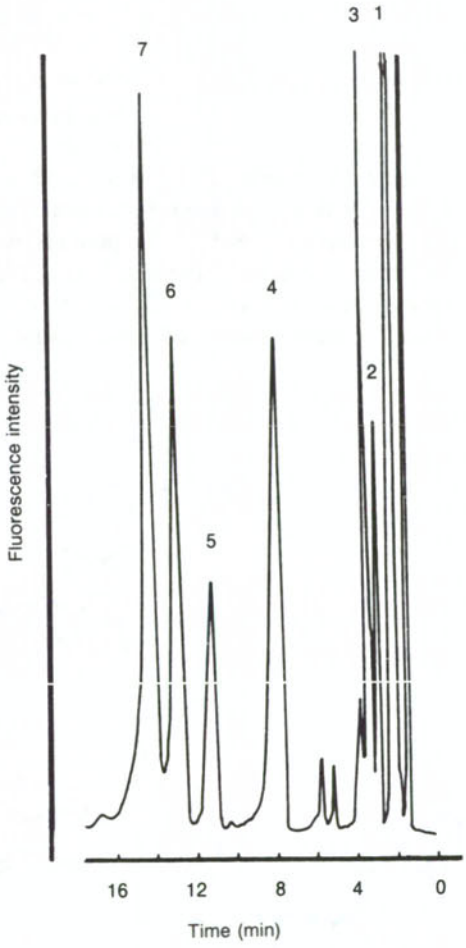

Fig. 2. Typical high-performance liquid chromatogram of the 3-minute plasma sample showing laudanosine (1), the quaternary alcohol (2 and 3), the internal standard hexafluorenium bromide (4) and atracurium (5, 6 and 7).

Urine was collected via an indwelling catheter from all patients with normal renal function. A control sample was taken before atracurium was injected and additional samples were collected at 30, 60, 90, 120, 180, 240, 300 and 360 minutes, and 12 and 18 hours, after administration of atracurium. The volume of urine excreted during each collection period was recorded, and from each

sample a 5ml aliquot was frozen at −20°C for later analysis. During each collection period, the pH of the urine was monitored and adjusted to approximately 3.5 with sulphuric acid 0.1 mol/L.

Monitoring of neuromuscular blockade began immediately after induction of anaesthesia. Measurements of the single twitch of the adductor pollicis were taken every 10 seconds by supramaximal stimulation of the ulnar nerve at the wrist via surface electrodes ('Grass S88' stimulator). The resultant contraction of the adductor pollicis muscle was measured using a 'Statham UC3' force-displacement transducer, and recorded on a 'Gould Brush 220' pen recorder. The onset time (time from the end of injection to the moment of 100% block-

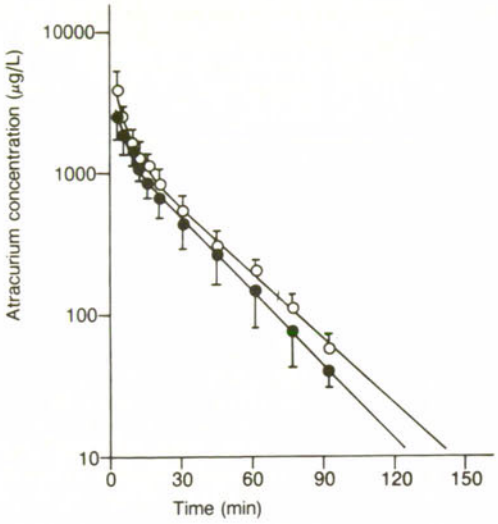

Fig. 4. Mean (± SD) plasma concentration decay curves of total atracurium in patients with normal renal function (●) and those with renal failure (○) following a bolus dose of atracurium 0.5 mg/kg.

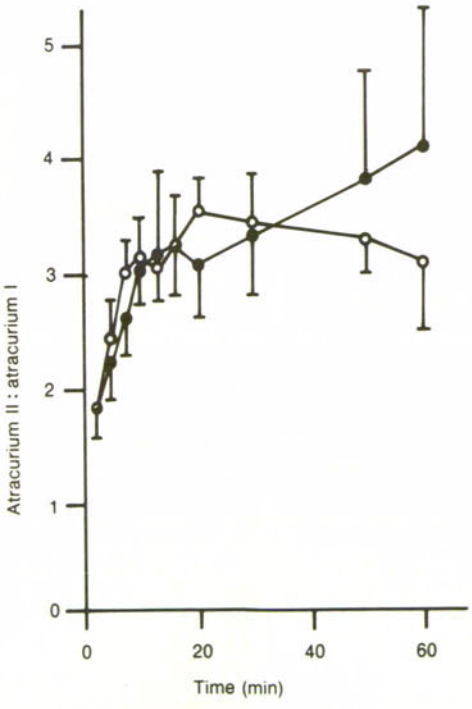

Fig. 3. Mean (± SD) ratio between the plasma concentrations of atracurium II (*cis-cis* isomer) and atracurium I (*cis-trans* isomer) over time in patients with normal (●) and impaired (○) renal function.

ade of neuromuscular transmission), the total duration of relaxation (time from end of injection to the return of 90% of control twitch height) and the recovery index (time needed for the recovery of the twitch height from 25 to 75% of the control value) were measured for both patient groups.

Atracurium and its breakdown products were measured in the samples of plasma and urine using high performance liquid chromatography (HPLC) [Uges et al. 1984], as described in the Appendix. This method is suitable for simultaneous quantitative determination of atracurium, laudanosine and the quaternary alcohol.

Multiexponential equations of up to 5 exponential terms were fitted to each of the individual experimental plasma concentration curves by means of a computer program (RUGFIT). This program carries out, by means of linear least square regression, iterative peeling of the experimental curves plotted on a semilogarithmic scale (Scaf 1988). The mathematically derived optimal number of exponential terms required to describe the plasma concentrations was selected according to the criteria

Table I. Mean (± SD) pharmacokinetic parameters of atracurium following an intravenous bolus dose of 0.5 mg/kg

Parameter	Normal renal function	Renal failure
C_1 (μg/L)	3070 ± 1453	4072 ± 3280
C_2 (μg/L)	1540 ± 791	1531 ± 576
$t_{½\lambda_1}$ (min)	2.5 ± 1.1	3.7 ± 1.7
$t_{½\lambda_2}$ (min)	17.3 ± 3.8	19.7 ± 2.7
λ_1 (min^{-1})	0.325 ± 0.118	0.219 ± 0.080
λ_2 (min^{-1})	0.0421 ± 0.0103	0.0358 ± 0.0048
V_c (ml/kg)	129 ± 88	93 ± 55
AUC (mg/L · h)	0.86 ± 0.27	1.13 ± 0.30
CL (L/h/kg)	0.65 ± 0.23	0.47 ± 0.13
Vd (ml/kg)	280 ± 153	165 ± 69

Abbreviations: C_1 (C_2) = extrapolated theoretical plasma concentration for the distribution (elimination) phase for time zero; $t_{½\lambda_1}$ ($t_{½\lambda_2}$) = half-life associated with the first (second) exponent of the biexponential equation; λ_1 (λ_2) = rate constant for distribution (elimination) phase; V_c = volume of the central compartment; AUC = area under the plasma concentration-time curve; CL = total body clearance; Vd = apparent volume of distribution.

described by Boxenbaum et al. (1974). In addition, the computer program calculates the derived pharmacokinetic parameters. Thus, C_1 and C_2 are the extrapolated theoretical plasma concentrations for the distribution and elimination phases, respectively, for time zero (t = 0 minutes); λ_1 and λ_2 are the rate constants for the 2 phases. The volume of the central compartment (V_c) is calculated by dividing the dose (D) of atracurium by the sum of C_1 and C_2. Whole body clearance (CL) and the volume of distribution (Vd) are calculated using the area under the curve (AUC): $AUC = C_1/\lambda_1 + C_2/\lambda_2$; $CL = D/AUC$ and $Vd = D/AUC \cdot \lambda_2$.

It was not possible to calculate V_c, CL and Vd of either laudanosine or the monoquaternary alcohol since the total amount of both substances, formed via degradation of atracurium, was unknown. Student's t-test was used to determine statistical significance of differences between the mean values for pharmacokinetic and pharmacodynamic parameters of the 2 patient groups. A value of $p < 0.05$ was considered statistically significant.

Results

Atracurium produces 3 peaks on the chromatogram, while the quaternary alcohol has a double peak (fig. 2). Analysis of pure atracurium and of the quaternary alcohol revealed identical peaks. The pharmacokinetics of the atracurium components corresponding to the middle and highest peaks (fig. 2, nos 6 and 7) have been determined and are designated as atracurium I and atracurium II, respectively.

Pharmacokinetic analysis of the total amount of atracurium was carried out using the sum of the 3 peaks; similarly, that of the quaternary alcohol was performed using the sum of its 2 peaks. The ratio between the plasma concentrations of the 2 atracurium components was not constant in time. In the commercial preparation of atracurium ('Tracrium'), the ratio between the amounts of atracurium II and atracurium I is about 1.5, while the ratio in the plasma samples varied with time (from 1.8 to 4.1, see fig. 3).

Figure 4 shows the change in the plasma concentration of atracurium after intravenous administration to patients with normal and decreased renal function. Table I gives the corresponding parameters. No significant differences in any of the parameters were found between the 2 groups.

Plasma concentrations of laudanosine are shown in figure 5 and the derived parameters for the patients with normal renal function are listed in

Table II. Mean (± SD) pharmacokinetic parameters of laudanosine after an intravenous bolus dose of atracurium 0.5 mg/kg

Parameter	Normal renal function
C_1 (μg/L)	151 ± 60
C_2 (μg/L)	109 ± 49
$t_{½\lambda_1}$ (min)	3.3 ± 2.0
$t_{½\lambda_2}$ (min)	176 ± 84
λ_1 (min^{-1})	0.294 ± 0.178
λ_2 (min^{-1})	0.0050 ± 0.0029
AUC (mg/L · h)	0.47 ± 0.22

Abbreviations: see table I.

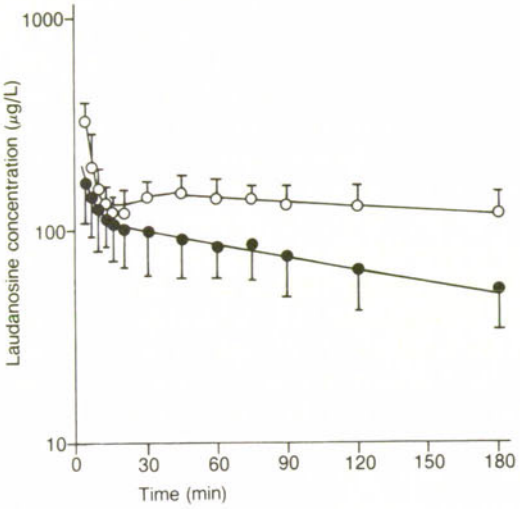

Fig. 5. Mean (± SD) plasma concentration decay curves of laudanosine in patients with normal renal function (●) and those with renal failure (○; n = 4) following a bolus dose of atracurium 0.5 mg/kg.

table II. In all patients the concentration of laudanosine was maximal in the first collected sample and decreased thereafter. However, in the patients with impaired renal function, the plasma concentration of laudanosine showed a second peak approximately 40 minutes after injection, decreasing subsequently with a half-life of 516 ± 262 minutes. The height of the second peak of laudanosine showed a wide variation among the patients, in 2 individuals exceeding 2600 μg/L. For clarity, the data of these 2 patients were excluded for calculation of the mean plasma laudanosine concentrations.

Figure 6 shows the plasma concentration of the quaternary alcohol in plasma. Because of the marked fluctuations in plasma concentrations during the early sampling periods, the first parts of both graphs are not drawn. The corresponding pharmacokinetic parameters are presented in table III. Only the half-life of the terminal phase could be calculated, because of these early fluctuations. The half-life and λ were significantly different between the 2 groups.

Table IV shows the amounts of atracurium and the 2 metabolites excreted in urine. Of the bolus dose of atracurium (402.1 nmol/kg), 43.9 ± 23.7 nmol/kg (10.9 ± 5.9%) was excreted as unchanged atracurium. Renal excretion of laudanosine and the quaternary alcohol amounted to 57.4 ± 44.8 and 108.6 ± 58.6 nmol/kg, respectively.

The mean values of the pharmacodynamic parameters are presented in table V, and show a shorter duration of action and a faster rate of recovery in patients with renal failure.

The duration of neuromuscular block and the corresponding plasma concentrations when recovery amounted to 10, 25, 50, 75 and 90% of the control value are listed in table VI for the 2 groups, although it should be noted that the values are drawn from only 9 patients with normal renal function. All plasma concentrations except that corresponding to 10% recovery were significantly different between the 2 groups, as were the times required to reach 75% and 90% recovery. Figure 7 shows the relationship between the mean plasma concentration of atracurium and the degree of recovery from the neuromuscular blockade in the 2 groups of patients.

Discussion

After a bolus dose of intravenous atracurium 500 μg/kg the plasma samples show 3 atracurium peaks on the chromatogram. As noted in the Results section above, analysis of pure atracurium revealed 3 identical peaks. According to Stenlake et al. (1984), these peaks may be ascribed to the *cis-cis*, *cis-trans* and *trans-trans* isomers of atracurium (see fig. 2,

Table III. Mean (± SD) pharmacokinetic parameters of the quaternary alcohol after an intravenous bolus dose of atracurium 0.5 mg/kg

Parameter	Normal renal function	Renal failure
C (μg/L)	1060 ± 672	982 ± 362
$t_{½\lambda}$ (min)	27.1 ± 8.3	42.5 ± 8.3[a]
λ (min^{-1})	0.0280 ± 0.0092	0.0168 ± 0.0035[a]
AUC (mg/L · h)	0.81 ± 0.39	1.10 ± 0.58

a Significantly different from normal renal function group ($p < 0.05$).

Abbreviations: see table I.

Table IV. Mean (± SD) elimination of atracurium and 2 of its breakdown products in the urine of patients with normal renal function. The dose of atracurium administered was 402 nmol/kg

Substance	Amount (nmol/kg)	Time[a] (h)
Atracurium	43.9 ± 23.7	6.0 ± 2.8
Laudanosine	57.4 ± 44.8	11.5 ± 4.6
Quaternary alcohol	108.6 ± 58.6	9.4 ± 5.6

a Time after which substances no longer detectable.

Table V. Mean (± SD) neuromuscular blocking effect of atracurium 0.5 mg/kg

Group	No. of pts	Onset (min)	Duration (min)	Recovery index (min)
Normal renal function	9	2.5 ± 0.2	64.1 ± 7.2	16.7 ± 4.1
Renal failure	6	3.0 ± 0.6	51.8 ± 11.5[a]	9.6 ± 2.0[a]

a Significantly different from normal renal function group ($p < 0.05$).

Table VI. Mean (± SD) values of time and plasma concentration of atracurium, corresponding to 10, 25, 50, 75 and 90% recovery of the single twitch height

Rec %	Time (min)		Concentration (μg/L)	
	normal renal function[a]	renal failure[b]	normal renal function[a]	renal failure[b]
10	34.8 ± 2.6	32.1 ± 8.0	411 ± 78	471 ± 85
25	40.5 ± 2.8	35.7 ± 8.1	315 ± 68	408 ± 70[c]
50	48.1 ± 3.1	40.2 ± 8.7	225 ± 66	342 ± 60[c]
75	57.2 ± 5.6	45.1 ± 9.9[c]	152 ± 58	284 ± 62[c]
90	64.1 ± 7.2	51.8 ± 11.5[c]	115 ± 52	240 ± 75[c]

a n = 9.
b n = 6.
c Significantly different from normal renal function group ($p < 0.05$).
Abbreviation: Rec = recovery of single twitch height.

nos 7, 6 and 5, respectively). The initial ratio of peak 7 to peak 6 (atracurium II to atracurium I, respectively) was found to be 1.5. With time, this ratio increased to 3.4 and 4.1 at 30 and 60 minutes, respectively, for patients with normal renal function (fig. 3). The changing values of these ratios are in agreement with those found by Tsui et al. (1987) [an initial ratio of *cis-cis* to *cis-trans* isomers of 1.5, increasing to 3.3 and 4.0 after 30 and 60 minutes). Because the present findings are comparable with those of Stenlake and Tsui, the conclusion is drawn that the 3 peaks on the chromatogram correspond with the 3 isomers of atracurium mentioned. Unfortunately, due to industrial, technical and analytical difficulties, it is not possible to isolate the isomers separately from the mixture. Therefore, no further chromatographic studies with the individual isomers can be properly carried out. Although not a goal of this study, it would be very interesting to know more about the pharmacokinetics and pharmacodynamics of the isomers, because it might be possible that only 1 of the isomers is mainly responsible for the neuromuscular blocking effects and that the other isomers are more or less impurities. There was no difference in ratio between patients with normal and impaired renal function, indicating that the pharmacokinetic profile of both isomers is not altered by renal failure. By analogy with atracurium, the 2 peaks of the quaternary alcohol probably correspond to the *cis* and *trans* isomers; because laudanosine does not have a *cis* or *trans* configuration, it produced a single peak on the chromatogram. Unfortunately, neither the quaternary acid nor the quaternary monoacrylate could be measured. Measurement of the monoacrylate moiety would have been particularly interesting since it is suspected that this metabolite, a potentially highly reactive substance, may possess cytotoxic properties (Nigrovic & Pandya 1989). This also could be one of the reasons that the plasma concentration of the acrylate has never been measured, since it may react with suitable endogenous substances present in plasma immediately following its formation, giving low plasma concentrations as a result. However, as laudanosine and the monoquaternary acrylate are formed with a ratio

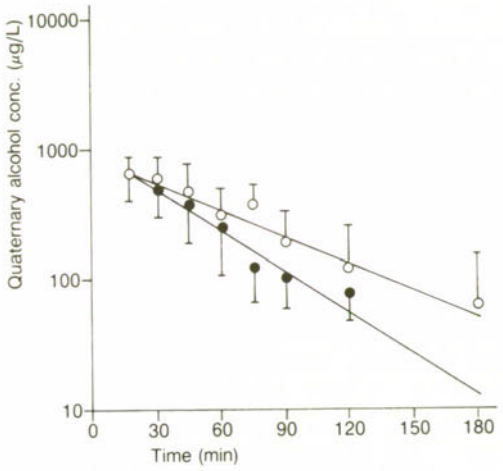

Fig. 6. Mean (± SD) plasma concentration decay curves of the quaternary alcohol in patients with normal renal function (●) and those with renal failure (○) following a bolus dose of atracurium 0.5 mg/kg.

of I via Hofmann elimination (Stenlake et al. 1983), changes in the plasma concentration of laudanosine may reflect corresponding changes in the formation of the acrylate.

The pharmacokinetic analysis confirmed the observations of others that the time course of the plasma concentrations of atracurium is best described by a biexponential function. The presence of renal failure had no perceptible effect on the pharmacokinetic profile of atracurium (De Bros et al. 1986; Fahey et al. 1984; Ward & Weatherley 1986). Ward et al. (1987) described the pharmacokinetics of atracurium and of its metabolites, laudanosine and monoquaternary alcohol, both in healthy subjects and in patients with renal disease. However, since that paper is apparently a compilation of selected data from previously published work presented as a properly performed study, their results must be rejected. The present study demonstrates that the total clearance of atracurium is not significantly lower in patients with impaired renal function (0.648 versus 0.474 L/h/kg). Fahey et al. (1984) and Ward and Weatherley (1986), however, observed a small increase in the total clearance. A more detailed pharmacokinetic analysis is not feasible and microparameters cannot be derived in this clinical study, since the breakdown of atracurium is not restricted to the central compartment (Hull 1983).

In patients with normal renal function the plasma concentration of laudanosine after a bolus dose of atracurium was best described as a biexponential function. The early presence of high concentrations of laudanosine in plasma is remarkable because this substance is a breakdown product of atracurium. On theoretical grounds, low plasma concentrations of laudanosine would be expected immediately after administration of atracurium, with a subsequent increase as the degradation of atracurium progresses. The result of this finding implies, however, that atracurium may already have been partly broken down in the ampoule and, therefore, that laudanosine was injected along with atracurium. Analysis of a properly treated, unexpired ampoule of 'Tracrium' revealed 1.4% laudanosine. This small amount does not explain the initial high plasma concentration; it seems, therefore, that other processes are involved, yielding an

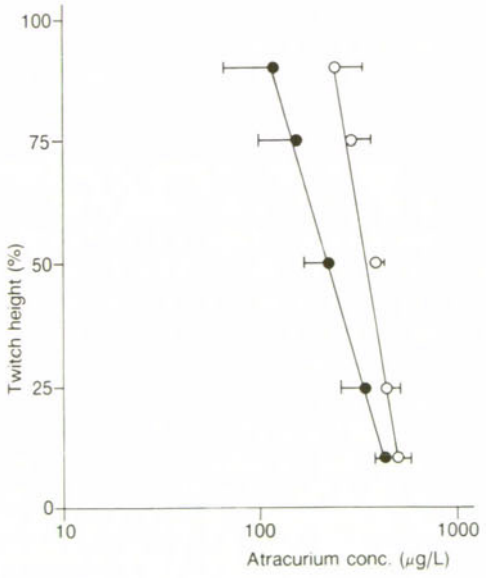

Fig. 7. Recovery of the single twitch height against the mean plasma log concentration (± SD) of atracurium from patients with normal renal function (●) and those with renal failure (○) following a bolus dose of atracurium 0.5 mg/kg.

accelerated rate of chemical breakdown. One of the possibilities could be that the highly reactive quaternary acrylate reacts immediately with suitable agents present in the blood, enhancing the rate of Hofmann elimination and giving rise to the high initial plasma concentration of laudanosine.

Experiments carried out by other researchers justify this hypothesis (Nigrovic & Smith 1987; Nigrovic et al. 1989). In patients with impaired renal function, the mean plasma concentration of laudanosine was significantly higher than in those with normal renal function. Significantly higher plasma laudanosine concentrations in patients with renal failure were also reported by Fahey et al. (1985). In addition to the increase in concentration, the plasma concentration-time curve was also of a different shape. This phenomenon is probably caused by the decreased renal elimination of laudanosine. Hence, soon after the rapid initial distribution phase, the formation of laudanosine via Hofmann elimination gives rise to the increase of the plasma concentration. At this second peak, there is a balance between formation and elimination, subsequently followed by the elimination phase. In 2 patients with impaired renal function the concentration of laudanosine increased, exceeding 2600 μg/L. It has been known for many years that laudanosine acts as a CNS stimulant (Babel 1899; Mercier & Mercier 1955). The pharmacological effect is ascribed to a strychnine-like mode of action (Curtis et al. 1971; Pong & Graham 1976).

Pharmacological experiments performed by Chapple et al. (1985) demonstrate that such concentrations can cause an increase in frequency and amplitude of the EEG of dogs. During surgery, no signs of excitation were observed in these 2 patients, but it is possible that total relaxation may abolish the clinical signs of excitation. Ward and Weatherley (1986) found a nonsignificant increase in terminal half-life, from 197 ± 38 to 234 ± 81 minutes, in patients with chronic renal failure. However, they did not define chronic renal failure, nor were the anaesthetic, statistical and analytical methods described. Therefore, their results cannot be compared with the present authors' data, which showed that this half-life is increased 3-fold (176 ± 84 and 516 ± 262 minutes for patients with normal and impaired renal function, respectively). This implies that kidney function plays an important role in the elimination of laudanosine, and that other nonrenal elimination pathways (e.g. metabolism or hepatic excretion) are not capable of taking over the loss of renal function. This finding is supported by the results of a study by Parker et al. (1988), who performed a continuous infusion of atracurium 0.6 mg/kg/h, after an initial bolus dose of 0.6 mg/kg, for 10 to 47 hours in critically ill patients with normal renal function or renal failure in the Intensive Therapy Unit. The mean elimination half-life for laudanosine increased significantly from 375 minutes in patients with normal renal function to 1418 minutes in renal failure. The pharmacokinetics of atracurium were unaffected by renal failure.

Soon after administration of atracurium the concentration of the quaternary alcohol was high, and fluctuated markedly for about 10 minutes before starting to decrease progressively. Again, low concentrations would be expected immediately following the administration of atracurium, subsequently followed by an increase: analysis of an ampoule of 'Tracrium' demonstrated that 2.3% of the contents consisted of the quaternary alcohol. Renal failure caused a significant increase in half-life of the quaternary alcohol from 27.1 to 42.5 minutes. The findings of Ward and Weatherley (1986) were similar, including the high initial plasma concentration. To date, no explanation is known for this phenomenon. Perhaps the ester hydrolysis is accelerated by nonspecific carboxy esterases, as a result of the large amount of atracurium available immediately after injection or due to the increase in pH from 3.5 (in the ampoule) to physiological values.

A study by Neill and Chapple (1982) in cats demonstrated that the role of the kidneys in the elimination of atracurium and its metabolites should not be underestimated. Following the intrajugular administration of radiolabelled atracurium, 47% of the radioactivity was excreted by the liver within 5 hours and 18% by the kidneys. After intraportal injection in other cats, however, 43%

was excreted by the kidneys and 38% by the liver. The authors have omitted to explain these different findings. In cats, after 2 hours, 6.9% of the dose is found in the urine as unchanged atracurium; whereas in cats made functionally anephric by the ligation of both renal arteries the excretion of radioactivity in the bile increased by almost 60%; this implies that the kidneys do play an important role in the excretion of atracurium and its metabolites. The present study shows that, after 18 hours in humans, 10.9 ± 5.9% of the administered dose of atracurium is excreted unchanged by the kidneys (see table IV). Approximately 109 nmol/kg of the quaternary alcohol was excreted via the kidneys in humans (table IV). Assuming that the quaternary alcochol is formed only by ester hydrolysis (Stenlake et al. 1983) of the dose of parent drug (402.1 nmol/kg), then at least 27% of the total degradation of the administered dose of atracurium must have occurred via ester hydrolysis. Although in humans only a small fraction of atracurium is excreted in the form of laudanosine, it appears that the elimination of the latter is heavily dependent on renal function.

This study shows that in patients with renal failure the plasma concentrations of atracurium corresponding to 25% or greater recovery from the neuromuscular blockade were significantly higher than those in patients with normal renal function. The plasma concentrations in the latter group that correspond to 10% and 50% recovery agree with those found by Ward and Wright (1983). In patients with impaired renal function, the onset time was slightly prolonged compared with the normal kidney function group, and the total duration and the recovery index were significantly shortened. It appears that patients with renal failure need higher plasma concentrations of atracurium in order to maintain a certain degree of blockade than do those with normal renal function. The same phenomenon has been demonstrated by others both for atracurium and vecuronium (Bencini et al. 1986; Hunter et al. 1984; Nguyen et al. 1985), but no explanation is known to date. It might be possible that the presence of uraemia or of other substances, such as methyl-guanidine derivatives, whose concentration is higher in patients with renal failure, are responsible for this resistance to the effect of nondepolarising neuromuscular blocking agents.

Therapeutic Implications

The conclusion is drawn that renal failure has only minimal influence on the pharmacokinetic profile of atracurium, while prolonging the terminal half-life of laudanosine; the elimination half-life of the quaternary alcohol is also increased, but to a lesser extent. The apparent resistance of renal failure patients to the neuromuscular blocking action of atracurium is not of great clinical importance. However, because of the changes in the pharmacokinetic profile of laudanosine, and possibly also of the potential toxic monoquaternary acrylate, prolonged administration of atracurium (e.g. multiple maintenance doses or lengthy infusions) requires caution in patients with decreased metabolic or elimination pathways, with monitoring of the neuromuscular function and, preferably, the plasma laudanosine concentrations.

Appendix

The following is a description of the technique employed in this study to achieve quantitative estimates of the plasma and urine concentrations of atracurium and its 2 breakdown products. The measurements were obtained in one procedure by an ion-pair extraction in acid medium, followed by HPLC.

To 1.0ml acidified plasma was added: 100μl of internal standard (hexafluorenium bromide 10 mg/L), 100μl of a solution of potassium iodide 50 g/L and dichloromethane 7.0ml. In the assay to determine concentrations in urine, 100μl of urine was made up to 1.0ml with water, after which the sample was treated in the same way as the plasma sample. Following vigorous mixing for 2 minutes, the solution was centrifuged for 5 minutes at approximately 3000 rpm, after which the whole organic layer was separated and concentrated at ambient temperature by evaporation. To this extract was added 100μl of eluate, consisting of acetonitril and

a solution of sodium sulphate 0.03 mol/L (27.5 + 72.5 v/v%), adjusted to pH = 3.5 with sulphuric acid 1 mol/L. An aliquot of 50μl of each sample was injected into an HPLC unit ('M6000A', Waters Associates Inc.) by an automatic injector ('Whisp 710A', Waters Associates Inc.). The column of 150 × 4.6mm internal diameter was packed with 'Nucleosil 5C18' (Chromopack). The eluent flow rate was 2 ml/min. Detection was undertaken by a fluorescence meter ('Kontron SFM23/B') with excitation at 280nm and emission at 320nm. The concentrations were calculated by a Hewlett Packard 2645 terminal by reference to a calibration curve. All assays were undertaken in duplicate and the mean of the 2 determined concentrations calculated. The lowest detection limit and the coefficient of variation for atracurium was 25 μg/L and 8% at 800 μg/L, for laudanosine 5 μg/L and 11% at 200 μg/L and for the quaternary alcohol 10 μg/L and 16% at 1500 μg/L, respectively.

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