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Drug Kinetics in Low-Flux (Small) Anatomic Compartments

Keyphrases □ Pharmacokinetics—low-flux peripheral compartment □ Cochlear perilymph—aminoglycoside kinetics

To the Editor:

Small anatomic compartments may be the site of action or toxicity of drugs. Because the kinetics in the anatomic compartment may differ significantly from those in the sampled compartment, pharmacokinetic modeling of such drugs requires the development of explicit expressions for the time course of drug concentrations in the anatomic compartment. Classical compartmental analysis is based on large (kinetic) compartments, which exchange enough drug that measurable alterations in the concentration of drug in the sampled compartment result. A small (anatomic) compartment may not give rise to a detectable alteration in drug concentration in the sampled compartment, because its drug flux is small. In such a case, the anatomic compartment can not be represented by a peripheral kinetic compartment. This communication describes the derivation of an equation for the time course of drug concentrations in such small compartments based on a modified compartmental analysis.

Consider an n-compartment linear mammillary system with first-order rate constants and elimination from the central compartment (denoted by subscript 1) only. Let there be an $(n + 1)$th compartment that exchanges drug with the central compartment but for which the flux of drug into and out of the compartment is so minute that it does not measurably alter levels of the drug in the central compartment. This compartment will be called the low-flux peripheral compartment and will be labeled LF.

The differential equations governing this model are:

$$\frac{dC_1}{dt} = \sum_{j=2}^{n}\left(k_{j1}\frac{V_j}{V_1}C_j - k_{1j}C_1\right) - k_{10}C_1 \quad \text{(Eq. 1)}$$

$$\frac{dC_j}{dt} = k_{1j}\frac{V_1}{V_j}C_1 - k_{j1}C_j,\ n \geq j > 1 \quad \text{(Eq. 2)}$$

$$\frac{dC_{LF}}{dt} = k_{1LF}\frac{V_1}{V_{LF}}C_1 - k_{LF1}C_{LF} \quad \text{(Eq. 3)}$$

where

C_j = concentration of drug in the jth compartment;
V_j = pharmacokinetic volume of distribution of drug in the jth compartment;
k_{ab} = first-order transfer rate constant from the ith to the jth compartment;
k_{10} = first-order elimination rate constant from the central compartment;
C_{LF} = concentration of drug in the low-flux compartment;
k_{1LF}, k_{LF1} = first-order transfer rate constants into and out of the low-flux compartment.

If the drug enters the central compartment as a result of bolus injection, the drug concentration in that compartment, as a function of time, will be a sum of exponentials (1):

$$C_1(t) = \sum_{i=1}^{n} a_i e^{-\lambda_i t} \quad \text{(Eq. 4)}$$

where a_i = coefficient of ith exponential term and λ_i = exponent of the ith exponential term. The general equation for the drug concentration in the jth peripheral compartment is found by the use of Laplace transforms (2):

$$C_j(t) = \frac{V_1}{V_j}\sum_{i=1}^{n}\frac{k_{1j}}{(k_{j1} - \lambda_i)}a_i(e^{-\lambda_i t} - e^{-k_{j1}t}) \quad \text{(Eq. 5)}$$

The equation for the drug concentration in the low flux compartment is:

$$C_{LF}(t) = \frac{V_1}{V_{LF}}\sum_{i=1}^{n}\frac{k_{1LF}}{(k_{LF1} - \lambda_i)}a_i(e^{-\lambda_i t} - e^{-k_{LF1}t}) \quad \text{(Eq. 6)}$$

By similar means, expressions can be found for the drug concentration in the low-flux compartment following entry of the drug into the central compartment by first-order absorption or continuous infusion.

As an example of the application of this model, Eq. 6 is used to describe the kinetics of amikacin, an aminoglycoside antibiotic, in cochlear perilymph, presumably a low-flux compartment. The data are taken from a study performed in guinea pigs, as reported by Brummett *et al.* (3). The concentrations of amikacin were determined in serum and in cochlear perilymph over time following a single subcutaneous injection of the drug (as detailed in Ref. 3). The subcutaneous absorption of amikacin was very rapid, resulting in a monoexponential serum drug concentration *versus* time curve. Therefore, Eq. 4, and consequently Eq. 6, can be used in this case even though the injection was not intravenous.

The equation for the serum drug concentration *versus* time curve is:

$$C_{serum}(t) = 489e^{-0.6992t\,(\text{in hr})} \text{ in micrograms per milliliter}$$

The experimental data and corresponding predicted values are presented in Table I. The perilymph drug concentration *versus* time curve is fitted to a biexponential

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Table I—Concentration of Amikacin in Serum Following a Bolus Subcutaneous Injection

Time, hr	Amikacin Concentration, μg/ml Experimental	Predicted Value
0.5	315	345
1.0	270	244
2.0	132	121
4.0	25	29
6.0	8	7

Table II—Concentration of Amikacin in Cochlear Perilymph Following a Bolus Subcutaneous Injection

Time, hr	Amikacin Concentration, μg/ml Experimental	Predicted Value
0.5	2.0	2.2
1.0	6	5.7
2.0	9	9.1
4.0	10	9.2
6.0	7	7.0
12.0	2.5	2.1

equation, which is the form prescribed by Eq. 6 and is also as many exponential terms as can confidently be generated for six data points:

$$C_{\text{perilymph}}(t) = 29e^{-0.2169t(\text{in hr})} - 32e^{-0.6019t(\text{in hr})}$$

in micrograms per milliliter

The experimental data and corresponding predicted values are listed in Table II. For both the serum and perilymph, the equations fit the data well.

If the model is appropriate, the values of k_{10} estimated from each of these two equations should be equal. The estimate of k_{10} from the serum drug concentration *versus* time equation is the exponent of the single exponential term, 0.6992 hr^{-1}. The estimate of k_{10} from the perilymph drug concentration *versus* time equation is the exponent for the exponential term with a negative coefficient, 0.6019 hr^{-1}. These estimates show a 16% difference. Such a small difference is within the limits of accuracy expected in such an experimental setting. The close agreement provides evidence of the validity of the model. This model might be found useful in describing other small anatomic compartments of pharmacological interest.

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BOOKS

REVIEWS

Encyclopedia of Emulsion Technology, Vol. 1: Basic Theory. Edited by PAUL BECHER. Marcel Dekker, Inc., New York, NY 10016. 1983. 744 pp. 17 × 25 cm. Price $95.00 (20% higher outside the U.S. and Canada).

This book is the first in a series of volumes devoted to various aspects of emulsion science and technology. It contains one of the most comprehensive and authoritative reviews of the basic principles underlying emulsification and emulsion properties now available. Each chapter has been prepared by individuals actively involved in the area about which they have written. The editor, himself widely recognized for his work with emulsions, has done an excellent job in bringing this work together in a well-edited volume.

The book contains nine chapters, all developed at a fairly fundamental level. In Chapter 1, the authors provide an excellent review of basic interfacial chemistry and physics using the oil–water interface as the main focus. The next two chapters address the fundamentals of emulsion formation and stabilization. The former is an extremely unique and in-depth treatment of droplet formation and coalescence and the underlying fluid dynamics involved, while the latter represents the most complete and up-to-date fundamental discussion of emulsion stability that this reviewer has seen.

The remaining chapters provide excellent in-depth coverage of such topics as: microemulsions, phase equilibria and phase inversion temperatures, particle size evaluation, rheology, optical properties, and dielectric properties. The chapter on rheology, written by P. Sherman, presents material which should be read by anyone seriously concerned with the complex problems of evaluating emulsion product stability. The material on the viscoelastic properties of emulsions is particularly relevant for this purpose. The very long chapter on the fundamental dielectric properties of emulsions (over 200 pages) is a unique resource of information which offers interesting possibilities for evaluating emulsion behavior in a new way. The proportion of the book devoted to this chapter, however, is much too large, relative to the importance of the other subjects presented. As in this latter chapter, all of the material in this volume is treated at a fairly fundamental level with the assumption that the reader has a reasonably good basic background in the physical chemistry of surfaces and disperse systems. Consequently, this book should be thought of as primarily suitable for a graduate-level course dealing with emulsions or for the pharmaceutical scientist seriously prepared to approach this subject at a very fundamental level.

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