method suggested by Tozer *et al.*, which corrects for both the volume shift and concentration-dependent binding, becomes necessary in calculating unbound fraction of a concentration-dependent binding drug such as prednisolone (1).

Although Eqs. 3 and 4 were derived under the assumption that drugs bind to a single-binding protein with multiple binding sites, the equations can be used as a good approximation to the correct unbound fractions for drugs that bind to two or more different binding proteins. For example, for a drug with two classes of binding sites, one having high capacity (600 μM) but low affinity (Kd = 100 μM), and the other having low capacity (20 μM) but high affinity (Kd = 1 μM), shows an unbound fraction of 0.04 at 0.1 μM drug concentration (Eq. 3A). A 30% volume shift gives a 40% error in unbound fraction ($f_{u'}$ = 0.056, Eq. 4A). Equation 4 can be used to convert $f_{u'}$ to f_u with good accuracy (f_u calculated = 0.04).

The extent of volume shift is usually determined by measuring the sample volume before and after equilibrium dialysis. Practically, it is not easy to determine the sample volume accurately after dialysis. It would be advisable instead to measure the binding protein concentration before and after dialysis and apply for correction calculations.

APPENDIX

The unbound fraction of a drug is by definition:

$$f_u = C_u \Big/ \left(C_u + \sum_{i=1}^{n} Cb_i\right) \qquad \text{(Eq. 1A)}$$

where $\sum_{i=1}^{n} Cb_i$ is the sum of concentrations of drugs bound to different binding sites. Based on the law of mass action, Cb_i can be expressed as:

$$Cb_i = C_u \cdot Pt_i/(Kd_i + C_u) \qquad \text{(Eq. 2A)}$$

and Eq. 1A can be written as:

$$f_u = 1 \Big/ \left[1 + \sum_{i=1}^{n} Pt_i/(Kd_i + C_u)\right] \qquad \text{(Eq. 3A)}$$

and

$$f_{u'} = 1 \Big/ \left[1 + \sum_{i=1}^{n} Pt_{i'}/(Kd_i + C_u)\right] \qquad \text{(Eq. 4A)}$$

Assuming a single binding protein with multiple binding sites, Eq. 3A can be simplified to be Eq. 1 and $f_{u'}$ is equal to:

$$f_{u'} = 1 \Big/ \left[1 + Pt' \sum_{i=1}^{n} 1/(C_u + Kd_i)\right] \qquad \text{(Eq. 5A)}$$

Letting

$$S = \sum_{i=1}^{n} 1/(C_u + Kd_i) \qquad \text{(Eq. 6A)}$$

Eq. 1 can be rearranged to:

$$S = (1 - f_u)/(f_u \cdot Pt) \qquad \text{(Eq. 7A)}$$

Substituting Eq. 7A into Eq. 5A, gives:

$$f_{u'} = 1/[1 + Pt' \cdot (1 - f_u)/(f_u \cdot Pt)] \qquad \text{(Eq. 8A)}$$

where Pt'/Pt is equal to F (Eq. 2). Substituting F into Eq. 8A gives Eq. 3. Similarly, Eq. 5A can be rearranged to:

$$S = (1 - f_{u'})/(f_{u'} \cdot Pt') \qquad \text{(Eq. 9A)}$$

Substituting Eqs. 2 and 9A into Eq. 1, Eq. 4 is derived.

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Rate of Recovery from Fazadinium: Relationship to the Rate of Decline of its Plasma Concentration

Keyphrases □ Fazadinium—rate of recovery, relationship to plasma concentration, pharmacokinetics □ Pharmacokinetics—fazadinium, rate of recovery, relationship to plasma concentration

To the Editor:

Fazadinium bromide, introduced into anesthetic practice in 1972, is of clinical interest as a short-acting neuromuscular blocking agent. An approach is presented here which strongly suggests that the differences in the rate of recovery from the neuromuscular blocking effects of fazadinium are solely dependent on the pharmacokinetics of the relaxant. This approach is not new in that it was first presented on theoretical grounds more than a decade ago and utilized with recovery data for succinylcholine in both neonates and adults (1, 2).

If the claim (3) that fazadinium is eliminated by apparent first-order kinetics is true, and if it can be assumed that its metabolite(s) are inactive (4), then the duration (t) of the neuromuscular blocking action of fazadinium and the rate of decline (R) of the effect (paralysis) in the linear (20–80% or 25–75%) range can be related according to the following equations, as derived for succinylcholine (1, 2):

$$t = (2.3/k_{10})(\log A^0 - \log A_{min}) \qquad \text{(Eq. 1)}$$

$$R = m(k_{10}/2.3) \qquad \text{(Eq. 2)}$$

Table I—Pharmacokinetic Analysis of Recovery from the Neuromuscular Blocking Effects of Fazadinium [a]

Patient	Duration (t)[b], min	Rate of Decline (R)[c], % min^{-1}	$t \times R$, %	$k_{app\ 25\text{–}75}$[d], min^{-1}
3	14	3.57	49.98	−0.0382
4	22	2.27	49.94	−0.0286
5	24	2.08	49.92	−0.0210
1	26	1.92	49.92	−0.0251
2	27	1.85	49.95	−0.0219
6	34	1.47	49.98	−0.0149

[a] Based on data from ref. 3. [b] Time interval when the twitch height was depressed between 25 and 75% of its control value: between 75 and 25% muscle paralysis. [c] Rate of recovery in the 75–25% paralysis range. [d] $k_{app\ 25\text{–}75} = (\log C_{25} - \log C_{75}/t_{25} - t_{75})$ where C and t are the plasma concentrations and times respectively at 25 and 75% effect levels.

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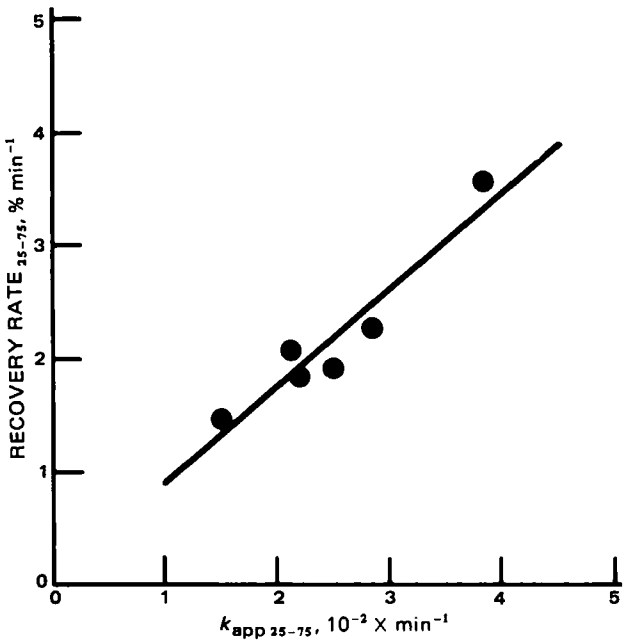

Figure 1—*Relationship between the rate of recovery from the neuromuscular blocking effects of fazadinium and the calculated* $k_{app\ 25-75}$. *Individual patient data are shown as solid circles while the solid line represents the linear regression line* ($r^2 = 0.897$, $p < 0.005$).

$$t \times R = m(\log A^0 - \log A_{min}) \qquad \text{(Eq. 3)}$$

where k_{10} is the apparent first-order rate constant for drug elimination from its site of action, A_{min} is the minimum effective dose, and m is the slope of the log dose (A^0) response relationship for the relaxant. Thus, according to the above three equations, four pharmacokinetic factors determine the duration and rate of decline of effect, with three of these terms (m, A^0, and A_{min}) appearing on the right side of Eq. 3, while k_{10} is implicit on the left-hand side but cancels out as such. Thus, in a group of patients given the same drug dose but showing different durations of effect, the product of duration (t) and rate of decline (R) of effect will yield a constant value if the differences in the observed time course of effect are solely the result of differences in k_{10}, the elimination rate constant. If, however, the values of $t \times R$ differ between the patients, then it must be concluded that these patients differ with respect to m and/or A_{min} and/or k_{10}.

The results obtained from the six patients in the study by D'Hollander *et al.* (3) are listed in Table I, with the numerical designations used by these authors but in order of increasing duration of effect. It can be seen that although the six patients differed in the duration (t) and the rate of decline (R) from the effects of fazadinium, the $t \times R$ values were identical for all the patients, implying that the differences in the rate of recovery from the neuromuscular effects of fazadinium in these six patients were solely due to a difference in the rate of elimination of the relaxant from the body. This claim is further supported by the finding that $k_{app\ 25-75}$, the apparent rate of decline of the (log) plasma concentration, which is a measure of the elimination rate of the relaxant during the linear (25–75%) phase of recovery, was different in each of the six patients and there was an excellent linear relationship between the *rate* of recovery from fazadinium and the calculated $k_{app\ 25-75}$ (Fig. 1).

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BOOKS

REVIEWS

Pharmacokinetics, 2nd Ed. By MILO GIBALDI and DONALD PERRIER. Marcel Dekker, 270 Madison Avenue, New York, NY 11016. 1982. 494 pp. 16 × 23 cm. Price: $34.50 (20% higher outside the U.S. and Canada).

The second edition of this now classic text detailing the mathematical description of pharmacokinetics has been greatly expanded and updated over the previous edition. One of the most important new aspects to be presented is the comprehensive discussion of clearance concepts, flow models, and physiological modeling, which has given the new text a much broader scope while at the same time introduces the reader to new concepts presented over the last few years. In addition, an overview depicting the usefulness of statistical moments in pharmacokinetics is presented, a concept being explored extensively in the pharmacokinetic literature today which should prove useful to both the established researcher and the student. The new material added to the text is, in general, approached (as is the mark of these authors) in a detailed, step-by-step procedure that renders the work especially useful to novices and subsequently makes it an important teaching tool.

It is important to note that not only have new chapters and topics been added, but that the majority of the original text has undergone revision, expansion, and addition of new material. The majority of the equations have been generalized, thereby making them useful in a variety of models. Although the generalization makes the edition slightly less useful as a reference book for pharmacokinetic relationships, it is most illustrative for teaching purposes in demonstrating the generalities of kinetic models. Without too much effort, the generalized equations can readily be converted to relationships that can be applied in specific situations. The authors have also added a more philosophical overview to the various concepts that increase the understanding of many of the equations and relationships presented.

Other interesting additions to the second edition are the kinetics of irreversible pharmacological response, product inhibition aspects of nonlinear kinetics, and various aspects of protein binding in relation in pharmacokinetics. Although the discussion dealing with protein binding is often divergent from what this reviewer believes to be a rational development of the relationship between protein binding and pharmacokinetics, it is a valuable and instructive addition, especially in lieu of the paucity of such discussions.