CLEARANCE OF ATRACURIUM AND LAUDANOSINE IN THE URINE AND BY CONTINUOUS VENOVENOUS HAEMOFILTRATION†

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SUMMARY

We have measured the steady state urinary clearances of atracurium, given by constant infusion, and laudanosine in eight patients undergoing artificial ventilation; all had normal renal function (mean creatinine clearance 81 ml min⁻¹). Mean (SD) urinary clearance of atracurium was 0.55 (0.5) ml kg⁻¹ min⁻¹; that of laudanosine was 0.33 (0.2) ml kg⁻¹ min⁻¹. Simultaneous plasma clearances were 7.1 (1.4) ml kg⁻¹ min⁻¹ and 3.8 (1.5) ml kg⁻¹ min⁻¹, respectively. Notional haemofiltration clearances of the two substances were measured also in seven critically ill patients with renal and respiratory failure undergoing continuous venovenous haemofiltration. Mean (SD) clearances of atracurium and laudanosine in the haemofiltrate fluid were 0.11 (0.06) ml kg⁻¹ min⁻¹ and 0.09 (0.02) ml kg⁻¹ min⁻¹, respectively whilst plasma clearances were atracurium 6.7 (1.8) ml kg⁻¹ min⁻¹ and laudanosine 4.5 (1.8) ml kg⁻¹ min⁻¹. There were no significant differences between the plasma clearances of the drugs in the two groups, despite the difference in severity of sickness. Urinary clearance rates of atracurium and laudanosine were approximately 8 and 9% of that in the plasma, but the haemofiltration clearance of both substances was only 2%.

KEY WORDS


Although it was thought originally that atracurium was eliminated solely in the plasma and extracellular fluid by means of Hofmann degradation and ester hydrolysis, Fisher and his colleagues in 1986 [1] offered evidence from in vivo and in vitro work suggesting that organ elimination is responsible for the clearance of at least 60% of a dose of atracurium. Measuring organ clearance of atracurium through the kidney during anaesthesia is relevant to this problem, but is impracticable: a good urine output is difficult to establish, especially during the first 1 h of anaesthesia [2] and it necessitates catheterization of the bladder, which may not be clinically indicated; in addition, steady state plasma concentrations of atracurium, which are necessary if true urinary clearance is to be measured, may not be obtained unless an infusion of the drug is used. It was decided, therefore, to study the urinary clearance of atracurium and its metabolite, laudanosine, in intensive care patients (with normal renal function) who were receiving atracurium by constant infusion during intermittent positive pressure ventilation (IPPV).

Continuous venovenous haemofiltration (CVVH), used in the treatment of patients with acute renal failure [3], is known to contribute to the elimination from the circulation of many drugs used in intensive care [4]. It was decided also to investigate the plasma and haemofiltration clearances of atracurium and laudanosine in a group of acute renal failure patients undergoing IPPV and to compare this route of clearance with that in the urine.

PATIENTS AND METHODS

Ethics Committee approval was obtained for this study and informed written consent obtained from the patient's next-of-kin before sample
collection. We studied eight patients undergoing IPPV with normal renal function (mean creatinine clearance = 81 ml min⁻¹, range 40-110 ml min⁻¹) (group 1) and seven patients in acute renal failure on IPPV who were undergoing CVVH with a creatinine clearance of less than 5 ml min⁻¹ (group 2). All were receiving constant infusions of atracurium 0.3—0.8 mg kg⁻¹ h⁻¹ in addition to analgesia and sedation with constant i.v. infusions of morphine 2–10 mg h⁻¹ and midazolam 2–10 mg h⁻¹ as indicated clinically. Clinical details of the patients are given in table I. All those in group 1 had an indwelling urinary catheter as part of their clinical management.

Blood 5 ml was taken from an arterial cannula at least every 4 h during infusion of the drug for measurement of plasma concentrations of atracurium and laudanosine. In patients in group 1, urine 5 ml was collected from the connection of the bladder catheter to the urine collecting bag at the same time as the blood sample. The volume of urine produced in the next 60 min was noted and the urine flow derived (ml min⁻¹). Blood was collected at similar intervals from the patients in group 2 when they were receiving CVVH. Haemofiltration fluid 5 ml was collected simultaneously from the exit port of the dialysis machine (Gambro AK 10 system with FH66 fibre haemofilters). The blood flow through the filter was maintained at 125 ml min⁻¹ and the outflow from the filter restricted to give an average haemofiltrate flow of 19 ml min⁻¹ (27.4 litre day⁻¹).

The plasma samples were assayed in this department as described previously [5]. Immediately after collection, specimens of urine (50 µl)
and haemofiltrate (200 µl) were added to 1.5-ml microtest tubes containing potassium hydrogen phthalate buffer 950 µl and 800 µl, respectively; the pH had previously been adjusted to 2.5. The tubes and contents were frozen in liquid nitrogen and stored at −20 °C. The urine and haemofiltrate samples were assayed using the same HPLC technique as that used for the plasma specimens.

After the samples were analysed and it was determined which were recorded when plasma concentrations of both atracurium and laudanosine were at steady state, the corresponding plasma, urine and haemofiltration samples were used to derive the appropriate clearance values. Steady state was accepted as four consecutive plasma samples showing a variation in plasma concentration of less than 15%. The steady state plasma clearances (C/P) of atracurium were derived using the formula:

\[ \frac{C}{P} = \frac{\text{Infusion rate (ng kg}^{-1} \text{ min}^{-1})}{C_p} \]

where \( C_p \) = steady state plasma concentration.

For laudanosine, the infusion rate was calculated by assuming that one molecule of atracurium eventually breaks down to yield two molecules of laudanosine [6].

The urinary clearance for each set of estimations was derived using the formula \( UV/P \), where \( U = \) urinary concentration (ng ml\(^{-1}\)), \( V = \) urinary flow rate (ml min\(^{-1}\)) and \( P = \) plasma concentration (ng ml\(^{-1}\)). The clearance achieved with CVVH was derived using the Sieving coefficient, \( S \):

\[ Cl = S \times HF \]

where \( HF = \) haemofiltrate flow (ml min\(^{-1}\)), the Sieving coefficient being derived from the ratio of the haemofiltrate to plasma concentration, as described by Golper and others [7].

The mean plasma clearances of atracurium and laudanosine in groups 1 and 2 were compared using the Mann–Whitney \( U \) test.

### RESULTS

The mean plasma, urine and haemofiltrate concentrations of atracurium and laudanosine for each patient in groups 1 and 2, and the number of paired samples collected from each patient are shown in table II.

The mean (sd, range) plasma clearances of atracurium and laudanosine at steady state in group 1 patients are shown in table III, with the mean urinary clearances of the two substances. The renal clearances of atracurium and laudanosine were approximately 8% and 9% of the plasma clearances, respectively.

The mean plasma clearances of atracurium and laudanosine in the renal failure patients (group 2)
are also shown in Table III, with the mean notional haemofiltration clearances. The haemofiltration clearances of atracurium and laudanosine were only 1.6% and 2% of the plasma clearances, respectively.

There was no significant difference in the plasma clearances of atracurium and laudanosine between the two groups.

**DISCUSSION**

Work in cats first demonstrated that not all of a bolus dose of atracurium is degraded in the plasma: 6.9% is excreted in the urine [8]. In the first human study (1987), it was estimated that the amount of atracurium and laudanosine excreted in the urine over a period of 500 min after a bolus dose of the drug, given to three healthy, uncatheterized patients, was 2–10% [9]. No precautions could be taken to prevent further breakdown of atracurium in the urine present in the bladder in this study. More recent work by Vandenbrom, Wierda and Agoston on the pharmacokinetics of a bolus dose of atracurium, which included measurement of urinary clearance in catheterized patients, has supported the earlier findings [10].

The urinary clearances reported here are the first estimated at steady state. The mean urinary clearance of atracurium (0.6 ml kg⁻¹ min⁻¹; 8% of the plasma clearance) may be an underestimate, for atracurium breakdown may be assumed to have continued in the urine as it passed down the ureter and through the bladder. This continued degradation tended to reduce the value for the urinary concentration of atracurium (U), thus decreasing the clearance value. In contrast, the urinary concentration of laudanosine must have been increased by the same process; thus the actual urinary clearance of laudanosine should be slightly less than that reported here (0.3 ml kg⁻¹ min⁻¹; 9% of the plasma clearance). The urinary clearances of both atracurium and laudanosine are much less than those of plasma and are probably of limited clinical significance, certainly when atracurium is used as a bolus dose during general anaesthesia. However, the relevance of this route of excretion when the drug is given for hours, even days, by constant infusion in the intensive care unit is more difficult to assess.

Intensive care patients with "normal" renal function have lower creatinine clearances (mean 80 ml min⁻¹) than those of truly healthy individuals, although the difference is of little clinical significance. Renal clearance of atracurium and laudanosine during anaesthesia in healthy subjects may be expected to be greater than that reported here, but renal function during anaesthesia is usually impaired, especially during the first 60 min, and is probably not dissimilar to that found in the intensive care patient [11].

It is interesting that the plasma clearances of both atracurium and laudanosine in the more critically ill patients with renal failure were similar to those in the patients with normal renal function—findings which are compatible with those reported previously by Parker, Jones and Hunter, who used a method which did not rely on achievement of a steady state [12]. Although it has been demonstrated that the use of high doses of inotropic agents such as dopamine, dobutamine, noradrenaline and adrenaline (as used in our patients in group 2) may constrict hepatic blood flow, thus reducing hepatic metabolism of other drugs [13], there is no evidence in this study to suggest that the clearance of each substance was decreased in these ill patients.

When elimination of drugs by CVVH (or haemodialysis) is considered, only plasma protein binding and volume of distribution have been shown to be important, although these measures are not totally reliable indicators of drug clearance [14]. The haemofiltrate composition is essentially the same as that of plasma water. Thus it may be
expected that drugs which are highly protein bound or have large volumes of distribution (and are therefore found only in low concentrations in the plasma water compartment)—for example propranolol—would be cleared poorly by CVVH [14]. The protein binding of atracurium is not known for certain, although a value of 80% has been obtained by an indirect method [15]. This relatively high degree of binding, coupled with a volume of distribution in the range 172–280 ml kg\(^{-1}\) [5, 10], would suggest only limited elimination of atracurium by CVVH and, indeed, this was found to be the case in our study. The volume of distribution of the more lipophilic laudanosine is much greater (1730 ml kg\(^{-1}\) [15], which would imply even less clearance of the metabolite by CVVH, although this study does not substantiate such a hypothesis.

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REFERENCES


