and for nonylphenol adducts,

$$HLB_G = 1.55 + 0.380\,\gamma \qquad \text{(Eq. 12)}$$

The significance of these simple relations is questionable, however, in view of the different and varying behavior of the o/w interfacial tensions (9).

REFERENCES

(1) W. C. Griffin, *J. Soc. Cosmetic Chemists*, **1**, 311(1949).

(2) *Ibid.* **5**, 249(1954).

(3) J. T. Davies, *Proc. Intern. Congr. Surface Activity, 2nd, London*, **1**, 426(1957).

(4) S. Ross, E. S. Chen, P. Becher, and H. J. Ranauto, *J. Phys. Chem.*, **63**, 1681(1959).

(5) L. Hsiao, H. N. Dunning, and P. B. Lorenz, *ibid.*, **60**, 657 (1956).

(6) M. J. Schick, S. M. Atlas, and F. R. Eirich, *ibid.*, **66**, 1326 (1962).

(7) M. J. Schick, *J. Colloid Sci.*, **17**, 801(1962).

(8) H. Schott, *J. Phys. Chem.*, **68**, 3612(1964), **70**, 2966(1966).

(9) P. Becher, *J. Colloid Sci.*, **18**, 665(1963).

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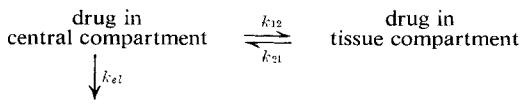
Estimation of the Pharmacokinetic Parameters of the Two-Compartment Open Model from Post-Infusion Plasma Concentration Data

MILO GIBALDI

Abstract □ A model is presented which can serve as a means for obtaining the pharmacokinetic parameters of the two-compartment open system for drugs which are too poorly soluble or too irritating to be administered by rapid intravenous injection. Experimentally, this method involves administering the drug by a constant rate intravenous infusion, until the attainment of infusion equilibrium, and determining the plasma concentrations of drug in the postinfusion period. This approach has been applied to literature data and has resulted in the evaluation of the two-compartment pharmacokinetics of oxacillin.

Keyphrases □ Pharmacokinetic parameters—two-compartment open model □ Infusion equilibrium—i.v. administration □ Post-infusion period—plasma concentration

The kinetics of distribution and elimination of a number of drugs may be described adequately by the two-compartment open model shown in Scheme I (1, 2).



Scheme I

The usual method of calculating the rate constants is to first determine the parameters A, B, α, and β (see Fig. 1 in *Reference 3*) from the plasma concentration of drug *versus* time plot obtained after rapid intravenous injection of the drug and to use these values for calculating the rate constants k_{12}, k_{21}, and k_{el}. However, a number of drugs are too poorly soluble, irritating, or acutely toxic to be injected rapidly. In these cases it is difficult or impossible to obtain the parameters of Scheme I. A method is presented here for determining the rate constants of the two-compartment open model which does not require rapid intravenous injection.

Often, drugs which cannot be administered as a rapid intravenous injection may nevertheless be introduced to the body in the form of a slow intravenous infusion of a dilute solution of the drug. When the drug is infused at a constant rate and is eliminated by first-order kinetics, drug levels in both the central and tissue compartments asymptotically approach, with time, a constant value and infusion equilibrium occurs. The present method is based on evaluation of plasma concentration of drug with time after attainment of infusion equilibrium. Where a drug is eliminated very slowly, then the infusion should be preceded by an intravenous loading dose (administered as rapidly as

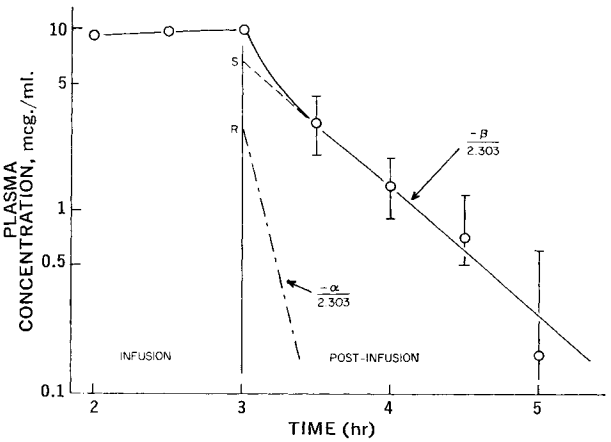


Figure 1—*Average plasma concentrations of oxacillin in four healthy subjects receiving a constant rate (0.25 g./hr.) intravenous infusion of drug for 3 hr. Experimental data* (O) *from* Reference *5. Solid curve represents nonlinear least-squares regression fit to the data.*

possible) to reduce the time required to attain infusion equilibrium.

THEORETICAL

The amounts of drug in the central compartment (X_c) and in the tissue compartments (X_T) at infusion equilibrium are given by

$$(X_c)_{\text{inf. eq.}} = k_0 k_{21}/\alpha\beta \qquad \text{(Eq. 1)}$$

and

$$(X_T)_{\text{inf. eq.}} = k_0 k_{12}/\alpha\beta \qquad \text{(Eq. 2)}$$

where k_0 is the constant intravenous infusion rate of drug (see *Appendix*). After cessation of a constant-rate intravenous infusion, which was administered over a sufficiently long period of time to achieve constant levels of drug in each compartment, the drug levels in the central compartment may be described by the following Eq. (4):

$$X_c = (X_c)_{\text{inf. eq.}} \left[\frac{(\beta - k_{el})}{\beta - \alpha} e^{-\alpha t} - \frac{(\alpha - k_{el})}{\beta - \alpha} e^{-\beta t}\right] \qquad \text{(Eq. 3)}$$

where X_c represents the amount of drug in the central compartment in the postinfusion period. Equation 3 may be rewritten in terms of plasma concentration (C_p), so that

$$C_p = Re^{-\alpha t} + Se^{-\beta t} \qquad \text{(Eq. 4)}$$

where

$$R = \frac{(X_c)_{\text{inf. eq.}}(\beta - k_{el})}{V_c(\beta - \alpha)} \qquad \text{(Eq. 5)}$$

and

$$S = -\frac{(X_c)_{\text{inf. eq.}}(\alpha - k_{el})}{V_c(\beta - \alpha)} \qquad \text{(Eq. 6)}$$

The term V_c represents the apparent volume of distribution of drug in the central compartment, *i.e.*, the amount of drug (X_c) divided by the concentration (C_p). From a mathematical point of view it is assumed that the plasma concentration corresponds to the drug concentration in the central compartment of the two-compartment open model. Hence, according to Eq. 4, the decline of drug concentration in the plasma after attainment of infusion equilibrium may be described by a bi-exponential equation with exponents identical to the exponents of the bi-exponential equation required to describe the decline of plasma level of drug after rapid intravenous injection (see Fig. 1).

The parameters α, β, R, and S are readily obtained from sufficiently intensive plasma concentration of drug *versus* time data in the postinfusion period as shown in Fig. 1. The rate constants and other parameters of the two-compartment open model may be calculated from the following equations. Dividing Eq. 5 by Eq. 6 yields

$$\frac{R}{S} = \frac{\beta - k_{el}}{k_{el} - \alpha} \qquad \text{(Eq. 7)}$$

which upon rearrangement yields

$$k_{el} = \frac{R\alpha + S\beta}{R + S} \qquad \text{(Eq. 8)}$$

It has been noted (1) that $\alpha\beta = k_{21}k_{el}$ and $\alpha + \beta = k_{el} + k_{12} + k_{21}$. Accordingly,

$$k_{21} = \frac{\alpha\beta}{k_{el}} \qquad \text{(Eq. 9)}$$

and

$$k_{12} = \alpha + \beta - k_{el} - k_{21} \qquad \text{(Eq. 10)}$$

The volume of the central compartment is given by the ratio of the amount of drug in this compartment to the concentration of drug in the plasma at infusion equilibrium, so that

$$V_c = \frac{k_0 k_{21}}{\alpha\beta(R + S)} \qquad \text{(Eq. 11)}$$

The apparent volumes of distribution, $(V_d)_\beta$ and $(V_d)_{\text{inf. eq.}}$, which relate plasma concentration of drug to the total amount of drug in the body during pseudo-distribution equilibrium (3) and at infusion equilibrium (4), respectively, may be calculated from Eqs. 12 and 13

$$(V_d)_\beta = \frac{k_0 k_{21} k_{el}}{\alpha\beta^2(R + S)} \qquad \text{(Eq. 12)}$$

and

$$(V_d)_{\text{inf. eq.}} = \frac{k_0(k_{12} + k_{21})}{\alpha\beta(R + S)} \qquad \text{(Eq. 13)}$$

APPLICATION

Rosenblatt *et al.* (5) have reported average (four human subjects) plasma concentrations of oxacillin during and after the administration of 750-mg. dose by constant-rate intravenous infusion over a 3-hr. period. Since the drug has a biologic half-life of about 30 min., this period of infusion was sufficient to essentially attain infusion equilibrium. The average plasma concentrations in the postinfusion period were given equal weight and were used as input data for the digital computer program of Marquardt (6) to provide a bi-exponential least-squares regression fit to the data. The constants thus obtained were used with the appropriate equations outlined above to estimate the rate constants of the two-compartment open model shown in Scheme I.

A bi-exponential fit of the oxacillin data in the postinfusion period as a function of time (t) in minutes yielded the following expression:

$$C_p = 2.942\, e^{-0.127\, t} + 6.758\, e^{-0.027\, t} \qquad \text{(Eq. 14)}$$

with a zero-time (postinfusion) intercept of 9.70 mcg./ml.

The rate constants obtained according to Scheme I are

$$k_{el} = 0.057 \text{ min.}^{-1}$$
$$k_{12} = 0.037 \text{ min.}^{-1}$$
$$k_{21} = 0.060 \text{ min.}^{-1}$$

Figure 1 shows the plasma concentrations of oxacillin calculated according to Eq. 14 as well as the experimentally determined plasma levels of drug. The sum of the squared deviations of the observed from the calculated plasma concentrations is 0.291. The volume of the central compartment, calculated according to Eq. 11, is 7.5 l. The apparent volumes of distribution, $(V_d)_\beta$ and $(V_d)_{\text{inf. eq.}}$, are 15.9 and 12.1 l., respectively.

It has been noted in a previous report (4) that the distribution ratios at pseudo-distribution equilibrium $[(X_T/X_c)_\beta]$ and at infusion equilibrium $[(X_T/X_c)_{\text{inf. eq.}}]$ are not equivalent. In theory, the tissue compartment : central compartment distribution ratio is predicted to be higher at pseudo-distribution equilibrium than at infusion equilibrium. With oxacillin, this difference appears to be considerable; in the order of 1.8-fold. Thus, assuming a homogeneous tissue compartment, it is anticipated that at equivalent plasma concentrations, the "tissue" concentration of oxacillin would be about twice as great during pseudo-distribution equilibrium than during infusion equilibrium.

APPENDIX

During constant rate infusion of the central compartment the rate of change of drug levels in each compartment of the two-compartment open model shown in Scheme I is given by

$$dX_c/dt = k_0 - (k_{el} + k_{12})X_c + k_{21}X_T \qquad \text{(Eq. 1}a\text{)}$$

and

$$dX_T/dt = k_{12}X_c - k_{21}X_T \qquad \text{(Eq. 2}a\text{)}$$

respectively. Some time after initiation of infusion the rate of entry of drug into each compartment is equal to the rate of exit, *i.e.*, $dX_c/dt = 0$ and $dX_T/dt = 0$. After attainment of this steady-state condition (infusion equilibrium), then it follows from Eqs. 1*a* and 2*a* that

$$(X_c)_{\text{inf. eq.}} = k_0/k_{el} \qquad \text{(Eq. 3}a\text{)}$$

and

$$(X_T)_{\text{inf. eq.}} = k_{12}\, k_0/k_{21}\, k_{el} \qquad \text{(Eq. 4}a\text{)}$$

During the course of integration of Eqs. 1*a* and 2*a* to determine X_c and X_T explicitly, the constants α and β are defined so that

$$\alpha\beta = k_{21}\, k_{el} \qquad \text{(Eq. 5}a\text{)}$$

and

$$\alpha + \beta = k_{el} + k_{12} + k_{21} \qquad \text{(Eq. 6}a\text{)}$$

Substituting Eq. 5*a* in Eqs. 3*a* and 4*a* yields Eqs. 1 and 2 in the text.

REFERENCES

(1) S. Riegelman, J. Loo, and M. Rowland, *J. Pharm. Sci.*, **57**, 117(1968).

(2) *Ibid.*, **57**, 128(1968).

(3) M. Gibaldi, R. Nagashima, and G. Levy, *ibid.*, **58**, 193(1969).

(4) M. Gibaldi, *ibid.*, **58**, 327(1969).

(5) J. E. Rosenblatt, A. C. Kind, J. L. Brodie, and W. M. M. Kirby, *Arch. Internal Med.*, **121**, 345(1968).

(6) D. W. Marquardt, *DPE-NLIN*, Share General Library Program No. 7-1354.

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Ultrasonic Extraction of *Cassia acutifolia*

INDUKUMAR C. PATEL and DONALD M. SKAUEN

Abstract □ *Cassia acutifolia* has been extracted using ultrasonic energy in the form of a powerful step-horn converter. The amount of aglycones extracted by this means was compared with aglycones extracted by a standard infusion method. Under similar conditions ultrasonic extraction was more rapid and produced more aglycones than the infusion method. The amount of heat applied has an important effect in the extraction of *Cassia acutifolia*.

Keyphrases □ Ultrasonic extraction—*Cassia acutifolia* □ Extraction comparison—boiling water, ultrasonic □ Temperature effect—*Cassia acutifolia* extraction

Under appropriate conditions, ultrasound has been shown to be very effective in extracting various principles from biological cells. In the majority of the studies reported in the pharmaceutical literature, low power, tank type generators were used (1–4). Ovadia and Skauen (5) reported their experiences with a step-horn ultrasonic generator of high power in extraction experiments with *Cinchona*, *Cephaëlis*, and *Pilocarpus* species. Morrison and Woodford (6) utilized a similar ultrasonic probe for an aqueous extraction of senna pericarps.

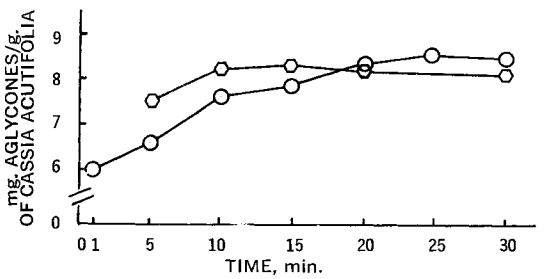

Figure 1—*Comparison of ultrasonic extraction without boiling water and infusion extraction with boiling water. Key:* ○, *ultrasonic extraction (without boiling water);* ○, *infusion extraction (boiling water).*

This investigation was conducted to determine the effects of a more powerful step-horn converter[1] on the extraction of *Cassia acutifolia*,[2] and to compare those results with a standard infusion technique.

EXPERIMENTAL

Ten-gram samples of powdered *Cassia acutifolia*, No. 40 mesh, were weighed and placed into 240-ml. polyethylene containers. One hundred milliliters of water was added and the drug macerated for 10 min. Fifty milliliters of water, brought to pH 8 with 1 *N* NaOH, was added and the samples insonated for the required periods of time. The mixture was then cooled, made up to 300 ml. with water, filtered, and the residue washed with 50 ml. of water in divided portions.

Ten milliliters of the combined filtrate was used to determine the amount of aglycones present after hydrolysis of the extracted glycosides. This assay method was a modification of the method introduced by Fairbairn and Michaels (7).

The glycosides extracted without ultrasound were treated in a similar manner using boiling water and eliminating the maceration step.

When it became necessary to compare ultrasonic extraction without maceration with similar infusion extraction, the general pro-

[1] Model S-125 Sonifier, Branson Sonic Power Co., Danbury, Conn.

[2] Courtesy of Meer Corp., New York, N. Y. 10036