DEPENDENCE OF THE NEUROMUSCULAR BLOCKING EFFECT OF ATRACURIUM UPON ITS DISPOSITION

C. J. R. PARKER AND J. M. HUNTER

SUMMARY

We have assessed the profiles of plasma concentration of atracurium and its neuromuscular blocking effect on the first response of the train-of-four measured by electromyography after a short infusion of atracurium 0.25 mg kg\(^{-1}\), in 38 patients anaesthetized by one of three techniques. Measures of the temporal profile of neuromuscular block were found to correlate with pharmacokinetic variables. When anaesthetic technique was taken into account in a multivariate model, the time to onset of 10\% depression of T\(_{1:0}\) correlated positively with the central volume of distribution (P < 0.05). The change in T\(_{1:0}\) during the 1 min after 10\% depression, and the logit of maximum depression were both correlated negatively with the central volume of distribution (P < 0.05 and P < 0.01, respectively). Both the times to 20\% and 50\% recovery of T\(_{1:0}\) correlated strongly negatively with clearance (P < 0.0001 for both measures). The findings support the conclusion that the effect of atracurium is dependent upon its disposition.

KEY WORDS

Neuromuscular relaxants: atracurium Pharmacodynamics Pharmacokinetics.

Whilst it is now generally assumed that the magnitude and duration of effect of the non-depolarizing neuromuscular blocking drugs are dependent upon the time course of their disposition, direct evidence for this supposition is scant. Early attempts by Aladjemoff, Dikstein and Shafrir [1] and by Cohen, Paulsen and Elert [2] to define the relationship between the plasma concentration of tubocurarine and its effects met with limited success because of the difficulty of the assay for tubocurarine, and the qualitative assessment of effect [1]. Matteo, Spector and Horowitz [3], in 1974, defined a correlation between the plasma concentration of tubocurarine and its effects met with limited success because of the difficulty of the assay for tubocurarine, and the qualitative assessment of effect [1]. Matteo, Spector and Horowitz [3], in 1974, defined a correlation between the plasma concentration of tubocurarine and depression of the twitch tension of the adductor pollicis during recovery from a single dose, albeit with considerable scatter in individual results.

It was argued, however [4, 5], that such a correlation between plasma concentration and effect during recovery from a bolus of a neuromuscular blocking drug is only weak evidence for a causal dependence of effect upon disposition, as both plasma concentration and effect predictably decline in parallel during the recovery phase. The controversy surrounding this question has abated since the demonstration that tubocurarine and the nicotinic acetylcholine receptor dissociate over a time course of milliseconds, and the wide acceptance of a biophase model proposed by Hull and colleagues [6, 7] and by Sheiner and colleagues [8]. Perhaps the strongest evidence for a link between disposition and effect was provided for pancuronium by Shanks, Somogyi and Triggs [9], who demonstrated, in 27 patients, a strong positive correlation between the rate of recovery of the evoked twitch height and the elimination rate constant.

Although the biophase model has been applied to atracurium [10–14], the dependence of effect upon disposition has not been established for this drug. The main aim of the present study is to attempt to do so, in the paradigm of Shanks, Somogyi and Triggs [9].

PATIENTS AND METHODS

We studied 38 patients; all were healthy and undergoing elective 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 all patients. The patients were studied in three groups, which differed only in the technique used to maintain anaesthesia and were comparable for age, weight and sex (table I).

<p>| TABLE I. Physical characteristics of the patients in the three groups (mean (range or SD) or number) |
|---------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Sex (M:F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoflurane (n = 14)</td>
<td>36.4 (19.7–65.1)</td>
<td>63.0 (11.3)</td>
</tr>
<tr>
<td>Halothane (n = 14)</td>
<td>39.7 (22.1–54.8)</td>
<td>67.4 (11.1)</td>
</tr>
<tr>
<td>Midazolam (n = 10)</td>
<td>37.3 (15.3–57.2)</td>
<td>66.8 (14.2)</td>
</tr>
</tbody>
</table>

C. J. R. PARKER, M.A., M.B., B.CHIR., F.C.ANAES.; J. M. HUNTER, M.B., CH.B., F.C.ANAES.; University Department of Anaesthesia, 4th Floor, Royal Liverpool Hospital, Prescot Street, P.O. Box 147, Liverpool L69 3BX. Accepted for Publication: December 16, 1991.
and thiopentone 250–500 mg, and maintained with 66% nitrous oxide in oxygen. In one group this was supplemented with 0.9% isoflurane (end-tidal); in a second group 0.5% halothane (end-tidal) was used; in a third group no volatile anaesthetic agent was given, but the nitrous oxide in oxygen was supplemented with midazolam 3–10 mg i.v. End-tidal concentrations of volatile anaesthetic agents were monitored using an infra-red analyser (Datex “Normac”).

After induction of anaesthesia, we commenced electromyographic monitoring of the height of the surface compound action potential of the adductor pollicis of one hand in response to supramaximal stimuli to the ulnar nerve. Trains of four stimuli at 2 Hz were repeated every 12.5 s throughout the study. The ratio of the height of the first response to the control height (T1:T0), and the ratio of the height of the fourth to the first response (T4:T1) were measured.

A cannula was placed in a vein in the antecubital fossa of the arm used for electromyographic monitoring, and used for obtaining blood samples. Another cannula was placed in a vein in the opposite forearm, for the administration of atracurium.

After a period of 20 min when the end-tidal concentration of volatile anaesthetic agent (if used) stabilized and the electromyographic baseline established, 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; neuromuscular monitoring was continued until both the ratios T1:T0 and T4:T1 were 80% or greater (in one patient in the isoflurane group, electromyographic monitoring was discontinued when the ratio T1:T0 had recovered to 78.5%). After recovery from neuromuscular block and the end of surgery, anaesthesia was discontinued, spontaneous ventilation re-established and the trachea extubated.

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, 40, 50, 60, 75 and 90 min after the end of the infusion. The samples were immediately acidified and cooled and the plasma separated promptly. The plasma was frozen rapidly in liquid nitrogen and stored at −20 °C until subsequent analysis. Three plasma samples were stored at each time; two were used for analysis of atracurium concentration in duplicate, one was held in reserve in case of technical problems.

An internal standard of tubocurarine 4 μg was added to each plasma sample, and the drugs were extracted from the plasma using solid phase cartridges with an active phenyl group (“Bond Elut”). At this time a standard curve was prepared which simulated plasma concentrations of atracurium 100, 200, 500, 1000 and 2000 ng ml\(^{-1}\).

The extracted drug was assayed by high pressure liquid chromatography; an isocratic technique was used. Details of the column and mobile phase have been described previously [15]. A Perkin Elmer LS4 spectrofluorimeter, with a 3-μl flow cell was used for drug detection; the excitation wavelength was set to 280 nm and the detector to 320 nm. The method measures total plasma atracurium concentration, without separation of enantiomers.

The assay was sensitive to a plasma atracurium concentration of about 5 ng ml\(^{-1}\). The coefficient of variation between duplicates varied between 1.6% and 11.1%, and was typically less than 6%. The standard curve was linear; in no patient was the correlation coefficient for the standard curve less than 0.994, and it was usually greater than 0.998.

The heights of the first and fourth responses were measured for each train-of-four stimulus and T1:T0 calculated. The time course of the depression of T1:T0 was characterized by the summary measures shown in figure 1. These measures were chosen to indicate the time and rate of onset of block, of the maximum effect achieved, and of the time and rate of recovery.

**Data analysis**

In order to obtain estimates of the central volume of distribution and of the elimination half-life, equations arising from a pharmacokinetic model with two well-stirred compartments, with drug administration into and sampling from the central compartment, and with elimination allowed directly from both compartments, were fitted to the plasma concentration profile. As such a model is not uniquely identifiable [16], the following combination of parameters was identified: $V_\text{c} = \text{central volume of distribution}$

$\alpha = \text{hybrid distribution rate constant}$

$\beta = \text{hybrid elimination rate constant}$

$k_1 + k_\text{en} = \text{sum of the rate constants for transfer of drug from the peripheral to the central compartment, and for direct elimination from the peripheral compartment, respectively.}$

These parameters were fitted to the data using the least squares criterion with each plasma concentration weighted as its inverse. Data obtained both during and after the end of the infusion were used simultaneously to fit the model, with the exception of the points 1 min after the start of the infusion and 1 min after its end, which were excluded; at these times, systematic discrepancy between the data and the model predictions was noted, which arose presumably from circulatory delay. The fit was obtained using the Gauss–Newton algorithm; partial derivatives were obtained numerically and convergence was accepted when each Gauss–Newton step changed the estimate of each parameter by less than 0.1%.

The area under the curve (AUC) was calculated by the trapezoidal rule up to the last data point, together with the AUC extrapolated beyond the last data point using the previously estimated value of $\beta$. The area under the first moment curve (AUMC) was calculated in a similar manner. These areas were used to provide estimates of clearance and steady state volume of distribution using standard formulae [17].
ATRACURIUM EFFECT AND DISPOSITION

The possible relationship between each of the measures of effect and measures of disposition was explored initially by calculation of Pearson's correlation coefficient. Multivariate regression, with two dummy parameters to separate the groups, was applied to allow account to be taken of the influence of anaesthetic technique upon the measure of effect. Thus the linear multivariate model was fitted:

\[ y = \alpha_0 + \beta_1 x + \beta_2 i + \beta_3 h + \varepsilon \]

where \( y \) = effect variable of interest, e.g. time to 50% recovery; \( x \) = a pharmacokinetic variable, e.g. clearance; \( \alpha_0 \) = an intercept; \( \beta_1 \) = slope of the relationship between \( y \) and \( x \); \( i \) and \( h \) = dummy variables which take the value 1 if the patient received isoflurane or halothane respectively, and 0 otherwise; \( \beta_2 \) and \( \beta_3 \) = corresponding regression coefficients; \( \varepsilon \) = residual error not explained by the regression model; its size forms the basis of comparison between alternative regression models.

Added variable plots [18] were used to illustrate graphically the dependence of an effect variable on a pharmacokinetic variable in the multivariate context. This is a plot of the residuals (\( \varepsilon \)) of the regression for the model without the added variable (i.e. without the \( \beta_1 x \) term above), plotted against the residuals of the regression of the added variable on the explanatory variables already in the model (i.e. the residuals of the regression of \( x \) on the dummy variables \( i \) and \( h \) above). The slope of the relationship between these two sets of residuals is equivalent to \( \beta_1 \); the strength of the correlation between the two sets of residuals represents the strength of the relationship between \( y \) and \( x \) in the multivariate model above.

RESULTS

The measures of the time course of depression of T1:T0 are summarized, together with pharmacokinetic measures, in table II.

The plasma atracurium concentration profile for each group is given as mean (SD) at each time in figure 2.

The univariate correlation coefficient between each of the measures of the depression of T1:T0 and each of the measures of disposition is shown in table III. Of the 30 possible comparisons, eight achieved statistical significance at the 5% level. There was no significant correlation between any of the measures of effect and either \( T^0 \) or the rate constants \( \alpha \) or \( k_{21} + k_{20} \).

The positive findings have been analysed further.

Time to 10% depression of T1:T0

When all patients are considered together, the time to 10% depression correlated positively with the central volume of distribution (\( r = +0.33; 36 \) d.f.; \( P < 0.05 \)) (fig. 3). Taking account of the anaesthetic technique, multivariate analysis revealed a stronger underlying relationship (\( F = 5.68; 1,34 \) d.f.; \( P < 0.05 \)).

Change during 1 min after 10% depression of T1:T0

Amongst all the patients, the percentage change during the 1 min after the achievement of 10% depression of T1:T0 correlated negatively with the central volume of distribution (\( r = -0.34; P < 0.05 \)). Taking account of the anaesthetic technique, multivariate regression with separation of the three groups revealed a stronger underlying relationship (\( F = 7.34; 1,34 \) d.f.; \( P < 0.05 \)).

Maximum block

As the data for maximum block had a variance which is not homogeneous between groups (table II), the logit transformation was applied before correlation with indices of disposition was attempted. There was a weak negative correlation with the central volume of distribution (\( r = -0.32; 36 \) d.f.; \( 0.05 < P < 0.1 \)). Taking account of the anaesthetic technique, multivariate analysis revealed a stronger relationship (\( F = 11.5; 1,34 \) d.f.; \( P < 0.01 \)).
TABLE II. Measures of the time course of depression of T1: T0 of the train-of-four, and measures of the pharmacokinetic profile for each group (mean (SD))

<table>
<thead>
<tr>
<th></th>
<th>Isoflurane (n = 14)</th>
<th>Halothane (n = 14)</th>
<th>Midazolam (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacodynamics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to 10% depression (min)</td>
<td>4.3 (0.6)</td>
<td>4.2 (0.6)</td>
<td>4.8 (0.9)</td>
</tr>
<tr>
<td>Change in the 1 min after 10% depression (%)</td>
<td>32.6 (5.9)</td>
<td>32.1 (7.9)</td>
<td>27.8 (6.0)</td>
</tr>
<tr>
<td>Maximum depression (%)</td>
<td>97.0 (1.4)</td>
<td>95.8 (2.1)</td>
<td>93.8 (4.5)</td>
</tr>
<tr>
<td>Logit maximum depression</td>
<td>1.56 (0.21)</td>
<td>1.42 (0.25)</td>
<td>1.26 (0.32)</td>
</tr>
<tr>
<td>Time to 20% recovery (min)</td>
<td>34.7 (6.0)</td>
<td>34.9 (6.8)</td>
<td>29.2 (7.8)</td>
</tr>
<tr>
<td>Time to 50% recovery (min)</td>
<td>45.6 (7.5)</td>
<td>45.3 (8.6)</td>
<td>39.0 (8.0)</td>
</tr>
<tr>
<td><strong>Pharmacokinetics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_e$ (ml kg$^{-1}$)</td>
<td>72.2 (12.6)</td>
<td>58.3 (10.2)</td>
<td>62.6 (21.7)</td>
</tr>
<tr>
<td>$V^m$ (ml kg$^{-1}$)</td>
<td>141 (21.4)</td>
<td>120 (15.7)</td>
<td>125 (37.1)</td>
</tr>
<tr>
<td>Clearance (ml min$^{-1}$ kg$^{-1}$)</td>
<td>6.9 (1.1)</td>
<td>5.4 (0.7)</td>
<td>5.8 (1.0)</td>
</tr>
<tr>
<td>$T_1$ (min)</td>
<td>18.8 (2.8)</td>
<td>20.2 (3.2)</td>
<td>19.4 (3.2)</td>
</tr>
<tr>
<td>$\alpha$ (min$^{-1}$)</td>
<td>0.26 (0.12)</td>
<td>0.24 (0.06)</td>
<td>0.24 (0.06)</td>
</tr>
<tr>
<td>$\alpha + k_p$ (min$^{-1}$)</td>
<td>0.10 (0.04)</td>
<td>0.09 (0.02)</td>
<td>0.09 (0.02)</td>
</tr>
</tbody>
</table>

FIG. 2 Mean (SD) plasma concentration of atracurium at each time point for the isoflurane (×), halothane (▲) and midazolam (□) groups. For clarity, the points for the isoflurane group have been displaced to the left by 0.2 min and those for the midazolam group to the right by 0.2 min.

TABLE III. Univariate correlation between each of the measures of disposition and each of the descriptors of effect on T1: T0. Values shown are those for Pearson's product moment correlation coefficient, in each instance with 36 degrees of freedom. Eight significant correlations from amongst the 30 possible: * P < 0.05; ** P < 0.01

<table>
<thead>
<tr>
<th></th>
<th>$V_e$</th>
<th>$V^m$</th>
<th>Clearance</th>
<th>$T_1$</th>
<th>$\alpha$</th>
<th>$\alpha + k_p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to 10% depression</td>
<td>+0.33*</td>
<td>+0.29</td>
<td>+0.22</td>
<td>+0.10</td>
<td>-0.18</td>
<td>-0.12</td>
</tr>
<tr>
<td>Change in the 1 min after 10% depression</td>
<td>-0.34*</td>
<td>-0.24</td>
<td>-0.13</td>
<td>-0.09</td>
<td>+0.26</td>
<td>+0.16</td>
</tr>
<tr>
<td>Logit maximum depression</td>
<td>-0.32</td>
<td>-0.25</td>
<td>-0.15</td>
<td>-0.08</td>
<td>+0.22</td>
<td>+0.15</td>
</tr>
<tr>
<td>Time to 20% recovery</td>
<td>-0.40*</td>
<td>-0.38*</td>
<td>-0.48**</td>
<td>+0.19</td>
<td>-0.05</td>
<td>-0.17</td>
</tr>
<tr>
<td>Time to 50% recovery</td>
<td>-0.35*</td>
<td>-0.33*</td>
<td>-0.48**</td>
<td>+0.26</td>
<td>-0.11</td>
<td>-0.24</td>
</tr>
</tbody>
</table>
**ATRACURIUM EFFECT AND DISPOSITION**

The time from the start of the infusion of atracurium to 20% recovery of T1 :T0 correlated negatively with both measures of volume of distribution, but even more strongly with clearance ($r = -0.48; 36$ d.f.; $P < 0.01$). When the difference between the three groups was taken into account using multivariate regression, the relationship was strong ($F = 28.7; 1,34$ d.f.; $P < 0.0001$). The negative correlation between time to 20% recovery and clearance is shown by the added variable plot in figure 4.

**Time to 50% recovery of T1 :T0**

The results for time to 50% recovery of T1 :T0 paralleled those for the time to 20% recovery. There was a univariate negative correlation with clearance ($r = -0.48; 36$ d.f.; $P < 0.01$). When the groups were separated in a multivariate regression the underlying relationship was strong ($F = 31.7; 1,34$ d.f.; $P < 0.0001$).
DISCUSSION

Several groups have defined the pharmacodynamics and pharmacokinetics of atracurium, and data on the effect and disposition of atracurium have been united formally in five reports [10-14]. In all these studies, the measured effect and plasma concentration profiles were used to find the parameter values which provided the best fit of a biophase model with a predetermined structure. Whilst making the maximal use of the data gathered from the study of a single subject, this powerful method of analysis takes the structure of the model as given. Of course, the model is not a perfect representation of the patient, and in practice the data contain errors; consequently, the pharmacodynamic data and the predictions of the model of best fit do not match perfectly. The issue as to how much discrepancy may be present before the model is re-evaluated has not been examined for atracurium.

The present approach is radical: no prior assumptions have been made on the structure or even the existence of a link between the disposition and effect of atracurium. The pharmacokinetic and pharmacodynamic analyses were carried out independently; the attempt to find a link between the two data sets was carried out at the level of the whole population. This exploratory approach has certain weaknesses.

One potential criticism is that only positive results have been presented in detail; this criticism is ameliorated by several considerations. First, some of the correlations presented are extremely strong. As five summary measures of effect were tested for correlation with each of the six summary pharmacokinetic measures here calculated, 30 correlations were possible. Thus there is still less than a 1 in 300 chance of finding a correlation as strong as that which was found to exist in the multivariate context between the time to 20% recovery and clearance.

Second, the somewhat arbitrary summary measures of both effect and disposition are themselves correlated. Thus the tests of the relationship between, say, the clearance and both the times to 20% and to 50% recovery are not totally independent, and correction of the significance levels on the assumption that the comparisons were independent would be too harsh.

Third, the correlations presented are feasible. In a review of the relationship between the pharmacokinetics and pharmacodynamics of the non-depolarizing neuromuscular blocking drugs in 1984, Hennis and Stanski [19] listed the central volume of distribution as one of the factors which affects onset time; they cited pharmacokinetic results obtained in patients with cirrhosis but failed to cite any evidence that onset time is increased in this group. The present report provides the first firm evidence for a link between the central volume of distribution and the time to onset of effect and maximum block are measures of some practical importance. The maximum block is a measure of effect used frequently, and is used sometimes as the sole measure [20]. Different measures of the temporal profile of effect would not have produced different conclusions.

It is, unfortunately, not possible to use the present results to enable prediction of the response of future individual patients; variability in the population would make such an estimate prone to considerable error. However, the present report has defined, within a large population of subjects, relationships between the disposition and effect of atracurium which are statistically very strong, which are feasibly compatible with prior understanding, and yet which do not depend upon the validity of any particular structural model. They are the first of their kind to be reported for atracurium and they form a necessary preliminary to the definition of a structural model of the pharmacodynamics of atracurium.

ACKNOWLEDGEMENTS

The electromyograph was purchased with a grant from the Mersey Regional Health Authority; the equipment required to measure the plasma concentration of atracurium was purchased in part with a grant from the Wellcome Foundation Ltd. We thank Mr A. Dixon for expert technical assistance.

REFERENCES


