PHARMACOKINETICS OF ATRACURIUM IN ANAESTHETIZED INFANTS AND CHILDREN


Atracurium, a non-depolarizing neuromuscular blocking drug with an intermediate duration of action, is metabolized by non-specific esterases and decomposes spontaneously via Hofmann elimination (Basta et al., 1982; Merrett, Thompson and Webb, 1983). In vitro about two-thirds of atracurium is degraded by ester hydrolysis and one-third by the Hofmann reaction (Stiller, Brandom and Cook, 1985; Stiller, Cook and Chakravorti, 1985). Thus, each pathway plays an important role in the degradation of atracurium; laudanosine is the major end product of each pathway. Neither true- or pseudo-cholinesterase has any effect on the inactivation of atracurium, and the nature of the non-specific esterases has been poorly defined. In patients with liver disease, esterase activity may be reduced, the protein binding of drugs may be affected, body fluid compartments may be altered, and the renal excretion of drugs decreased (Duvaldestin et al., 1978). These changes could affect the pharmacokinetics of atracurium.

In addition, age-related differences in dose requirements and duration of action of atracurium between infants, children and adults have been reported (Brandom, Rudd and Cook, 1983; Brandom et al., 1984). Since these changes could be the result of age-related alterations in either the pharmacokinetics or pharmacodynamics of atracurium, we have studied the pharmacokinetics of atracurium in infants and in children with normal or abnormal liver function.

SUMMARY

The pharmacokinetics of atracurium were studied in infants and children anaesthetized with isoflurane and nitrous oxide in oxygen. There were no significant differences in volume of distribution (area) (139 v. 152 ml kg⁻¹), clearance (5.1 v. 5.3 ml kg⁻¹ min⁻¹), T½ (2.1 v. 2.0 min), or T₁/2 (19.1 v. 20.3 min) between children with normal hepatic and renal function and those with moderately impaired hepatic function presenting for hepatic transplantation. There were significant differences in volume of distribution (area) (176 v. 139 ml kg⁻¹) and in clearance of atracurium (9.1 v. 5.1 ml kg⁻¹ min⁻¹) between infants and children with normal excretory function. In infants the clearance of atracurium in ml m⁻² min⁻¹ (153 v. 133) tended to be greater and the T½ and T₁/2 tended to be shorter (1.0 v. 2.0 and 13.6 v. 19.1) than in children with normal excretory function; however, these trends did not reach statistical significance. Plasma laudanosine concentration was around 100 ng ml⁻¹ greater in patients with liver disease than in normal children from 15-45 min following a bolus of atracurium 0.5 mg kg⁻¹.

PATIENTS AND METHODS

Two groups of eight children aged between 2 and 10 yr, inclusive, and one group of six infants aged between 1 and 8 months, inclusive, were studied.
All patients were about to undergo surgical procedures during which tracheal intubation and the monitoring of intra-arterial pressure would be beneficial. The study was approved by the institutional review board and informed consent was obtained from a parent. The control group of children had a mean age of 6.1 yr (±1.1 SEM), body weight 24.8 kg (±5.5), and a body surface area 0.9 m² (±0.13). These patients had normal hepatic and renal function and acid-base balance was normal. The children with liver disease had a mean age of 3.3 yr (±0.6), weight of 15.3 kg (±1.4) and a surface area of 0.62 m² (±0.04). Children in the control group were older (P < 0.05) and tended to be larger (as reflected by weight and surface area) than those with liver failure, but all children in both groups were near the 50th percentile (± 13) by weight for their age. Three of the patients with liver disease had chronic rejection of transplanted livers and five had biliary atresia with failed Kasai procedures and evidence of portal hypertension; all were producing urine in clinically adequate volumes. Prothrombin and partial thromboplastin times, and total bilirubin, alkaline phosphatase, GGT, SGOT, SGPT and albumin concentrations were obtained in both groups of children at the time of the study (table I). Patients requiring liver transplantation had statistically significant increases in the total bilirubin, alkaline phosphatase, SGOT, and SGPT concentrations (P < 0.05); GGT concentration tended to be lower in the control patients. Thus, these patients had moderate to severely impaired hepatic function (Class B–C of Child’s classification) (Child, 1964).

The infants had a mean age of 5.5 months (±1.1), weight 5.1 kg (±0.7), and a surface area 0.29 m² (±0.25). They were presenting for a variety of cardiovascular or pulmonary procedures; all were producing urine in clinically adequate volumes.

General anesthesia was induced in all patients with either nitrous oxide and isoflurane in oxygen (by inhalation) or thiopentone 4–7 mg kg⁻¹ i.v.; anesthesia was maintained with nitrous oxide and isoflurane (1% end-tidal) in oxygen during the placement of intravascular catheters. Fentanyl 3–5 µg kg⁻¹ was given as a supplement, if needed.

Atracurium 0.5 mg kg⁻¹ was administered i.v. over 10 s. Heparinized arterial blood samples (1–2 ml) were drawn at 1.5, 3, 5, 7.5, 10, 15, 30, 45 and 60 min after the bolus was given. If clinically necessary, additional doses of fentanyl or a dose of pancuronium 0.1 mg kg⁻¹ were given during this period. These drugs have been shown not to interfere with the assay of atracurium. Because of the time required for the positioning of the patient and preparation of the skin, little blood loss and only minimal cardiovascular change occurred during the period of arterial blood sampling. The blood sample was promptly dispensed into polypropylene vials and spun in an Eppendorf Model 5412 high-speed centrifuge for 20 s. Plasma was transferred quickly into another polypropylene vial containing 3N HCl 0.01 ml and frozen in dry ice-acetone slush (−70 °C). Measurement of the concentrations of atracurium and laudanosine was by specific high pressure liquid chromatography (Stiller, Brandom and Cook, 1985).

The plasma atracurium concentration against time curve for each patient was fitted to a two-compartment exponential equation using a non-linear least square analysis adapted from Yamaoka, Tanigowakay and Uno (1981). From the macrokinetic parameters (A, α, B, β) the volume of the first compartment (V₁), volume of distribution (area) (Vₕarea), plasma half-lives (T₁α and T₁β) and plasma clearance (Cl) were determined from standard formulae as used by Ward and Neill (1983). Since the elimination of atracurium is presumed to be from both compartments, estimation of microkinetic constants is impossible. The volumes and clearance were expressed in terms of both body weight and surface area.

The pharmacokinetic variables for the two groups of children, and the normal children v.
TABLE II. Atracurium pharmacokinetics in children (mean ± SEM)  

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<tr>
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<th>Normal liver function (n = 8)</th>
<th>Impaired liver function (n = 8)</th>
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<tr>
<td>$T_{1/2}^a$ (min)</td>
<td>2.1 ± 0.2</td>
<td>2.0 ± 0.2</td>
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<tr>
<td>$T_{1/2}^b$ (min)</td>
<td>19.1 ± 1.6</td>
<td>20.3 ± 1.4</td>
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<tr>
<td>$V_t$ (ml kg$^{-1}$)</td>
<td>52.6 ± 2.0</td>
<td>46.0 ± 2.6</td>
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<tr>
<td>$V_{area}$ (ml kg$^{-1}$)</td>
<td>139.0 ± 8.3</td>
<td>152.2 ± 9.1</td>
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<tr>
<td>$Cl$ (ml kg$^{-1}$ min$^{-1}$)</td>
<td>5.1 ± 0.2</td>
<td>5.3 ± 0.4</td>
</tr>
<tr>
<td>$V_{D}$ (ml m$^{3}$)</td>
<td>3590.5 ± 236</td>
<td>3729.6 ± 340</td>
</tr>
<tr>
<td>$Cl$ (ml m$^{-2}$ min$^{-1}$)</td>
<td>133.4 ± 14.3</td>
<td>128.7 ± 11.3</td>
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TABLE III. Atracurium pharmacokinetics in infants (n = 6) (mean ± SEM). *Significantly different than children (table II)  

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<th>Normal liver function (n = 8)</th>
<th>Impaired liver function (n = 8)</th>
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<tr>
<td>$T_{1/2}^a$ (min)</td>
<td>1.0 ± 0.2</td>
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<tr>
<td>$T_{1/2}^b$ (min)</td>
<td>13.6 ± 0.6</td>
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<tr>
<td>$V_t$ (ml kg$^{-1}$)</td>
<td>50.55 ± 2.6</td>
<td></td>
</tr>
<tr>
<td>$V_{area}$ (ml kg$^{-1}$)</td>
<td>176.7 ± 9.1*</td>
<td></td>
</tr>
<tr>
<td>$Cl$ (ml kg$^{-1}$ min$^{-1}$)</td>
<td>9.1 ± 0.7*</td>
<td></td>
</tr>
<tr>
<td>$V_{D}$ (ml m$^{3}$)</td>
<td>2994.0 ± 136.3</td>
<td></td>
</tr>
<tr>
<td>$Cl$ (ml m$^{-2}$ min$^{-1}$)</td>
<td>153.2 ± 9.6</td>
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FIG. 1. Mean plasma laudanosine concentrations (ng ml$^{-1}$) over time in normal children and those with liver failure following a bolus of atracurium 0.5 mg kg$^{-1}$.

infants, were compared by Student’s $t$ test or the Mann–Whitney test where appropriate. Differences were considered significant when $P < 0.05$. Two-tailed tests were used.

RESULTS

There was no difference in the pharmacokinetic variables when expressed in terms of either weight or surface area between the two groups of children (table II). When the infants were compared with the control children, the $\alpha$ and $\beta$ half-lives tended to be shorter, clearance (ml m$^{-2}$ min$^{-1}$) tended to be more rapid, and there were significant differences in the volume of distribution (ml kg$^{-1}$) and in clearance (ml kg$^{-1}$ min$^{-1}$) (table III). Volume of distribution (area) (ml m$^{-2}$) was similar in infants and children.

Laudanosine was detectable in the plasma in all patients studied. However, the shape of the laudanosine concentration–time curve was different in the two groups of children. In children without liver disease, laudanosine concentrations peaked early (within 3–4 min), reaching approximately 600 ng ml$^{-1}$, and then decreased (fig. 1). In patients with liver disease, two peak plasma laudanosine concentrations were observed; however, the maximum plasma laudanosine concentrations reached was no more than 400 ng ml$^{-1}$. The rate of decline of plasma laudanosine concentrations in the patients with liver failure appeared to parallel that in the children without liver disease.

DISCUSSION

This study was designed to assess the influence of both liver function and age on the pharmacokinetics of atracurium. Atracurium is not significantly metabolized in or excreted through the liver, nor cleared through the kidney. Thus, conceptually, atracurium is internally cleared through ester hydrolysis and Hofmann elimination. In this study moderate to severely impaired liver function had no effect on the kinetics of atracurium; clearance and the volume of distribution were similar in the normal and in the patients with liver failure. Hence, $T_{1/2}^b$ was similar. Ward and Neill (1983) evaluated the kinetics of atracurium in adults with acute hepatic failure self-induced by paracetamol. In their study the volume of distribution of atracurium was statistically larger in the patients with liver failure than in normal patients, and the clearance of atracurium tended to be greater in these patients. Because of the relationship between these variables, $T_{1/2}^b = 0.693 V_D/Cl$, changes in the volume of distribution ($V_D$) and in clearance ($Cl$) can offset one another and result in similar $T_{1/2}^b$. In patients hypoproteininaemic from severe chronic liver disease, pseudocholines- terase activity, coagulation factors and drug metabolizing activity may be limited (Duvaldestin, Lebrault and Chauvin, 1983). Although the
kinetics of atracurium have not been studied in such patients, one suspects that non-specific esterase activity and, hence, the metabolism of atracurium may be severely limited.

Changes in the volume of distribution, protein binding and kinetics have been noted for other myoneural blockers in patients with moderate liver disease. For example, the metabolism and biliary excretion of pancuronium and vecuronium are decreased in patients with liver disease (Duvaldestin et al., 1978; Somogyi, Shanks and Triggs, 1977; Duvaldestin et al., 1982). Thus, only extremely severe liver disease has any potential influence on the kinetics of atracurium; renal disease has no influence (Fahey et al., 1984). Although the kinetics of atracurium are normal in patients with renal and liver failure, laudanosine tends to accumulate in such patients. This is not unexpected, since laudanosine is excreted by the kidney and metabolized by the liver (Fahey et al., 1984; Sharma et al., 1984). The secondary peaks of laudanosine seen in our patients with liver failure may be a reflection of alternative routes of atracurium metabolism.

The infants tended to have shorter $\alpha$ and $\beta$ half-lives than the children; the volume of distribution and the clearance (ml kg$^{-1}$) were significantly greater in infants than in children. If the $T_{1/2}^{\beta}$ were constant, the clearance of atracurium would be linearly related to the volume of distribution with a slope of 0.693/$T_{1/2}^{\beta}$. The correlation coefficient between clearance (ml kg$^{-1}$ min$^{-1}$) and volume of distribution (ml kg$^{-1}$) was 0.68 in our normal infants and children. Age-related differences in the extracellular fluid volume are mirrored by differences in the volume of distribution for other blocking agents (for example, tubocurarine and vecuronium) (Fisher et al., 1982; Fisher, Castagnoli and Miller, 1985). Specifically, infants have a large extracellular fluid volume (ml kg$^{-1}$) and a large volume of distribution for myoneural blocking drugs. Indeed, the volume of distribution of atracurium decreased with advancing age ($r = -0.73$); clearance, likewise, decreased with age ($r = -0.60$); $T_{1/2}^{\beta}$ did not correlate with age. In contrast to those of tubocurarine and vecuronium, the $T_{1/2}^{\beta}$ of atracurium was not prolonged in infants as the volume of distribution increased. The more rapid elimination half-life and higher clearance of atracurium in infants is consistent with the previously observed shorter duration of neuromuscular blockade in this age group (Brandon et al., 1984). Untested pharmacodynamic differences might also exist.

ACKNOWLEDGEMENT

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REFERENCES


