Anesthesiology
65:6–12, 1986

Elimination of Atracurium in Humans: Contribution of Hofmann Elimination and Ester Hydrolysis versus *Organ-based Elimination*

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ABBREVIATIONS

- $A_{1_{ss}}$ = amount of drug in the central compartment at steady state
- $A_{2_{ss}}$ = amount of drug in the peripheral compartment at steady state
- AUC = area under the plasma concentration *vs.* time curve
- $AUC_{portal\ vein}$ = area under the plasma concentration *vs.* time curve following administration into the portal vein
- $AUC_{systemic\ vein}$ = area under the plasma concentration *vs.* time curve following intravenous administration
- C = plasma drug concentration at time *t*
- C_{ss} = plasma drug concentration at steady state
- Cl_{total} = total drug clearance
- $Cl_{hepatic}$ = hepatic clearance
- $Cl_{nonorgan}$ = drug clearance from the central and peripheral compartments by Hofmann elimination and ester hydrolysis
- Cl_{organ} = drug clearance from the central compartment by pathways other than Hofmann elimination and ester hydrolysis
- F_H = fraction of drug entering the liver that escapes elimination in that organ
- k_{10} = first-order mass rate constant associated with the elimination of drug from compartment 1
- k_{12} = first-order mass rate constant associated with the movement of drug from compartment 1 to compartment 2
- k_{20} = first-order mass rate constant associated with the elimination of drug from compartment 2
- k_{21} = first-order rate constant associated with the movement of drug from compartment 2 to compartment 1
- $k_{ester\ hydrolysis}$ = rate constant for ester hydrolysis
- $k_{Hofmann\ elimination}$ = rate constant for Hofmann elimination
- $k_{in\ vitro}$ = rate constant obtained in the *in vitro* studies
- $k_{nonorgan}$ = sum of rate constants for Hofmann elimination and ester hydrolysis
- k_{organ} = rate constant for hepatic and/or renal elimination
- $Q_{hepatic}$ = hepatic blood flow
- V_1 = volume of central compartment
- V_2 = volume of peripheral compartment at steady state
- V_{ss} = volume of distribution at steady state

Atracurium, a nondepolarizing muscle relaxant, is eliminated through several pathways, including Hofmann elimination (spontaneous degradation in plasma and tissue at normal body *p*H and temperature) and ester hydrolysis (catalysis by nonspecific esterases). Because elimination of atracurium occurs in both tissue and plasma, traditional pharmacokinetic models assuming elimination from a single central compartment are inaccurate for atracurium. The authors developed a two-compartment pharmacokinetic model in which hepatic and/or renal elimination occurs from the central compartment (Cl_{organ}), and Hofmann elimination and ester hydrolysis occur from both central and peripheral compartments ($Cl_{nonorgan}$). To determine the *in vitro* rate constant for Hofmann elimination and ester hydrolysis, atracurium was added to whole blood kept at each patient's *p*H and temperature. The values for this rate constant ranged from 0.0193 to 0.0238 per min. When these values were applied to the pharmacokinetic model, Cl_{total}, Cl_{organ}, and $Cl_{nonorgan}$ were 4.8 ± 1.1, 3.0 ± 0.9, and 1.9 ± 0.6 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively. The authors conclude that more than one-half of the clearance of atracurium occurs *via* pathways other than Hofmann elimination and ester hydrolysis. (Key words: Metabolism: ester hydrolysis; Hofmann elimination. Neuromuscular relaxants: atracurium. Pharmacokinetics: atracurium.)

AT NORMAL BODY *p*H and temperature, atracurium undergoes spontaneous degradation through Hofmann elimination and ester hydrolysis. Because the elimination of atracurium occurs in both tissue and plasma, traditional pharmacokinetic models characterizing elimination from only one compartment describe the pharmacokinetics of atracurium inaccurately.[1] We devised a model for atra-

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Received from the Departments of Anesthesia and Laboratory Medicine, University of California, San Francisco, California. Accepted for publication February 4, 1986. Dr. Fisher is the recipient of a New Investigator Award from the National Institutes of Health. Presented in part at the Annual Meeting of the Association of University Anesthetists, Los Angeles, May, 1985 and the Annual Meeting of the American Society of Anesthesiologists, San Francisco, October, 1985.

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curium** in which elimination occurs from both the central and peripheral compartments and quantified elimination using data from five subjects.

Methods

Pharmacokinetic Model

The pharmacokinetic properties of atracurium can be described using a two-compartment model (fig. 1*A*) in which atracurium is administered into the central compartment and moves between the central and peripheral compartments at rate constants traditionally called k_{12} and k_{21} (see abbreviations). Elimination from the central compartment occurs at rate k_{10}, which is the sum of $k_{\text{Hofmann elimination}}$, $k_{\text{ester hydrolysis}}$, and k_{organ}. If the eliminating organ(s) is in the central compartment, the rate constant for elimination from the second compartment (k_{20}) would be equal to $k_{\text{Hofmann elimination}}$ plus $k_{\text{ester hydrolysis}}$. The sum of $k_{\text{Hofmann elimination}}$ and $k_{\text{ester hydrolysis}}$ can also be called k_{nonorgan} (fig. 1*B*).

Using the appropriate transforms (see appendix), the plasma concentration of atracurium *versus* time can be expressed as the sum of two exponential terms. We determined plasma concentration *versus* time for five subjects who were given atracurium and fit the sum of two exponentials to these values. The pharmacokinetic model also requires an estimate for the value for $k_{\text{ester hydrolysis}}$ plus $k_{\text{Hofmann elimination}}$ in each of the central and peripheral compartments. Assuming that the sum of $k_{\text{ester hydrolysis}}$ plus $k_{\text{Hofmann elimination}}$ is the same in both compartments, we estimated its value *in vitro* by simulating physiologic conditions under which elimination would occur *in vivo* (the *in vitro* rate constant is called k_{nonorgan}). These *in vitro* studies were performed using blood obtained from the same subjects just described. The pharmacokinetic data obtained in both the *in vivo* and *in vitro* studies for each of the subjects were then used to determine Cl_{total}, Cl_{nonorgan}, Cl_{organ}, and V_{ss} for each subject.

In Vivo Studies

We obtained approval from the Committee on Human Research and informed consent to study eight patients (22–43 yr of age, ASA PS I and II) who were undergoing elective procedures not involving the liver or kidney. Anesthesia was induced with thiopental, 100 mg iv, nitrous oxide, and halothane. The trachea was intubated without the aid of muscle relaxants. Anesthesia was maintained with 60% nitrous oxide and halothane, 0.7% end-expired concentration, monitored by mass spectrometry. Ventilation was controlled to keep end-expired P_{CO_2} at 30–40 mmHg. Nasopharyngeal temperature was maintained at 35–37° C. After anesthetic conditions were stable for 15 min, atracurium was administered by continuous iv infusion at a rate of 17.2 ± 1.6 (mean ± SD) $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 8.0 ± 1.4 min. The infusion was ter-

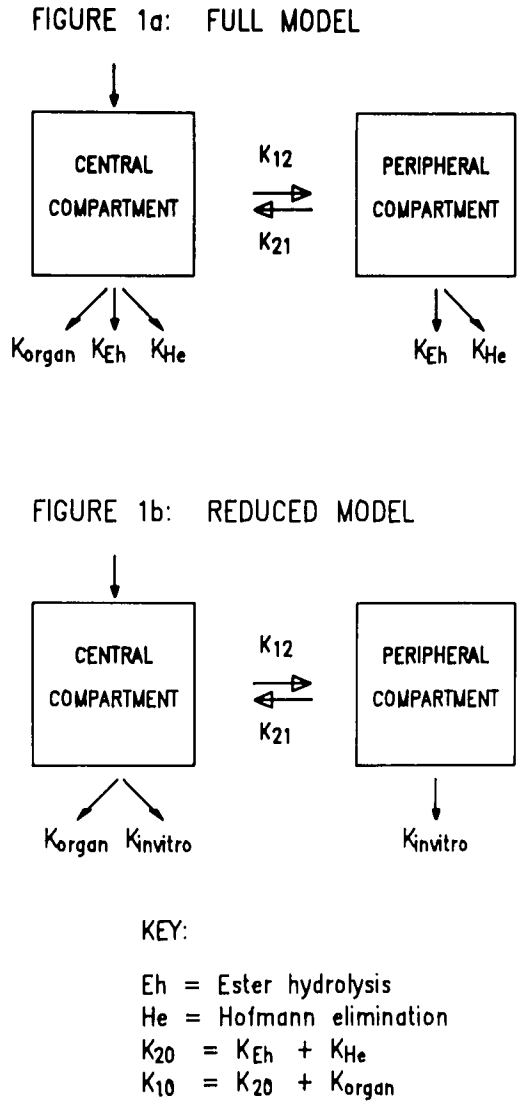

FIG. 1. In our pharmacokinetic model for atracurium, atracurium is administered into the central compartment and moves between the central and peripheral compartments at rate constants k_{12} and k_{21}. Elimination occurs from both compartments through pathways shown in *A*. We used a reduced model (fig. 1*B*) and rate constants k_{organ} (rate constant for renal and hepatic elimination) and k_{nonorgan} (rate constant for Hofmann elimination and ester hydrolysis) to determine the pharmacokinetic values.

** Similar pharmacokinetic models have been used for comparing data fit with one- and two-compartment models[2] and to quantify the reversible metabolism of prednisone to prednisolone.[3] This model has not been applied previously to determine the pharmacokinetics of atracurium.

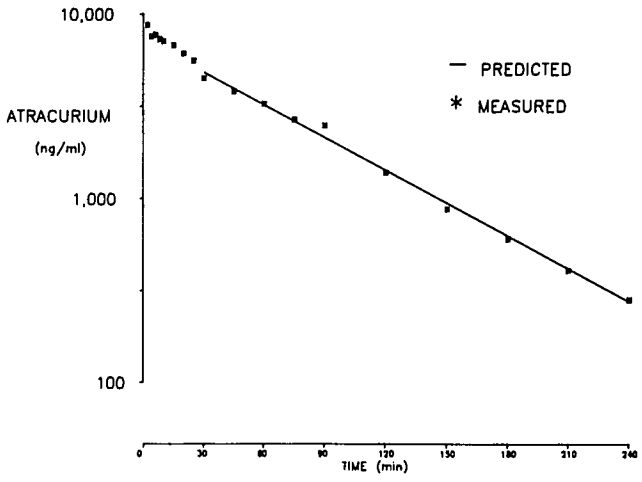

FIG. 2. Data obtained from one *in vitro* pharmacokinetic study. Atracurium (400 μg) was added to 100 ml of whole blood maintained at physiologic *p*H and temperature. Samples were obtained at the indicated time intervals for determination of the concentration of atracurium. For this subject and one other subject in whom extended *in vitro* pharmacokinetic studies were performed, there was a more rapid decline initially, followed by a slower, linear decline of log atracurium concentration with time.

minated when twitch tension of the adductor pollicis was depressed approximately 70% and no additional atracurium was given. Five milliliter heparinized venous blood samples were obtained from the contralateral arm before administration of atracurium and at 1, 2, 4, 6, 8, 10, 15, 20, 25, 30, 35, 40, 45, 52.5, 60, 75, 90, and 120 min after the beginning of the infusion. These samples were acidified immediately with 3 N sulfuric acid and centrifuged; the plasma was frozen at −20° C. The concentration of atracurium was determined by liquid chromatography.[4] This assay is sensitive to 10 ng/ml and has a coefficient of variation of 7% at a concentration of 50 ng/ml.

Serum concentrations of atracurium were plotted against time and fitted to a two-compartment pharmacokinetic model using nonlinear least-squares regression analysis.[5]

In Vitro Studies

To determine whether Hofmann elimination and ester hydrolysis were first-order pharmacokinetic processes (*i.e.*, the amount of drug eliminated per unit time is proportional to the concentration), we obtained 100 ml of blood from two additional subjects who were anesthetized in a similar manner but were not given atracurium. The blood was placed in a sealed vessel, equilibrated with a mixture of 5% CO_2 and 95% O_2, and agitated constantly. The blood was maintained at the same *p*H (7.35–7.45) and body temperature (35.0–37.0° C) as the subject from whom it came. Atracurium, 400 μg, was then added to the blood, and plasma samples were obtained for determination of the concentration of atracurium at time intervals similar to those for the *in vivo* study. Values for natural log atracurium concentration were plotted against time. The slope of the resulting line was determined using linear regression. Because the slope of the first part of the curve for each subject was slightly steeper than the rest of the curve, samples obtained earlier than 25 min after addition of atracurium were omitted from this analysis.

To determine whether the rate of *in vitro* degradation was altered by the initial concentration of atracurium, blood from an additional subject was divided into three 25 ml aliquots and maintained at physiologic conditions as just described. Atracurium (50, 100, or 200 μg) was then added to each aliquot and concentrations of atracurium were determined 30, 60, and 90 min after the addition of atracurium; additional samples were obtained at 120 min for two of these studies. The log of the concentration of atracurium was plotted against time and the slope of the resulting line was determined using least-squares linear regression.[6] The slope of these regression lines was compared by analysis of covariance.

To determine $k_{nonorgan}$ for the five subjects in the *in vivo* study, an additional 50 ml of blood was obtained before the administration of atracurium. This blood was treated in a manner similar to the *in vitro* studies described previously except that concentrations of atracurium were determined 30, 60, 90, and 120 min after the addition of atracurium.

The value for $k_{nonorgan}$ for each subject was then used in the pharmacokinetic model to calculate V_{ss}, $Cl_{nonorgan}$, and Cl_{organ}.

Results

For the two subjects participating in the extended *in vitro* studies, plotting log atracurium concentration *versus* time revealed a brief initial distribution phase followed by a linear elimination phase. The curve for concentration *versus* time for one of these subjects is shown in figure 2; the curve for concentration *versus* time for the other subject had a similar appearance. The addition of different quantities of atracurium to blood maintained at physiologic conditions *in vitro* did not alter the rate of degradation (fig. 3, $P > 0.2$).

Data obtained in the *in vivo* and *in vitro* studies for a representative subject are shown in figures 4 and 5, respectively. V_{ss} was 87.4 ± 31.0 (mean ± SD) ml/kg (table 1). Total clearance, $Cl_{nonorgan}$, and Cl_{organ} were 4.8 ± 1.1, 1.9 ± 0.6, and 3.0 ± 0.9 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively; Cl_{organ} represented 61% ± 10% of Cl_{total}.

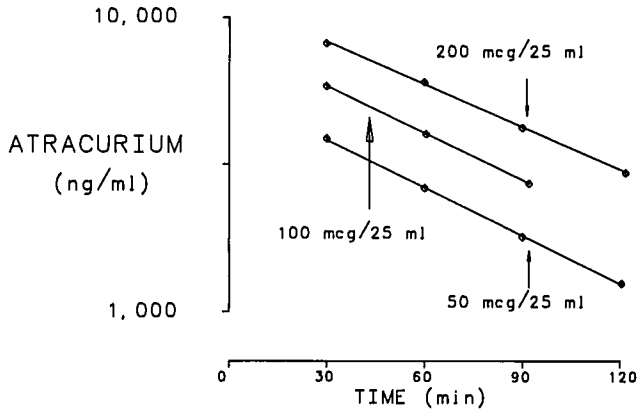

FIG. 3. Atracurium, 50, 100, or 200 μg, was added to 25 ml aliquots of whole blood maintained at physiologic *p*H and temperature. Samples were obtained at the indicated time intervals for determination of the concentration of atracurium. The rate of decline was similar regardless of the dose of atracurium added to the blood, suggesting that *in vitro* elimination of atracurium is a first-order process.

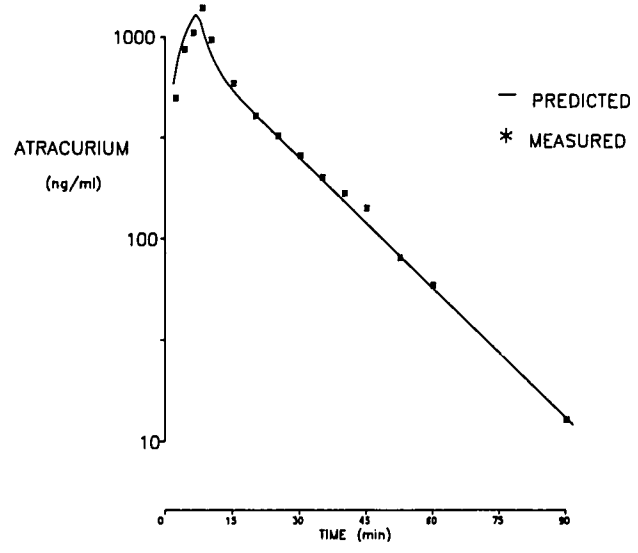

FIG. 4. Pharmacokinetic data from a representative *in vivo* study. Atracurium was administered at a rate of 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the first 7.5 min. Stars represent the measured concentrations, and the line represents the fitted function as determined by nonlinear regression.

Discussion

If Hofmann elimination and ester hydrolysis are assumed to occur *in vivo* at the same rate as observed *in vitro*, our data suggest that approximately 40% of the *in vivo* clearance of atracurium results from Hofmann elimination and ester hydrolysis. The remaining 60% occurs through other processes, presumably metabolism or excretion by the liver and/or kidney. In humans, elimination of atracurium appears to depend little on renal function. Data from Fahey *et al.*[7] demonstrated that the total clearance of atracurium in subjects having no renal function was similar to the clearance in subjects having normal renal function (6.7 ± 1.8 and 6.1 ± 0.8 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively). In addition, the duration of action of atracurium is not prolonged in patients with renal failure.[8]

Three studies have examined the contribution of the liver to the elimination of atracurium. Neill and Chapple[9] found 9.9% of a radiolabeled dose of atracurium in the bile (and 6.9% in urine) of cats 2 h after administration of atracurium. For three cats in which atracurium was administered into the portal vein, AUC was similar to the value obtained with administration into the jugular vein. Neill and Chapple concluded that, in cats, there was little hepatic clearance of atracurium. However, after administration into the portal vein, $AUC_{portal\ vein}$ is equal to $F_H \times AUC_{systemic\ vein}$ where $F_H = 1 - (Cl_{hepatic}/Q_{hepatic})$. Because $Q_{hepatic}$ (plasma) is approximately 500–800 ml/min,†† $Cl_{hepatic}$ can be appreciable, while F_H still remains close to unity. In addition, administration into the portal vein might saturate the ability of the liver to metabolize atracurium, further mitigating the deviation of F_H from unity. Thus, the observations of Neill and Chapple do not contradict our results. Nagashima *et al.*,[10] using a continuous iv infusion, demonstrated that the infusion rate required to maintain a constant 50% depression of twitch tension was lower in rats that had undergone portacaval shunt than in either rats that had undergone renal ligation or control animals (3.56, 4.67, and 4.50 $mg \cdot kg^{-1} \cdot h^{-1}$, respectively). Because the infusion rate required to maintain a given steady-state plasma concentration is the product of clearance and the plasma concentration, and because there is no reason that portacaval shunt or renal

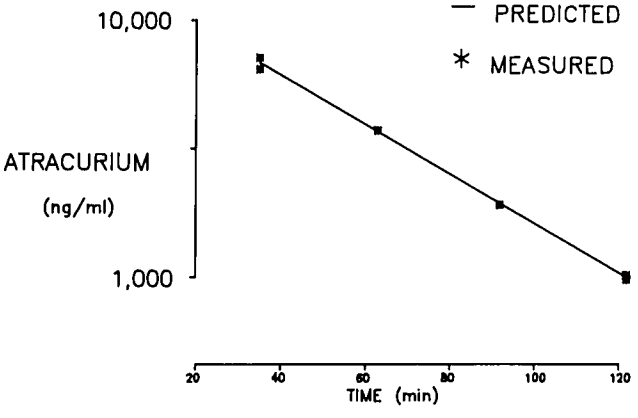

FIG. 5. Data obtained *in vitro* for the subject described in figure 4. Atracurium (400 μg) was added to 50 ml of whole blood maintained at physiologic *p*H and temperature. Blood samples were obtained at the indicated time intervals to determine the concentration of atracurium.

†† We used $Q_{hepatic}$ (plasma) in these calculations because penetration of erythrocytes by atracurium is minimal.[9]

TABLE 1. Pharmacokinetic Values Obtained in the *in Vitro* and *in Vivo* Studies of Atracurium in Humans

Age (yr)	Temperature (° C)	*p*H	$k_{nonorgan}$ (min/kg)	V_{ss} (ml/kg)	Cl_{total} ($ml \cdot kg^{-1} \cdot min^{-1}$)	$Cl_{nonorgan}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	Cl_{organ} ($ml \cdot kg^{-1} \cdot min^{-1}$)
22	35.8	7.38	0.0220	98.4	5.4	2.2	3.3
25	36.3	7.34	0.0209	133.3	5.5	2.8	2.7
29	35.0	7.35	0.0193	77.0	5.9	1.5	4.4
42	36.0	7.37	0.0238	49.4	3.5	1.2	2.3
43	35.5	7.35	0.0210	78.7	3.8	1.7	2.1

$k_{nonorgan}$ = the rate constant Hofmann elimination and ester hydrolysis; V_{ss} = volume of distribution at steady state; Cl_{total} = total clearance; $Cl_{nonorgan}$ = clearance through Hofmann elimination and ester hydrolysis; and Cl_{organ} = clearance by the liver and/or kidneys.

ligation should alter sensitivities of the neuromuscular junction acutely, we can estimate that the liver provides approximately 20% of total clearance in rats. This value is smaller than the value for Cl_{organ}/Cl_{total} obtained in the present study.

The third study compared the values for pharmacokinetic properties of atracurium in critically ill subjects having acute liver and kidney failure with values obtained in anesthetized subjects having normal liver and kidney function.[11] For five subjects whose liver failure resulted from ingestion of paracetamol, elimination half-life was not prolonged. For the remaining subject, who had undergone an unsuccessful liver transplant, elimination half-life was prolonged nearly 50%. These studies suggest that although the liver may represent an elimination pathway for atracurium, this pathway is not altered by paracetamol-induced liver failure.

Neill *et al.*[12] suggested that atracurium may be eliminated solely by Hofmann elimination and ester hydrolysis rather than by organ-based metabolism or excretion. However, there is no reason why atracurium should not undergo organ-based metabolism and excretion. In fact, the value for Cl_{organ} for atracurium is similar to the values for Cl_{total} for pancuronium,[13] *d*-tubocurarine,[14] and metocurine[15] (1.8 ± 0.4, 3.0 ± 0.8, and 1.2 ± 0.7 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively). These nondepolarizing muscle relaxants do not undergo Hofmann elimination or ester hydrolysis.

The values for $k_{in\ vitro}$ obtained in this study differ from those reported by Stiller *et al.*[16] who determined the half-life for atracurium in plasma at *p*H 7.3 and 37° C. Their value for half-life of 21 min corresponds to an elimination rate constant of 0.033/min, in contrast to our mean value of 0.021/min. The design of their study differs from ours in several ways, including the use of plasma rather than whole blood and of a slightly lower initial *p*H. Furthermore, we document the stability of *p*H throughout our *in vitro* studies (*p*H never deviated more than 0.05 *p*H units from the initial measurement), whereas Stiller *et al.* do not report on the stability of *p*H in their studies. Possibly, the difference in values calculated for *in vitro* half-lives results from either the use of different medium (blood *vs.* plasma) or the instability of *p*H in their studies.

The pharmacokinetic model that we propose makes several assumptions. First, we assumed that the combined processes of Hofmann elimination and ester hydrolysis were first-order. We tested this assumption by performing more extensive *in vitro* studies in three subjects. For two of these subjects in whom samples were obtained at a greater number of time intervals, we observed that the elimination of atracurium *in vitro* was slightly nonlinear (fig. 2). Perhaps the steeper initial portion of the elimination curve obtained *in vitro* results from passage of atracurium into erythrocytes; regardless of the cause of more rapid elimination initially, subsequent *in vitro* elimination of atracurium appears to be first-order. In the third subject, addition of different quantities of atracurium to blood maintained at physiologic conditions *in vitro* resulted in a similar rate of degradation (fig. 3).

Second, we assumed that the rate constant for Hofmann elimination and ester hydrolysis *in vitro* would be the same as the rate constant *in vivo*. Although we simulated physiologic conditions for temperature and *p*H, *in vitro* results may differ from *in vivo* results.

Third, we assumed that the $k_{Hofmann\ elimination}$ and $k_{ester\ hydrolysis}$ would be similar throughout both compartments. Because the rate of Hofmann degradation depends predominantly on two factors, temperature and *p*H (for which the physiologic range is small), *in vitro* estimates for Hofmann elimination should be valid. However, esterase activity may differ markedly between tissues, depending on the local concentration and activity of enzymes. Because the experimental conditions closely approximate those *in vivo*, these values are likely to provide a reliable estimate for elimination in blood. If esterase activity were markedly higher in the tissues to which atracurium is distributed, it is possible that the *in vitro* rate constants underestimate the role of ester hydrolysis in the elimination of atracurium.

One advantage of our pharmacokinetic model is that it permits an estimate of V_{ss} for atracurium. The traditional techniques used for estimating V_{ss} for other drugs are not applicable to atracurium because its elimination occurs from more than one compartment. For example, noncompartmental techniques require the assumption that all clearance occurs from the central compartment.[17]

If pharmacokinetic variables for atracurium were determined using traditional models (*i.e.*, those assuming clearance from the central compartment only), estimates for total clearance would be identical to those in the present study. However, because the traditional model ignores elimination of atracurium from the peripheral compartment, the quantity of drug in the peripheral compartment, and hence its volume of distribution, would be underestimated. Similarly, if the true rate constant for elimination from the peripheral compartment is greater than the value obtained in the *in vitro* studies, we might still be underestimating V_{ss}; however, we would be doing so to a lesser degree than if elimination from the peripheral compartment were ignored completely. Perhaps through quantitation of metabolites and determination of their pharmacokinetics this issue can be resolved.

In summary, we developed a model to describe the pharmacokinetic properties of atracurium, a muscle relaxant that is eliminated from both the central and peripheral compartments. We evaluated our model using data from five subjects. Using this model and an *in vitro* rate constant for Hofmann elimination and ester hydrolysis, we found that the elimination of atracurium occurs through three major pathways. Hepatic (or other nonrenal) pathways account for 61% of the clearance, and Hofmann elimination and ester hydrolysis account for the remaining 39%. We have not determined the relative contributions of Hofmann elimination and ester hydrolysis.

The fact that atracurium is eliminated through several pathways is an advantage in clinical use. For example, *in vitro* studies suggest that atracurium is degraded as rapidly in the plasma of patients with pseudocholinesterase deficiency as in patients with normal pseudocholinesterase activity.[18] In addition, if hepatic failure resulted in a marked decrease in the Cl_{total} of atracurium, Cl_{total} would still exceed the clearance of pancuronium in subjects with normal renal function.[10] Thus, in patients with hepatic failure, atracurium-induced neuromuscular blockade should not be prolonged excessively. These considerations explain why atracurium is an excellent muscle relaxant for patients with multiorgan failure.

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Appendix

The pharmacokinetic model for atracurium shown in figure 1 can be represented by:

$$C = Ae^{-\alpha t} + Be^{-\beta t};‡‡ \quad (1)$$

where:

$$V_1 = Dose/(A + B); \quad (2)$$

$$A = Dose \times (k_{20} + k_{21} - \alpha)/[V_1 \times (\beta - \alpha)]; \quad (3)$$

$$B = Dose \times (k_{20} + k_{21} - \beta)/[V_1 \times (\alpha - \beta)]; \quad (4)$$

$$\alpha + \beta = k_{10} + k_{12} + k_{20} + k_{21}; \quad (5)$$

$$\alpha \times \beta = (k_{10} \times k_{20}) + (k_{10} \times k_{21}) + (k_{12} \times k_{20}). \quad (6)$$

‡‡ Equation 1 applies when atracurium is administered by bolus. Because we administered atracurium by infusion, our pharmacokinetic calculations were performed using a modified equation that requires no additional parameters.

By definition,

$$C_{ss} \times V_1 = A_{1_{ss}}; \quad \text{and,} \tag{7}$$

$$C_{ss} \times V_{ss} = A_{1_{ss}} + A_{2_{ss}}, \tag{8}$$

where $A_{1_{ss}}$ and $A_{2_{ss}}$ are the amounts of drug in the central and peripheral compartments, respectively, at steady state. The quantity of atracurium entering the peripheral compartment at steady state is equal to the quantity of drug leaving that compartment. Therefore:

$$k_{12} \times A_{1_{ss}} = (k_{21} + k_{20}) \times A_{2_{ss}}, \quad \text{and} \tag{9}$$

$$A_{1_{ss}} + A_{2_{ss}} = A_{1_{ss}} \times [1 + k_{12}/(k_{21} + k_{20})]. \tag{10}$$

Dividing both sides of the equation by C_{ss} produces

$$V_{ss} = A_{1_{ss}} \times [1 + k_{12}/(k_{21} + k_{20})]/C_{ss}. \tag{11}$$

This is equivalent to:

$$V_{ss} = V_1 \times [1 + k_{12}/(k_{21} + k_{20})]. \tag{12}$$

At steady state,

$$\text{input rate} = \text{elimination rate} = C_{ss} \times Cl_{total}. \tag{13}$$

Because:

$$\text{elimination rate} = [k_{10} \times A_{1_{ss}}] + [k_{20} \times A_{2_{ss}}], \tag{14}$$

$$Cl_{total} = [k_{10} \times A_{1_{ss}} \times V_1/A_{1_{ss}}] + [k_{20} \times A_{2_{ss}} \times V_1/A_{1_{ss}}]; \tag{15}$$

or:

$$Cl_{total} = (k_{10} \times V_1) + [(k_{12} \times k_{20})/(k_{21} + k_{20}) \times V_1]. \tag{16}$$

By definition,

$$V_2 = V_{ss} - V_1. \tag{17}$$

Therefore,

$$V_2 = V_1 \times k_{12}/(k_{21} + k_{20}). \tag{18}$$

Hence,

$$Cl_{total} = (k_{10} \times V_1) + (k_{20} \times V_2). \tag{19}$$

Using the appropriate transforms produces a value for Cl_{total} that is identical to the value when the dose is divided by the AUC. Assuming that Cl_{organ} occurs only in the central compartment and that $k_{nonorgan}$ is the same in the central and peripheral compartments, we can further divide clearance as follows:

$$Cl_{nonorgan} = k_{nonorgan} \times V_{ss}, \tag{20}$$

and:

$$Cl_{organ} = Cl_{total} - Cl_{nonorgan}. \tag{21}$$

As a result:

$$k_{organ} = Cl_{organ}/V_1. \tag{22}$$