Assay of Chlordiazepoxide and Demoxepam in Chlordiazepoxide Formulations by Difference Spectrophotometry

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Abstract □ Rapid difference spectrophotometric methods for chlordiazepoxide and demoxepam in chlordiazepoxide formulations are described which overcome the nonspecificity of the official spectrophotometric assays. The procedures are based on the measurement of the difference absorbance at 269 nm of equimolar solutions of chlordiazepoxide at pH 8 and pH 3 and the difference absorbance at 263 nm of equimolar solutions of demoxepam at pH 13 and pH 8. The methods are specific for chlordiazepoxide and demoxepam in the presence of both compounds, 2-amino-5-chlorobenzophenone, certain coformulated drugs, and formulation excipients. Analyses of commercial dosage forms of chlordiazepoxide have shown the presence of demoxepam at concentrations in excess of the pharmacopoeial specifications in some aged samples.

Keyphrases □ Chlordiazepoxide—assay with demoxepam in formulations, difference spectrophotometry □ Demoxepam—assay with chlordiazepoxide in chlordiazepoxide formulations, difference spectrophotometry □ Difference spectrophotometry—assay of chlordiazepoxide and demoxepam in chlordiazepoxide formulations

Methods of analysis of benzodiazepine drugs and their respective hydrolysis products in pharmaceutical formulations based on the direct measurement of absorbance in the UV region lack selectivity. For example, chlordiazepoxide (I) and its major hydrolysis product demoxepam (7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide, II) have very similar UV spectra resulting in their mutual interference in direct spectrophotometric procedures. The presence of a minor hydrolysis product 2-amino-5-chlorobenzophenone (III) and absorbing coformulated drugs in certain chlordiazepoxide–drug combinations may further reduce the accuracy of direct spectrophotometric methods for I and II.

Current pharmacopoeial specifications in the United States (1) limit the content of II to 0.1% in chlordiazepoxide drug substance, 3% in capsules of the hydrochloride salt, and 4% in tablets of the free base. The British Pharmacopoeia 1980 (2) also specifies limits for II and other related substances in chlordiazepoxide and its formulations based on a comparison of the intensities of impurity spots on a thin-layer chromatogram of the sample with that of a specified quantity of I obtained by a dilution of the sample. The maximum permissible content of III is 0.01% (1) or 0.05% (2) in chlordiazepoxide drug substance and 0.1% in solid dosage forms (1, 2).

A variety of techniques have been used to assay chlordiazepoxide formulations including HPLC (3–5) and GLC (6) which quantitatively determine I and its hydrolysis products, spectrofluorometry (7, 8), polarography (9, 10), colorimetry (11, 12), and UV spectrophotometry (1, 2, 13). A column chromatographic–UV spectrophotometric assay has also been described for II (14).

Difference spectrophotometry has proved particularly useful in the assay of medicinal substances by eliminating specific interference from degradation products and coformulated drugs (15, 16) and also nonspecific irrelevant absorption from the formulation matrix. The technique may be applied to substances that exhibit a difference in absorbance between two equimolar solutions which has been induced by the addition of reagents to one or both of the solutions. The difference spectrophotometric assay of these substances in samples that also contain other absorbing components may be carried out provided the absorbances of the interfering substances remain unaltered by the reagents. This paper describes pH-induced simultaneous difference spectrophotometric procedures that are specific for I and II in the presence of III, certain coformulated drugs, and formulation excipients.

EXPERIMENTAL

Apparatus—Absorption and difference absorption spectra were recorded in 1-cm silica quartz cells using a recording double-beam spectrophotometer[1]. To measure the small difference absorbance of demoxepam accurately, the cells were carefully matched for transmission and path length so that the absorbance difference at 269 nm of neither a solution of I (10 μg/mL) at pH 8 nor of water in the two cells exceeded 0.001 AU.

Reagents—Chlordiazepoxide BP[2], demoxepam[2], and 2-amino-5-chlorobenzophenone[2] were dried as described in the USP XX (1). All other reagents and solvents were of analytical reagent quality. Stock pH 3 buffer was prepared by diluting 37.53 g of glycine and 114 mL of 1.00 M HCl to 1 L with water. Stock pH 8 buffer was prepared by diluting 60.57 g of Tris and 292 mL of 1.00 M HCl to 1 L with water.

Chlordiazepoxide Standard Solutions—Approximately 25 mg of chlordiazepoxide was accurately weighed into a 250-mL volumetric flask and dissolved in 20 mL of ethanol. The solution was slightly acidified by the addition of 0.4 mL of 1 M HCl and diluted to volume with water. A 5.0-mL aliquot was transferred to each of two 50-mL volumetric flasks containing stock pH 3 buffer (5 mL) and stock pH 8 buffer (5 mL), respectively, and diluted to volume with water. The difference absorbance at 269 nm (ΔA_{269}^{Std}) of the pH 8 solution in the sample cell was measured relative to the pH 3 solution in the reference cell after the zero absorbance had been set with the pH 8 buffer (stock buffer diluted 1:9 with water) in the sample cell and the pH 3 buffer (stock buffer diluted 1:9 with water) in the reference cell.

Demoxepam Standard Solutions—Approximately 25 mg of demoxepam, accurately weighed into a 250-mL volumetric flask, was dissolved in 20 mL of ethanol and diluted to volume with water. A 5.0-mL aliquot was transferred to two 50-mL volumetric flasks containing stock pH 8 buffer (5 mL) and 1 M NaOH (5 mL), respectively, and diluted to volume with water. The difference absorbance at 263 nm (ΔA_{263}^{Std}) of the pH 13 solution (in 0.1 M NaOH) in the sample cell was measured relative to the pH 8 solution in the reference cell after the zero absorbance had been set with 0.1 M NaOH and the pH 8 buffer in the sample and reference cells, respectively.

Sample Solutions—Twenty tablets or the contents of twenty capsules were thoroughly triturated. A quantity of powder containing ~10 mg of chlordiazepoxide or 11.2 mg of chlordiazepoxide hydrochloride was ac-

[1] Model 552 Spectrophotometer; Perkin-Elmer Ltd., Beaconsfield, Bucks, HP9 1QA, U.K.
[2] Roche Products Ltd., Welwyn Garden City, Herts AL7 3AY, U.K.

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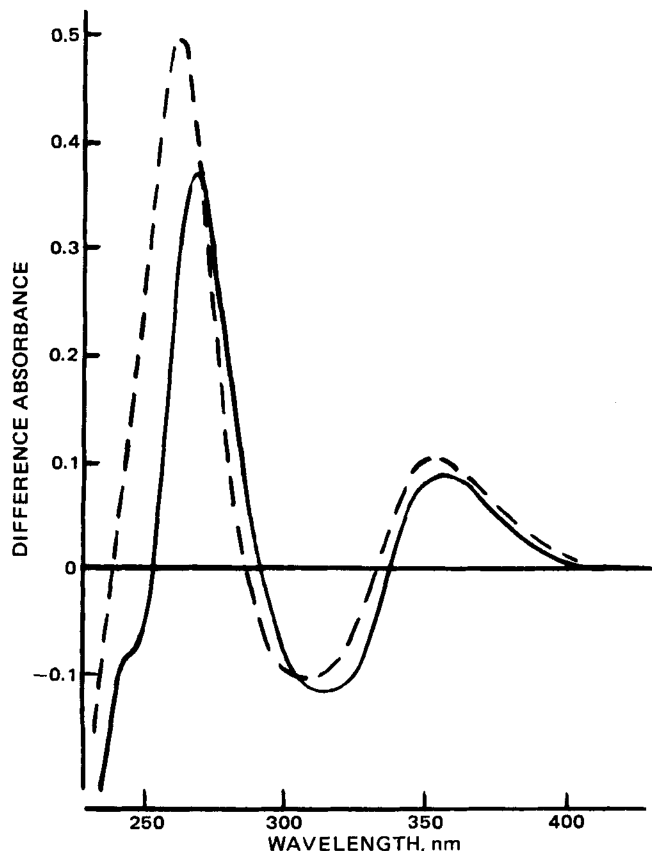

Figure 1—*Difference absorption spectra of chlordiazepoxide (10μg/mL) in pH 8 versus pH 3 solutions (—) and demoxepam (10 μg/mL) in pH 13 versus pH 8 solutions (- - -).*

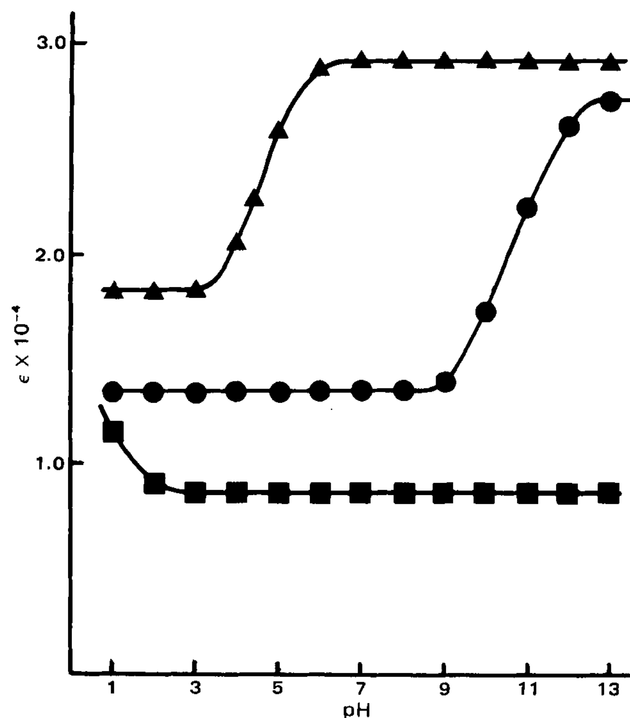

Figure 2—*Variation of molar absorptivity (ε) of chlordiazepoxide (▲) at 269 nm, demoxepam (●) at 263 nm, and 2-amino-5-chlorobenzophenone (■) at 269 nm with pH.*

curately weighed into a 100-mL volumetric flask and shaken for 10 min with 10 mL of ethanol. Water (60 mL) and 0.1 M HCl (10 mL) were added and the flask was shaken for an additional 20 min. The extract was diluted to volume with water and clarified by passing it through a filter paper[3] or membrane filter[4], with the first 10 mL of filtrate being discarded. Aliquots (5.0 mL) of the filtrate were transferred to three 50-ml volumetric flasks containing stock pH 3 buffer (5 mL), stock pH 8 buffer (5 mL), and 1 M NaOH (5 mL), respectively, and diluted to volume with water. The $\Delta A_{269}{}^{sample}$ of the pH 8 and pH 3 solutions were measured as described above for the standard chlordiazepoxide solutions, and the $\Delta A_{263}{}^{sample}$ of the solutions in 0.1 M NaOH and pH 8 buffer were measured as described above for the standard demoxepam solutions.

The concentrations of chlordiazepoxide (C_C) and demoxepam (C_D) in a tablet or capsule contents of average weight (AW) as a percentage of the stated quantity of chlordiazepoxide (C_t) were calculated using:

$$C_C = \frac{\Delta A_{269}{}^{sample} \times C_C{}^{std} \times AW \times 100}{\Delta A_{269}{}^{std} \times \text{weight of sample} \times C_t} \quad \text{(Eq. 1)}$$

$$C_D = \frac{\Delta A_{263}{}^{sample} \times C_D{}^{std} \times AW \times 100}{\Delta A_{263}{}^{std} \times \text{weight of sample} \times C_t} \quad \text{(Eq. 2)}$$

where $C_C{}^{std}$ and $C_D{}^{std}$ are the concentrations of the buffered standard solutions of I and II, respectively, in μg/mL and weights are in mg.

RESULTS AND DISCUSSION

Choice of Assay Conditions—The specificity of the difference spectrophotometric assays of I and II is due to the different spectral changes exhibited by these substances in aqueous solution on alteration of the pH. Chlordiazepoxide displays a bathochromic shift of its λ_{max} at 245 nm in acidic solution to 260 nm in alkaline solution (17). The difference absorption spectrum (Fig. 1) of a solution of I buffered at pH 8 relative to an identical solution buffered at pH 3 in the reference cell shows that the maximum difference occurs at 269 nm. The spectra of II are identical at pH 3 and pH 8, but basification to pH 13 results in a bathochromic shift of the maximum at 237 nm to 242 nm with a shoulder at 255 nm (17). The maximum difference absorbance of equimolar solutions of II at pH 13 (in 0.1 M NaOH) and at pH 8 occurs at 263 nm (Fig. 1).

Absorptivity—pH plots of equimolar solutions (3.34×10^{-5} M) of I, II, and III over the pH range of 1–13 (Fig. 2) show that each exhibits only one inflexion and that the pH regions over which these occur (pH ~4.6, ~10.5, and ~1.0, respectively) are sufficiently well separated to permit the selective determination of I and II in the presence of each other and in the presence of III. Buffers of pH 8 and pH 3 have been selected for the determination of I at 269 nm and buffers at pH 13 and pH 8 for the assay of II at 263 nm. The assay of III utilizing the spectral changes of pH ~1 has not been attempted in this work owing to the very low levels found in formulations, typically <0.03% (3, 6).

The sites of ionization which affect the absorption spectra of I and II are, respectively, the *N*-oxide oxygen atom where protonation in acidic solution occurs (18) and the C-3 position where deprotonation occurs in alkaline solution with stabilizing enolization in the direction of C-2 (19). An ionization of II (pK_a 4–5) associated with protonation of the *N*-oxide oxygen atom has been found in this work and previously (19) to have no effect on its absorption spectrum.

The midpoint of the sigmoidal curve (Fig. 2) for I occurred at pH 4.6, in agreement with the pK_a measured spectrophotometrically at 265 nm (18). However the midpoint of the inflexion given by II occurred at pH 10.5, considerably lower than 11.5, the pK_{a2} which has been determined spectrophotometrically at an unspecified wavelength (19). To resolve this difference, the pK_a of II (concentration, 10 μg/mL) was determined

Table 1—Recovery of Chlordiazepoxide and Demoxepam in Standard Mixtures

Composition of Mixture, μg/mL			Concentration Found			
			I		II	
I	II	III	μg/mL	Percent Added	μg/mL	Percent Added
99.2	0.0	0.0	99.2	100.0	0.0	—
98.2	1.05	0.0	98.0	99.8	0.92	87.6
96.2	2.10	0.0	96.6	100.4	2.23	106.2
94.2	4.20	1.02	93.6	99.4	4.30	102.4
89.3	8.40	2.04	89.9	100.7	8.16	97.1
79.4	16.80	4.07	79.9	100.6	16.83	100.2
59.5	31.49	10.18	60.2	101.2	31.40	99.7
19.8	62.99	20.36	20.1	101.5	63.40	100.7

[3] Whatman No. 1.
[4] Millipore Filter, 0.45 μm, 25 mm diameter.

Table II—Means, Standard Deviations (*SD*), and Coefficients of Variation (*CV*) for Standard Solutions of Chlordiazepoxide and Demoxepam

Composition of Mixture, μg/mL		ΔA_{269}			ΔA_{263}		
I	II	Mean[a]	$SD \times 10^3$	CV, %	Mean[a]	$SD \times 10^3$	CV, %
100.0	0.0	0.3704	1.30	0.35	0.0001	0.70	—
0.0	100.0	0.0008	0.92	—	0.4903	0.91	0.19
96.0	4.0	0.3551	1.13	0.32	0.0194	0.69	3.57
80.0	20.0	0.2960	1.05	0.36	0.0982	0.62	0.63

[a] Ten replicate measurements.

Table III—Assay of Chlordiazepoxide Formulations by the Difference (ΔA) and Official Spectrophotometric Procedures

Sample	Formulation	Coformulated Drug	Age, years	ΔA I[a]	ΔA II[a]	USP (1)[a]	BP (2)[a]
A	5-mg Capsule of I·HCl	—	New	102.7	<L.D.[b]	101.7	101.9
B	10-mg Capsule of I·HCl	—	New	98.9	<L.D.[b]	101.0	100.4
C	5-mg Capsule of I·HCl	—	6	98.1	2.47	100.0	100.9
D	10-mg Capsule of I·HCl	—	6	86.8	6.80	95.0	94.4
E	25-mg Tablet I (base)	—	1	99.0	<L.D.[b]	102.2	102.0
F	5-mg Tablet I (base)	—	5	98.2	1.91	100.2	99.7
G	5-mg Tablet I (base)	Clidinium bromide, 2.5 mg	4	92.1	8.31	—	—
H	5-mg Capsule I·HCl	Amitriptyline HCl, 12.5 mg	New	98.3	—	—	—
I	10-mg Capsule I·HCl	Amitriptyline HCl, 25.0 mg	4	96.8	—	—	—

[a] Expressed as percent of stated content. [b] Less than the limit of detection.

at 263 nm in seven buffers of 0.3 pH increments from pH 9.6 to 11.4 (20). The average pK_a was 10.55 ± 0.05.

Beer's Law and Specificity—Beer's law graphs for I showed that a proportional relationship exists between the ΔA_{269} of solutions at pH 8 and pH 3 and the concentration of I in the range 0–12.5 μg/mL. The regression equation obtained with six pairs of solutions was $y = 0.0370x - 0.0023$ and the correlation coefficient (r) was 0.99997, where y is the ΔA_{269} in 1-cm cells and x μg/mL is the concentration. An almost identical line ($y = 0.0369x - 0.0010$; $r = 0.99994$) was obtained for a similar series of solutions of I (0–12.5 μg/mL) containing II (2 μg/mL) confirming that the presence of II does not affect the absorptivity of I. Similarly, a proportional relationship exists between the ΔA_{263} of pH 13 and pH 8 solutions of II and their concentration in the range 0–12.5 μg/mL ($y = 0.0490x + 0.0020$; $r = 0.99994$) which is almost identical to that of a series of six mixtures containing a varying concentration of II (0–2.5 μg/mL) and a constant concentration (10 μg/mL) of I ($y = 0.0492x + 0.0020$; $r = 0.9994$). The chosen analytical concentration of I (10 μg/mL) gives absorbance values for the standard solution of I and sample solutions at pH 8 of ~1.0 at 269 nm and 1.2 at 263 nm, which are within the optimum range of absorbance providing minimum relative error.

To assess further the specificity of the method in samples containing I and II, two series each of six solutions were assayed using the procedures. The solutions in the first series contained a constant concentration of I (100 μg/mL) and a varying concentration (0–25 μg/mL) of II. The solutions in the second series contained a constant concentration of II (20 μg/mL) and a varying concentration of I (0–125 μg/mL). The ΔA_{269} of the pH 8 and pH 3 solutions of the first series all fell within 99.4–100.6% of that of the solutions of I containing no added II; in the second series, the ΔA_{263} of the pH 13 and pH 8 solutions fell within 97.6–101.3% of the solutions of II only. These results confirm that the concentrations of I and II may be selectively determined in mixtures by measurement of the ΔA_{269} of equal dilutions at pH 8 and pH 3 and of the ΔA_{263} of equal dilutions at pH 13 and pH 8, respectively.

Amitriptyline hydrochloride and clidinium bromide, coformulated with I in two commercial preparations, give zero ΔA_{269} and do not interfere in the assay of I in these formulations. Amitriptyline, however, precipitates in pH 13 solution, and the assay of II in amitriptyline–chlordiazepoxide combinations cannot, therefore, be carried out by the procedure. Clidinium bromide gives zero ΔA_{263} and does not affect the assay of II in clidinium–chlordiazepoxide combinations.

Isosbestic points (*i.e.*, wavelengths of zero difference absorbance owing to the equal absorptivity of the protonated and nonprotonated species) in the difference absorption spectra (Fig. 1) of I at 291 nm and 252 nm and of II at 287 nm and 240 nm were found to be identical in standard and sample solutions, which indicates that there was no interference from the formulation excipients of the samples (15).

Accuracy, Precision, and Limit of Detection of II—The accuracy of the procedures was assessed by analyzing in duplicate standard mixtures containing I, II, and III, prepared to simulate solutions of I which had undergone varying degrees of hydrolytic decomposition. The results in Table I show that the accuracy of the assay of I is excellent even in the presence of high concentrations of hydrolysis products. The recoveries of II, at and above the USP limit of 4% in chlordiazepoxide capsules, were also satisfactory. At lower concentrations of II, near the limit of detection, the recoveries of 87.6 and 106.2%, at approximate concentrations of II of 1 and 2%, respectively, reflect the difficulty of accurately measuring very small values of ΔA_{263}. At the specified analytical concentration of I, each 1% of II gives a ΔA_{263} value of ~0.005 AU. A high-performance spectrophotometer is therefore essential for the accurate and precise measurement of these small values.

Satisfactory precision was achieved in 10 replicate measurements of ΔA_{269} and ΔA_{263} of solutions of I and II separately and mixtures containing 4 and 20% of II (Table II). The limit of detection of II in I, calculated as twice the standard deviation of the ΔA_{263} of the solution containing no II (21), corresponded to a concentration of 0.286%.

Assay Results—To test the application of the methods, the levels of I and II were determined in a number of chlordiazepoxide tablets and capsules both newly purchased and stored for several years at room temperature. Tablets containing I and clidinium bromide were assayed for I and II and tablets containing I and amitriptyline hydrochloride were assayed for I only. For comparison, the chlordiazepoxide tablets and capsules were also assayed by the official procedures of the USP XX (1) and BP 1980 (2). The results (Table III) show that the new formulations contained undetectable levels of II, and that the levels of I were in good agreement with the declared content and, where appropriate, with those found by the official procedures. In the samples which had been stored, the levels of I were lower than label strength and significant amounts of II were found. In most of these samples the total content of I and II were in reasonable agreement with the declared strength and, where appropriate, with the concentration found by the official procedures. These results confirm the findings of other investigations using chromatographic techniques (3, 6) which showed that levels of II in excess of pharmacopoeial limits may be found in aged chlordiazepoxide samples and that the official nonspecific spectrophotometric procedures do not measure the concomitant loss of chlordiazepoxide.

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Initial Slope Technique for Estimation of the Apparent Volume of Distribution During Constant-Rate Intravenous Infusion

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Received August 19, 1982, from the **School of Chemical Engineering, Cornell University, Ithaca, NY 14853-0294*, the ‡*Division of Clinical Pharmacology, Departments of Pharmacology and Medicine, Box 3813, Duke University Medical Center, Durham, NC 27710*, and the §*Department of Microbiology, Institute of Pharmacy, University of Oslo, Blindern, Oslo 3, Norway.* Accepted for publication October 21, 1982. ¶Present address: Merck Sharp and Dohme Research Laboratories, West Point, PA 19486.

Abstract □ A new technique is presented for estimating the apparent volume of distribution of drugs during constant-rate intravenous infusion. It is based on the initial slope of the plasma drug concentration *versus* time profile during the infusion. Equations are derived to provide estimates of the apparent volume of distribution for a one-compartment drug and for the central compartment of a two-compartment drug. The utility of the technique is illustrated by data obtained during constant-rate infusion of metronidazole in 11 healthy subjects. The average estimated value of the volume of the central compartment of metronidazole was 12% higher than the average value obtained by conventional pharmacokinetic analysis. The systematic error associated with this volume estimation procedure was assessed through the use of dimensionless concentration *versus* dimensionless time plots. The initial slope technique should prove useful in providing initial estimates of volume terms.

Keyphrases □ Pharmacokinetics—apparent volume of distribution, constant-rate infusion, estimation by an initial slope technique, application to metronidazole □ Initial slope technique—estimation of apparent volume of distribution, constant-rate infusion, application to metronidazole pharmacokinetics □ Infusion, constant-rate—estimation of apparent volume of distribution, initial slope technique, application to metronidazole pharmacokinetics

During the past few years, three research groups have described approaches for determining the apparent volume of distribution after administration of single and multiple intermittent, constant-rate, intravenous infusions. Sawchuk *et al.* (1, 2) derived an equation from which the apparent volume of distribution for a drug that follows a one-compartment open model can be calculated, based on knowledge of (*a*) the elimination rate constant, (*b*) the preinfusion residual plasma drug concentration, and (*c*) the plasma drug concentration at the end of infusion. Chiou *et al.* (3, 4) extended the technique by using post-infusion data and the midpoint back-extrapolation method to calculate the apparent volume of distribution for drugs that exhibit linear one-compartmental or multicompartmental characteristics. In addition, application of the Chiou–Hsu equation (5–7) to accurately estimate total body clearance during a constant-rate intravenous infusion requires an accurate estimate of the apparent volume of distribution. Barzegar-Jalali (8) used equally spaced sampling times during a zero-order intravenous infusion and the first derivative of the plasma drug concentration *versus* time profile to directly estimate both the elimination rate constant and steady-state plasma drug concentration for a drug with linear one-compartmental characteristics. The apparent volume of distribution could then be estimated from the latter two quantities.

Unfortunately, none of these approaches can be used to estimate directly the apparent volume of distribution or total body clearance from individual patient plasma drug concentration data gathered during the ongoing infusion. The purpose of this paper is to detail a method for estimating the apparent volume of distribution of a drug from the initial slope of the plasma drug concentration *versus* time profile during a constant-rate intravenous infusion.

THEORETICAL

If instantaneous drug distribution and first-order drug elimination are assumed, the plasma concentration of a drug given as a constant-rate intravenous infusion can be described by the following equation (9):

$$C = \frac{k_0}{KV}(1 - e^{-Kt}) \qquad \text{(Eq. 1)}$$

where C is concentration, k_0 is the zero-order infusion rate, K is the first-order elimination rate constant, V is the apparent volume of distribution, and t is time. Taking the first derivative of Eq. 1 with respect to time yields:

$$\frac{dC}{dt} = \frac{k_0 e^{-Kt}}{V} \qquad \text{(Eq. 2)}$$

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