British Journal of Anaesthesia 1995; 75: 431–435

Pharmacokinetics of 1R-*cis* 1′R-*cis* atracurium besylate (51W89) and plasma laudanosine concentrations in health and chronic renal failure

N. B. EASTWOOD, A. H. BOYD, C. J. R. PARKER AND J. M. HUNTER

Summary

To ascertain the effects of chronic renal failure on the pharmacokinetics of 1 R-*cis* 1′R-*cis* atracurium besylate (a stereoisomer, designated 51W89), we gave a bolus dose of 0.1 mg kg^{-1} (2 × ED_{95}) to 17 patients with end-stage renal failure and to 15 patients with normal renal function undergoing elective surgery. All patients received thiopentone, fentanyl and midazolam i.v. and 70 % nitrous oxide in oxygen. Blood samples were obtained over 8 h and plasma analysed for 51W89 and laudanosine concentration, using high pressure liquid chromatography. A two-compartment model was fitted to the 51W89 plasma concentration data using the NONMEM program, to estimate pharmacokinetic variables and to determine the influence of renal failure, age, weight and sex. Clearance of 51W89 was found to be reduced by 13 % in renal failure. The typical value of $T_{\frac{1}{2}}^{\beta}$ was 4.2 min longer in renal failure than in the healthy patients (34.2 *vs* 30.0 min, $P < 0.005$). In the healthy patients, clearance of 51W89 was greater in males, but it decreased with increasing age by approximately 1.5 ml min^{-1} yr^{-1}. Mean plasma laudanosine concentrations were significantly higher in the renal failure group; nevertheless, they were approximately one-tenth of those reported after atracurium. (*Br. J. Anaesth*. 1995; **75**: 431–435)

Key words

Pharmacokinetics, atracurium. Neuromuscular block, atracurium. Pharmacokinetics, 51W89. Neuromuscular block, 51W89. Pharmacokinetics, laudanosine. Pharmacokinetics, stereoisomers. Complications, renal.

Atracurium besylate is a benzylisoquinolinium non-depolarizing neuromuscular blocking agent, with a kinetic profile which is unchanged by renal impairment [1, 2]. It is therefore a popular agent to use in patients with chronic renal failure, because the duration of its clinical effect is unchanged [1, 3]. Clearance of atracurium is unaltered because of the safety net of Hofmann elimination [2, 4], whereby spontaneous breakdown of the drug occurs at body temperature and pH.

Laudanosine is a product of this metabolic pathway. In animal studies, laudanosine has been shown to stimulate abnormal electroencephalographic activity and epileptic convulsions [5, 6], although this has not been reported in humans. Laudanosine is cleared in part by the kidney [7], and probably also by the liver [8].

The atracurium molecule has four chiral centres; 10 distinct stereoisomers are found in the commercial preparation [9]. Several of these compounds have undergone laboratory investigation and one (1R-*cis* 1′R-*cis* atracurium besylate, designated 51W89) is currently undergoing phase III clinical trials. This isomer is more potent than atracurium [10, 11]; animal studies have shown it to be more selective for the postsynaptic nicotinic receptor, with less autonomic effect [12].

We examined the pharmacokinetics of 51W89 in health and chronic renal failure and measured the plasma concentration of its metabolite, laudanosine.

Patients and methods

After approval by the Committee on Safety of Medicines and the hospital Ethics Committee, we obtained written informed consent from 32 patients to take part in the study; 17 with end-stage chronic renal failure undergoing regular dialysis and 15 healthy patients. The pharmacodynamics of 51W89 in these patients have been reported previously [13]. The renal failure patients were not undergoing renal transplantation; they were scheduled for either dialysis access procedures ($n = 14$), renal transplant nephrectomy ($n = 2$) or femoropopliteal bypass ($n = 1$). The healthy patients were undergoing elective surgery, for example, inguinal hernia repair or laparoscopic cholecystectomy.

Patients were excluded if there was a history, or physical signs, of any neuromuscular disorder, obesity, asthma, cardiac failure or liver disease, and also if they were receiving drugs thought to interfere with neuromuscular transmission, including anticonvulsants, aminoglycoside antibiotics, antihistamines, antidepressants and anti-arrhythmics. None of the females was pregnant or breast feeding.

Before operation, haemoglobin, blood glucose, plasma urea and electrolyte concentrations were measured. Liver function tests were also carried out. All patients were weighed and their heights recorded. The ideal weight for each patient was obtained from published insurance tables [14].

N. B. EASTWOOD, BSC, MB, BS, FRCA, A. H. BOYD, MB, CHB, FRCA, C. J. R. PARKER, MA, MD, FRCA, J. M. HUNTER, MB, CHB, PHD, FRCA, University Department of Anaesthesia, Royal Liverpool University Hospital, Prescot Street, Liverpool L69 3BX. Accepted for publication: May 12, 1995.

Patients received diazepam 5–10 mg orally 2 h before surgery. Anaesthesia was induced with midazolam 0.05 mg kg^{-1}, fentanyl 1 g kg^{-1} and thiopentone 2–5 mg kg^{-1}, and maintained with inhalation of 70 % nitrous oxide in oxygen. Additional increments of thiopentone and fentanyl were administered as indicated clinically. Monitoring included non-invasive arterial pressure measurement, three-lead electrocardiography, pulse oximetry, inspired oxygen analyser, capnography and nasopharyngeal and forearm skin temperatures.

After induction of anaesthesia, a 14-gauge cannula was placed into a vein in one arm for blood sampling and a baseline 5-ml blood sample was obtained. A fast-flowing i.v. infusion was commenced in the other arm for 51W89 administration. A bolus dose of 51W89 0.1 mg kg^{-1} (2 × ED_{95} [10, 11]) was then given into the infusion over 10 s. Additional blood samples were obtained at 2, 4, 6, 8, 10, 12, 15, 20, 25, 30, 45, 60, 90, 120, 240 and 480 min. After preliminary results were available from the first 12 patients, an additional sample was obtained at 150 min (this included the last eight healthy patients and the last 13 renal failure patients). Each blood sample was placed in a lithium heparin tube, acidified immediately with 0.02 ml of sulphuric acid 1.5 mol litre^{-1} and centrifuged. Plasma (2 ml) was then decanted into 8 ml of sulphuric acid 15 mmol litre^{-1} to prevent degradation of the isomer. The acidified plasma was kept on ice and deep frozen within 30 min.

Plasma samples were analysed using a gradient method of high pressure liquid chromatography (HPLC) with fluorescence detection; the method used was similar to that reported for atracurium [15]. The concentration of 51W89 was expressed as that of the bis-cation, which has 75 % of the mass of the dibenzene sulphonate salt (as has been used to express the dose of atracurium). The accuracy of the analysis was assessed by the use of standards of 51W89 15–1500 ng ml^{-1} and laudanosine 15–750 ng ml^{-1} in pooled bank human plasma. The coefficient of variation of the analysis for 51W89 varied from 14 % at the lower limit of detection to 10 % at 1500 ng ml^{-1}, and that for laudanosine from 10 % at the lower limit of detection to 4 % at 750 ng ml^{-1}.

On the day after surgery, each patient was examined clinically and blood was again obtained for chemical and haematological analyses.

A two-compartment model was fitted to the plasma concentrations of 51W89, using the NONMEM (nonlinear mixed effects model) program [16]. Unlike traditional pharmacokinetic analysis where the data from each individual are analysed separately, this method deals with all patients simultaneously. Variables are not derived for each individual; instead, a population mean for each pharmacokinetic variable is derived, together with an estimate of the random variability of that variable within the population.

In addition to defining a population mean for each variable, it is also possible to determine the influence of such factors as age, weight, sex and the presence of renal failure on each variable. The statistical significance of such factors is assessed by the change which their inclusion in the model makes to the goodness of fit of the model to the data, defined by the objective function (actually, 2 × log likelihood of the model).

The model was characterized in terms of central volume of distribution (V_1) and the volume of the peripheral compartment (V_2), plasma clearance (Cl) and intercompartmental clearance (Q) (which is the product of the central volume of distribution V_1 and the rate constant for transfer from the central to the peripheral compartment). This set of four variables completely defines a basic two-compartment model. In order to determine the distribution ($T_{\frac{1}{2}}^{\alpha}$) and elimination ($T_{\frac{1}{2}}^{\beta}$) half-lives, additional runs were performed using alternative variables.

Mean plasma laudanosine concentrations in each group at each time were compared using the Mann–Whitney U test.

Results

All patients completed the study. The physical characteristics of the two groups were similar (table 1). The high plasma creatinine concentrations in the renal failure group are typical of patients in a dialysis programme.

A semi-logarithmic plot of mean (SD) plasma concentrations of 51W89 *vs* time for each group is shown in figure 1. 51W89 was not detectable in plasma after 150 min. A linear plot of laudanosine

Table 1 Patient characteristics (mean (SD) [range])

	Normal renal function (n = 15)	Renal failure (n = 17)
Age (yr)	42.9 [21.8–64.0]	43.9 [25.7–62.4]
Weight (kg)	69 (13) [55–98]	66 (12) [45–95]
Sex (M/F)	7/8	8/9
Height (cm)	170 (10) [157–190]	168 (11) [152–190]
Plasma creatinine (μmol litre^{-1})	84 (16) [60–121]	823 (265) [361–1221]
Serum albumin (g litre^{-1})	44 (5) [35–50]	39 (5) [31–47]

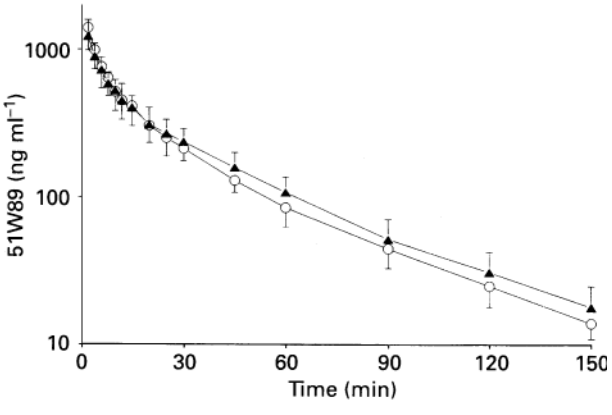

Figure 1 Semi-logarithmic plot of mean (SD) plasma 51W89 concentrations against time in health (○) and end-stage chronic renal failure (▲).

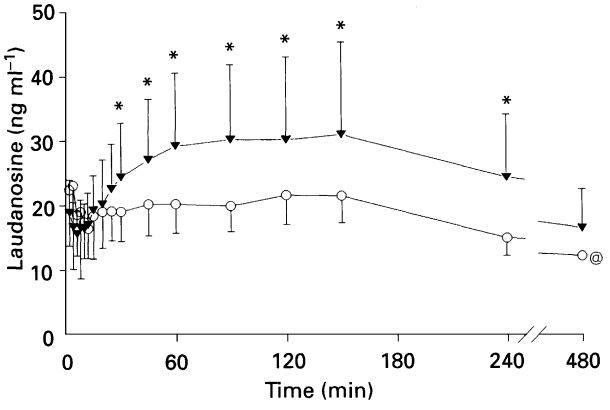

Figure 2 Mean (SD) plasma concentrations of laudanosine against time after a bolus of 51W89 0.1 mg kg^{-1} in health (○) and end-stage chronic renal failure (▼). @ = Single observation. * $P < 0.05$.

Table 2 Decrease in the objective function when "typical values" of clearance (*Cl*), V_1 and V_2 are permitted to vary between healthy and renal failure groups. **$P < 0.01$ compared with a model with fewer additional variables

Variables varying between groups	Decrease in objective function
One additional variable	
Cl	15.9**
V_1	8.1**
V_2	2.4
Two additional variables	
Cl and V_1	16.7
Cl and V_2	15.9
V_1 and V_2	12.5
Three additional variables	
Cl, V_1 and V_2	17.0

concentrations *vs* time is shown in figure 2. Mean laudanosine concentrations in the healthy group were significantly lower than in the renal failure patients from 30 to 240 min ($P < 0.05$); the plasma laudanosine concentration was above the lower limit of detection in only one healthy patient at 480 min.

A two-compartrment model was fitted to the plasma 51W89 data and plots of predicted *vs* observed concentrations, and of weighted residuals *vs* predicted plasma concentrations, suggested the model was adequate. Normalization of volume terms for body weight (thus expressing volumes in units of ml kg^{-1} and *Cl* in ml min^{-1} kg^{-1}) worsened the fit of the model, and their volume terms are therefore presented throughout without weight correction.

When the effect of renal failure was examined similarly, fitting models of the form, for example:

$$Cl = \Theta_3 + \text{renal function}.\Theta_5$$

where renal function has a value of 1 or 0, an apparently significant decrease in the objective function was found for the effects of renal function on *Cl* and on V_1. When further variables were added to test for the simultaneous effect of renal function on, for example, both *Cl* and V_1, the fit was not improved further than when renal function was allowed to influence *Cl* alone. This information is given in detail in table 2.

Table 3 Pharmacokinetic variables using the optimal model for the effect of renal function on clearance (*Cl*) of 51W89. *Q* = Intercompartmental clearance, V_1 = volume of the central compartment, V_2 = volume of the peripheral compartment

	Typical value	Standard error	Coefficient of interindividual variation
Cl (ml min^{-1})			
Healthy	293	9.9	20.1 %
Renal failure	254	12.2	20.1 %
V_1 (ml)	4520	281	34.6 %
V_2 (ml)	4650	239	22.2 %
Q (ml min^{-1})	288	22.9	Not estimated

Table 4 Distribution ($T_{\frac{1}{2}}^{\alpha}$) and elimination ($T_{\frac{1}{2}}^{\beta}$) half-lives of 51W89 in health and renal failure

	Typical value	Standard error
$T_{\frac{1}{2}}^{\alpha}$ (min)		
Healthy	4.2	0.3
Renal failure	4.2	0.5
$T_{\frac{1}{2}}^{\beta}$ (min)		
Healthy	30.0	1.2
Renal failure	34.2	1.2

Pharmacokinetic variables for the optimal model, including the effect of renal function on *Cl*, are given in table 3.

The distribution and elimination half-lives ($T_{\frac{1}{2}}^{\alpha}$ and $T_{\frac{1}{2}}^{\beta}$) for the healthy and renal failure groups are given in table 4. There was no difference between the groups in the distribution half-life ($T_{\frac{1}{2}}^{\alpha}$) The typical value of $T_{\frac{1}{2}}^{\beta}$ was 4.2 min longer in renal failure than in healthy patients ($P < 0.005$).

Consideration of the effect of weight, ideal body weight, age and sex in the healthy patients was undertaken by allowing each individual characteristic, in turn, to influence *Cl*. A highly significant effect was found for sex (a reduction in objective function of 11.3), and minor effects for weight and ideal body weight (reductions of 6.4 and 5.5). Combination of sex and age produced a further slight improvement (total reduction in objective function of 17.2), but incorporation of weight terms gave no further improvement. In the renal failure group, no significant effect on *Cl* was found for weight, ideal weight, age or sex. The optimal model for *Cl* in the healthy group was:

$$Cl = 327 \text{ ml min}^{-1} - 1.53 \text{ ml min}^{-1} \text{ year}^{-1} + 53.9 \text{ ml min}^{-1}, \text{ if male}$$

The standard errors of the estimates are given in table 5.

Table 5 Effect of age and sex on clearance (*Cl*) of 51W89 in health

Model for *Cl*	Estimate	Standard error
Intercept: ml min^{-1}	327	27
Effect of age: ml min^{-1} yr^{-1}	−1.53	0.54
Effect of sex: ml min^{-1}, if male	+53.9	12.02

Discussion

In common with attracurium, estimation of the pharmacokinetic variables of 51W89 is complicated by the problem of spontaneous peripheral degradation of the drug outside the plasma. Standard pharmacokinetic methods assume that all of the drug is eliminated from a central, homogeneous compartment into which the drug is administered. While attempts have been made to allow for this by performing a simultaneous *in vitro* experiment [17], this was not done here. A standard compartment model, embodied in the NONMEM program, was applied to provide objective data reduction within a context which would allow the delineation of the factors affecting drug disposition.

The mean clearance rate of 51W89 (293 ml min^{-1} in health) was found to be lower than that of atracurium (372 ml min^{-1}), using a similar neurolept anaesthetic technique [18], but the central volume of distribution of the two drugs was similar (4520 ml for 51W89; 3940 ml for atracurium). It is known that differences in anaesthetic technique may alter the pharmacokinetic variables of atracurium; for example, patients receiving isoflurane were reported to have higher rates of clearance than patients receiving halothane or midazolam [18], but this would not explain the difference reported here.

The variables derived for 51W89 were similar to those obtained for a combination of all of the *cis-cis* isomers together, analysed using a stereospecific analysis after a dose of atracurium; mean clearance was reported as 5.3 (SEM 0.4) ml kg^{-1} min^{-1}, with a mean central volume of distribution of 60.2 (11.9) ml kg^{-1} and a mean total volume of distribution of 154.2 (12.7) ml kg^{-1} [19].

We found a highly significant difference in mean clearance of 51W89 between healthy patients (293 ml min^{-1}) and those with end-stage renal failure (254 ml min^{-1}) ($P < 0.005$); this amounts to a reduction of approximately 13 %. It contrasts with atracurium, where clearance was similar in the two groups [1, 2]. It may be that 51W89 undergoes less Hofmann elimination than atracurium, and conversely urinary excretion of this isomer may be greater. These pharmacokinetic differences confirm the findings of a pharmacodynamic study of the recovery characteristics of 51W89 0.1 mg kg^{-1} in healthy and renal failure patients. The mean values for 75 % and 90 % recovery of T1/T0 and the recovery index (25–75 % Tl/T0) were longer in the renal failure patients, although the differences did not reach statistical significance [13].

Age and sex also seem to affect the clearance of 51W89 in healthy patients; older patients had a reduced clearance and males had a greater clearance. This effect was not observed in patients with chronic renal failure and may be a reflection of the effect of these factors on renal function. Such an effect of age on the pharmacokinetics of atracurium is now well accepted [15, 18, 20]. The effect of sex found in the present study is similar to a single previous report [18], but remains unexplained and requires further confirmation.

Plasma concentrations of laudanosine observed after administration of 51W89 are much lower than those after an equipotent dose of atracurium. After atracurium 0.5 mg kg^{-1}, the mean peak plasma laudanosine concentration in healthy patients was between 200 and 300 ng ml^{-1}, and between 300 and 400 ng ml^{-1} in chronic renal failure: in each group, the peak concentration occurred within 10 min of the dose of atracurium [7]. The mean peak plasma laudanosine concentration after 51W89 0.1 mg kg^{-1} was 23.1 ng ml^{-1} at 4 min in the healthy group and 31 ng ml^{-1} at 150 min in the renal failure group; these values are one-tenth of those seen after approximately four times the mass of atracurium. This adds further weight to the suggestion that 51W89 is less susceptible to Hofmann elimination than atracurium.

The delay in peak plasma laudanosine in the renal failure group suggests that the source of much of this laudanosine may be another metabolite, such as the product of ester hydrolysis, monoquaternary alcohol, which is also broken down to laudanosine [2]. The degree of ester hydrolysis may be increased in the renal failure group, in whom the absence of renal clearance increases the amount available for breakdown in plasma. Plasma laudanosine concentrations were significantly higher in the renal failure group from 30 to 240 min ($P < 0.05$); at 480 min the concentration of laudanosine in the renal failure group was higher than that in the single healthy patient in whom laudanosine remained detectable.

The early peak in plasma laudanosine concentration after a bolus of atracurium may result from the formation of laudanosine in the ampoule [15] or rapid metabolism of other shorter lived isomers [21]. We observed less prominent peaks in plasma laudanosine concentration after 51W89 than those observed after atracurium, and this strengthens the hypothesis that the short-lived isomers which exist in a solution of atracurium are responsible for the early peak in the laudanosine concentration.

Acknowledgement

This work was supported in part by a grant from the Wellcome Foundation plc, who also supplied 51W89.

References

1. Fahey MR, Rupp SM, Fisher DM, Miller RD, Sharma M, Canfell C, Castagnoli K, Hennis PJ. The pharmacokinetics and pharmacodynamics of atracurium in patients with and without renal failure. *Anesthesiology* 1984; **61**: 699–702.
2. Ward S, Boheimer N, Weatherley BC, Simmonds RJ, Dopson TA. Pharmacokinetics of atracurium and its metabolites in patients with normal renal function, and in patients in renal failure. *British Journal of Anaesthesia* 1987; **59**: 697–706.
3. Hunter JM, Jones RS, Utting JE. Use of atracurium in patients with no renal function. *British Journal of Anaesthesia* 1982; **54**: 1251–1258.
4. Stenlake JB, Waigh RD, Urwin J, Dewar GH, Coker GG. Atracurium: conception and inception. *British Journal of Anaesthesia* 1983; **55**: 3S–10S.
5. Chapple DJ, Miller AA, Ward JB, Wheatley PL. Cardiovascular and neurological effects of laudanosine. Studies in mice and rats, and in conscious and anaesthetized dogs. *British Journal of Anaesthesia* 1987; **59**: 218–225.
6. Ingram MD, Sclabassi RJ, Stiller RL, Cook DR, Bennett

MH. Cardiovascular and electroencephalographic effects of laudanosine in "nephrectomized" cats. *Anesthesia and Analgesia* 1985; **64**: 232.
7. Fahey MR, Rupp SM, Canfell C, Fisher DM, Miller RD, Sharma M, Castagnoli K, Hennis PJ. Effect of renal failure on laudanosine excretion in man. *British Journal of Anaesthesia* 1985; **57**: 1049–1051.
8. Lawhead RG, Matsumi M, Peters KR, Landers DF, Becker GL, Earl RA. Plasma laudanosine levels in patients given atracurium during liver transplantation. *Anesthesia and Analgesia* 1993; **76**: 569–573.
9. Stenlake JB, Waigh RD, Dewar GH, Dhar NC, Hughes R, Chapple DJ, Lindon JC, Ferrige AG, Cobb PH. Biodegradable neuromuscular blocking agents. Part 6—Stereochemical studies on atracurium and related polyalkylene diesters. *European Journal of Medicinal Chemistry* 1984; **19**: 441–450.
10. Lien CA, Belmont MR, Abalos A, Abou-Donia M, Savarese JJ. Dose response relations of 51W89 under nitrous oxide–opioid–barbiturate anesthesia. *Anesthesiology* 1993; **79**: A948.
11. Lepage JY, Malinovsky JM, Malinge M, Cozian A, Pinaud M. 51W89: Dose response, neuromuscular blocking profile and cardiovascular effects. *Anesthesiology* 1993; **79**: A945.
12. Wastila WB, Maehr RB. The pharmacological profile of 51W89, the R, cis-R cis isomer of atracurium in cats. *Anesthesiology* 1993; **79**: A946.
13. Boyd AH, Eastwood NB, Parker CJR, Hunter JM. Pharmacodynamics of the 1R *cis*-1 R *cis* isomer of atracurium (51W89) in health and chronic renal failure. *British Journal of Anaesthesia* 1995; **74**: 400–404.
14. 1983 Metropolitan Height and Mass Tables. *Statistical Bulletin Metropolitian Foundation* 1983; **64**: No 1, 4.
15. Kent AP, Parker CJR, Hunter JM. Pharmacokinetics of atracurium and laudanosine in the elderly. *British Journal of Anaesthesia* 1989; **63**: 661–666.
16. Beal SL, Sheiner LB. *NONMEM User's Guide*. San Francisco: University of California, 1979.
17. Fisher DM, Canfell PC, Fahey MR, Rosen JI, Rupp SM, Sheiner LB, Miller RD. Elimination of atracurium in humans: contribution of Hofmann elimination and ester hydrolysis versus organ-based elimination. *Anesthesiology* 1986; **65**: 6–12.
18. Parker CJR, Hunter JM, Snowdon SL. Effect of age, sex and anaesthetic technique on the pharmacokinetics of atracurium. *British Journal of Anaesthesia* 1992; **69**: 439–443.
19. Tsui D, Graham GG, Torda TA. The pharmacokinetics of atracurium isomers in vitro and in humans. *Anesthesiology* 1987; **67**: 722–728.
20. Kitts JB, Fisher DM, Canfell PC, Spellman MJ, Caldwell JE, Heier T, Fahey MR, Miller RD. Pharmacokinetics and pharmacodynamics of atracurium in the elderly. *Anesthesiology* 1990; **72**: 272–275.
21. Nigrovic V, Fox JL. Atracurium decay and the formation of laudanosine in humans. *Anesthesiology* 1991; **74**: 446–454.