PHARMACOKINETIC MODELLING OF MIVACURIUM

Sir,—Cook and colleagues [1] recently proposed an unconventional approach to estimating the pharmacokinetics of mivacurium, because of inability of their assay to distinguish the three stereoisomers of mivacurium, one of which (cis–cis) appears to have pharmacokinetics markedly different from those of the others [2] (and is believed to be only 10% as potent). When re-analysis of certain samples from the terminal phase using a stereospecific assay suggested that only the cis–cis isomer persisted, Cook’s group assumed that the cis–cis isomer distributed to only one compartment and that its concentration throughout distribution and elimination could be estimated by extrapolating the log-linear terminal portion of the plasma concentration vs time curve to time zero (fig. 1). The difference between this curve and the total mivacurium concentration (the sum of the three isomers) was assumed to represent the sum of the two “active” isomers (trans–trans and cis–trans). We disagree with the assumption by Cook and colleagues that the cis–cis isomer should distribute to only one compartment. Neuromuscular blockers, being polar, typically distribute to at least two compartments: central compartment volume is typically similar to that of plasma volume and volume of distribution at steady state generally approximates that of the extracellular fluid space. Mivacurium should distribute to similar body compartments.

Assuming that the isomers of mivacurium obey these principles, an alternate time course for the cis–cis isomer is likely; one possible curve for this isomer is shown in figure 1. The resulting values for the active isomers differ markedly from those proposed by Cook and colleagues [1] (fig. 2) and the true area under the curve (AUC) and area under the moment curve (AUUMC) are likely to be smaller than Cook’s group estimated. As a result, the reported estimates of clearance (calculated as dose divided by AUC) and volume of distribution (calculated using both AUC and AUUMC) are probably incorrect.

Pharmacokinetic modelling of mivacurium may provide insight into the clinical effects of this novel neuromuscular blocker. However, correct kinetic analysis of mivacurium requires use of a stereospecific assay such as that recently reported by Lien and colleagues [2]. In addition, the elimination of mivacurium via cholinesterase may necessitate using non-traditional pharmacokinetic models such as those suggested by Hull for atracurium [3, 4]. We eagerly await these studies.

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Sir,—Our study was originally designed to examine the pharmacodynamics and pharmacokinetics of a single dose of mivacurium in normal patients and in those with hepatic or renal failure. We and others have performed similar studies with a variety of non-depolarizing neuromuscular blockers and other anaesthetic agents. The pharmacokinetic data analysis in this mivacurium study was, indeed, complicated by our finding a terminal elimination half-life of an order of magnitude greater than that predicted from either the increase in duration of neuromuscular block in response to doubling the mivacurium dose in our other clinical studies or the plasma hydrolysis rates for mivacurium which we have studied in vitro. This conflict was largely resolved conceptually when a new stereospecific assay for mivacurium was later developed and differences in the rates of metabolism of the three mivacurium isomers and their neuromuscular potency ascertained. These studies demonstrated that the cis–cis isomer of mivacurium represents some 4–8% of an injected dose, has limited potency compared with the active cis–trans and trans–trans isomers, and is metabolized slowly. Our study was thus seminal in calling attention to this interesting pharmacokinetic/dynamic problem and serving as the impetus for its resolution. The studies by Lien and colleagues provide a natural sequel to our study.

In an attempt to estimate the pharmacokinetics of mivacurium, we assumed that the terminal phase represents primarily the cis–cis isomer. Standard curve-stripping techniques were used to subtract the presumed contribution of the cis–cis isomer from each...
plasma concentration–time data point. As stated clearly in our paper, one assumption of this method is that the cis–cis isomer obeys a one-compartment model and that the model does not account for the distribution of the cis–cis isomer. Thus we were quite aware that we had not accounted for a distribution phase for the cis–cis isomer and likewise quite aware of the principles of drug distribution. The purposes of pharmacokinetics are to facilitate calculations and to enhance our understanding of drug distribution. Our unconventional approach to modelling may introduce departure from mathematical "purity" and introduce some small computational error, but it certainly increased our understanding of the kinetics of mivacurium and provided a first estimate of its kinetic profile.

The distribution curve for the cis–cis isomer does have the shape proposed by Fisher and Hale in their figure 1. The area bounded by the cis–cis alternative values and the "cis–cis (Cook [1])" values (-----) represents largely the potential error produced by our methods. We have estimated that this segment (or small triangle) produces a 3–5% error in our computations. In the past, we have shared most of our published and unpublished data from this study with Fisher and Hale; thus we are quite perplexed at the alternative time course for the cis–cis isomer which they now propose. As the cis–cis isomer accounts for only 4–8% of the injected dose, one wonders how the time zero concentration (Co) of the cis–cis isomer mivacurium could be 35% of the total isomers as depicted by Fisher and Hale in their figure 1. In our paper, we estimated the Co cis–cis mivacurium concentration to be 6.5 (to 4.7)% of the estimated total mivacurium concentrations. This estimate seems much more realistic than that proposed by Fisher and Hale. Thus the distribution curve for the cis–cis isomers provided by Fisher and Hale seems of dubious relevance; the resulting value for the active isomers is probably equally flawed.

Various current investigations are studying the pharmacokinetics of mivacurium using stereospecific assays and various kinetic models. Such data will, indeed, provide further insights about the kinetics of this unique neuromuscular blocking drug. However, little insight and certainly no new information or new concepts are provided by drawing imaginary but unrealistic distribution curves for the cis–cis isomer.

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