Anesthesiology
72:272–275, 1990

Pharmacokinetics and Pharmacodynamics of Atracurium in the Elderly

John B. Kitts, M.D., F.R.C.P.C., Dennis M. Fisher, M.D.,† P. Claver Canfell, M.S.,‡ Michael J. Spellman, B.A.,§ James E. Caldwell, F.F.A.R.C.S.,¶ Tom Heier, M.D.,* Mark R. Fahey, M.D.,¶ Ronald D. Miller, M.D.***

To evaluate the effect of aging on the distribution, clearance, and neuromuscular junction sensitivity to atracurium, the authors determined the pharmacokinetics and pharmacodynamics of atracurium in five healthy elderly subjects (74–76 yr) during halothane–nitrous oxide anesthesia and compared these values to those obtained previously in five healthy young adults (22–44 yr). A brief (6.0–13.0 min) infusion of atracurium was administered until twitch tension was suppressed by approximately 70%, and atracurium plasma concentration and twitch tension data were used to determine pharmacokinetic and pharmacodynamic parameters for each patient. Total clearance (Cl_{total}) was similar in elderly and young adults. However, clearance *via* the liver and/or kidney (Cl_{organ}) was lower in elderly patients, whereas clearance due to Hofmann elimination and ester hydrolysis ($Cl_{nonorgan}$) was higher. Volume of distribution at steady state (V_{ss}) was larger in elderly patients. The increase in V_{ss} without an age-related increase in Cl_{total} resulted in a longer elimination half-life [21.8 ± 3.3 *vs.* 15.7 ± 2.5 min (mean ± SD)] in elderly patients. The steady state plasma concentration of atracurium required to suppress twitch tension by 50% was similar in elderly and young adults. The authors conclude that the pharmacokinetics, but not the pharmacodynamics, of atracurium differ significantly between elderly and young adults. As a result, repeated doses will be required with similar frequency in young and elderly adults, but recovery from comparable levels of neuromuscular blockade may be slightly prolonged in elderly patients. (Key words: Age factors. Neuromuscular relaxants: atracurium. Pharmacodynamics: atracurium. Pharmacokinetics: atracurium; kinetics; models.)

THE PROLONGED DURATION of action of pancuronium,[1] *d*-tubocurarine,[2] metocurine,[2] and vecuronium[3,4] in elderly patients is presumably, in part, due to age-related decreases in metabolic function of the kidney and/or liver. Other age-related changes in distribution, elimination, metabolism, and/or changes in sensitivity of the neuromuscular junction may also influence the response to nondepolarizing muscle relaxants.[1–4] Because atracurium, at physiologic *p*H and temperature, is eliminated by spontaneous degradation through Hofmann elimination and ester hydrolysis[5] (as well as other hepatic and/or renal pathways[6,7]), the response to atracurium might be less affected by age than are other nondepolarizing muscle relaxants. This speculation is supported by d'Hollander *et al.*,[8] who reported that the infusion rate of atracurium required to maintain constant neuromuscular depression did not differ between elderly and young adults. Accordingly, to determine whether age-related changes in response to atracurium occur, we determined the pharmacokinetics and pharmacodynamics of atracurium in elderly patients and compared these values with those obtained in young adults in a previous study.[6]

Methods

We obtained approval from the Committee on Human Research and informed consent to study five patients (74–76 yr of age, ASA Physical Status 1 or 2) who were undergoing elective surgical procedures not involving the liver or kidney. Patients had no historical or laboratory evidence of renal, hepatic, or neuromuscular disease.

Anesthesia was induced with 1–2 mg/kg thiopental iv and inhalation of halothane in 60% nitrous oxide *via* a face mask. The trachea was intubated without the aid of muscle relaxants. Anesthesia was maintained with 60% nitrous oxide and 0.5% end-tidal halothane (0.85 MAC, age-adjusted[9]), monitored by mass spectrometry. Ventilation was controlled to keep end-expired P_{CO_2} at 30–40 mmHg. Esophageal temperature was maintained at 35–37° C. The ulnar nerve was stimulated *via* subcutaneous needle electrodes placed at the wrist, using a Grass® S88 nerve stimulator. Supramaximal single stimuli of 0.15 ms duration were delivered at 0.1 Hz. The evoked twitch tension of the adductor pollicis muscle was measured by a Gould Statham® UTC3 force transducer attached to the thumb and recorded on a polygraph.

After anesthetic conditions and twitch tension were stable for at least 15 min, atracurium was infused at 16.3 ± 2.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (mean ± SD) until twitch tension was depressed approximately 70%; the duration of infusion was 10.2 ± 2.2 min. Heparinized venous blood samples (5 ml each) were obtained from the contralateral arm prior to and 2, 4, 6, 8, 10, 15, 20, 25, 30, 37.5, 45, 52.5, 60, 70, 80, 90, 100, 110, and 120 min after the start of the infusion. Samples were centrifuged immediately and the plasma was acidified with 3N sulfuric acid and stored at −20° C. The concentration of atracurium was deter-

* Fellow, Department of Anesthesia.
† Associate Professor of Anesthesia and Pediatrics.
‡ Associate Specialist.
§ Staff Research Associate.
¶ Assistant Professor of Anesthesia.
** Professor and Chairman of Anesthesia; Professor of Pharmacology.

Received from the Department of Anesthesia, University of California, San Francisco, California. Accepted for publication September 19, 1989. Supported in part by the National Institute of Aging (Grant No. P01 AG03104-07).

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

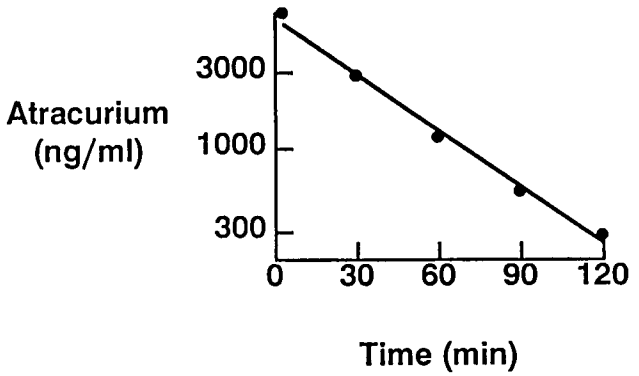

FIG. 1. Data obtained *in vitro* for a representative subject. Atracurium (100 μg) was added to 25 ml of whole blood maintained at physiologic *p*H and temperature. Blood samples were obtained at the indicated time intervals to determine the concentration of atracurium. Circles represent the measured concentration and the line represents the fitted function as determined by linear regression.

mined by ion-exchange liquid chromatography,[10] with the extraction modified to utilize AASP C_8 cartridges instead of SepPak C_{18} cartridges. This assay is sensitive to 10 ng/ml with a coefficient of variation of 7% at a concentration of 50 ng/ml.

Plasma concentrations of atracurium were plotted against time and fitted to a two-compartment pharmacokinetic model, modified to account for different elimination rate constants from the central ($k_{organ} + k_{nonorgan}$) and peripheral ($k_{nonorgan}$) compartments,[6] using nonlinear least-squares regression analysis.[11]

To determine $k_{nonorgan}$, the rate constant for elimination of atracurium from the peripheral compartment (sum of elimination rate constants for Hofmann elimination and ester hydrolysis[6]), an additional 25 ml of blood was obtained from each patient prior to administration of atracurium. This blood was placed in a sealed vessel, equilibrated with 5% CO_2 and 95% O_2 and agitated constantly. The blood was maintained at *p*H 7.35–7.45 and body temperature (35–37° C). Atracurium, 100 μg, was then added to the blood, and plasma samples were obtained at 3, 30, 60, 90, and 120 min to determine atracurium concentration. Values for natural log atracurium concentration were plotted against time, and the slope ($-k_{nonorgan}$) was calculated by least-squares linear regression. Values obtained *in vivo* and *in vitro* for each patient were then used in the pharmacokinetic model[6] to determine volume of distribution at steady state (V_{ss}), elimination half-life ($t_{1/2}\beta$), clearance by pathways other than Hofmann elimination and ester hydrolysis (Cl_{organ}), clearance by Hofmann elimination and ester hydrolysis ($Cl_{nonorgan}$), and total clearance (Cl_{total}).

The pharmacodynamic parameters, steady state plasma concentration producing 50% depression of twitch tension ($C_{ss_{50}}$), the term that describes sigmoidicity of the relationship between atracurium concentration at the neuromuscular junction and twitch depression (γ), and the rate of equilibration of the muscle relaxant between plasma and site of action (k_{eo}), were determined using the method of Sheiner *et al.*[12]

Results

For all subjects the plasma decay curve for atracurium *in vitro* was logarithmic, *i.e.*, log atracurium concentration *versus* time was linear (fig. 1). The elimination rate constant for Hofmann elimination and ester hydrolysis ($k_{nonorgan}$) was 0.025 ± 0.001 min^{-1} (mean ± SD) (table 1). Log atracurium concentration *versus* time from the data obtained *in vivo* and the fitted function for all subjects are shown in figure 2 along with data obtained from a previous study in young adults.[6] V_{ss} and $t_{1/2}\beta$ were 188 ± 61 ml/kg and 21.8 ± 3.3 min, respectively. Cl_{organ}, $Cl_{nonorgan}$, and Cl_{total} were 1.7 ± 0.9, 4.7 ± 1.6, and 6.5 ± 1.1 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively.

The twitch tension data and the fitted pharmacodynamic function for a representative subject are shown in figure 3. Pharmacodynamic parameters, $C_{ss_{50}}$, γ, and k_{eo}, were 449 ± 101 ng/ml, 4.1 ± 1.2, and 0.13 ± 0.08 min^{-1}, respectively (table 2).

Discussion

Because of its unique pathways of metabolism, atracurium is eliminated from both plasma (central compartment) and tissue (peripheral compartment). Traditional pharmacokinetic models, assuming elimination from the central compartment only, do not completely describe the pharmacokinetics of atracurium.[13] Using a traditional pharmacokinetic model, deBros *et al.*[14] determined $t_{1/2}\beta$

TABLE 1. Pharmacokinetic Values for Atracurium in the Elderly

Age (yr)	$k_{nonorgan}$ (min^{-1})	$t_{1/2}\beta$ (min)	V_{ss} (ml/kg)	Cl_{total} ($ml \cdot kg^{-1} \cdot min^{-1}$)	$Cl_{nonorgan}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	Cl_{organ} ($ml \cdot kg^{-1} \cdot min^{-1}$)
74	0.0241	20.4	154	6.1	3.7	2.4
74	0.0239	19.8	144	5.6	3.4	2.2
75	0.0262	18.2	147	6.4	3.9	2.5
76	0.0259	25.7	209	5.8	5.4	0.4
76	0.0252	24.8	287	8.4	7.2	1.2

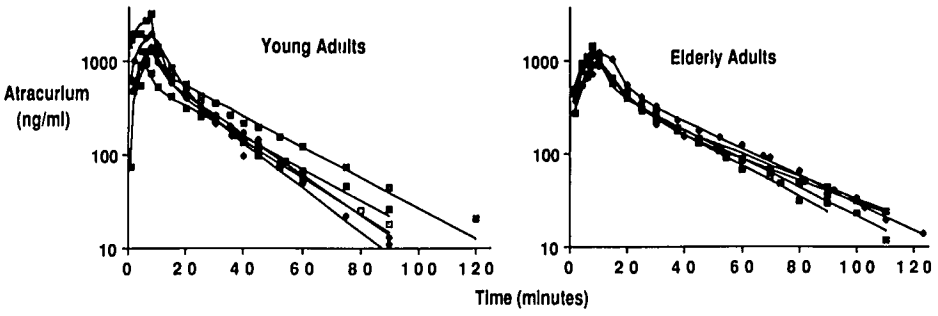

FIG. 2. Pharmacokinetic data obtained *in vivo* from all five elderly subjects in this study. Atracurium was administered at 16.3 ± 2.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (mean ± SD) for 10.2 ± 2.2 min. Circles represent the measured concentrations and the line represents the fitted function as determined by nonlinear regression. Pharmacokinetic data obtained from five young adults in a previous study are included for comparison.[6]

(19.1 ± 4.0 min, mean ± SE), Cl_{total} (6.4 ± 0.7 $ml \cdot kg^{-1} \cdot min^{-1}$), and V_β (171.8 ± 18.0 ml/kg) in the elderly. These values for $t_{1/2}\beta$ and Cl_{total} are similar to those obtained in the present study. By utilizing a model that accounts for elimination from both compartments,[6] we determined not only the parameters calculated by traditional pharmacokinetic models but also V_{ss} and the relative contributions of $Cl_{nonorgan}$ and Cl_{organ} to Cl_{total}.

We compared our results with those obtained previously in five young adults (table 3, fig. 2).[6] These young adults were anesthetized in a manner similar to that in the present study: end-tidal halothane concentrations were maintained at 0.85 MAC, age-adjusted[9,15] in both studies, *i.e.*, 0.7% in young adults and 0.5% in the elderly. Atracurium was infused using the same technique for both studies and blood samples were obtained and analyzed using the same personnel and analytic technique in each study. The major difference between studies was that the ulnar nerve was stimulated at 0.15 Hz in young adults and 0.1 Hz in the elderly. Pharmacokinetic values for four of these young adults have been reported previously.[6]

We found that V_{ss} was larger in elderly patients compared with that in young adults ($P < 0.05$ by the Mann-Whitney *U* test). Because atracurium probably distributes into the extracellular fluid (ECF) space, we expected maturational decreases in ECF volume to decrease V_{ss}. However, because atracurium is highly protein bound (80%[16]), the larger V_{ss} in the elderly may result from age-related decreases in protein binding.[17]

We found that Cl_{total} was similar in both groups. Because $Cl_{nonorgan}$ is the product of V_{ss} and $k_{nonorgan}$,[6] an increase in V_{ss} in elderly patients without a change in $k_{nonorgan}$ resulted in an increase in $Cl_{nonorgan}$ in elderly compared with young adults. However, Cl_{organ} was less in elderly patients, possibly a result of age-related decreases in metabolic function of the liver and kidney.[18] Changes in $Cl_{nonorgan}$ and Cl_{organ} counterbalanced to produce no age-related change in Cl_{total}.

We found no difference in neuromuscular junction sensitivity to atracurium between elderly and young patients. These results are consistent with those from previous studies with pancuronium,[1,4] *d*-tubocurarine,[2] metocurine,[2] and vecuronium[4] in which no significant age-related differences in neuromuscular junction sensitivity to these agents could be demonstrated.

The neuromuscular response of elderly subjects to atracurium has been investigated by d'Hollander *et al.*[8] Although they did not determine the pharmacokinetics of atracurium, their results can be interpreted in the context of our pharmacokinetic and pharmacodynamic data. They evaluated dose requirements for atracurium to maintain 90% twitch depression and found no difference between the different age groups. Because steady state infusion requirement is the product of steady state plasma concentration and Cl_{total}, our results (no change in $C_{ss_{50}}$ or Cl_{total} in the elderly) are consistent with their findings.

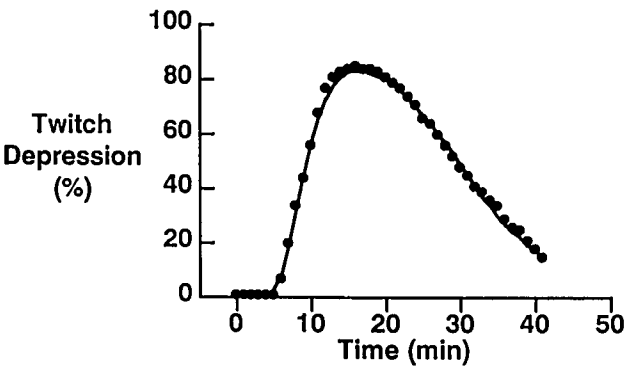

FIG. 3. Pharmacodynamic data obtained from the same subject as in figure 1. Atracurium was administered at 15.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 11.0 min. Solid circles represent the observed twitch depression and the line represents the fitted pharmacodynamic model. (Reprinted from Fisher *et al.*[6] Used with permission.)

TABLE 2. Pharmacodynamic Values for Atracurium in the Elderly

Age (yr)	$C_{ss_{50}}$ (ng/ml)	γ	k_{e0} (min^{-1})
74	566	4.2	0.087
74	546	5.0	0.125
75	360	3.9	0.119
76	422	2.2	0.265
76	353	5.2	0.078

TABLE 3. Values (mean ± SD) for Pharmacokinetic and Pharmacodynamic Parameters for Atracurium in Elderly and Young Adults

	Elderly Adults (n = 5)	Young Adults* (n = 5)
Age (yr)	75 ± 1†	33 ± 10
$k_{nonorgan}$ (min^{-1})	0.025 ± 0.001	0.022 ± 0.003
$t_{1/2}\beta$ (min)	21.8 ± 3.3†	15.7 ± 2.5
V_{ss} (ml/kg)	188 ± 61†	98 ± 23
Cl_{total} ($ml \cdot kg^{-1} \cdot min^{-1}$)	6.5 ± 1.1	5.3 ± 0.9
$Cl_{nonorgan}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	4.7 ± 1.6†	2.2 ± 0.6
Cl_{organ} ($ml \cdot kg^{-1} \cdot min^{-1}$)	1.7 ± 0.9†	3.1 ± 0.9
$C_{ss_{50}}$ (ng/ml)	449 ± 101	436 ± 121
γ	4.1 ± 1.2	4.6 ± 1.1
k_{e0} (min^{-1})	0.13 ± 0.08	0.12 ± 0.06

* From Fisher et al.[6] used with permission.
† Different ($P < 0.05$) from young adults by Mann-Whitney U test.

d'Hollander *et al.*[8] also reported that recovery (time required for twitch tension to recover from 25% to 75% of control) from a steady state infusion of atracurium in elderly patients was not different from young adults. Because recovery of neuromuscular function after a steady state infusion of atracurium varies as a function of $t_{1/2}\beta$, their results suggest that $t_{1/2}\beta$ is similar in elderly and young adults. This contrasts to our finding that $t_{1/2}\beta$ was slightly longer in the elderly (table 1). Although mean values for recovery time reported by d'Hollander *et al.*[8] were similar for different age groups, the large variability (10–24 min) in their results may prevent one from detecting small age-related differences.

We conclude that the pharmacokinetics, but not the pharmacodynamics, of atracurium differ between elderly and young adults. As a result, a slightly larger initial dose of atracurium may be required in elderly patients to account for the larger V_{ss} in these patients. Because Cl_{total} for atracurium is similar in both groups, second and subsequent doses of atracurium will be required with similar frequency in elderly and young adults. However, recovery from comparable levels of neuromuscular blockade might be slightly prolonged in elderly patients due to a slight increase in elimination half-life.

References

1. Duvaldestin P, Saada J, Berger JL, d'Hollander A, Desmonts JM: Pharmacokinetics, pharmacodynamics, and dose–response relationships of pancuronium in control and elderly subjects. ANESTHESIOLOGY 56:36–40, 1982
2. Matteo RS, Backus WW, McDaniel DD, Brotherton WP, Abraham R, Diaz J: Pharmacokinetics and pharmacodynamics of *d*-tubocurarine and metocurine in the elderly. Anesth Analg 64: 23–29, 1985
3. d'Hollander A, Massaux F, Nevelsteen M, Agoston S: Age-dependent dose–response relationship of Org NC45 in anaesthetized patients. Br J Anaesth 54:653–657, 1982
4. Rupp SM, Castagnoli KP, Fisher DM, Miller RD: Pancuronium and vecuronium pharmacokinetics and pharmacodynamics in younger and elderly adults. ANESTHESIOLOGY 67:45–49, 1987
5. Hughes R, Chapple DJ: The pharmacology of atracurium: A new competitive neuromuscular blocking agent. Br J Anaesth 53: 31–44, 1981
6. Fisher DM, Canfell PC, Fahey MR, Rosen JI, Rupp SM, Sheiner LB, Miller RD: Elimination of atracurium in humans: Contribution of Hofmann elimination and ester hydrolysis *versus* organ-based elimination. ANESTHESIOLOGY 65:6–12, 1986
7. Tsai SK, Lee C, Mok MS: Atracurium induced neuromuscular block is prolonged in hepatic vascular occlusion (abstract). ANESTHESIOLOGY 67:A605, 1987
8. d'Hollander AA, Luyckx C, Barvais L, De Ville A: Clinical evaluation of atracurium besylate requirement for a stable muscle relaxation during surgery: Lack of age-related effects. ANESTHESIOLOGY 59:237–240, 1983
9. Gregory GA, Eger EI II, Munson ES: The relationship between age and halothane requirement in man. ANESTHESIOLOGY 30: 488–491, 1969
10. Neill EAM, Jones CR: Determination of atracurium besylate in human plasma. J Chromatogr 274:409–412, 1983
11. Dixon WJ: BMDP Statistical Software. Berkeley, University of California Press, 1983, pp 305–327
12. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J: Simultaneous modeling of pharmacokinetics and pharmacodynamics: Application to *d*-tubocurarine. Clin Pharmacol Ther 25:358–371, 1979
13. Hull CJ: A model for atracurium (editorial). Br J Anaesth 55:95–96, 1983
14. deBros F, Okutani R, Lai A, Lawrence KW, Basta S: Pharmacokinetics and pharmacodynamics of atracurium in the elderly (abstract). ANESTHESIOLOGY 67:A604, 1987
15. Eger EI II: Anesthetic Uptake and Action. Baltimore, Williams & Wilkins, 1974, pp 13–14
16. Foldes FF, Deery A: Protein binding of atracurium and other short-acting neuromuscular blocking agents and their interaction with human cholinesterases. Br J Anaesth 55:31S–34S, 1983
17. Wood M: Plasma drug binding: Implications for anesthesiologists. Anesth Analg 65:786–804, 1986
18. Ouslander JG: Drug therapy in the elderly. Ann Intern Med 95: 711–722, 1981

Appendix

Pharmacokinetic properties of atracurium can be described using a two-compartment model in which atracurium is administered into the central compartment and moves between the central and peripheral compartments at rate constants k_{12} and k_{21}. Elimination from the central compartment is described by the sum of $k_{Hofmann\ degradation}$, $k_{ester\ hydrolysis}$, and k_{organ}. If organ elimination occurs only from the central compartment, the rate constant for elimination from the peripheral compartment ($k_{nonorgan}$) would equal the sum of $k_{Hofmann\ degradation}$ and $k_{ester\ hydrolysis}$. Assuming that the sum of $k_{Hofmann\ degradation}$ and $k_{ester\ hydrolysis}$ is the same in both compartments, its value may be estimated *in vitro* using blood maintained at physiologic *p*H and temperature. The *in vitro* rate constant is called $k_{nonorgan}$. Pharmacokinetic data were obtained by fitting the sum of two exponential terms ($C = Ae^{-\alpha t} + Be^{-\beta t}$) to the *in vivo* plasma concentration of atracurium *versus* time data. The pharmacokinetic data obtained from both *in vitro* and *in vivo* studies were used to determine $t_{1/2}\beta$, Cl_{organ}, $Cl_{nonorgan}$, Cl_{total}, and V_{ss} for each subject.