The Pharmacokinetics of Atracurium Isomers

In Vitro and in Humans

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Atracurium is a mixture of ten isomers. By high-performance liquid chromatography, using acidified methanol as the mobile phase and silica support, it was separated into its three geometrical isomer groups, cis-cis, cis-trans, and trans-trans, which contain three, four, and three isomers, respectively. The clinically available form of atracurium was made up of 58% cis-cis, 36% cis-trans, and 6% trans-trans isomers. In buffered saline, pH 7.4, at 37°C, the half-lives of the three isomer groups were 57.1 ± 0.9, 59.7 ± 0.9, and 66.4 ± 2.7 min, respectively, for the cis-cis, cis-trans, and trans-trans groups. In whole blood, under similar conditions, the three groups showed different behavior. The cis-cis group broke down in a monexponential manner with a half-life of 23.3 ± 2.8 min. The cis-trans group showed bi-exponential breakdown with a rapid phase of 2.5 ± 0.4 min and a slow phase of 22.1 ± 2.9 min. The trans-trans group decayed rapidly, but, because of the low concentration of this group in the mixture, kinetic parameters could not be obtained. In eight patients, the mean elimination half-life and apparent clearance of the cis-cis group were 20.6 ± 1.5 min and 5.3 ± 0.4 ml·kg⁻¹·min⁻¹, respectively. For the cis-trans group, the apparent elimination half-life and clearance were 17.7 ± 1.8 min and 9.0 ± 1.0 ml·kg⁻¹·min⁻¹, but these figures require care in interpretation, as this isomer group contains isomers of widely varying rates of decomposition. Quantitative pharmacokinetic data for the trans-trans group could not be obtained. The short half-life isomers of atracurium could be of practical usefulness in the future. (Key words: Biotransformation [drug]; Atracurium; in vitro; in vivo; Neuromuscular relaxants: Atracurium; isomers. Pharmacokinetics: atracurium.)

Atracurium (Fig. 1) is a non-depolarizing neuromuscular blocking drug, designed to decompose rapidly and spontaneously at physiological pH by the process of Hofmann degradation. There is, however, an alternate pathway of decomposition. Atracurium is an ester and enzymatic hydrolysis has been demonstrated in vitro.³ ⁴

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Atracurium consists of a mixture of ten isomers, but no previous reports have included any details of the breakdown of the isomers of the drug. By high pressure liquid chromatography (HPLC), atracurium can be separated into three groups of isomers which are termed cis-cis, cis-trans, and trans-trans from the configuration about the tetralydrosoquinoline ring system (fig. 1). These geometrical isomer groups contain three, four, and three individual optical isomers (R-R, S-S, and R-S), respectively, as in the cis-trans group the R-S and S-R are not congruent. In the present work, we have examined the rate of breakdown of these isomer groups in buffer and in blood in vitro and in eight patients. The studies in buffer were initially performed at concentrations higher than those encountered in vivo, but were then repeated at lower concentrations. The studies in blood were conducted at total concentrations of atracurium which are attained during clinical neuromuscular blockade.

Methods

In Vitro Studies

Materials. Atracurium was used as the commercially available solution for injection (Tracrium—Wellcome Foundation Ltd.) nominally containing 10 mg·ml⁻¹, but actually stated to contain 11.5 mg·ml⁻¹ at time of preparation (data from Wellcome, Australia Ltd.). Chromatographic analysis yielded the following concentrations of isomeric groups at the time of the study: cis-cis 6.07 mg·ml⁻¹; cis-trans 3.83 mg·ml⁻¹; trans-trans 0.60 mg·ml⁻¹; cis-trans to cis-cis ratio of 0.63. All other chemicals were of analytical reagent grade. Methanol was distilled before use.

Degradation in Buffered Saline. Solutions of atracurium were made up in phosphate buffered saline containing sodium chloride, 8 g·l⁻¹, potassium chloride 0.2 g·l⁻¹, sodium hydrogen phosphate (Na₂HPO₄) 1.15 g·l⁻¹, and potassium dihydrogen phosphate 0.2 g·l⁻¹. The solution was adjusted to pH 7.40 at 37°C. Duplicate incubations at 37°C were conducted at each of two concentrations of atracurium, 1 mg·l⁻¹ and 20 mg·l⁻¹. At various times up to 120 min, 20 μl of 30 millimol·l⁻¹ hydrochloric acid was added to 0.9 ml aliquots of the atracurium solutions to prevent further breakdown. The solutions were rapidly frozen and stored at −20°C for a maximum of 24 h before assay, although, on test-
ing, there was no significant change in the concentrations of the isomeric groups over a 2-week storage period under these conditions. At the higher concentration, tubocurarine (50 μg in 0.1 ml) was added to the acidified atracurium solution (0.92 ml) and 50 μl aliquots were chromatographed by direct injection into the HPLC apparatus. At the lower concentration, atracurium was extracted and assayed by the same method used for plasma.

**Degradation in Blood.** Atracurium, 200 μg, was mixed with 50 ml heparinized blood which was maintained at 37°C in an atmosphere of 5% carbon dioxide in oxygen. The pH of the blood was measured frequently. At various times up to 90 min, 5 ml aliquots of blood were withdrawn and added to ice-cold tubes containing EDTA sodium and 300 μm of hydrochloric acid in 0.1 ml. The plasma was then separated and stored at -20°C for a maximum of 24 h until assayed.

**Extraction of Atracurium.** Atracurium was extracted from plasma and buffered saline using the method described by Stiller et al. Aliquots (0.9 ml) of acidified plasma or saline were mixed with the internal standard, tubocurarine (10 μg in 0.1 ml). The solutions were then applied to C18 Sep Pak columns (J. T. Baker Chemical Co.) which had been previously washed twice with methanol and then twice with 50 millimol/L1 potassium dihydrogen phosphate (pH 4.8 ± 0.2). After application of the acidified plasma or saline, the columns were washed three times with the potassium dihydrogen phosphate solution and once with methanol/water (1:4) before elution with the mobile chromatographic phase of methanol/trifluoroacetic acid (85%); phosphoric acid: (600:1:1, v/v/v). Standards were made up in acidified saline or in plasma, according to the samples to be assayed.

**High Pressure Liquid Chromatography.** Fifty μl aliquots of the methanolic extracts or aqueous solutions were injected through a Rheodyne injector onto a silica column (Altex Ultrasphere Si, 5 μ, 25 × 0.46 cm). The mobile phase was pumped through the column using a Waters model 6000A pump set at a rate of 2 ml·min⁻¹. For the initial assay of the injectable solution, peaks were recorded by absorbance at 280 nm, measured in a Waters model 440 absorbance detector, and the relative proportions of the three isomeric groups were found after injection of all peaks present in the chromatograms, including those due to impurities. This analysis assumes that the absorbance of all isomeric components is equal; an assumption which was made by Stenlake et al. and is applied in quality control of the commercially available material. Because of its greater sensitivity, in the kinetic studies, peaks were detected by an Hitachi F1000 fluorometer set at 280 nm for excitation and 320 for emission. The quantitative aspects of the analysis assume that the isomer groups have similar fluorescent yields.

The chromatograms showed clear separation of the three isomeric groups of atracurium and separation from the internal standard d-tubocurarine (fig. 2). Standard curves were constructed from peak height ratios (atracurium isomeric group: tubocurarine) versus concentration and were linear with correlation coeffi

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**FIG. 1. Upper.** Structure of atracurium showing bonds which are broken by Hofmann degradation (h) and ester hydrolysis (e). Lower. Partial structures of atracurium showing stereochemistry of substituents on tetrahidroisoquinoline grouping producing cis and trans isomers. The pattern of substitution varies independently at the two isoquinoline groupings producing cis-cis, cis-trans, and trans-trans isomeric groups. The structures shown are the R-cis and R-trans isomers.

**FIG. 2.** Chromatograms of atracurium from injectable solution (lower) and extracted from plasma after incubation in blood for 21 min (upper). Note the difference in the ratios of the C-T to C-C peaks. T = tubocurarine (internal standard); C-C = cis-cis; C-T = cis-trans; T-T = trans-trans components.
ciences greater than 0.99 over the ranges used: 0.06–2.9 mg·l⁻¹ (cis-cis), 0.04–1.8 mg·l⁻¹ (cis-trans), and 0.03–0.29 mg·l⁻¹ (trans-trans).

The coefficients of variation when replicate plasma standards (n = 4) were assayed were: cis-cis, 0.06 mg·l⁻¹, 4.5%; 2.9 mg·l⁻¹, 3.0%; cis-trans, 0.04 mg·l⁻¹, 6.8%; 1.8 mg·l⁻¹, 4.5%; while the inter-run coefficients of variation (n = 5) were: cis-cis, 7.7 and 7.3%; and cis-trans, 8.0 and 7.7% at the same concentrations. The minimal assayable level of the isomeric groups was 0.015 mg·l⁻¹, about three times the limit of detection.

**Kinetic Analysis.** The time course of concentrations of all three isomeric groups in buffered saline and the concentrations of the cis-cis isomeric group in plasma were fitted by linear regression of the logarithm of the concentrations against time. The time courses of concentrations of the cis-trans isomeric group in plasma were fitted to the following biexponential function by the FUNFIT program⁷ using a weighting of C⁻¹:

\[
C = C_1 \cdot e^{-k_1 t} + C_2 \cdot e^{-k_2 t},
\]

where \(C_1\) and \(C_2\) are the concentrations of the kinetically distinguishable components at zero time, while \(k_1\) and \(k_2\) are the rate constants of degradation of these components. The sum of \(C_1\) and \(C_2\) was set by the relationship:

\[
C_1 + C_2 = 0.63 \cdot C_{cis},
\]

where \(C_{cis}\) is the concentration of the cis-cis isomer at zero time and 0.63 is the ratio of cis-trans to cis-cis isomers in atracurium, as shown by our initial assay of the injectable material.

**In Vivo Studies.** The study was carried out on eight consenting ASA physical status 1 or 2 patients, ages 37–68 yr, three males and five females, who underwent elective operations not requiring profound muscle relaxation but of sufficient duration to permit recovery from neuromuscular block without the need for pharmacological reversal. The patients were premedicated with 2 or 2.5 mg lorazepam, administered orally, 2 h prior to induction. On arrival in the operating suite, an intravenous infusion of Hartmann's solution was begun and topical lidocaine was applied to the pharynx and larynx following 1–2 mg·kg⁻¹ of fentanyl given intravenously. The patients were then pre-oxygenated and anesthesia was induced with thiopental 4–5 mg·kg⁻¹, and a further aliquot of 1–2 mg·kg⁻¹ fentanyl intravenously. Tracheal intubation was accomplished without neuromuscular blocking drugs, and the patients' ventilation was controlled at 70 ml·kg⁻¹·min⁻¹ with nitrous oxide and oxygen (67%;33%) for the remainder of the study. Further aliquots of fentanyl and thiopental were given to maintain anesthesia. The electrocardiogram and heart rate was displayed continuously and the blood pressure was recorded at 5-min intervals by non-invasive monitoring. The patients' temperature was monitored by nasopharyngeal thermistor, and, in all cases, remained in the 36–37° C range. Two of the patients received 500 μg·kg⁻¹ and, the remaining six, 300 μg·kg⁻¹ atracurium.

For determination of the plasma concentration of atracurium, 5-ml blood samples were taken from the subjects' external jugular veins into heparinized syringes at about 2, 4, 10, 20, 30, 45, 60, and 90 min after injection of the drug. The samples were immediately transferred into test tubes containing 0.1 ml 3 N hydrochloric acid and were packed in ice. The plasma was separated by centrifugation within 2 h, and the samples were then frozen at −20° C until assay, not later than 24 h after they were taken. Tubocurarine was added as an internal standard to the aliquots of plasma which were then assayed by HPLC.

For each subject, the concentration-time data for the two major isomer groups was fitted by the computer program, FUNFIT,⁷ simultaneously, again using a weighting factor of C⁻¹, each to a biexponential equation:

\[
C = C_1 \cdot e^{-λ_1 t} + C_2 \cdot e^{-λ_2 t},
\]

The fitting was constrained to allow for the initial ratio of the cis-trans isomers to the cis-cis group which was previously determined to be 0.63 in the injected material. This constraint increased the accuracy of the curve fit to the initial phase, but forced the estimates of the initial volume of distribution of the central compartment (V₁) of the two major isomer groups to be identical. The volume of distribution during the terminal log-linear phase (Vₙₑᵣₙₐ) was also calculated,⁸ but this volume must be regarded as "apparent" because of the hydrolysis of atracurium in the peripheral compartment.⁹,¹⁰ The presence of rapidly hydrolyzed isomers in the cis-trans group produces further inaccuracies in the value of Vₙₑᵣₙₐ of this isomeric group. The "apparent" values of Vₙₑᵣₙₐ are quoted only for comparison with such values reported in previous studies.⁷,⁸

Statistical comparisons between the half lives of the three isomer groups in buffered saline were made using one-way analysis of variance with contrasts to identify the differences. The difference between the rate of degradation of the cis-cis group and the slow phase of the cis-trans group in blood was tested by Student's t test. The differences among the in vivo pharmacokinetic parameters were tested using paired t tests.
BREAKDOWN OF ATRACURIUM ISOMERS

FIG. 3. Typical time courses of concentrations of cis-cis (C-C), cis-trans (C-T), and trans-trans (T-T) isomeric groups of atracurium in phosphate-buffered saline.

Results

DEGRADATION IN BUFFERED SALINE

The decay of all three isomeric groups in saline solutions was monoeXponential (fig. 3) with mean half-lives of 57.1 (cis-cis), 59.7 (cis-trans), and 66.4 min (trans-trans) (table 1). The differences between the trans-trans group and the other two groups were statistically significant ($P \leq 0.05$).

DEGRADATION IN BLOOD

The pH of all the sampled aliquots was in the range 7.35-7.55. The time course of decay of the cis-cis isomeric group in blood was also monoeXponential (fig. 4) with a mean half-life of 23.3 min (table 2). By contrast, the cis-trans isomeric group was degraded in a biexponential fashion. There was an initial phase of rapid decomposition whose half-life was 2.3 min followed by a slower phase during which the half-life was 22.1 min, similar to that of the cis-cis isomeric group (no significant difference). As a result, the ratio of cis-trans to cis-cis isomers decreased rapidly over the first 10 min, but was approximately constant thereafter. The decrease in the ratio of the geometrical isomers can also be seen from the relative peak heights shown in figure 2.

The relative amounts of the cis-trans isomers, whose breakdown was kinetically distinguishable, was determined from the values of $C_1$ and $C_2$ obtained by fitting the data to equation 1. The ratio $C_2/(C_1 + C_2)$ was $0.46 \pm 0.01$ (mean $\pm$ SEM, $N = 5$). Thus, the component which was degraded more slowly made up, on the average, 46% of the total cis-trans isomeric group, assuming equal fluorescent yield for the different cis-trans isomers.

The low concentrations of the trans-trans isomeric group declined very rapidly and could be assayed after incubation for only 15-30 min. The time course was also not log-linear suggesting components of differing half-lives. The initial half life was less than 5 min, but a detailed kinetic analysis was not possible at the low concentrations used in this study.

IN VIVO STUDIES

The pharmacokinetic parameters derived from the data of our patients are summarized in tables 3 and 4 for the cis-cis and cis-trans isomer groups, respectively. The correlation coefficients of the curve fits were 0.987 or higher (fig. 5). The peak of the trans-trans isomers could be detected in the chromatograms of the early samples, up to 15 min after injection, but no meaningful kinetic analysis of this group was possible. The initial half-lives of the two major isomer groups were $1.9 \pm 0.3$ min (mean $\pm$ SEM) for cis-cis and $1.6 \pm 0.3$ min for cis-trans, respectively (NS). The terminal half-lives were

FIG. 4. Typical time courses of plasma concentrations of cis-cis (C-C), cis-trans (C-T), and trans-trans (T-T) isomeric groups of atracurium during incubation in blood.
The terminal half-lives of the cis-cis and cis-trans isomeric groups were considerably shorter in blood than in buffered saline, and were very similar to those previously reported from chemical assays of total atracurium. The present study, however, shows that the breakdown of the cis-trans isomeric group is complex, with approximately 54% of this isomeric group being degraded much more quickly than the remaining 46%. The four isomers in the cis-trans group are formed in approximately equal amounts. Assuming that the four cis-trans isomers have similar fluorescent yield, the data is consistent, with two of the isomers being hydrolyzed more rapidly than the other two members of the group. Components of the trans-trans isomeric group may also be hydrolyzed at different rates, but these components make up only a small proportion of atracurium. The presence of these rapidly decomposed isomers explains the initial non-linearity reported by Fisher et al. in some of their in vitro experiments.

Inhibition of the rate of breakdown by diisopropylfluorophosphate indicates that an esterase is responsible for the increased rate of breakdown of total atracurium in plasma, but no detailed identification of the enzyme catalyzing the hydrolysis of atracurium has been made. A study which failed to demonstrate significant reduction of atracurium breakdown rate by enzyme inhibition was performed at an atracurium concentration of 1 g·l⁻¹, several orders of magnitude greater than that which would be attained clinically. This concentration is approximately ten times the \( I_{50} \) of atracurium for plasma butyrylcholinesterase and, although we know of no published data for carboxylesterase inhibition by atracurium, it is likely that such high concentration may either inhibit or saturate an enzyme system.

A previous finding which is not clarified by the results of the present study is the relatively long plasma half-life of total atracurium when determined by bioassay. This technique yielded a mean half-life of 44 min, a value which is approximately twice that obtained by chemical

### Table 2. Half-lives of Atracurium Isomeric Groups, in Minutes, in Whole Blood at pH 7.30–7.50, at 37°C. The Concentration of Atracurium was Approximately 4 mg·l⁻¹. The Trans-trans Group Was Detectable Only for a Short Time after Commencement of Incubation

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>pH</th>
<th>Gcisic</th>
<th>Gcis (Rapid)</th>
<th>Gcis (Slow)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>7.49</td>
<td>19.5</td>
<td>1.6</td>
<td>20.1</td>
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<td>2</td>
<td>7.29</td>
<td>29.8</td>
<td>3.9</td>
<td>30.5</td>
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<tr>
<td>3</td>
<td>7.31</td>
<td>30.5</td>
<td>2.3</td>
<td>27.0</td>
</tr>
<tr>
<td>4</td>
<td>7.47</td>
<td>17.1</td>
<td>2.6</td>
<td>15.1</td>
</tr>
<tr>
<td>5</td>
<td>7.49</td>
<td>19.5</td>
<td>1.5</td>
<td>18.0</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td></td>
<td>23.3 ± 2.8</td>
<td>2.3 ± 0.4</td>
<td>22.1 ± 2.9</td>
</tr>
</tbody>
</table>

20.6 ± 4.3 min for cis-cis and 17.7 ± 5.1 min for the cis-trans group, the difference being statistically significant (\( P < 0.02 \)). The volume of the central compartment (\( V_c \)) was 60.2 ± 11.9 ml·kg⁻¹. As stated above, this was not determined independently for the two isomeric groups. The "apparent" volume of distribution (\( V_{\text{app}} \)) of the cis-cis isomers was 154.2 ± 12.7 ml·kg⁻¹, smaller than the "apparent" volume for the cis-trans group, 212.1 ± 17.7 ml·kg⁻¹ (\( P < 0.001 \)). The "apparent" clearance of the cis-cis group was 5.5 ± 0.4 ml·kg⁻¹·min⁻¹, less than that of the cis-trans group, 9.0 ± 1.0 ml·kg⁻¹·min⁻¹ (\( P < 0.001 \)).

In our in vitro studies, the initial ratio of cis-trans to cis-cis isomers was found to be 0.63. This ratio was reduced in vivo, with time, to 0.31 ± 0.01 at 30 min and 0.25 ± 0.01 at 60 min.

### Discussion

The half-lives of the three isomeric groups in buffered saline were similar to those reported previously for total atracurium by Stiller et al. Since the breakdown of all three isomeric groups was monoeponential, with similar half-lives, agreement with data on total atracurium could be expected.

### Table 3. Pharmacokinetic Data for Gcisic Isomer Group. The Values for \( C_t \) and \( C_t \) Have Been Normalized to a Dose of 300 µg·kg⁻¹

<table>
<thead>
<tr>
<th>Pt</th>
<th>( C_{t_1} ) µg·ml⁻¹</th>
<th>( C_{t_2} ) µg·ml⁻¹</th>
<th>( \lambda_1 ) min⁻¹</th>
<th>( \lambda_2 ) min⁻¹</th>
<th>( t_{1/2}\lambda_1 ) min</th>
<th>( t_{1/2}\lambda_2 ) min</th>
<th>( V_{t_1} ) ml·kg⁻¹</th>
<th>( V_{t_2} ) ml·kg⁻¹</th>
<th>( C_t ) ml·min⁻¹·kg⁻¹</th>
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<tr>
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<td>29.3</td>
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<td>3</td>
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<td>0.650</td>
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<td>178.9</td>
<td>75.8</td>
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<td>6</td>
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<td>0.047</td>
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<td>0.294</td>
<td>0.031</td>
<td>2.96</td>
<td>22.4</td>
<td>193.1</td>
<td>74.0</td>
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<td>8</td>
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<td>1.313</td>
<td>0.405</td>
<td>0.037</td>
<td>1.71</td>
<td>18.8</td>
<td>136.5</td>
<td>48.8</td>
<td>5.0</td>
</tr>
<tr>
<td>Mean</td>
<td>4.481</td>
<td>1.119</td>
<td>0.418</td>
<td>0.055</td>
<td>1.91</td>
<td>26.6</td>
<td>154.2</td>
<td>60.2</td>
<td>5.3</td>
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<tr>
<td>SEM</td>
<td>1.629</td>
<td>0.105</td>
<td>0.054</td>
<td>0.002</td>
<td>0.29</td>
<td>1.5</td>
<td>12.7</td>
<td>11.9</td>
<td>6.4</td>
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</tbody>
</table>
BREAKDOWN OF ATRACURIUM ISOMERS

<p>| TABLE 4. Pharmacokinetic Data for Cis-trans Isomer Group. The Values for C1 and C2 Have Been Normalized to a Dose of 300 μg·kg⁻¹ |
|---|---|---|---|---|---|---|---|---|</p>
<table>
<thead>
<tr>
<th>Pt</th>
<th>C1 mg·ml⁻¹</th>
<th>C2 mg·ml⁻¹</th>
<th>λ1 min</th>
<th>λ2 min⁻¹</th>
<th>τ1 min</th>
<th>τ2 min⁻¹</th>
<th>Vd ml·kg⁻¹</th>
<th>V1 ml·kg⁻¹</th>
<th>C1 ml·min⁻¹·kg⁻¹</th>
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<td>0.431</td>
<td>0.528</td>
<td>0.041</td>
<td>1.31</td>
<td>16.7</td>
<td>223.6</td>
<td>58.4</td>
<td>9.3</td>
</tr>
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<td>8.002</td>
<td>0.195</td>
<td>0.308</td>
<td>0.023</td>
<td>1.76</td>
<td>20.7</td>
<td>197.1</td>
<td>16.1</td>
<td>4.6</td>
</tr>
<tr>
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<td>0.418</td>
<td>0.182</td>
<td>0.043</td>
<td>1.44</td>
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<td>11.9</td>
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<td>0.202</td>
<td>0.042</td>
<td>3.44</td>
<td>16.4</td>
<td>208.6</td>
<td>87.0</td>
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<td>0.583</td>
<td>0.042</td>
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<td>16.4</td>
<td>250.9</td>
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<td>0.593</td>
<td>0.053</td>
<td>1.17</td>
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<td>0.340</td>
<td>0.390</td>
<td>0.046</td>
<td>1.78</td>
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<td>0.038</td>
<td>0.97</td>
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<td>248.4</td>
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<tr>
<td>Mean</td>
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<td>0.405</td>
<td>0.485</td>
<td>0.041</td>
<td>1.63</td>
<td>17.7</td>
<td>212.1</td>
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<tr>
<td>SEM</td>
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<td>0.039</td>
<td>0.055</td>
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<td>1.8</td>
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methods. No component with such a long half-life was detected in our study.

In vivo, the pharmacokinetics of the atracurium isomers were in close conformity with the findings of the in vitro experiments in whole blood. The trans-trans isomers, only 6% of the total dose, were detectable in the early samples, but the data were insufficient for quantitative treatment. It did appear, however, that their half-life was short. The terminal half-life of the cis-cis isomers was 20.5 min in contrast to 23.3 min in whole blood in vitro. The in vivo terminal half-life of the cis-trans isomers was 17.7 min, while in blood in vitro degradation was biphase and the half-lives of the two detected components of the group were 2.3 and 22.1 min, respectively. The similar in vitro and in vivo halflives do not indicate, however, that blood is the only site of hydrolysis of atracurium. One kinetic analysis suggests that there is considerable hydrolysis of atracurium in a peripheral compartment and possibly in "organs" in the central compartment. This study, however, makes assumptions, such as equal rates of hydrolysis in the central and peripheral compartments, and does not take into account the rapidly degraded isomers. We believe that further work is required to localize the sites of atracurium hydrolysis.

Evidence pointing to the existence of a short-life component in the cis-trans isomer group in vivo can be found in the cis-trans/cis-cis ratio. The values of this ratio at 30 and 60 min were 0.31 and 0.25, contrasting with the initial ratio of 0.63. The plot of this ratio against time is clearly biphase (fig. 6), which is consistent with the in vitro data.

In general, our pharmacokinetic data are in good agreement with those previously published for $V_1$, $V_{area}$, elimination half-life, and clearance, although, as discussed previously, $V_{area}$ and clearance must be regarded as "apparent" values.

Our findings support the conclusions of Stilller et al. that enzyme hydrolysis, not Hofmann elimination, is the major breakdown path of atracurium. The differ-

Fig. 5. Typical biexponential curves fitted to the concentration data for the cis-cis and cis-trans isomer groups in one patient. The initial cis-trans/cis-cis ratio was fixed at 0.63.

Fig. 6. The ratio of cis-trans to cis-cis isomers plotted against time for all eight patients. The initial rapid decrease confirms the in vitro finding of short half-life isomers in the C-T group.
tential rate of hydrolysis of the cis-trans isomers may have considerable clinical significance. The identification and isolation of isomers which are hydrolyzed rapidly may allow the development of a neuromuscular blocking agent with similar kinetics to succinylcholine. Provided that this component possesses the non-depolarizing neuromuscular blocking activity shown by total atracurium, it will be a neuromuscular blocking drug of ultra-short duration of action.

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References