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More about the Pharmacokinetics of Vecuronium and Pancuronium

To the Editor:—Cronnelly and his colleagues[1] have reported a comparison of the pharmacokinetics and pharmacodynamics of vecuronium and pancuronium. I believe there are two problems with the articles that commonly are found in many similar articles.

First, they report the results of fitting the plasma concentrations of drug to a three-compartment model. The half-life of the fastest component with both drugs is of the order 2.5 min. However, on examining their sampling schedule they only obtained their first blood samples 10 min after the end of the infusion of the neuromuscular-blocking drugs. By this time, the rapid distribution phase would be about 94% complete. How much better a fit do they get using the three-compartment model rather than a two-compartment one?

Secondly and more importantly, the authors do not give all the parameters of the models they use. I believe that if pharmacokinetic and dynamic analysis is to be of use, then it must not only be descriptive of the results obtained in any one investigation but allow predictions of what may happen when different techniques of using the drugs are employed. With a three-compartment model it becomes necessary to give not only the three half-lives but also the three volumes. Better still would be the publication of all the intercompartmental rate constants.

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In reply: Dr. Norman has raised two questions with respect to our study. First, are the data really better characterized by a three-compartment model rather than a two-compartment model? We used the technique of Boxenbaum, which employs an F test to determine statistical preference for the number of compartments required to best characterize the data.[1] To demonstrate this by visual comparison, the concentrations of pancuronium measured in a patient are displayed in figure 1, along with the fitted functions generated with the two- and three-compartment models. The three-compartment model obviously characterizes the concentration-*versus*-time data "better" than the two-compartment model.

The second question raised by Dr. Norman involves our ability to characterize the distribution phase using our sampling schedule. Venous blood samples were obtained both *during* the infusion (at 2, 4, 6, 8 and 10 min) and at 5-min intervals for 20 min following the infusion. Perhaps this was misread by Dr. Norman. The pharmacokinetic model was modified for the drug infusion

TABLE 1. Rate Constants and Distribution Volumes

	k12 (min)	k13 (min)	k21 (min)	k31 (min)	k10 (min)	V_{2ss} l/kg	V_{ss} l/kg
Pancuronium	0.092	0.042	0.086	0.015	0.036	0.050	0.156
Vecuronium	0.607	0.085	0.305	0.024	0.116	0.056	0.157

Values are means.

(rather than injection of a drug bolus) by the technique of Loo and Riegelman.[2] Characterization of the distribution phase by this approach is not different from that obtained following the iv bolus techniques. Realizing that the accurate determination of a rapidly occurring event such as distribution of pancuronium is difficult, even if very frequent sampling were performed, we have attached minimal significance to this variable in the interpretation of our results.

Dr. Norman also requested that we provide additional pharmacokinetic data so that he can predict the concentrations of these drugs by using various methods of administration. Values for distribution volumes at steady state and intercompartmental rate constants are shown in table 1.

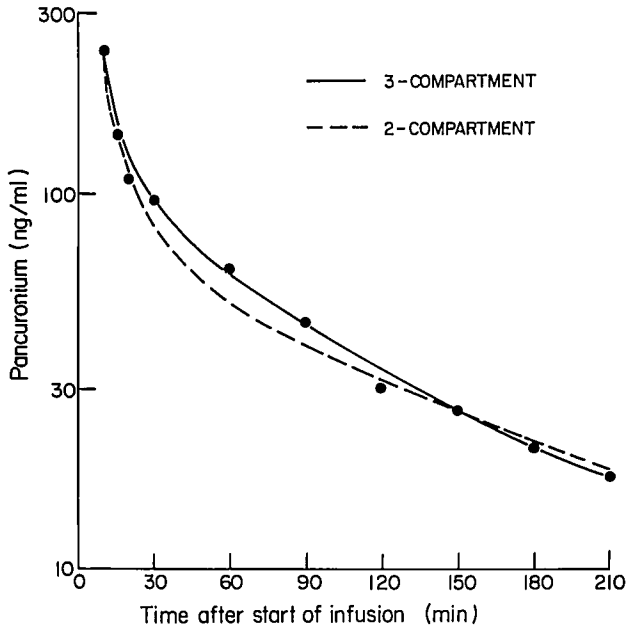

FIG. 1. Pharmacokinetic data for pancuronium. Pancuronium, 25 μg/kg, was administered by infusion during the first 10 min. Circles represent measured concentrations of pancuronium. The dashed line represents the fitted function determined using the two-compartment pharmacokinetic model. The solid line represents the fitted function determined using the three-compartment pharmacokinetic model.

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An Effective Way to Disseminate Protocols for Managing Malignant Hyperthermia

To the Editor:—Despite the increasing awareness of malignant hyperthermia as a life-threatening pharmacogenetic complication of anesthesia, there are still cases in which delayed or inappropriate treatment leads to an adverse outcome. The ASA and MHAUS both have published protocols for emergency treatment and referral that can be posted in anesthetizing locations throughout the hospital.