Volume of Distribution and Tissue Level Errors in Instantaneous Intravenous Input Assumptions

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Abstract □ A comparison was made between instantaneous input assumption and short-term zero-order infusion for 1 and 2 min for several drugs showing fast distribution to the tissue compartments. The errors ranged from 9 to 40% for the volume of the central compartment, from 0.7 to 11% for the volume of distribution following pseudo-distribution equilibrium, and from 11 to 34% for the volume of distribution change at the end of the 2-min infusion period. Significant errors in the tissue levels also were observed. It was suggested that all intravenous administrations be considered as short-term zero-order inputs.

Keyphrases □ Distribution, volume—comparison of instantaneous input assumption and short-term zero-order infusion, tissue compartments, various drugs □ Tissue levels—various drugs, comparison of instantaneous input assumption and short-term zero-order infusion, various drugs □ Intravenous input assumption, instantaneous—compared to short-term zero-order infusion, volume of distribution calculations, various drugs □ Volume of distribution—comparison of instantaneous input assumption and short-term zero-order infusion, tissue compartments, various drugs

The concept of possible errors in assuming that a drug can be instantaneously placed in the central compartment of a mammillary model was recently introduced (1). The simplifying assumption of instantaneous input invariably results in erroneous volume of distribution and tissue level calculations, the extent of which depends on the distribution half-lives in a mammillary model system. The purposes of this report are to cite several examples where such errors may have occurred and to review the pharmacokinetic and pharmacological aspects of these observations.

THEORY

In the conventional treatment of the data following a quick intravenous dose, the blood concentration, C_1, is expressed as:

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

where A_i = intercepts on the feathered plot, and a_i = hybrid rate constants. If, however, the intravenous administration is considered as short-term zero-order infusion (1), the blood concentration can be expressed as (1):

$$C_1 = \sum_{i=1}^{n} \frac{A_i(1 - e^{-a_i\theta})e^{-a_i t'}}{a_i\theta} \qquad \text{(Eq. 2)}$$

where θ = dosing duration, and t' = time following the infusion period $(t - \theta)$.

The volume of the central compartment, V_{d_0}, is expressed as:

$$V_{d_0} = \frac{\text{dose}}{\sum_{i=1}^{n} A_i} \qquad \text{(Eq. 3)}$$

Therefore, the corrected definition would read (1):

$$V_{d_0} = \frac{\text{dose}}{\sum_{i=1}^{n} \frac{\theta a_i A_i}{(1 - e^{-a_i\theta})}} \qquad \text{(Eq. 4)}$$

The volume of distribution following pseudo-distribution equilibrium is expressed as (2, 3):

$$V_{d_{eq}} = \frac{\text{dose}}{a_n x \sum_{i=1}^{n} \frac{A_i}{a_i}} \qquad \text{(Eq. 5)}$$

which can be corrected for short-term zero-order infusion to give:

$$V_{d_{eq}} = \frac{\text{dose}}{a_n x \sum_{i=1}^{n} \frac{\theta A_i}{(1 - e^{-a_i\theta})}} \qquad \text{(Eq. 6)}$$

A single definition of the volume of distribution, treating this term as a function of time, was proposed (3):

$$V_d = \frac{\text{dose} \sum_{i=1}^{n} \frac{A_i}{a_i} e^{-a_i t}}{\sum_{i=1}^{n} \frac{A_i}{a_i} \sum_{i=1}^{n} A_i e^{-a_i t}} \qquad \text{(Eq. 7)}$$

It can be modified for short-term zero-order infusion to give:

$$V_d = \frac{\text{dose} \sum_{i=1}^{n} \frac{\theta A_i e^{-a_i t'}}{(1 - e^{-a_i\theta})}}{\sum_{i=1}^{n} \frac{\theta A_i}{(1 - e^{-a_i\theta})} \sum_{i=1}^{n} \frac{\theta a_i A_i}{(1 - e^{-a_i\theta})} e^{-a_i t'}} \qquad \text{(Eq. 8)}$$

This equation has the same limits at $t = \theta$ and t = pseudo-distribution equilibrium time as expressed in Eqs. 4 and 6, respectively.

The concept of the volume of distribution as a function of time was applied to evaluate the thermodynamic activity of the drug in the central compartment (3). The rate of the volume of distribution change with time reflects the distribution to the tissues from the central compartment; at time $t = \theta$, the volume of distribution derivative, RV_{d_0}, will be maximum. Applied to the short-term zero-order infusion, this concept can be expressed as:

$$RV_{d_0} = \text{dose}\left[\frac{\sum_{i=1}^{n} \frac{\theta a_i^2 A_i}{(1 - e^{-a_i\theta})}}{\left\{\sum_{i=1}^{n} \frac{\theta a_i A_i}{(1 - e^{-a_i\theta})}\right\}^2} - \frac{1}{\sum_{i=1}^{n} \frac{\theta A_i}{(1 - e^{-a_i\theta})}}\right] \qquad \text{(Eq. 9)}$$

The fraction of the available dose remaining in the body, f_B, is expressed as (3, 4):

$$f_B = \frac{\sum_{i=1}^{n} \frac{A_i}{a_i} e^{-a_i t}}{\sum_{i=1}^{n} \frac{A_i}{a_i}} \qquad \text{(Eq. 10)}$$

and the fraction remaining in the central compartment, f_C, is expressed as:

$$f_C = \frac{\sum_{i=1}^{n} A_i e^{-a_i t}}{\sum_{i=1}^{n} A_i} \qquad \text{(Eq. 11)}$$

The fraction of the available dose in the tissues, f_T, can be expressed as the difference between Eqs. 10 and 11. By incorporating the correction due to short-term zero-order infusion, this fraction can be expressed as:

$$f_T = \frac{\sum_{i=1}^{n} \frac{\theta A_i e^{-a_i t'}}{(1 - e^{-a_i\theta})}}{\sum_{i=1}^{n} \frac{\theta A_i}{(1 - e^{-a_i\theta})}} - \frac{\sum_{i=1}^{n} \frac{\theta a_i A_i e^{-a_i t'}}{(1 - e^{-a_i\theta})}}{\sum_{i=1}^{n} \frac{\theta a_i A_i}{(1 - e^{-a_i\theta})}} \qquad \text{(Eq. 12)}$$

Therefore, it is possible to calculate the tissue levels without calculating the transfer rate constants and comparisons made at different values of θ.

DISCUSSION

For drugs exhibiting multicompartment pharmacokinetics, the nature of distribution can be expressed in terms of the volume of the central compartment, the volume of distribution following pseudo-

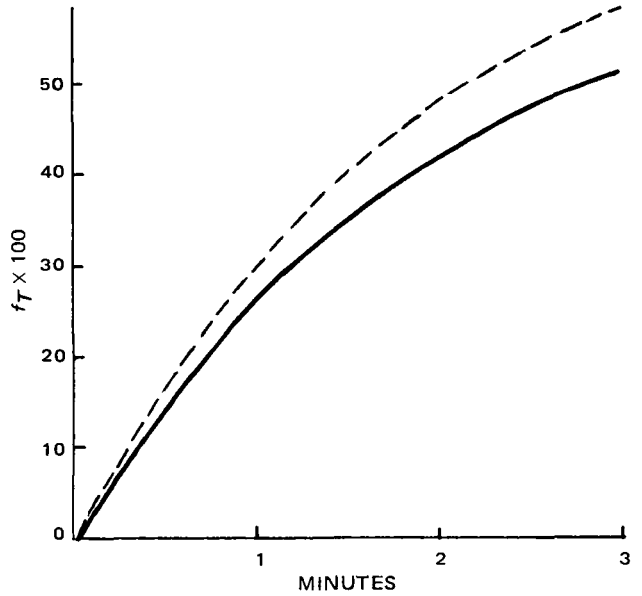

Figure 1—*Fraction of clonazepam remaining in the tissue compartment as a function of time according to the instantaneous input assumption (—) and short-term zero-order infusion for 2 min (----).*

distribution equilibrium, and, recently (3), the volume of distribution as a function of time and the change in the volume of distribution at time $t = \theta$. The assumption of instantaneous input will not affect these parameters significantly in most cases. However, where the distribution half-lives are short, an overestimation of these parameters will invariably result, as shown in Table I for several drugs where the volume terms were calculated for dosing intervals of 1 and 2 min and compared with the reported values. The selection of 1- and 2-min dosing intervals was based on the range of generally observed time intervals for intravenous injection. Of course, time periods greater than 2 min sometimes are necessary for administering an appropriate amount of the drug.

As shown in Table I, a 40% overestimation of volume of the central compartment was observed for clonazepam if the dose was administered over a 2-min period. The volume of distribution following pseudo-distribution equilibrium was little changed, but the RV_{d_0} showed a 23% overestimation. The largest overestimation of RV_{d_0} was observed for methohexital at 34% at the 2-min dosing interval. The overestimations of $V_{d_{eq}}$ were generally small, the highest being about 11% for aspirin.

Several interesting observations can be made from these analyses. First, the volume of the central compartment is much more sensitive to erroneous calculation if an instantaneous input assumption is made than is the volume of distribution following pseudo-distribution equilibrium. This observation was applicable to all but one situation for aspirin, where $V_{d_{eq}}$ values varied more (18%) than V_{d_0} values (11%). This discrepancy can be explained on the basis of the ratio of $V_{d_{eq}}$ and V_{d_0}. This ratio, 2.11, was the lowest for aspirin (compared to 36 for methohexital). Obviously, for aspirin the central compartment provides for a significant fraction of the total body distribution, increasing the error involved in $V_{d_{eq}}$. However, as shown in other examples, the volume of the so-called tissue compartments ($V_{d_{eq}} - V_{d_0}$) accounts for the major contribution to $V_{d_{eq}}$.

The rate of the volume of distribution change at time $t = \theta$ indicates the chemical potential of the drug in the central compartment (3). As shown in Table I, this parameter was overestimated in instantaneous input assumptions by 11–34% at the 2-min dosing interval. Such significant variations decrease its utility in various thermodynamic and pharmacological correlations.

The concept of the volume of distribution as a function of time makes it possible to compare tissue levels as a function of time in an instantaneous input assumption and the corresponding short-term zero-order infusion without any calculation of transfer rate constants between compartments. Figure 1 shows the tissue levels of clonazepam as determined from the reported pharmacokinetic parameters (5) assuming an instantaneous input and the tissue levels if the drug is

Table I—Reported and Corrected Pharmacokinetic Parameters for Several Drugs

Drug (Reference)	Dose, mg	A_1, mg/liter	A_2, mg/liter	A_3, mg/liter	a_1, hr^{-1}	a_2, hr^{-1}	a_3, hr^{-1}	V_{d_0}, liters	V_{d_0}', liters, θ = 1 min	V_{d_0}', liters, θ = 2 min	$V_{d_{eq}}'$ liters	$V_{d_{eq}}'$, liters, θ = 1 min	$V_{d_{eq}}'$, liters, θ = 2 min	RV_{d_0}', liters/hr	RV_{d_0}', liters/hr, θ = 1 min	RV_{d_0}', liters/hr, θ = 2 min
Aspirin (6)	650	67	33	—	13.880	2.976	—	6.50	5.97	5.49	13.72	13.02	12.35	26.00	23.88	21.92
Penicillin G (7)	100	8.4	2.3	—	6.250	1.351	—	9.34	8.95	8.58	24.29	23.59	22.91	15.74	14.93	14.17
Methohexital (8)	190	21.15	1.85	0.280	16.666	1.077	0.1234	8.16	7.20	6.39	292.95	282.09	271.24	88.13	76.04	65.73
Pralidoxime chloride (9)	411	14.94	3.73	—	7.060	0.531	—	22.01	20.98	20.01	84.68	83.24	81.80	81.74	77.76	73.94
Lysergide (10)	0.12	0.01464	0.002016	0.006531	26.230	2.480	0.2170	5.17	4.49	3.92	17.57	17.46	17.34	83.33	77.26	70.83
Pentazocine (11)	2.4	0.15412	0.04852	0.02112	25.000	1.100	0.2200	10.72	9.28	8.06	74.58	73.59	72.55	171.06	155.02	139.35
Clonazepam (5)	30	1.205	0.601	—	30.620	0.129	—	16.61	14.02	11.88	49.49	49.33	49.14	333.70	302.70	271.04

administered over 2 min. Such differences can result in correlation variations between pharmacological activity and blood concentration if the site of action resides in the tissue compartments. It would be reasonable to assume that the site of action probably will be, at least in part, in one or more of the tissue compartments, since the compartments simply represent time-dependent equilibration processes. Even if the organ on which the drug is acting can be clearly classified as part of the central compartment, such as the heart, the actual site of action may reside in tissue compartments because of the essential nature of time-dependent processes involved in the tissue equilibration.

From these data, it is clear that some degree of error will invariably result if an instantaneous input assumption is made. Therefore, all intravenous administrations should be considered as short-term zero-order inputs.

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Simple and Rapid Determination of a New Pharmaceutically Active Amine Hydrochloride

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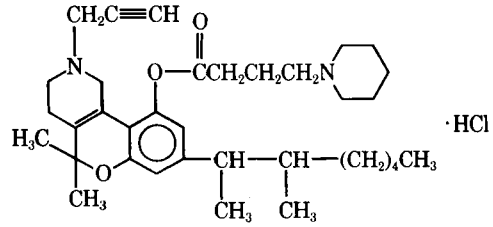
Abstract □ The quantitative analysis of a new pharmaceutically active amine hydrochloride is described. Samples are extracted with chloroform. A yellow amine–dye complex is formed by buffering a sample–bromthymol blue solution at pH 8.5 ± 0.1 and subsequently extracted with chloroform. The complex is treated with 0.01 *N* NaOH to convert it back to the sodium salt of bromthymol blue, which is then measured at 615 nm in the aqueous layer. The amount of complex extracted is linearly related to the amount of amine present, from 0.020 to 0.20 mg/ml. Under the selected conditions, the compound can be determined in the presence of degradation products and there is no interference from common pharmaceutical excipients. The method is suitable for stability studies.

Keyphrases □ Amine hydrochlorides—pharmaceutically active substituted benzopyranopyridine, complexation with bromthymol blue, colorimetric analysis □ Benzopyranopyridine, substituted—pharmaceutically active compound, colorimetric analysis □ Colorimetry—analysis, pharmaceutically active substituted benzopyranopyridine □ Bromthymol blue—use in colorimetric analysis of pharmaceutically active substituted benzopyranopyridine

A new biologically active compound with a benzopyran nucleus (I) was synthesized. Chemically, I is 5,5-dimethyl-10-[4-(1-piperidine)butyryloxy]-8-(3-methyl-2-octyl)-2-(2-propynyl)-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*d*]pyridine hydrochloride. It is readily soluble in water, chloroform, and ethanol, and its melting point[1] is 103–106°.



I

The method for the determination of amine salts, involving the formation of an ion-pair with indicator, is based on Prudhomme's (1) discovery that alkaloids form chloroform-soluble complexes with acid dyes such as eosin, the reaction being quantitative (2). The methods available for the determination of quaternary ammonium salts were reviewed previously (3). The extraction of the amine–bromthymol blue complexes of numerous compounds into methylene chloride was studied, and the optimum pH value was 7.4 (4). Thiamine was analyzed using bromthymol blue with a pH 6.6 buffer solution (5).

The indicator extraction method has the advantages of high sensitivity, rapidity, and partial selectivity and appeared to be of potential value for pharmaceutical preparations. The purpose of this investigation was to develop a stability method for the assay of a new pharmaceutically active amine hydrochloride (I) in various dosage forms.

EXPERIMENTAL

Instruments—The following were used: a UV–visible spectrophotometer[2] with 1-cm cells[3], a pH meter[4], a centrifuge[5], and an analytical balance[6].

[1] Thomas-Hoover, USP Class I.
[2] Beckman DU (or equivalent), Beckman Instruments, Fullerton, Calif.
[3] Bausch and Lomb.
[4] Beckman expandomatic instrument (or equivalent).
[5] International clinical centrifuge.
[6] Type H-51, Mettler Instrument Corp., Princeton, N.J.