CORRESPONDENCE

PHARMACOKINETICS OF ATRACURIUM

Sir,—We congratulate Drs Beemer, Bjorksten and Crankshaw on their description of the pharmacokinetics of atracurium [1]. As they observe correctly, the derivation of pharmacokinetic parameters after a single bolus dose is subject to difficulties because of the presumed degradation of atracurium in sites peripheral to the plasma.

In our view, however, the crucial flaw in previous attempts to describe the pharmacokinetics of atracurium (including our own [2]), is not that the observations were not made at steady state, but that it is impossible to define the rate of peripheral degradation of atracurium on the basis of measurements made on plasma samples alone [3]. The application of standard formulae allows an objective summary of data, and comparison between groups, and may thus be useful. It does not allow calculation of the plasma clearance or steady state volume of distribution as usually defined [4].

We wish to point out that the method of analysis used by Beemer and colleagues does not overcome the problems created by the peripheral degradation of atracurium. The application of his equation (3) gives an estimate of clearance which is not equivalent to plasma clearance, defined as the volume of plasma theoretically completely cleared of drug per unit time. Indeed it may be re-written:

\[
\text{Clearance} = \frac{\text{Rate of drug degradation from the plasma}}{\text{Rate of drug degradation outside the plasma}}
\]

Only the first of these terms represents the plasma clearance. Moreover, the authors then apply this value for clearance (obtained at steady state) when calculating the amount of drug eliminated during the first 1 h of drug administration. Their equation (6) refers, however, to data gathered during the whole of the first 1 h (much of which was not close to a steady state), for which this value is therefore not applicable. One might correctly write, instead of equation (6):

\[
\text{Amount of drug eliminated} = \text{from the plasma during 1 h} = \text{Plasma clearance} \times \text{AUC}_{0-1}
\]

Unfortunately, the amount of drug eliminated from sites peripheral to the plasma, and hence the total amount of drug eliminated from the body, remains unknown, for the data pertain only to the plasma.

Whilst Beemer, Bjorksten and Crankshaw have obtained an estimate of \(V_{ss}\) smaller than that produced by several other groups, it may be noted that the problems of defining a pharmacokinetic model for atracurium have been attacked more explicitly by Fisher and colleagues [5], albeit with the assumption that spontaneous degradation of atracurium occurs throughout the body at a rate comparable to that in plasma \textit{in vitro}. The latter group obtained values of \(V_{ss}\) considerably less than 130 ml kg\(^{-1}\) in four of their five patients.

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REFERENCES


