RELATIONSHIP BETWEEN VOLUME OF DISTRIBUTION OF ATRACURIUM AND BODY WEIGHT

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SUMMARY

We have determined the central and steady state volumes of distribution of atracurium 0.25 mg kg\(^{-1}\) in 41 healthy adult patients. Volume of distribution, corrected for body weight (ml kg\(^{-1}\)), correlated negatively with body weight (\(r = -0.612\) for central volume of distribution; \(r = -0.737\) for the steady state volume of distribution). When expressed as an absolute volume, neither central nor steady state volume of distribution correlated significantly with body weight (\(r = 0.120\) and \(r = 0.131\), respectively). These data cast doubt upon the necessity for the dose of atracurium to be related to body weight in the healthy adult population. (Br. J. Anaesth. 1993; 70: 443-445)

KEY WORDS


It is usual to administer non-depolarizing neuromuscular blocking drugs in a dose related to body weight, and to express volume terms in a pharmacokinetic analysis as a ratio to body weight, for example in the units ml kg\(^{-1}\). It has been shown, however, that for pancuronium the volume of distribution is not correlated closely with body weight [1]. Beemer, Bjorksten and Crankshaw [2] reported the volume of distribution of atracurium at steady state during an i.v. infusion given to a series of 20 patients, and noted that the variability within the population increased when the estimates were "corrected" for total body weight.

The question arises as to the nature of the relationship between volume terms in the description of atracurium pharmacokinetics, and body weight. The aim of the present study was to describe the relationship between volume of distribution of atracurium and body weight in healthy adults, who were studied as part of a project to determine the relationship between the pharmacokinetics and pharmacodynamics of atracurium.

METHODS AND RESULTS

Patients and anaesthesia

We studied 41 healthy patients undergoing minor surgery requiring the use of neuromuscular blocking drugs. The study was approved by the Ethics Committee of the Royal Liverpool Hospital and informed consent was obtained from all patients, who were studied in three groups, which differed only in the technique used to maintain anaesthesia.

The physical characteristics of the patients are summarized in table I. Other results from 38 of these patients have been reported previously [3]; the present series included three others in addition, in whom electromyographic recordings were technically unsatisfactory.

Premedication consisted of either 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. Premedication was omitted in those patients admitted to hospital on the day of surgery.

Anaesthesia was induced with fentanyl 25-200 \(\mu\)g and thiopentone 250-500 mg, and maintained with 66% nitrous oxide in oxygen. In group one this was supplemented with 0.9% isoflurane end-tidal; in group two supplementation was with 0.5% halothane end-tidal; in a third group no volatile anaesthetic agent was used, but midazolam 3-10 mg i.v. was given. End-tidal concentrations of volatile anaesthetic agents were monitored using an infra-red analyser (Datex Normac).

After induction of anaesthesia, electromyographic monitoring of the adductor pollicis of one hand was undertaken with a Medelec MS6. Two i.v. cannulae were sited: one for withdrawal of blood samples, the other for administration of atracurium.

After a period of 20 min during which 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 partial pressure was maintained in the range 4.0-5.3 kPa (Datex Capnomac). Pharmacological antagonism of neuromuscular block was not used.

Measurement of plasma concentrations of atracurium

Heparinized blood samples (2.5 ml) were taken 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,
Table I. Physical characteristics and pharmacokinetic results of the patients in each of the three groups (mean (range or SD)). No statistically significant difference in pharmacokinetic variables between the groups (P > 0.05)

<table>
<thead>
<tr>
<th></th>
<th>Isoflurane (n = 15)</th>
<th>Halothane (n = 16)</th>
<th>Midazolam (n = 10)</th>
</tr>
</thead>
<tbody>
<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>
<tr>
<td>Compartmental analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K (litre/min⁻¹)</td>
<td>4.48 (0.65)</td>
<td>4.00 (0.76)</td>
<td>3.94 (0.69)</td>
</tr>
<tr>
<td>p (min⁻¹)</td>
<td>0.038 (0.006)</td>
<td>0.035 (0.005)</td>
<td>0.036 (0.005)</td>
</tr>
<tr>
<td>a (min⁻¹)</td>
<td>0.26 (0.12)</td>
<td>0.23 (0.05)</td>
<td>0.24 (0.06)</td>
</tr>
<tr>
<td>kₐ1 + kₜ (min⁻¹)</td>
<td>0.10 (0.04)</td>
<td>0.09 (0.02)</td>
<td>0.09 (0.02)</td>
</tr>
<tr>
<td>Non-compartmental analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vd∞ (litre)</td>
<td>8.71 (0.70)</td>
<td>8.00 (1.02)</td>
<td>7.97 (1.26)</td>
</tr>
</tbody>
</table>

40, 50, 60, 75 and 90 min after the end of the infusion. The plasma was frozen rapidly and stored at −20 °C until subsequent analysis by HPLC, using the method described in detail previously [3]. Plasma concentrations were measured in duplicate, with a coefficient of variation typically less than 6% (range 1.6-11.1%).

Data analysis

In order to obtain an estimate of the central volume of distribution, 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. The Gauss–Newton algorithm was used to define the least squares solution, with each datum point weighted as its inverse. The fit was implemented by a program written by the authors in Microsoft “Quickbasic” v4.0, and run on an 8086-based IBM-compatible personal computer. A two-compartment model was preferred to a simpler one-compartment model in all cases using the F test of residual variance (values of F ranged from 19.1 (2, 37 d.f.) to 1193 (2, 38 d.f.)). The individual rate constants of a two-compartment model with elimination from both compartments are not identifiable; the following combination of parameters was identified:

\[ V_1 = \text{central volume of distribution} \]
\[ \alpha = \text{hybrid distribution rate constant} \]
\[ \beta = \text{hybrid elimination rate constant} \]
\[ k_1 + k_p = \text{sum of exit rate constants from the peripheral compartment} \]

In order to obtain a measure of total volume of distribution, the steady state volume of distribution (Vd∞) was estimated using the standard non-compartmental formula [4]:

\[ V_{d∞} = \left[ \frac{\text{infused dose}}{AUC} \right] \left[ \frac{\text{AUMC} \cdot T}{AUC} \right] \]

where AUC = area under the curve; AUMC = area under the first moment curve.

Linear correlations were evaluated with Pearson’s product–moment correlation coefficient.

The profile of mean plasma concentration for 38 of the 41 patients has been illustrated previously [3].

The mean central and steady state volumes of distribution, for each group are shown in table I, as absolute values. The central volume of distribution, expressed as an absolute volume (in litre) is plotted against body weight for isoflurane (+), halothane (V) and midazolam (D). Upper panel: central volume of distribution; lower panel: steady state volume of distribution. No significant correlation is evident between each measure of volume of distribution and body weight (r = +0.120 for central volume of distribution; r = +0.131 for steady state volume of distribution).

When the central and steady state volumes of distribution were normalized for body weight (units ml kg⁻¹) there was a highly significant negative correlation of both measures of volume of dis-

Fig. 1. Volume of distribution (in litre) plotted against body weight for isoflurane (+), halothane (V) and midazolam (D). Upper panel: central volume of distribution; lower panel: steady state volume of distribution. No significant correlation is evident between each measure of volume of distribution and body weight (r = +0.120 for central volume of distribution; r = +0.131 for steady state volume of distribution).
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tribution with body weight: central volume of distribution \( r = -0.612, P < 0.0001 \); steady state volume of distribution \( r = -0.737, P < 0.0001 \).

COMMENT

Although the pharmacokinetics of atracurium have been studied extensively in the adult patient, the volume of distribution (the ratio of the amount of drug present to the plasma concentration) has generally been expressed in the units ml kg\(^{-1}\). This practice can be justified only if the volume of distribution is proportional to body weight. It has been noted, within one population studied by Beemer, Bjorksten and Crankshaw [2], that the variance of the estimated steady state volume of distribution is increased on division of the absolute volume by body weight.

The present results are similar to those obtained for pancuronium by McLeod, Hull and Watson [1], who showed that volume of distribution, estimated by either \( V^\theta \) or \( V^\omega \), did not correlate significantly with body weight. The negative correlations between volume of distribution in ml kg\(^{-1}\) and weight presently reported simply represent the negative correlation of weight with its inverse. Their strength does, however, emphasize that the use of an inappropriate correction for body weight complicates rather than simplifies the comparison of results from subjects of differing weights. It is possible that this may have reduced the power of previous studies in which the volumes of distribution of groups of subjects were compared on an ml kg\(^{-1}\) basis.

Clearly, the present results apply only within the adult range in which they were obtained. Some relationship between body size and volume of distribution presumably exists in children but, although Brandom and colleagues were careful to consider an appropriate correction for body size in this group [5], it is not clear that this should be body weight. Indeed, volume terms were more nearly comparable between infants and children when comparison was based on body surface area.

One corollary of the present finding is that, if atracurium is administered in a dose related to body weight (that is, a fixed mg kg\(^{-1}\) dose), a relatively greater plasma concentration may be produced in heavier than in lighter adults; presumably, the drug may therefore achieve a greater effect. In a retrospective study in which the dose requirement for tubocurarine was judged on clinical grounds [6], Dundee showed that the dose administered during the first 2 h of anaesthesia was not related closely to body weight. Furthermore, division of the dose given by body weight did not diminish significantly the interindividual variability in the dose given.

The finding that the volume of distribution is independent of body weight is consistent with the water solubility of the drug and the fact that at least some of the variation in body weight between healthy adults is a result of variation in adiposity. The result cannot be extrapolated to more lipophilic drugs.

In retrospect, it would have been desirable to have assessed the physique of the present series of patients more thoroughly, for example with the use of skinfold thickness, to ascertain if it is possible to derive an index of body size which is related closely to the volume of distribution of atracurium. It does, however, remain clear that body weight is an unsuitable measure.

REFERENCES