Area under the Plasma Concentration–Time Curve Resulting from Constant-Rate Drug Input

Keyphrases □ Drug infusion—relationship with area under the plasma concentration–time curve □ Equations—relationship between infusion equation and area under the plasma concentration–time curve

To the Editor:

Plasma concentration–time data obtained from constant-rate drug input (*i.e.*, intravenous infusion or constant-rate absorption) are frequently analyzed by dividing the resulting curve into two segments: concentrations achieved during and those obtained after stopping the infusion. However, equations are available for analyzing the entire curve, and computer programs are capable of fitting such data to the appropriate equation. Benet (1) encouraged use of the equation describing the entire concentration–time curve. This communication reports on the relationship between the parameters of an infusion equation and the total area under the plasma concentration–time curve (AUC_0^∞).

THEORY

Assuming, for simplicity, a one-compartment model, the equation describing the entire concentration–time curve is given by:

$$C = \left(\frac{FK_0}{KV}\right)(e^{KT} - 1)\,e^{-Kt} \qquad \text{(Eq. 1)}$$

where F is the fraction of the dose absorbed ($F = 1$ for intravenous infusion), K_0 is the constant rate of drug input, K is the elimination rate constant, V is the apparent volume of distribution, t is the time beginning from the start of infusion, and T is the time of infusion (which equals t during infusion). In fitting Eq. 1, it will generally appear in the form:

$$C = (A)(e^{KT} - 1)e^{-Kt} \qquad \text{(Eq. 2)}$$

where A equals FK_0/KV. The terms A and K are treated as parameters and T is fixed for intravenous infusion. In the case of constant-rate drug absorption (*e.g.*, sustained-release products), T should also be treated as a parameter rather than holding it constant at some arbitrary value. The solid line shown in Fig. 1 represents plasma concentrations resulting from constant-rate drug input up to time T and exponential decline in concentrations at later times.

The term A in Eq. 2 may be recognized as the steady-state plasma concentration (C_{ss}) that would be achieved if infusion were to continue for a sufficiently long period of time. This value is denoted in Fig. 1 as the dashed line. The total area under the solid line in Fig. 1 may be shown to be equal to:

$$AUC_0^\infty = \frac{FK_0T}{KV} \qquad \text{(Eq. 3)}$$

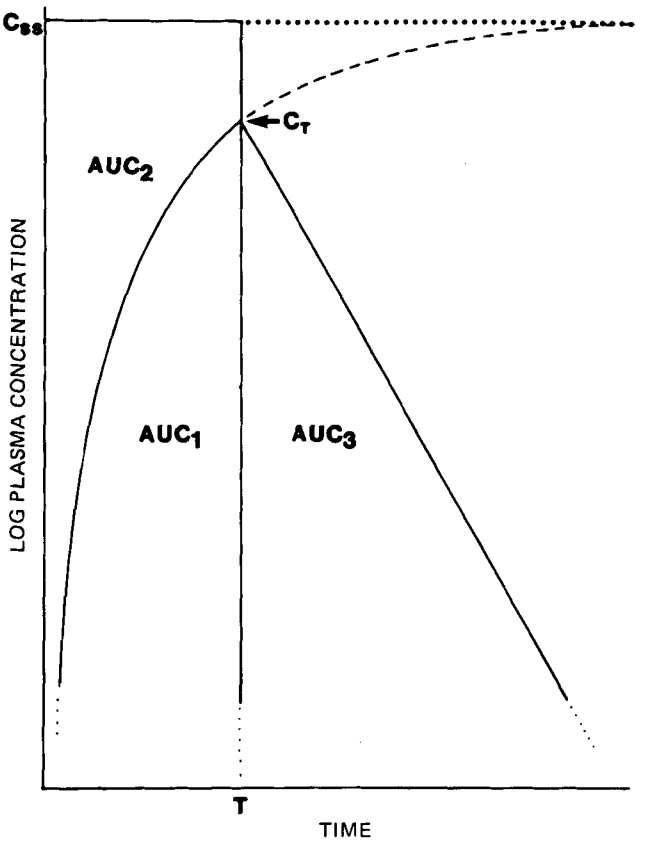

Figure 1—*Log-plasma concentration as a function of time during and after constant-rate drug infusion (solid line). Drug is infused for a time* T *and results in a maximum concentration,* C_T. *The dashed line represents the approach to a steady-state plasma concentration,* C_{ss}, *if infusion were to continue indefinitely. Also,* AUC_1 *is the area under the curve during infusion and up to time* T, AUC_3 *is the postinfusion area from time* T *to time* ∞, *and* AUC_2 *is the difference between,* $C_{ss}T$ *and* AUC_1.

where the product FK_0T equals the dose absorbed.

Therefore, the product of the term A (in Eq. 2) and T will equal AUC_0^∞:

$$AUC_0^\infty = \frac{FK_0T}{KV} = C_{ss}T = AT \qquad \text{(Eq. 4)}$$

Equation 4 may also be viewed by considering the geometric areas indicated in Fig. 1. The total area under the curve is equal to:

$$AUC_0^\infty = AUC_1 + AUC_3 \qquad \text{(Eq. 5)}$$

The calculated AUC_0^∞ in Eq. 4, AT, is given by:

$$AUC_0^\infty = AUC_1 + AUC_2 = C_{ss}T = AT \qquad \text{(Eq. 6)}$$

Since AUC_1 is common to both Eqs. 5 and 6, AUC_2 must be equal to AUC_3.

$$AUC_2 = C_{ss}T - AUC_1 \qquad \text{(Eq. 7)}$$

$$AUC_2 = \frac{FK_0T}{KV} - \int_0^T \frac{FK_0}{KV}(1 - e^{-kt})\,dt \qquad \text{(Eq. 8)}$$

The integral in Eq. 8 may be shown to be equal to:

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$$\int_0^T \frac{FK_0}{KV}(1 - e^{-Kt})\,dt = -\frac{FK_0T}{KV} + \frac{FK_0}{KVK}(1 - e^{-KT}) \quad \text{(Eq. 9)}$$

Placing Eq. 9 into Eq. 8 gives:

$$AUC_2 = \frac{FK_0}{KVK}(1 - e^{-KT}) \quad \text{(Eq. 10)}$$

Equation 10 is equal to the plasma concentration at time T, divided by K:

$$AUC_2 = \frac{C_T}{K} \quad \text{(Eq. 11)}$$

This expression may be recognized as being equal to AUC_3 which is conventionally used to calculate the postinfusion area and, therefore, $AUC_2 = AUC_3$.

The relationship indicated in Eq. 4, that area is the product of C_{ss} and T, appears not to have been previously reported. Furthermore, assuming linear kinetics, this relationship is model independent. The only difference in calculation for multicompartment models is that AUC_0^∞ is the product of T and the sum of all the appropriate coefficients (*e.g.*, $A + B$, in a two-compartment model).

(1) L. Z. Benet, *J. Pharm. Sci.*, **61**, 536 (1972).

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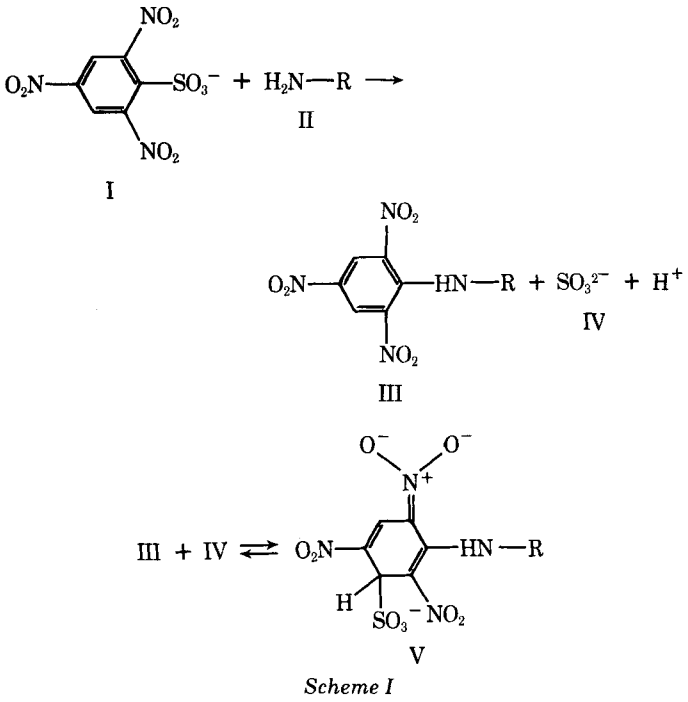
Kinetic Study on Rapid Reaction of Trinitrobenzenesulfonate with Human Serum Albumin

Keyphrases □ Trinitrobenzenesulfonate—kinetics of reaction with human serum albumin □ Kinetics—of reaction of trinitrobenezenesulfonate with human serum albumin □ Albumin, human serum—kinetics of reaction with trinitrobenzenesulfonate

To the Editor:

Trinitrobenzenesulfonate (I) has been used as a reagent for the chemical modification of amino groups in amino acids, peptides, and proteins (1–4). The basic mechanism for the reaction of I with amines (II) was proposed previously (5, 6) (Scheme I). The trinitrophenylated II (III) reacts further with sulfite ion (IV) to form the sulfite monoadduct (V). It was reported that III and V have UV absorption maxima at 340 and 420 nm, respectively, giving an isosbestic point at 367 nm during the reaction of III and IV (5, 6).

The distinction between, and identification of, the drug binding sites on human serum albumin were made previously by us on the basis of the inhibition of the reaction of *p*-nitrophenyl acetate with the albumin caused by several drugs (7). When the albumin was modified with I to characterize the drug binding sites, rapid reaction of I with the albumin was found. In this communication, we describe the localization of the reactive site on the albumin



Scheme I

for I and the kinetics and mechanism for the reaction.

All reactions in this study were carried out in pH 7.4, 0.067 *M* phosphate buffer ($\mu = 0.2$, adjusted with sodium chloride) at 25°. To localize the reactive site on the albumin for I, the fluorescence spectra of the albumin excited at 300 nm were measured[1]. The intensity of the emission

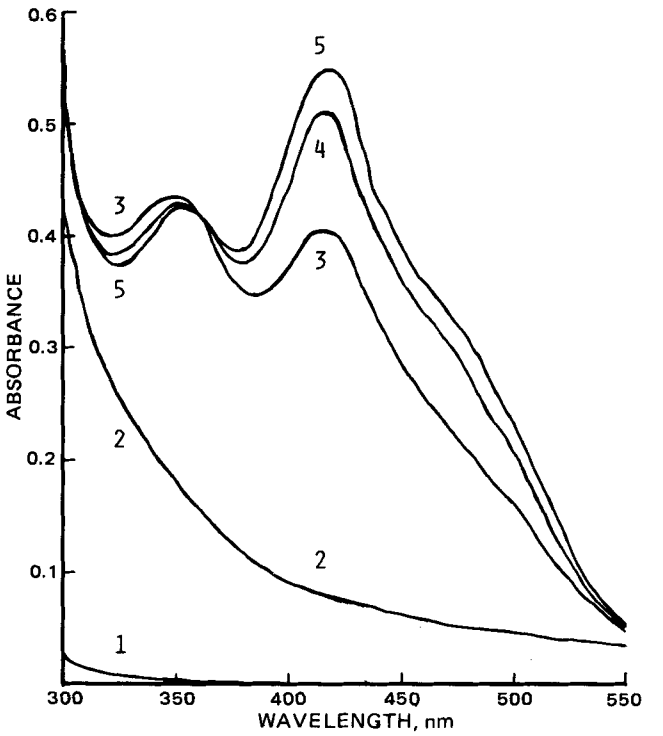


Figure 1—*UV absorption spectra. 1, 2.5 × 10⁻⁵ M I; 2, 1.0 × 10⁻⁴ M albumin; 3, 2.5 × 10⁻⁵ M I and 1.0 × 10⁻⁴ M albumin; 4, 2.5 × 10⁻⁵ M I, 1.0 × 10⁻⁴ M albumin, and 5.0 × 10⁻⁵ M NaHSO₃; and 5, 2.5 × 10⁻⁵ M I, 1.0 × 10⁻⁴ M albumin, and 1.0 × 10⁻⁴ M NaHSO₃.*

[1] RF-510 spectrofluorophotometer, Shimadzu, Kyoto, Japan.

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