Simplified Physiologically Based Method to Estimate Steady-State Volume of Distribution

Keyphrases □ Pharmacokinetics—simplified physiologically based method to estimate steady-state volume of distribution □ Volume of distribution—estimation, simplified physiologically based method

To the Editor:

Until recently (1–4), few investigators studied the potential effect of arterial–venous plasma concentration differences on the determination of the apparent steady-state volume of distribution (V_{ss}) of drugs. When standard methods in linear pharmacokinetics were used, the calculated V_{ss} values based on venous plasma data were invariably greater than those based on arterial data from the same animals (2–4). Differences as much as 2.4-fold were found.

From a physiological point of view, the driving force for elimination and distribution of a drug in the body should generally be its concentration in arterial plasma (especially for elimination by renal filtration) and not in peripheral venous plasma (commonly sampled for assay). Therefore, it seems appropriate to use the arterial data (if possible) for V_{ss} calculations (1–3). A new arterial plasma area method for V_{ss} determinations was proposed earlier (4).

In view of the difficulty and risk involved in arterial blood sampling, two physiologically based venous and excretion rate methods were derived (4).

Method I, the intravenous bolus injection method, is described by:

$$V_{ss} = \frac{\int_0^\infty (D - Ae_t/fe)\,dt}{AUC^V} \qquad \text{(Eq. 1)}$$

where D is the bolus dose, Ae_t is the cumulative urinary excretion of unchanged drug from time zero to t, fe is the fraction of the dose excreted unchanged up to time infinity, and AUC^V is the total area under the venous plasma drug concentration–time curve between time zero and time infinity. This method was verified experimentally[1].

Method II, the short-term intravenous infusion method, is described by:

$$V_{ss} = \frac{\int_0^\infty (D_t - Ae_t/fe)\,dt}{AUC^V} \qquad \text{(Eq. 2)}$$

where D_t is the cumulative amount of drug infused up to time t.

Both Methods I and II require frequent and accurate urine collection and extensive blood sampling to estimate the AUC^V. This report describes a simpler physiologically based method, called the steady-state plasma–urinary method, for calculating V_{ss}.

By definition, V_{ss} can be defined as (4 and references cited therein):

$$V_{ss} = \frac{A_{ss}}{C_{ss}} \qquad \text{(Eq. 3)}$$

where A_{ss} is the amount of drug in the body at steady state following a constant-rate infusion and C_{ss} is the steady-state plasma drug concentration. Therefore, V_{ss} can be estimated after the attainment of steady state by:

$$V_{ss} = \frac{D_{ss} - (\text{total amount eliminated up to } t_{ss})}{C_{ss}} \qquad \text{(Eq. 4)}$$

$$V_{ss} = \frac{D_{ss} - Ae_{ss}Cl/Cl_R}{C_{ss}} \qquad \text{(Eq. 5)}$$

where D_{ss} is the total amount of drug infused up to the steady state at time t_{ss}, Ae_{ss} is the total cumulative amount of drug excreted unchanged up to time t_{ss}, Cl is the total plasma drug clearance (*i.e.*, infusion rate/C_{ss}), and Cl_R is the renal drug clearance. The value of Cl_R can be determined by the conventional method, *i.e.*, urinary excretion rate at steady state divided by the C_{ss}. The times to reach various fractions of the steady-state plasma level during intravenous infusion initially can be estimated by a noncompartmental plasma area method described previously (5).

Equation 5 has several advantages over Eqs. 1 and 2. First, Eq. 5 requires only one or two venous blood samples at steady state. Second, all urinary samples can be pooled together (both convenient and economical in drug assay), except for the last one or two that are used for renal clearance measurement. Third, a loading bolus and/or loading infusion dose can be given to achieve the steady state rapidly with the final maintenance infusion; with Eq. 1 or 2, the study may have to be carried out for several half-lives. Fourth, the mathematical operation is much easier with Eq. 5. And fifth, it often may be more accurate to assay steady-state specimens due to higher concentrations. Furthermore, the described method is independent of the source of plasma sample since both arterial and venous (usually from a noneliminating leg or arm vein) plasma drug concentrations should be theoretically identical at steady state (4, 6, 7).

The limitation of the proposed method is that it can only be used for drugs excreted to some extent in the urine. Fluctuations in urine pH and flow rate should be minimized during the entire study period if either or both of them have been shown to significantly affect the renal clearance of drug. Several commonly used method to calculate V_{ss} were recently reviewed (4, 8, 9). The use of the steady-state infusion method employing the measurement of plasma concentrations for calculating V_{ss} were described previously (10–12). The recommended symbols in pharmacokinetics (12) are adopted in this communication.

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Win L. Chiou ˣ
Gilbert Lam
Department of Pharmacy
College of Pharmacy
University of Illinois Medical Center
Chicago, IL 60612

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Modified USP Assay of Calcium Gluceptate

Keyphrases □ Calcium gluceptate—modified USP assay □ USP assay—modification for calcium gluceptate

To the Editor:

The USP assay procedure for calcium gluceptate consists of the complexometric estimation of calcium with ethylenediaminetetraacetic acid (1). To an accurately weighed amount of calcium gluceptate (~800 mg), 150 ml of water containing 2 ml of 3 *N* HCl is added. While stirring, ~25 ml of 0.05 *M* ethylenediaminetetraacetate disodium is added from a buret. Then 15 ml of 1 *N* NaOH and 300 mg of hydroxy naphthol blue indicator are added, and the titration is continued to a blue end-point.

A similar procedure is described for the assay of precipitated calcium carbonate, calcium chloride, calcium gluconate, calcium hydroxide, calcium lactate, and calcium levulinate and for the calcium content analysis of calcium pantothenate and racemic calcium pantothenate. Although each assay calls for the addition of hydrochloric acid, this step is only necessary where the calcium salt has a limited aqueous solubility (2, 3). Since calcium gluceptate is freely soluble in water (4), we suggest that the addition of hydrochloric acid should be omitted. Table I shows that assay results are not affected by the presence or absence of hydrochloric acid.

Table I—Assay of Calcium Gluceptate in the Presence and Absence of Hydrochloric Acid

Calcium Gluceptate	Assay Value, %[a]	
	USP Method	Modified USP Method
Source A[b]	96.80 ± 0.42 (96.55–97.43)	96.82 ± 0.32 (96.54–97.10)
Source B[c]	97.02 ± 0.39 (96.51–97.42)	97.16 ± 0.21 (96.97–97.41)
Source C[d]	101.15 ± 0.08 (101.04–101.24)	100.86 ± 0.49 (100.14–101.17)

[a] Mean ± *SD*, $n = 4$; range is given in parentheses. [b] Pfanstiehl. [c] Givaudan. [d] Italsintex.

The sodium hydroxide solution and the hydroxy naphthol blue indicator can be added to the calcium gluceptate solution at the beginning of the assay; thus, it is unnecessary to interrupt titration to make these additions. The estimation of calcium with ethylenediaminetetraacetic acid using hydroxy naphthol blue as the indicator is carried out at pH 12–13 (5). The addition of 15 ml of 1 *N* NaOH solution in the official assay brings the pH to this range. In the absence of hydrochloric acid, ~10 ml of 1 *N* NaOH solution would be sufficient to bring the pH to the required range. Thus, omitting the hydrochloric acid both simplifies the procedure and enables the amount of sodium hydroxide to be reduced.

We suggest that hydrochloric acid might be omitted in the assay of other freely soluble calcium salts.

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R. Suryanarayanan
A. G. Mitchell ˣ
Faculty of Pharmaceutical Sciences
University of British Columbia
2146 East Mall
Vancouver, B.C. V6T 1W5
Canada

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Observed Artifacts due to Pellet Preparation in IR Spectrometry

Keyphrases □ IR spectrometry—observed artifacts due to pellet preparation □ Pellets—observed artifacts due to preparation, IR spectrometry

To the Editor:

IR spectrometry is required for identifying organic substances by most pharmacopeia and official compendia such as the USP XIX and the NF XIV (1, 2). The USP recommends: "Chemically identical substances of differing polymorphic forms often exhibit different infrared spectra when examined in the solid state. If a difference appears in the spectra, dissolve portions of both the sample and the reference standard in a suitable solvent, evaporate the solution to dryness, and repeat the test on the residues" (1). Differences resulting from polymorphism are considered to be the major reason for errors.

Certain secondary and tertiary amine derivatives such as bupivacaine, cinnarizine, and many butyrophenones have the same spectrum, in part or in whole, for their hydrochloride, hydrobromide, and free base forms when they are dissolved in methanol, ethanol, or isopropanol and if grinding with potassium bromide is prolonged.

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