monitoring. This is manufactured in a variety of lengths. Another very satisfactory tubing that is more flexible and of lower volume is the 60-inch Microbore Extension Set made by Bruce Medical (product code ET-60M). These products have the additional advantages of having Luer lock ends, low volume, and excellent transparency. It is probably a good idea to also color code any connection sites, or to identify this tubing in some other way to further prevent accidental addition of medications into the epidural line.

PHILLIPA L. ZYLANOFF, M.D.
*Department of Anesthesiology*
*University of South Alabama*
*Mobile, Alabama 36617*

## REFERENCE

1. Lin D, Becker K, Shapiro HM: Neurologic changes following epidural injection of potassium chloride and diazepam: A case report with laboratory correlations. ANESTHESIOLOGY 65:210–212, 1986

*(Accepted for publication September 25, 1986.)*

Anesthesiology
66:95–96, 1987

# Elimination of Atracurium in Humans

*To the Editor:*—Fisher and colleagues propose a two-compartment model for atracurium and report that "more than one-half of the clearance of atracurium occurs via pathways other than Hofmann elimination and ester hydrolysis."[1] In the following, a different yet simpler and model-independent pharmacokinetic analysis of their data is offered.

1) The authors make an *a priori* assumption that the pharmacokinetic properties of atracurium can be described using a two-compartment model, and propose that atracurium leaves the central compartment (Fig. 1b) *via* three processes characterized by the rate constants $k_{organ}$, $k_{in\ vitro}$, and $k_{12}$. Since the authors did not determine either the amount of atracurium eliminated from the body (hepatic or renal excretion) or the arterio-venous concentration difference for atracurium across the excretory organs, $k_{organ}$ (*i.e.*, the rate constant for hepatic and/or renal elimination) was not amenable to independent estimation. Therefore, $k_{organ}$ becomes pharmacokinetically indistinguishable from, and merges with, $k_{12}$. This consideration leads to a simplified pharmacokinetic model represented by a *single* compartment out of which atracurium disappears *via* processes controlled by two rate constants: $k_{in\ vitro}$ and a composite rate constant $k_x$.

2) The data presented in figures 2, 3, and 5 convincingly document a monoexponential degradation of atracurium starting approximately 30 min after its addition to blood *in vitro*. (The derived rate constants $K_{nonorgan}$ presented in Table 1 display incorrect units, *viz.*, min/kg instead of reciprocal time.)

3) Allowing for a lag period identical to that found necessary in the *in vitro* experiments, plasma concentration of atracurium *in vivo* (Fig. 4) also decays monoexponentially.

4) The analysis presented in 2) and 3) demonstrates that the degradation of atracurium in human plasma proceeds monoexponentially *in vitro* as well as *in vivo;* the decay is faster *in vivo* than *in vitro*. Therefore, the simplest and the most plausible descriptions of how atracurium disappears from *plasma* are (using the authors' abbreviations)

$$\textit{in vitro}: \quad C = A \cdot e^{-(k_{in\ vitro}) \cdot t} \qquad (a)$$

$$\textit{in vivo}: \quad C = A \cdot e^{-(k_{in\ vivo}) \cdot t} \qquad (b)$$

where

$$k_{in\ vivo} = k_{in\ vitro} + k_x \qquad (c)$$

The rate constant $k_x$ characterizes the additional disappearance for atracurium *in vivo*. In agreement with the theoretical considerations outlined in 1), the data of Fisher *et al.* may be interpreted as follows: intravenous administration of atracurium leads to its distribution into a *single* volume, approximately equal to between 2 and 3 times the plasma volume (an amazingly small volume of distribution). From here, atracurium disappears by the known processes of Hofmann elimination and ester hydrolysis (represented by $k_{in\ vitro}$ in equations (a) and (c)), as well as by one or more unknown processes (characterized by the rate constant $k_x$ in equation (c)). These postulated, but unknown, decay processes could be: (1) a chemical degradation of atracurium not evident *in vitro*, (2) tissue uptake, and/or (3) elimination of atracurium from the body by the excretory organs. Data on plasma concentrations of atracurium alone cannot differentiate among them. Equation (c) permits partitioning the *in vivo* decay rate constant into two parts of which the unknown part ($k_x$) contributes about 60% of the total (from Table 1, the average $k_{in\ vitro} = 0.0214\ min^{-1}$ and the average $k_{in\ vivo} = 0.0584\ min^{-1}$; hence, $k_x = 0.0370\ min^{-1}$. The contribution of the rate constant $k_x$ to the total rate constant $k_{in\ vivo}$ is thus about 63%).

In summary, the *a priori* assumption by Fisher *et al.*[1] of a two-compartment pharmacokinetic model for atracurium is not necessary to interpret their experimental data, nor is it supported by these data. Similarly, since no ex-

perimental attempt was made to measure $k_{organ}$, the underlying process cannot be evaluated in their model. The estimate that the unknown elimination process accounts for 60% of the total *plasma* clearance of atracurium *in vivo*[1] remains valid, since it can be derived independently of the model (as demonstrated in 4)). However, this information has been available from earlier reports. We have indicated previously[2] that the faster degradation of atracurium *in vivo* than *in vitro* points to an additional inactivation process *in vivo*. From the data of Ward *et al.*[3] ($t_{1/2\ in\ vivo}$ = approx. 20 min; $k_{in\ vivo}$ = approx. 0.0347 $min^{-1}$) and of Merrett *et al.*[4] ($t_{1/2\ in\ vitro}$ = approx. 45 min; $k_{in\ vitro}$ = approx. 0.0154 $min^{-1}$), it can be estimated that the unknown mechanism accounts for 56% of the *in vivo* rate constant. Thus, the results of Fisher *et al.*[1] support the old data, but do not offer any new insights. Specifically, the pharmacokinetic model, though plausible, needs appropriate experimental verification.

VLADIMIR NIGROVIC, M.D.
*Departments of Anesthesiology and Pharmacology*
*Medical College of Ohio*
*Toledo, Ohio 43699*

## REFERENCES

1. 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
2. Nigrovic V, Auen M, Wajskol A: Enzymatic hydrolysis of atracurium *in vivo*. ANESTHESIOLOGY 62:606–609, 1985
3. Ward S, Neill EAM, Weatherley BC, Corall IM: Pharmacokinetics of atracurium in healthy patients (after a single i.v. bolus dose). Br J Anaesth 55:113–118, 1983
4. Merrett RA, Thompson CW, Webb FW: *In vitro* degradation of atracurium in human plasma. Br J Anaesth 55:61–66, 1983

*(Accepted for publication September 16, 1986.)*

Anesthesiology
66:96, 1987

*In reply:*—Dr. Nigrovic agrees with our finding[1] that approximately 60% (63%, according to his calculations) of atracurium's elimination cannot be explained by degradation occurring *in vitro*. In addition, he contends that our results "support the old data but do not offer any new insights." In contrast, I believe that the "old data" bears little relevance to our study. For example, the study by Nigrovic *et al.*[2] demonstrated that inactivating enzymatic (*i.e.*, ester) hydrolysis markedly prolonged the duration of action of atracurium-induced neuromuscular blockade. However, these authors did not determine the relative contribution of Hofmann elimination and organ-based elimination to the rate of recovery. In addition, the study was conducted in rats, and Nigrovic *et al.* noted that "the rat is generally not considered to be the most suitable animal for the study of muscle relaxants."

I agree with Dr. Nigrovic that Ward *et al.*[3] reported an *in vivo* elimination half-life of approximately 20 min. However, I question the applicability of the data obtained by Merrett *et al.*[4] Although the latter investigators determined a "half-life" *in vitro*, they evaluated the neuromuscular effects of atracurium which had been incubated in plasma or buffer for varying periods of time (using a bioassay), rather than the rate of decline of plasma concentration of atracurium (using a biochemical assay, as in our study). I accept the findings of Merrett *et al.* regarding the comparisons of patients with normal or absent pseudocholinesterase activity. However, I question the advisability of comparing the data obtained by Merrett *et al.* to the data obtained in studies using biochemical assays.

Finally, Nigrovic advocates a single-compartment pharmacokinetic model for atracurium, claiming that our figure 4 suggests a monoexponential decline of atracurium plasma concentrations *in vivo*. However, because the data in figure 4 were obtained during and after an infusion, the ability to demonstrate a distribution phase is minimized. Fahey *et al.*,[5] in figure 3 of their paper, demonstrated that following administration by bolus, a two-compartment model is necessary to describe the pharmacokinetics of atracurium.

In summary, I believe that our study is the first demonstration in humans that Hofmann elimination and ester hydrolysis are not the sole major elimination pathways for atracurium.

DENNIS M. FISHER, M.D.
*Assistant Professor of Anesthesia and Pediatrics*
*Department of Anesthesia*
*University of California*
*San Francisco, California 94143-0648*

## REFERENCES

1. 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
2. Nigrovic V, Auen M, Wajskol A: Enzymatic hydrolysis of atracurium *in vivo*. ANESTHESIOLOGY 62:606–609, 1985
3. Ward S, Neill EAM, Weatherley BC, Corall IM: Pharmacokinetics of atracurium besylate in healthy patients (after a single I.V. bolus dose). Br J Anaesth 55:113–118, 1983
4. Merrett RA, Thompson CW, Webb FW: *In vitro* degradation of atracurium in human plasma. Br J Anaesth 55:61–66, 1983
5. Fahey MR, Rupp SM, Fisher DM, Miller RD, Sharma M, Canfell C, Castagnoli K, Hennis PJ: The pharmacokinetics and pharmacodynamics of atracurium in patients with and without renal failure. ANESTHESIOLOGY 61:699–702, 1984

*(Accepted for publication September 10, 1986.)*