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.

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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)

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

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

where

$$k_{in\ vivo} = k_{in\ vitro} + k_x \tag{c}$$

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.

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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.

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