EFFECT OF AGE, SEX AND ANAESTHETIC TECHNIQUE ON THE PHARMACOKINETICS OF ATRACURIUM

C. J. R. PARKER, J. M. HUNTER AND S. L. SNOWDON

SUMMARY

We have defined the pharmacokinetics of atracurium besylate 0.25 mg kg⁻¹ in 41 patients anaesthetized with 0.9% isoflurane end-tidal, 0.5% halothane end-tidal or midazolam 3–10 mg as a supplement to 66% nitrous oxide in oxygen. The pharmacokinetic profile was affected by age, sex and anaesthetic technique. Advancing age was associated with a reduced clearance and a longer elimination half-time; clearance was greater and elimination half-time was shorter in males than in females. Clearance was also greater in patients anaesthetized with isoflurane than with the two other techniques. Age, sex and anaesthetic technique did not significantly affect the volume of distribution. (Br. J. Anaesth. 1992; 69: 439-443)

KEY WORDS


Age is known to affect the pharmacokinetics of several non-depolarizing neuromuscular blocking drugs including pancuronium [1, 2], tubocurarine and dimethyltubocurarine [3], and vecuronium [4]; in general the plasma clearance is reduced and the elimination half-time prolonged in the elderly. The pharmacokinetics of atracurium have been studied in the elderly in two previous investigations [5, 6], but there are some discrepancies in the results. Kent, Parker and Hunter [5] found the sole difference between elderly and young adults to be an increase in elimination half-time in the elderly. This finding was confirmed in a later, smaller study by Kitts and others [6], in which the mean elimination half-time of the younger group (15.7 min), studied previously by those authors, was the shortest reported in any group of anaesthetized healthy adults. Kitts and colleagues [6] also found a greatly increased volume of distribution in the elderly and an unchanged total clearance, despite a reduction in the calculated organ-dependent clearance.

Whilst previous pharmacokinetic studies have generally used a standardized anaesthetic technique, for example 0.5% halothane in nitrous oxide and oxygen [6] or 0.8% enflurane end-tidal in nitrous oxide and oxygen [5], none has so far investigated the influence of anaesthesia on the pharmacokinetics of atracurium. The effects of sex on the disposition of atracurium are also unknown; indeed, the sex of the patients has not been stated in some previous reports.

The aim of this study was to describe the pharmacokinetic profile of atracurium in healthy adults anaesthetized by one of three different techniques, and to explore the influence of age, sex and anaesthetic technique. Some other findings in this group of patients have been reported previously [7].

PATIENTS AND METHODS

We studied 41 patients (table I). All were healthy and were undergoing minor surgery requiring the use of neuromuscular block. The study was approved by the Ethics Committee of the Royal Liverpool Hospital and informed consent was obtained from each patient, in the ward before surgery. The patients were studied in three groups, which differed only in the technique used to maintain anaesthesia.

Premedication consisted of promethazine 50 mg or diazepam 10 mg, orally on the night before surgery, or cyclizine 37.5–50 mg with morphine 7.5–10 mg i.m. 1 h before surgery. In patients admitted to hospital on the day of surgery, premedication was omitted.

Anaesthesia was induced with fentanyl 25–200 μg and thiopentone 250–500 mg. In one group, anaesthesia was maintained with 0.9% isoflurane end-tidal and 66% nitrous oxide in oxygen; in a second group, maintenance was with 0.5% halothane end-tidal in nitrous oxide and oxygen; in the third group, no volatile anaesthetic agent was used, but the nitrous oxide in oxygen was supplemented with i.v. midazolam 3–10 mg.

The volatile anaesthetic concentrations were chosen to be comparable fractions of MAC [8]. End-tidal concentrations of volatile anaesthetic agents were monitored using an infra-red absorption monitor (Datex Normac). This was calibrated before the outset of the study with reference to a flame ionization detector (W.T.I.), and on each day of the study using a standard calibration cylinder (Datex Quickcal).

After induction of anaesthesia, electromyographic monitoring of the response of the adductor pollicis of one hand was commenced. Two i.v. cannulae were inserted: one was used for withdrawal of blood...
TABLE I. Physical characteristics of the patients in the three groups (mean (range or SD))

<table>
<thead>
<tr>
<th></th>
<th>Isoflurane</th>
<th>Halothane</th>
<th>Midazolam</th>
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</thead>
<tbody>
<tr>
<td>Number</td>
<td>15</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>37.0 (19.7-65.1)</td>
<td>37.8 (21.6-54.7)</td>
<td>37.3 (15.3-57.2)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.7 (11.2)</td>
<td>68.2 (7.6)</td>
<td>66.8 (14.2)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>8:7</td>
<td>8:8</td>
<td>4:6</td>
</tr>
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TABLE II. Pharmacokinetic variables for each group (mean (SD)).

<table>
<thead>
<tr>
<th></th>
<th>Isoflurane</th>
<th>Halothane</th>
<th>Midazolam</th>
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</thead>
<tbody>
<tr>
<td>Vd** (litre)</td>
<td>4.48 (0.65)</td>
<td>4.00 (0.76)</td>
<td>3.94 (0.69)</td>
</tr>
<tr>
<td>Cl (ml min⁻¹)**</td>
<td>424 (54)</td>
<td>362 (44)</td>
<td>372 (37)</td>
</tr>
<tr>
<td>T1/2 (min)</td>
<td>18.7 (2.8)</td>
<td>20.0 (3.0)</td>
<td>19.4 (3.2)</td>
</tr>
</tbody>
</table>

FIG. 1. Values of atracurium clearance for each patient according to the anaesthetic technique and sex (■ = male; □ = female).

samples; the other, in a vein in the opposite forearm, was used for administration of atracurium.

After 20 min, when the end-tidal concentration of volatile anaesthetic agent (if used) was stabilized, atracurium 0.25 mg kg⁻¹ was given by constant rate infusion over a period of 10 min. Ventilation was controlled and the trachea intubated when appropriate; end-tidal carbon dioxide tension was maintained in the range 4.0-5.3 kPa (Datex Capnomac). Pharmacological antagonism of neuromuscular block was not used.

Blood samples (2.5 ml) were obtained before and at 1, 2, 4, 6, 8 and 10 min after the start of the infusion, and at 1, 2, 4, 6, 8, 10, 15, 20, 25, 30, 40, 50, 60, 75 and 90 min after the end of the infusion. The heparinized blood samples were immediately acidified and cooled, and plasma was separated promptly. The plasma was frozen rapidly in liquid nitrogen and stored at -20 °C, until subsequent analysis. Details of the analysis of plasma concentration of atracurium have been given previously [7].

Data analysis

Equations arising from a two-compartment pharmacokinetic model with elimination from both compartments were fitted to the plasma concentration profile, using non-linear least squares regression as described previously [7]. This allows the identification of the central volume of distribution, V1, and the hybrid elimination rate constant, β, and hence the elimination half-time. The clearance and steady state volume of distribution were estimated using standard non-compartmental formulae [9]. Volume terms were expressed as absolute values, and not divided by body weight [10].

Comparisons between the groups and between the sexes were performed using the Kruskal-Wallis and Mann-Whitney rank sum tests, respectively. The relationship between pharmacokinetic variables and age was examined using Pearson’s correlation coefficient. Where a pharmacokinetic variable appeared to be affected by more than one explanatory factor, multivariate linear regression was applied; the significance of added regressors was tested using the F test.

RESULTS

Estimates of the pharmacokinetic variables are summarized for each group in table II as mean (SD).

Effect of anaesthetic technique

The clearance was greater in the group anaesthetized with isoflurane than in the two other groups (Kruskal-Wallis H = 10.4, P < 0.01). This is illustrated in figure 1, in which the values of clearance are shown for each patient by anaesthetic technique and sex.

Both the central and steady state volumes of distribution were also greater in the group anaesthetized with isoflurane, but these differences were not significant (central volume of distribution: Kruskal-Wallis H = 4.52, P > 0.1; steady state volume of distribution: H = 5.84, P > 0.05). Although the elimination half-time was shortest in the group anaesthetized with isoflurane, and longest in the group anaesthetized with halothane, the differences between the groups are small and not significant.

Effect of age

The univariate correlation of each of the pharmacokinetic variables with age when all the patients are considered together is shown in table III. There is a
significant negative correlation between clearance and age, and a significant positive correlation between elimination half-time and age (fig. 2). The two measures of volume of distribution were not significantly correlated with age.

Effect of sex

The possible difference in volume of distribution between the sexes was evaluated using the Mann-Whitney rank sum test, considering the patients from all the three groups together. There was no significant difference between the sexes in either the central volume of distribution (Mann-Whitney $U = 162; P > 0.1$) or the steady state volume of distribution (Mann-Whitney $U = 170; P > 0.1$).

In view of the relationships demonstrated above between elimination half-time and age, and between clearance and both age and anaesthetic technique, further analysis was undertaken using multiple linear regression. The details of the effect of sex on clearance in the context of a regression of clearance on age, sex and two dummy parameters to separate the three groups is shown in table IV (upper panel); clearance was greater in male subjects, by an average of $49 \text{ ml min}^{-1}$.

The influence of sex on elimination half-time in the context of a bivariate regression of half-time on age and sex is shown in table IV (lower panel). There was a significant difference between the sexes, the elimination half-time being greater by a mean of about $1.9 \text{ min}$ in females. Addition of two further parameters to the regression (not shown in table IV), to separate the three groups, failed to reduce the residual error significantly.

DISCUSSION

Description of the pharmacokinetics of atracurium is complicated by its unique mechanisms of degradation; it may be expected to undergo spontaneous decomposition at any site in the body. However, the identification of a compartmental pharmacokinetic model with peripheral degradation is not possible

![Fig. 2. Values of atracurium elimination half-time plotted against the age of the patient; there is a significant positive correlation ($r = +0.58; P < 0.001$). The least squares regression line is shown. + = Isoflurane; ▲ = halothane; □ = midazolam.](https://academic.oup.com/bja/article-abstract/69/5/439/303493/1)

<table>
<thead>
<tr>
<th>TABLE IV. Relationship between clearance and sex of the patients, in the context of a multivariate linear regression of clearance on age, sex and anaesthetic technique, and relationship of elimination half-time to sex in the context of a bivariate regression on age and sex: regression coefficients and their standard errors, values of $F$ and $P$ for the inclusion of sex in the final model and degrees of freedom of the numerator and denominator</th>
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<tbody>
<tr>
<td>Regression coefficient</td>
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<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Clearanee (ml min$^{-1}$)</td>
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<tr>
<td>Sex ($m = 1; f = 0$)</td>
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<tr>
<td>$T_{1/2}^p$ (min)</td>
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<tr>
<td>Sex ($m = 1; f = 0$)</td>
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The present finding that the elimination half-time was increased with advancing age is consistent with both previous reports on the subject [5, 6], although none of the patients in the present study was as old as those studied by either Kitts and others [6] (whose elderly patients were aged 74-76 yr) or by Kent, Parker and Hunter [5] (71-97 yr). When the present results are considered together with those two previous studies, and in the absence of any conflicting evidence, we may have considerable confidence in the conclusion that the elimination half-time of atracurium increases with advancing age.

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In the present study, this was related to a reduced clearance in the elderly, in contrast with the two previous studies [5, 6]. The isolated finding of Kitts and others [6] that distribution volume increased in the elderly has not been confirmed. Indeed, the volume of distribution was found to be reduced in the elderly for tubocurarine, dimethyltubocurarine [3] and vecuronium [4], and to be unchanged for pancuronium [1, 2].

It seems difficult to account for the presently reported effects of age in terms of the spontaneous degradation of atracurium, for all the patients were normothermic, without metabolic derangement and were undergoing artificial ventilation to normocapnia. It is tempting to point to a deterioration in function of liver and kidneys with advancing age [14], and in this respect the present finding that clearance is reduced with advancing age lends at least qualitative support to the finding by Fisher and others [13] that about 61% of total atracurium clearance is organ dependent.

There have been no formal studies of the effect of sex or of anaesthetic technique on the pharmacokinetics of the non-depolarizing neuromuscular blocking drugs, and so direct comparison of the present results, on the effect of sex, with previous work is not possible. It is clear, however, that sex exerts an influence on the pharmacokinetics of several drugs [15], and the sexes differ in the activity of plasma esterases [16]. Whilst the role of esterases in the metabolism of atracurium is uncertain, the degradation of atracurium in vitro is more rapid in plasma than in buffer at the same pH, and the rate of degradation is slowed by the esterase inhibitors [17]. Thus the present finding of a difference between the sexes in the clearance and half-time of atracurium awaits confirmation and remains unexplained; to suggest a role for ester hydrolysis is speculative.

There is a paucity of information on the effects of anaesthesia on the pharmacokinetics of the non-depolarizing neuromuscular blocking drugs. Plainly, the pharmacokinetics of therapeutic doses of atracurium cannot be studied in the absence of an anaesthetic, and so the elucidation of the effects of anaesthesia must be comparative. In a study similar to this, it was found that halothane (0.5-0.7% or 1.0-1.2% end-tidal) did not affect the pharmacokinetics of tubocurarine, compared with a neuroleptanaesthetic technique [18]. Likewise, the clearances of vecuronium was found to be similar in three groups of patients anaesthetized with enflurane, isoflurane or fentanyl [19]. The present finding, that the clearance of atracurium was reduced by halothane and by midazolam supplementation of anaesthesia compared with isoflurane, finds no precedent amongst previous studies of the non-depolarizing neuromuscular blocking drugs.

It is increasingly clear that volatile anaesthetic agents influence the disposition of several drugs including fentanyl [20] and verapamil [21] in the dog, and lignocaine in man [22]. Moreover, different volatile anaesthetic agents may have different effects [23]. Fentanyl and verapamil are more lipophilic than atracurium, and have a different pharmacokinetic profile, yet it is clear that anaesthesia has a profound effect on the disposition of several drugs, and on regional blood flow distribution [24].

Whilst hepatic blood flow is better preserved during anaesthesia with isoflurane than with halothane [24], the clearance of atracurium is considerably less than the hepatic blood flow, and its hepatic extraction must be low. In view of other evidence that atracurium undergoes substantial organ-dependent metabolism [13], it is conceivable that the present finding that clearance is affected by the anaesthetic technique reflects the effect of anaesthetic agents on organ blood flow or function.

ACKNOWLEDGEMENTS

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REFERENCES

3. Matteo RS, Backus WW, McDaniel DD, Brotherton WP,
ATRACURIUM PHARMACOKINETICS


