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Pharmacokinetics and Pharmacodynamics of Atracurium in Infants and Children

Dennis M. Fisher, M.D., P. Claver Canfell, M.S.,† Michael J. Spellman, B.A.,‡ Ronald D. Miller, M.D.§*

To determine whether maturational changes in body composition and organ function affect distribution and elimination of and sensitivity to atracurium, the authors determined the pharmacokinetics and pharmacodynamics of atracurium in six infants and five children and compared these results with those obtained in five adults. Atracurium, 15.8 ± 1.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$, was infused iv for 6–11 min to subjects anesthetized with nitrous oxide (60%) and halothane (0.9 MAC, age-adjusted) and twitch tension of the adductor pollicis muscle was measured. Plasma samples were obtained for 120 min; concentrations of atracurium were determined using a liquid chromatographic assay. A two-compartment pharmacokinetic model, adapted to account for elimination of atracurium from both central and peripheral compartments, was fit to the plasma concentration data; an effect–compartment model was fit to the twitch tension data. Volume of distribution at steady state (210 ± 118, 129 ± 44, and 100 ± 22 ml/kg for infants, children, and adults, respectively) and total clearance (7.9 ± 2.0, 6.8 ± 1.6, and 5.3 ± 0.9 $ml \cdot kg^{-1} \cdot min^{-1}$ for the three groups) decreased with increasing age. Neither elimination half-life (20.0 ± 5.1, 17.2 ± 5.1, and 15.7 ± 2.5 min for the three groups) nor the steady state plasma concentration that resulted in 50% neuromuscular blockade (363 ± 118, 444 ± 121, and 436 ± 122 ng/ml for the three groups) varied with age. The authors conclude that these results are consistent with and explain the previously reported findings that recovery from the neuromuscular effects of atracurium is minimally affected by age. In addition, age-related changes in atracurium's volume of distribution at steady state are similar to those for vecuronium and *d*-tubocurarine; these changes presumably result from these muscle relaxants distributing into the extracellular fluid space the volume of which decreases during the first year of life. (Key words: Anesthesia, pediatric. Neuromuscular relaxants: atracurium. Pharmacokinetics: atracurium.)

RECOVERY from the neuromuscular effects of atracurium, a nondepolarizing muscle relaxant, is similar in infants and children.[1–5] In contrast, recovery from the neuromuscular effects of vecuronium is prolonged in infants.[6] We previously demonstrated that the longer recovery from vecuronium-induced paralysis in infants could be explained by age-related changes in its volume of distribution at steady state (V_{ss}) rather than age-related changes in plasma clearance.[7] Pharmacokinetic and pharmacodynamic data for atracurium would identify whether maturational changes in body composition or organ function affected distribution or elimination of atracurium and would explain the minimal changes in recovery time with age. Although Brandom *et al.*[8] previously reported the pharmacokinetics of atracurium in infants and children, they did not determine either V_{ss} or the contribution of organ-based and non-organ-based pathways to clearance nor did they obtain comparable data in adults. Thus, we determined the pharmacokinetics of atracurium in infants and children using a pharmacokinetic model that permitted determination of V_{ss} and compared our results with those obtained in adults.[9]

Methods

After obtaining approval from the local committee on human research and informed consent, we studied six infants (4–11 months) and five children (14 months–4 yr), none of whom had renal, hepatic, or neuromuscular diseases. Anesthesia was induced with nitrous oxide and halothane, and the trachea was intubated without the aid of muscle relaxants. Anesthesia was maintained with nitrous oxide, 60–70%, and halothane, 0.9 MAC end-tidal concentration (age-adjusted,[10] and monitored by mass spectrometry). $P_{ET_{CO_2}}$ was maintained at approximately 35 mmHg and temperature kept in a normal range.

We stimulated the ulnar nerve with supramaximal squarewave pulses of 0.15-ms duration using needle electrodes and measured twitch tension of the adductor pollicis muscle using a Grass® FT-10 force transducer. After achieving stable values for twitch tension and anesthetic concentrations, we administered atracurium, 15.8 ± 1.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (mean ± SD), until twitch tension of the adductor pollicis was depressed 70% (6.0–11.0 min); twitch tension continued to decline to approximately 10% of control. Blood samples, 0.5 ml each, were obtained frequently (approximately 16 samples per patient) during a 2-h sampling period. (In preliminary studies we observed that, following these doses, atracurium could not be detected beyond 2 h.) Arterial samples were obtained in four infants and four children, venous samples in the remainder. Samples were acidified immediately to prevent degradation of atracurium; plasma concentrations were determined using a liquid chromatographic assay[11] sensitive to 10 ng/ml, with a coefficient of variation < 10% at concentrations > 25 ng/ml and 20% at 10 ng/ml.

Plasma atracurium concentrations were then plotted against time, and a two-compartment pharmacokinetic model adjusted for the infusion[12] was fit to these data

* Associate Professor of Anesthesia and Pediatrics.

† Specialist.

‡ Staff Research Associate.

§ Professor and Chairman of Anesthesia; Professor of Pharmacology.

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Address reprint requests to Dr. Fisher: Department of Anesthesia, S-436, University of California, San Francisco, California 94143-0648.

using a derivative-free nonlinear regression.[13] Because atracurium is eliminated from the central and peripheral compartments *via* Hofmann elimination and ester hydrolysis, and from the central compartment, probably *via* the liver and kidneys, we used a pharmacokinetic model considering these multiple pathways. (We have described this model previously[9]; modifications applied for this study appear in the Appendix.) The model requires that we estimate the rate at which atracurium is eliminated *in vivo* ($k_{nonorgan}$) by Hofmann elimination and ester hydrolysis.

To determine $k_{nonorgan}$ 15 ml of blood was obtained from an additional six infants and six children similar in age to those described previously and anesthetized in a similar manner. The blood was placed in a sealed vessel, equilibrated wtih 5% CO_2 and 95% O_2, and agitated constantly; it was maintained at the same *p*H (7.35–7.45) and 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 to determine the concentration of atracurium 30, 60, 90 and 120 min after addition of atracurium. Values for natural log atracurium concentration were plotted against time, and the slope of the resulting line was determined using linear regression. The negative of this value is $k_{nonorgan}$. Mean values for patients in each age group were determined.

To determine pharmacokinetic parameters, we used the average value for $k_{nonorgan}$ for patients in the appropriate age group and the values obtained from the nonlinear regression to determine distribution half-life ($t_{1/2}\alpha$), elimination half-life ($t_{1/2}\beta$), volume of the central compartment (V_1), volume of distribution at steady state (V_{ss}), total clearance (Cl), clearance that could be explained by Hofmann elimination and ester hydrolysis ($Cl_{nonorgan}$), and clearance that resulted from pathways other than Hofmann elimination and ester hydrolysis (Cl_{organ}).

Then, using an effect–compartment pharmacodynamic model,[14,15] we fit the estimates of the pharmacokinetic model to the twitch tension data using non-linear regression. This permitted us to determine the steady state plasma concentration that produces 50% neuromuscular blockade ($C_{ss_{50}}$), the factor that describes the sigmoid relationship between the concentration of atracurium and effect (γ), and the rate constant for equilibration between the neuromuscular junction and plasma (k_{eo}). We also calculated the product of V_{ss} and $C_{ss_{50}}$, which is the quantity of atracurium in the body at steady state at 50% paralysis (D_{50}); this is the steady state equivalent of an ED_{50} (the bolus dose required to produce 50% paralysis).

We compared these results with those obtained concurrently in five adults 22–44 yr of age. (Pharmacokinetic, but not pharmacodynamic, data for four of these adults have been published previously.[9]) Anesthetic technique (N_2O, 60%; halothane, 0.9 MAC end-tidal concentration), neuromuscular stimulation and monitoring, atracurium administration, and analytic techniques for these subjects were similar to those of the present study. Venous blood samples were obtained in these subjects. The *in vitro* rate constant was determined for six additional adults of comparable age and anesthetized in a similar manner; these values were then used to calculate a pooled estimate for $k_{nonorgan}$. Pharmacokinetic parameters for the five adults were then estimated using this pooled estimate for $k_{nonorgan}$. Mean values for the three groups were compared using a nonparametric analysis of variance and a nonparametric Student-Newman-Keuls test; $P < 0.05$ was considered statistically significant.

Results

In the *in vitro* studies there was an excellent correlation between the observed values and the regression line for each subject (r^2 always exceeded 0.98, fig. 1). The *in vitro* elimination rate constant, $k_{nonorgan}$, was similar for infants, children, and adults (0.023 ± 0.002, 0.020 ± 0.002, and 0.025 ± 0.002 min^{-1}, respectively).

In the *in vivo* studies there was an excellent fit of the pharmacokinetic and pharmacodynamic models to the plasma concentration and twitch tension data (figs. 2 and 3). In all subjects the plasma concentration *versus* time curve appeared to enter a well-defined elimination phase despite sampling for only 2h. Total clearance, V_{ss}, $Cl_{nonorgan}$, and D_{50} decreased with age (table 1). We could not demonstrate that distribution or elimination half-lives, V_1, Cl_{organ}, $C_{ss_{50}}$, γ, or k_{eo} changed with age.

Discussion

Although atracurium has been used in pediatric anesthesia for many years, this is the first study to demonstrate that elimination half-life is similar for infants, children,

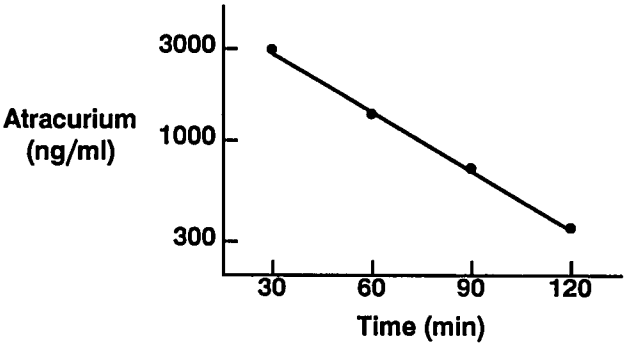

FIG. 1. Data obtained *in vitro* from a representative subject. Atracurium, 400 μg, was added to 15 ml blood maintained as physiologic *p*H and temperature. Blood samples were obtained 30, 60, 90, and 120 min after addition of atracurium, and the concentration of atracurium was determined. Circles represent the measured concentrations; the line represents the fitted function as determined by linear regression.

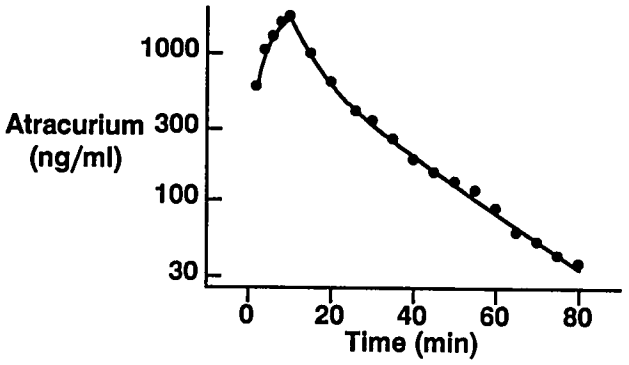

FIG. 2. Pharmacokinetic data obtained *in vivo* from a 19-month-old infant. Atracurium was administered at 15.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 10 min. Circles represent the measured concentrations; the line represents the fitted function as determined by nonlinear regression.

and adults; this absence of age-related change in elimination half-life results from parallel changes in V_{ss} and Cl. Because of the relationship between elimination half-life and recovery from the neuromuscular effects of atracurium,[16] our findings suggest that recovery from the neuromuscular effects of this drug should vary minimally with age. Several studies in pediatric patients confirm these expectations. For example, Meretoja and Kalli[5] demonstrated that recovery time for atracurium varied minimally between infants and children (11.6 ± 1.2, 10.2 ± 0.5, and 10.2 ± 0.6 min [mean ± SE] for patients weighing 5–10 kg, 15–20 kg, and >30 kg, respectively). Brandom *et al.*[1,2] and Goudsouzian *et al.*[3,4] have reported similar findings comparing infants, children, and adolescents. Of note, Meretoja and Kalli[5] reported that recovery time was slightly longer in neonates (14.2 ± 1.8 min in patients weighing <5 kg) than in older subjects. However, we were unable to determine the pharmacokinetics of atracurium in neonates because of the large amount of blood required for an adequate pharmacokinetic analysis.

In contrast, vecuronium's neuromuscular effects vary markedly with age, recovery time following a dose of 70 μg/kg being notably longer in infants than in older subjects.[6] We previously demonstrated that vecuronium's longer recovery time in infants could be explained by age-related changes in its pharmacokinetics: V_{ss} decreased with age while Cl did not change, resulting in a longer mean residence time and, thus, recovery time in infants.[7] In contrast, because atracurium's V_{ss} and Cl both decreased with age, elimination half-life varies minimally with age.

Our finding that the V_{ss} of atracurium, like vecuronium, decreased with age is consistent with these nondepolarizing muscle relaxants being highly polar. We previously reported that V_{ss} for both *d*-tubocurarine (*d*Tc)[17] and vecuronium[7] decreased with age paralleling maturational decreases in the volume of extracellular fluid (ECF).[18] Because atracurium, like *d*Tc and vecuronium, is polar, its distribution should similarly be limited to ECF.

Unlike vecuronium and *d*Tc, total clearance of atracurium decreased with age. We believe that this results from atracurium having both organ-based and non-organ-based elimination pathways. Atracurium's organ-based elimination (Cl_{organ}) did not vary with age, a finding similar to that for *d*Tc[17] and vecuronium,[7] which are eliminated *via* the kidney[19] and liver,[20] respectively. Atracurium, however, is eliminated *via* two additional pathways, Hofmann elimination and ester hydrolysis, in both the central and peripheral compartments. $Cl_{nonorgan}$, elimination *via* these two additional pathways, is lower in older patients because of age-related decreases in V_{ss}.

Atracurium's $C_{ss_{50}}$ did not change with age, whereas for both vecuronium[7] and *d*Tc,[17] $C_{ss_{50}}$ was lower in patients younger than 1 yr of age. Previously, we speculated that age-related increases in $C_{ss_{50}}$ of vecuronium and *d*Tc resulted from immaturity of the neuromuscular junction in infants. However, because infants in the three pharmacodynamic studies are comparable in age, we are unable to explain why similar age-related changes in $C_{ss_{50}}$ do not occur for atracurium.

Our results can be used to predict whether age affects the rate at which atracurium must be administered during steady state infusion. At steady state the amount of drug administered is equal to the amount of drug eliminated, the product of Cl, and the desired steady state plasma concentration of atracurium. We calculated the infusion rate for two degrees of neuromuscular blockade, 50% and 90% depression, for each subject. Mean values for 50% depression (2.7 ± 0.5, 2.9 ± 0.6, 2.3 ± 0.9 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for infants, children, and adults, respectively) and for 90% depression (4.4 ± 0.7, 5.1 ± 1.3, 4.1 ± 2.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) were similar for the three age groups. Thus, during the anesthetic conditions in our

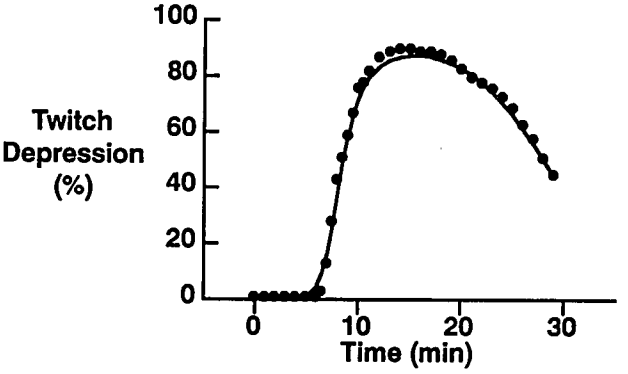

FIG. 3. Pharmacodynamic data obtained *in vivo* from the same infant as in figure 2. Atracurium was administered at 15.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 10 min. Circles represent the measured depression of twitch tension; the line represents the fitted function as determined by nonlinear regression.

TABLE 1. Pharmacokinetic and Pharmacodynamic Values (mean ± SD) for Atracurium for Infants, Children, and Adults

	Infants	Children	Adults*
N	6	5	5
$t_{1/2}\alpha$ (min)	3.8 ± 2.9	3.5 ± 2.2	1.5 ± 1.0
$t_{1/2}\beta$ (min)	20.0 ± 5.1	17.2 ± 5.1	15.7 ± 2.5
V_1 (ml/kg)	100 ± 95	63 ± 38	32 ± 16
V_{ss}† (ml/kg)	210 ± 118	129 ± 44	100 ± 22
Cl‡ ($ml \cdot kg^{-1} \cdot min^{-1}$)	7.9 ± 2.0	6.8 ± 1.6	5.3 ± 0.9
Cl_{organ} ($ml \cdot kg^{-1} \cdot min^{-1}$)	3.0 ± 1.1	4.2 ± 1.2	2.8 ± 0.9
$Cl_{nonorgan}$† ($ml \cdot kg^{-1} \cdot min^{-1}$)	4.8 ± 2.7	2.6 ± 0.9	2.5 ± 0.5
$C_{ss_{50}}$ (ng/ml)	363 ± 118	444 ± 121	436 ± 122
γ	4.9 ± 1.7	4.8 ± 2.2	4.6 ± 1.1
k_{eo} (min^{-1})	0.188 ± 0.117	0.159 ± 0.107	0.116 ± 0.060
F_{50}‡ ($\mu g/kg$)	66 ± 14	54 ± 10	41 ± 9

* Pharmacokinetic data for four of these five subjects were reported previously.[9]

† Infants differ from children and adults ($P < 0.05$).
‡ All groups differ ($P < 0.05$).

study, predicted infusion requirements do not appear to change with age.

Steady state infusion requirements for atracurium in pediatric patients have been examined in two studies, one by Kalli and Meretoja[21] during narcotic anesthesia and the other by Goudsouzian *et al.*[22,23] during halothane anesthesia. In both studies infusion requirements were similar for infants and children, consistent with our predictions. The fact that our predicted requirements are lower than those measured by Kalli and Meretoja[21] and by Goudsouzian *et al.*[22,23] probably results from their infusing atracurium at a rate sufficient to depress neuromuscular function 90–95% rather than the 90% used in our calculations; in addition, Kalli and Meretoja[21] did not administer halothane.

Our study could be criticized because, unlike our previous study,[9] we were unable to perform both *in vivo* and *in vitro* studies in the same subjects. Instead, for patients in each age group, we used the average value for $k_{nonorgan}$ for patients of the same age. The small variability observed for $k_{nonorgan}$ within each age group suggests that this study design should influence the results minimally. However, we recognize that using an average value for $k_{nonorgan}$ rather than the value obtained for each individual patient may influence our estimates of V_{ss} and the relative contributions of $Cl_{nonorgan}$ and Cl_{organ} to Cl. It is worth noting that using the average value, rather than individual values, for $k_{nonorgan}$ will not influence Cl. A second potential criticism of our study is that we sampled for only 2 h, unlike the 4-h sampling period used in our earlier studies of vecuronium and *d*Tc. However, examining the plasma concentration *versus* time curves suggests that we sampled for a sufficient period of time to define the elimination half-life and, thereby, estimate the pharmacokinetic parameters accurately. Finally, examining the pharmacodynamic data (*e.g.*, fig. 3) suggests that there is a systematic error with the pharmacodynamic model for many subjects. Because the error is small (typically less than a 1% difference between the observed and predicted values for twitch tension), we chose to not utilize a more complex pharmacodynamic model.

The pharmacokinetics of atracurium in infants and children were reported previously by Brandom *et al.*[8] Because these investigators used a model that does not account for elimination from both the central and peripheral compartments, they were unable to determine V_{ss}.[24] As a result, they reported V_{area}, a pharmacokinetic parameter of unknown physiologic significance. Of note, we calculated V_{area} for our subjects and found, similar to the results of Brandom *et al.*,[8] that it decreased with age (235 ± 115, 170 ± 70, and 119 ± 18 ml/kg for infants, children, and adults, respectively). Brandom *et al.*[8] also reported that clearance was greater in infants than in children (9.1 ± 0.7 *vs.* 5.1 ± 0.2 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively), but age-related differences were greater in their study than in ours. However, their sampling time of only 60 min may have been inadequate to define the terminal portion of the plasma concentration *versus* time curve, not permitting them to estimate total clearance or elimination half-life accurately.

In summary, age-related changes in V_{ss} for atracurium are similar to those for vecuronium and *d*Tc, whereas age-related changes in total clearance distinguish atracurium. Because atracurium's age-related changes in V_{ss} and Cl are parallel, its elimination half-life does not change with age. These results are consistent with the finding that recovery from atracurium-induced neuromuscular blockade changes minimally with age.

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Appendix

The pharmacokinetics of atracurium can be described by a two-compartment model in which atracurium is administered into the central compartment. Atracurium moves to the peripheral compartment at a rate k_{12} or is eliminated by organs (at a rate k_{organ}) or by non–organ-based pathways (at a rate $k_{nonorgan(central)}$, the sum of $k_{Hofmann\ degradation}$ and $k_{ester\ hydrolysis}$). Atracurium leaves the peripheral compartment by non–organ-based elimination (at a rate $k_{nonorgan(peripheral)}$) or by entering the central compartment (at a rate k_{21}). Assuming that $k_{nonorgan}$ is the same in the central and the peripheral compartments (this assumption is likely to be true because the rates of Hofmann elimination and ester hydrolysis are influenced predominantly by temperature and *p*H, both of which are relatively constant throughout the body), we can estimate $k_{nonorgan}$ *in vitro* by measuring the rate of degradation of atracurium in blood maintained under physiologic conditions. In previous studies we estimated $k_{nonorgan}$ *in vitro* for each subject for whom the pharmacokinetics of atracurium was determined *in vivo*. However, the quantity of blood that would be required to determine the pharmacokinetics of atracurium *in vivo* and *in vitro* exceeded that which we could ethically obtain from infants. Fortunately, our previous study demonstrated that $k_{nonorgan}$ varies little within an age group, suggesting that using an average value of $k_{nonorgan}$ obtained from patients of the same age would not influence the results. Consequently, we determined the pharmacokinetics of atracurium *in vivo* in one group of subjects and estimated $k_{nonorgan}$ in a second group.