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PHARMACOKINETICS OF ATRACURIUM AND LAUDANOSINE IN PATIENTS WITH HEPATIC CIRRHOSIS

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SUMMARY

The pharmacokinetic profiles of atracurium and one of its derivatives, laudanosine were studied following an i.v. bolus of atracurium 0.6 mg kg^{-1} administered to eight patients with hepatic cirrhosis and to seven healthy controls. The central volume of distribution of atracurium was greater in the patients with cirrhosis (104.6 ml kg^{-1}) compared with the controls (69.6 ml kg^{-1}) ($P < 0.05$), as was the total volume of distribution (281.8 ml kg^{-1} and 202.1 ml kg^{-1}, respectively) ($P < 0.05$). There was no significant difference in the elimination half-life of atracurium between the two groups. The total volume of distribution of laudanosine was increased in cirrhotic patients (2.68 litre kg^{-1}) compared with healthy controls (1.97 litre kg^{-1}) ($P < 0.05$), as was its elimination half-life (277 min in cirrhotic individuals; 168 min in controls) ($P < 0.05$). There was no significant difference in the clearance of laudanosine between the two groups.

Patients with hepatic cirrhosis are known to be resistant to the action of several non-depolarizing neuromuscular blocking drugs. The phenomenon was described first by Dundee and Gray for tubocurarine in 1953 [1], and has since been demonstrated for pancuronium [2] and, more recently, for vecuronium and atracurium [3]. However, the mechanism of such resistance is not clear. Furthermore, the route of elimination of laudanosine, one of the principal metabolites of atracurium, is not clearly defined. It has been shown that patients with renal failure develop greater plasma concentrations of laudanosine than do normal controls [4], but more recent work suggests that the renal clearance of laudanosine is a minor fraction of total clearance [5], as has been shown in the dog [6] and rat [7]. It is known that laudanosine undergoes significant hepatic excretion in the cat [8], although not in the dog [6]. The importance of the hepatic route of laudanosine excretion in man is not clear, although laudanosine excretion is altered in patients with biliary obstruction [9].

The present study was designed to define the pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis in comparison with a group of healthy patients undergoing general surgical procedures.

PATIENTS AND METHODS

Patients (table I)

We studied eight patients with hepatic cirrhosis scheduled to undergo elective sclerotherapy of oesophageal varices. Seven healthy patients undergoing minor surgery requiring the use of neuromuscular blockade (for example inguinal hernia repair, closure of colostomy) served as controls. All patients gave informed consent and the study was approved by the Hospital Ethics Committee.

In six of the patients with cirrhosis, the diagnosis had been confirmed by liver biopsy. In the other two, who had refused to undergo liver biopsy, the diagnosis of cirrhosis rested on the history, clinical examination and biochemical data. The aetiology of the cirrhosis was alcoholic in four patients, chronic active hepatitis in one patient, primary biliary cirrhosis in one patient and was unknown in two patients.

None of the control patients was receiving regular oral medication. Of the patients with cirrhosis, six received regular diuretics (four

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TABLE I. *Age and weight (mean (SD)) and sex of the patients studied*

	Control group ($n = 7$)	Cirrhotic group ($n = 8$)
Age (yr)	56.1 (10.7)	59.3 (14.6)
Weight (kg)	69.4 (14.7)	68.9 (8.9)
Sex (M:F)	5:2	5:3

spironolactone and two frusemide) and four were receiving H_2-receptor antagonists (three ranitidine and one cimetidine).

The preoperative laboratory data for the two groups are summarized in table II. Functional classification [10] of the patients with cirrhosis is given in table III.

Anaesthesia

Patients were premedicated with promethazine 50 mg on the evening before the operation, except

TABLE II. *Mean (SD) biochemical and haematological data (with normal range) for the control and cirrhotic groups. *Significant difference between the two groups, Mann–Whitney rank sum test: $P < 0.05$*

	Control group ($n = 7$)	Cirrhotic group ($n = 8$)	
Urea (mmol litre^{-1}) (3.0–7.0)	4.5 (0.7)	6.3 (3.9)	ns
Creatinine (μmol litre^{-1}) (60–110)	95 (17.2)	87 (12.0)	ns
Alkaline phosphatase (u. litre^{-1}) (35–130)	75 (24)	182 (116)	*
Total protein (g litre^{-1}) (57–76)	69.7 (3.3)	68.8 (5.2)	ns
Albumin (g litre^{-1}) (30–50)	42.5 (3.0)	36.2 (5.6)	*
Globulin (g litre^{-1}) (23–35)	27.2 (4.4)	32.5 (3.6)	*
Total bilirubin (μmol litre^{-1}) (2.0–17.0)	7 (2.3)	36 (24.9)	*
Alanine aminotransferase (u. litre^{-1}) (7–45)	26 (6.4)	37 (16.3)	*
Gamma-glutamyl transferase (u. litre^{-1}) (0–65)	49 (28.7)	119 (133)	ns
Haemoglobin (g dl^{-1})	13.9 (1.47)	11.1 (1.48)	*
Platelets (10^9 litre^{-1}) (150–400)	260 (23)	109 (40.2)	*
Prothrombin ratio (1.0)	—	1.56 (0.26)	

TABLE III. *Classification of the patients with cirrhosis in terms of hepatic functional reserve [10] and numbers in each group*

	Child's group [10]		
	A	B	C
Serum bilirubin (μmol litre^{-1})	< 34	34–50	> 50
Serum albumin (g litre^{-1})	> 35	30–35	< 30
Ascites	None	Easily controlled	Poorly controlled
Neurological disorder	None	Minimal	Advanced
Nutrition	Excellent	Good	Poor
No. patients	4	3	1

one patient with cirrhosis who exhibited signs of encephalopathy (Child's group C), in whom it was omitted. Anaesthesia was induced with thiopentone 150–400 mg; opioids were omitted in the patients with cirrhosis, but the control group received fentanyl 75–200 μg at induction. Neuromuscular blockade was provided by atracurium 0.6 mg kg^{-1}. The trachea was intubated and anaesthesia was maintained by controlled ventilation with 66% nitrous oxide in oxygen, supplemented with enflurane up to 1%. End-tidal carbon dioxide concentration was monitored using a Datex "Normocap" and maintained in the range 4–5.5%. After the completion of surgery, residual neuromuscular blockade was antagonized with neostigmine 2.5 mg and atropine 1.2 mg. All i.v. drugs were given through a cannula in a vein in the dorsum of one hand; the cannula was flushed with 0.9% saline 5 ml before and immediately after the administration of atracurium. Venous blood samples were taken from a 14-gauge cannula placed in an antecubital vein of the opposite arm.

Analytical technique

Blood samples (2.5 ml) were taken into heparinized syringes before injection of atracurium and at 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, 60, 75, 90, 120, 150, 180, 210, 240, 300 and 360 min after the administration of atracurium. The sample was transferred immediately to a tube containing 0.02 ml of sulphuric acid 1.5 mol $litre^{-1}$ and cooled in ice for 30 s during transfer to an adjacent laboratory. Plasma was separated without delay using an MSE Centaur 2 centrifuge and four 0.2-ml aliquots were transferred into 1.5-ml polypropylene tubes containing 0.8 ml of sulphuric acid 0.015 mol $litre^{-1}$. These samples were frozen immediately in liquid nitrogen and stored at −20 °C until required for analysis.

Fresh standards were prepared for each patient. Using 0.2-ml aliquots of the patient's plasma taken before injection of atracurium, and a series of five drug dilutions, a standard curve was constructed for a range of plasma concentrations up to 10 μg ml^{-1} for atracurium and 500 ng ml^{-1} for laudanosine.

Extraction of atracurium and laudanosine from plasma (by the method of Simmonds [11]) was undertaken separately, in duplicate, for each drug. Before extraction, an internal standard of N-methyl laudanosine 20 μl (2.5 μg ml^{-1}) was added to each sample for assay of laudanosine; an internal standard of tubocurarine 20 μl (150 μg ml^{-1}) was added to each sample for the assay of atracurium.

Extracted samples were assayed by high performance liquid chromatography (HPLC). Each drug was assayed separately using an isocratic elution. For atracurium, a Spherisorb CN 5-μm column and a mobile phase of acetonitrile: sodium sulphate 0.02 mol $litre^{-1}$ in sulphuric acid 0.005 mol $litre^{-1}$ (60:40) was used. For the laudanosine assay a Partisil 10-μm strong cation exchange column and a mobile phase of acetonitrile:sodium sulphate 0.012 mol $litre^{-1}$ in sulphuric acid 0.005 mol $litre^{-1}$ (70:30) was used. For both drugs the column temperature was 50 °C and the mobile phase flow rate was 2 ml min^{-1}.

A 3000 Perkin–Elmer fluorescence detector was used for drug detection with excitation set at 280 nm and emission at 320 nm. Peak heights were measured directly from a chart recorder and peak height ratios of drug to internal standard were used to calculate drug concentration.

Analyses were completed within 4 days of sample collection. Because of technical problems, some samples were lost during analysis. Results for atracurium were available therefore for all but one of the patients with cirrhosis and for laudanosine in all but one of the controls. In two of the eight patients with cirrhosis, plasma laudanosine concentration was measured only up to 240 min after atracurium injection.

Data for plasma concentrations of atracurium were fitted to a two-component exponential by weighted non-linear least squares analysis and kinetic parameters calculated using the convention of Ward and colleagues [12].

Plasma concentrations of laudanosine between 180 and 360 min after atracurium injection were fitted to a single exponential term from which the elimination half-life was calculated. Total area under the plasma concentration–time curve was calculated as the sum of the area up to 360 min, evaluated by the trapezoidal rule, plus the area under the extrapolated plasma concentration curve from 360 min to infinity [13]. The total area under the curve was used to calculate the plasma clearance of laudanosine and, together with the terminal half-life, the volume of distribution was calculated. As laudanosine was not injected as a single bolus, but formed *in vivo* from atracurium, it was not possible to calculate model compartmental volumes or distribution rate constants.

The Mann–Whitney rank sum test was used for

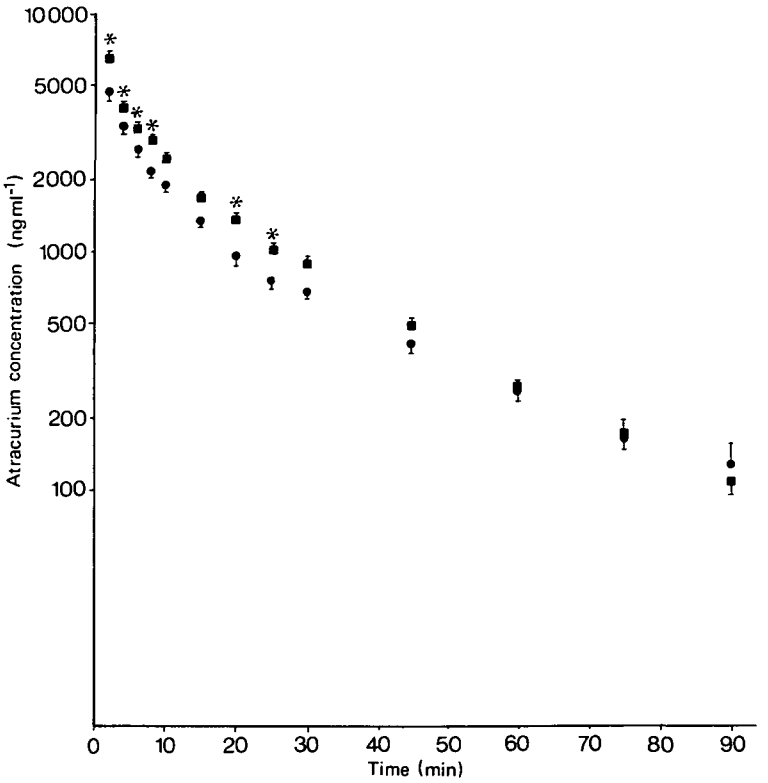

FIG. 1. Mean (SEM) plasma atracurium concentration (ng ml^{-1}) with time (min). ■ = Healthy group; ● = cirrhotic group. *Significant difference between the two groups using the Mann–Whitney rank sum test: $P < 0.05$.

statistical comparisons between the different groups of data [14].

RESULTS

Standard curves were linear over the measured range of drug concentration. The laudanosine assay was sensitive to 5 ng ml^{-1} and the coefficient of variation was typically 9 % at 100 ng ml^{-1}. The atracurium assay was sensitive to 25 ng ml^{-1} and had a coefficient of variation of 8 %.

Atracurium

Comparisons at each sample time revealed that the atracurium concentration was significantly lower in the patients with cirrhosis at 2, 4, 6, 8, 20 and 25 min after injection, although the difference failed to reach significance at the 10- and 15-min sample times (fig. 1).

The derived pharmacokinetic indices are shown in table IV. No significant difference was found in the distribution ($T_{\frac{1}{2}}^{\alpha}$) or elimination ($T_{\frac{1}{2}}^{\beta}$) half-lives of atracurium in the patients with cirrhosis compared with the healthy controls. Both the central (V_1) and the total (V^{β}) volumes of distribution, and the clearance (Cl) were significantly greater in the cirrhosis group.

Laudanosine

Analysis at each time shows that the plasma concentration of laudanosine in the cirrhosis group was significantly lower than the controls at 2, 4, 6, 8 and 10 min, and significantly greater at 360 min after the injection of atracurium. At other times there was no significant difference between the two groups (fig. 2).

Derived parameters are compared in table V for the control group and for the six patients with cirrhosis in whom sampling extended to 360 min. Both the elimination half-life and the total volume of distribution were significantly greater in the cirrhotic patients than in the controls. There was no significant difference in the clearance of laudanosine between the two groups.

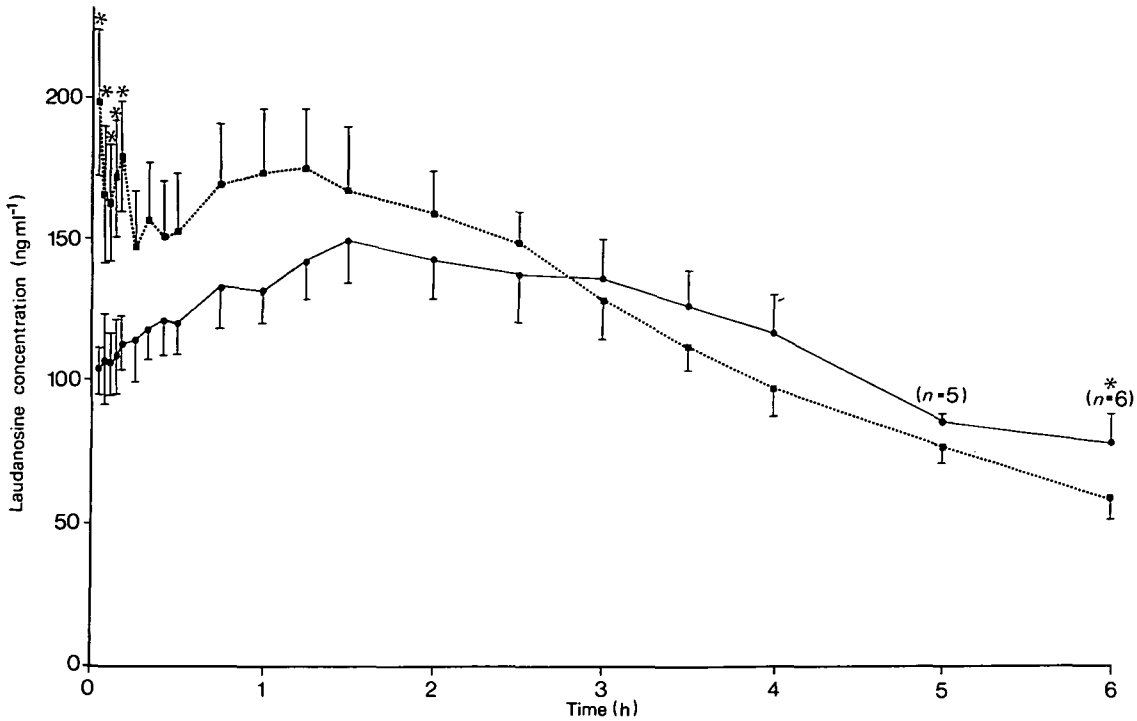

FIG. 2. Mean (SEM) plasma laudanosine concentration (ng ml^{-1}) with time (h). ■ = Healthy group; ● = cirrhotic group. *Significant difference between the two groups using the Mann–Whitney rank sum test: $P < 0.05$.

TABLE IV. *Derived pharmacokinetic parameters for atracurium (mean (SD)). *Significant difference between the two groups using the Mann–Whitney rank sum test: P < 0.05*

	Control group ($n = 7$)	Cirrhotic group ($n = 7$)	
$T_{\frac{1}{2}}^{\alpha}$ (μιν)	3.00 (1.01)	3.75 (1.56)	ns
$T_{\frac{1}{2}}^{\beta}$ (μιν)	20.9 (5.3)	24.5 (4.9)	ns
V_1 (*ml kg*$^{-1}$)	69.6 (22.6)	104.6 (39.7)	*
V^{β} (ml kg^{-1})	202.1 (71.4)	281.8 (71.2)	*
Cl (ml min^{-1} kg^{-1})	6.6 (1.2)	8.0 (1.7)	*

TABLE V. *Pharmacokinetic parameters for laudanosine (mean (SD)). *Significant difference between the two groups using the Mann–Whitney rank sum test: P < 0.05*

	Control group ($n = 6$)	Cirrhotic group ($n = 6$)	
$T_{\frac{1}{2}}$ (min)	168 (51.3)	277 (71.8)	*
V (litre kg^{-1})	1.97 (0.58)	2.68 (0.75)	*
Cl (ml min^{-1} kg^{-1})	8.3 (2.1)	6.9 (1.7)	ns

DISCUSSION

The pharmacokinetics of atracurium and its derivative, laudanosine have been studied previously in healthy patients and patients in renal failure [4,5,15,16] and in patients suffering from acute hepatic failure [17]. The present study has compared the pharmacokinetics of atracurium and laudanosine in adult patients chronically ill from hepatic cirrhosis with a group of healthy patients well matched for age, weight and sex.

The patients with cirrhosis in the present study, who were undergoing an elective course of treatment, had much less derangement of hepatic function than those suffering from acute hepatic failure reported by Ward and Neill [17]. Indeed, most of the present patients were classified to Child's groups A and B (table III). However, the degree of liver dysfunction was similar to that of a group of patients in whom resistance to atracurium was demonstrated [3].

It is accepted that elimination of atracurium from the body is dependent chiefly upon Hofmann elimination and ester hydrolysis, rather than organ-based metabolism and excretion [16]. The present finding that the elimination half-life of atracurium is similar in patients with hepatic cirrhosis and patients with normal hepatic function lends support to this concept. The tendency to a small and statistically insignificant prolongation of elimination half-life in the patients with cirrhosis (table IV), is similar to that reported in a group of patients with acute hepatic failure [17], and in patients with chronic renal failure [5,15].

Both the central and total volumes of distribution of atracurium were increased in the cirrhosis group. The volumes of distribution of several other non-depolarizing neuromuscular blocking drugs, for example pancuronium and fazadinium, are also increased in patients with cirrhosis [18,19]. An increased volume of distribution may provide a kinetic correlate for the earlier pharmacodynamic findings of Bell and colleagues [3] that, in patients with cirrhosis, the time to maximum depression of the twitch response following a bolus dose of atracurium was prolonged from 109 to 186 s, whilst time to 20% recovery of A′/A of the train-of-four was shortened from 43 to 34 min. The volumes of distribution of atracurium in the healthy patients reported here are similar to those found by Fahey and co-workers (V_1 60 ml kg^{-1}; V_{area} 182 ml kg^{-1}) [15], although they are rather larger than those reported by Ward and colleagues [12].

The clearance of atracurium was greater in patients with cirrhosis. Presumably, this reflects the spontaneous degradation of atracurium throughout its increased total volume of distribution, rather than any difference in its treatment by specific organs.

Taking into account the different doses of atracurium used in different studies, the magnitude and time course of the plasma concentration of laudanosine in the healthy patients reported here are in good agreement with previous results [4,5]. The peak laudanosine concentration, 198 ng ml^{-1}, was reached 2 min after the injection of atracurium. The time course of the plasma laudanosine concentration in the patients with cirrhosis was different, however, achievement of the peak laudanosine concentration (149 ng ml^{-1}) being delayed until 90 min after the administration of atracurium.

In descriptive terms, the present results demonstrate that, during the first 10 min after a bolus of atracurium, the plasma concentration of laudanosine was lower in patients with cirrhosis, whereas after 6 h the plasma concentration was significantly higher in that group.

Detailed consideration of the pharmacokinetics of laudanosine in man following a bolus of atracurium is complicated, as the extent, rate and time course of generation of laudanosine are not easily defined. Although there is evidence from *in vitro* work [20] that each molecule of atracurium is degraded to two molecules of laudanosine, there are many available pathways and it is conceivable that some of the intermediary metabolites are metabolized or excreted by routes which do not lead to the appearance of laudanosine in plasma. Although attempts have been made to overcome the limitations of a descriptive approach by fitting data on plasma concentration of laudanosine to a simple model [5], the model-independent ap- [5]. The clearance of laudanosine in the patients certain parameters. Thus it has been found that the terminal half-life of laudanosine, estimated from plasma concentration between 3 and 6 h after atracurium injection, was prolonged significantly, by a factor of about 1.6, in patients with cirrhosis. The clearance of laudanosine in the present group of healthy patients (8.3 ml kg^{-1} min^{-1}) is in reasonable agreement with the value of 10 ml kg^{-1} min^{-1} found by Ward and colleagues [5]. The clearance of laudanosine in the patients

with cirrhosis was not significantly lower than in the healthy group, suggesting that the main cause for the prolonged elimination of laudanosine from the patients with cirrhosis lies with the expanded distribution volume.

It is tempting to relate the increased volumes of distribution of atracurium and laudanosine in the patients with cirrhosis to the salt and water retention which occur in this condition. In individual patients, however, the volume of distribution of atracurium was not related to the degree of ascites, which was severe in only one patient. Furthermore, the lipophilicity of laudanosine and its high volume of distribution render salt and water retention unlikely as the sole explanation for our findings. The extent of plasma protein and tissue binding of both atracurium and laudanosine is uncertain, and so it is difficult to speculate on the influence of these processes on the present results. At present, therefore, the cause of the alterations in the pharmacokinetics of atracurium and laudanosine in patients with cirrhosis remains uncertain.

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REFERENCES

1. Dundee JW, Gray TC. Resistance to d-tubocurarine chloride in the presence of liver damage. *Lancet* 1953; **2**: 16–17.
2. Ward ME, Adu-Gyamfi Y, Strunin L. Althesin and pancuronium in chronic liver disease. *British Journal of Anaesthesia* 1975; **47**: 1199–1204.
3. Bell CF, Hunter JM, Jones RS, Utting JE. Use of atracurium and vecuronium in patients with oesophageal varices. *British Journal of Anaesthesia* 1985; **57**: 160–168.
4. 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.
5. 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.
6. Hennis PJ, Fahey MR, Canfell PC, Shi W-Z, Miller RD. Pharmacology of laudanosine in dogs. *Anesthesiology* 1986; **65**: 56–60.
7. Scheepstra, GL, Vree TB, Crul JF, van der Pol F, Reekers-Ketting J. Convulsive effects and pharmacokinetics of laudanosine in the rat. *European Journal of Anaesthesiology* 1986; **3**: 371–383.
8. Neill EAM, Chapple DJ. Metabolic studies in the cat with atracurium: a neuromuscular blocking agent designed for non–enzymic inactivation at physiological pH. *Xenobiotica* 1982; **12**: 203–210.
9. Vine P, Boheimer N, Ward S, Weatherley BC, Buick A, Smith I. Laudanosine pharmacokinetics after bolus atracurium in patients with hepato–biliary dysfunction. *British Journal of Anaesthesia* 1986; **58**: 1327P.
10. Child CG. Major problems in clinical surgery. In: Child CG, ed. *The Liver and Portal Hypertension*, Vol. 1. Philadelphia: Saunders, 1964; 50.
11. Simmonds RJ. Determination of atracurium, laudanosine and related compounds in plasma by high-performance liquid chromatography. *Journal of Chromatography* 1985; **343**: 431–436.
12. Ward S, Neill EAM, Weatherley BC, Corrall JM. Pharmacokinetics of atracurium besylate in healthy patients (after a single i.v. bolus dose). *British Journal of Anaesthesia* 1983: **55**: 113–118.
13. Gibaldi M, Perrier D. *Pharmacokinetics*, 2nd Edn. New York: Marcel Dekker, 1982; 433.
14. Mosteller F, Rourke REK. *Sturdy Statistics*, 1st Edn, Reading, Massachusetts: Addison-Wesley, 1972; 54.
15. 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.
16. Ward S, Weatherley BC. Pharmacokinetics of atracurium and its metabolites. *British Journal of Anaesthesia* 1986; **58**: 6S–10S.
17. Ward S, Neill EAM. Pharmacokinetics of atracurium in acute hepatic failure (with acute renal failure). *British Journal of Anaesthesia* 1983; **55**: 1169–1172.
18. Duvaldestin P, Agoston S, Henzel D, Kersten UW, Desmonts JM. Pancuronium pharmacokinetics in patients with liver cirrhosis. *British Journal of Anaesthesia* 1978; **50**: 1131–1136.
19. Duvaldestin P, Saada J, Henzel D, Saumon G. Fazadinium pharmacokinetics in patients with liver disease. *British Journal of Anaesthesia* 1980; **52**: 789–794.
20. Stiller RL, Ryan Cook D, Chakravorti S. (1985) *In vitro* degradation of atracurium in human plasma. *British Journal of Anaesthesia* 1985; **57**: 1085–1088.