Noncompartmental Determination of the Steady-State Volume of Distribution During Multiple Dosing

Keyphrases □ Pharmacokinetics—noncompartmental determination of the steady-state volume of distribution during multiple dosing. □ Volume of distribution—steady-state, noncompartmental determination during multiple dosing

To the Editor:

A noncompartmental approach, based on statistical moment analysis, has been used by Benet and Galeazzi (1) to estimate the volume of distribution at steady-state, V_{ss}, following an intravenous bolus injection. This analysis is applicable at present to systems characterized by first-order kinetics, and assumes that drug elimination occurs exclusively from the central compartment. Exactly the same limitations apply to V_{ss} calculated from distributional rate constants (2) or from the coefficients and exponents of exponential equations (3). Perrier and Mayersohn (4) have extended the analysis of Benet and Galeazzi to allow the calculation of V_{ss} for other modes of drug administration. However, these methods can only be applied to single-dose concentration–time profiles. For multiple-dose data, V_{ss} will be overestimated. Straughn (5) has addressed this problem, but the area analysis is not valid in the situation where residual drug is present prior to data collection. This communication shows how, at steady-state, this difficulty can be overcome by using the identity:

$$\mathrm{AUC_{IV}}|_0^\infty = \mathrm{AUC_{ss}}|_0^\tau \qquad \text{(Eq. 1)}$$

The notation used expresses the area under the plasma concentration–time curve (AUC) after either a single intravenous bolus (IV) or a dose given at steady state (ss) over the time limits indicated. Area under the first moment curve (AUMC) is similarly denoted. The dosing interval is τ.

Following a single bolus dose, the mean residence time ($\bar{t}_{IV}$) for the drug in the body is given by:

$$\bar{t}_{IV} = \frac{\mathrm{AUMC_{IV}}|_0^\infty}{\mathrm{AUC_{IV}}|_0^\infty}$$

V_{ss} can be calculated from the product of total body clearance and $\bar{t}_{IV}$ (1, 6):

$$V_{ss} = \frac{\mathrm{A_{IV}}|_0^\infty}{\mathrm{AUC_{IV}}|_0^\infty}\left(\frac{\mathrm{AUMC_{IV}}|_0^\infty}{\mathrm{AUC_{IV}}|_0^\infty}\right) = \frac{\mathrm{Dose}\left(\sum_{i=1}^{n}\frac{C_i^0}{\lambda_1^2}\right)}{\left(\sum_{i=1}^{n}\frac{C_i^0}{\lambda_i}\right)^2} \qquad \text{(Eq. 2)}$$

$\mathrm{A_{IV}}|_0^\infty$ is the total amount of drug cleared, *i.e.*, the dose administered. C_i^0 and λ_i are the coefficients and exponents in a polyexponential equation.

Area under the moment curve for a single bolus dose until time τ, can be evaluated using:

$$\mathrm{AUMC_{IV}}|_0^\tau = \sum_{i=1}^{n}\left\{\frac{C_i^0}{\lambda_i^2} - \frac{C_i^0 e^{-\lambda_i\tau}}{\lambda_i^2} - \tau\frac{C_i^0 e^{-\lambda_i\tau}}{\lambda_i}\right\}$$

After multiple dosage at steady state:

$$\mathrm{AUMC_{ss}}|_0^\tau = \sum_{i=1}^{n}\left\{\left(\frac{1}{1-e^{-\lambda_i\tau}}\right) \times \left(\frac{C_i^0}{\lambda_i^2} - \frac{C_i^0 e^{-\lambda_i\tau}}{\lambda_i^2} - \tau\frac{C_i^0 e^{-\lambda_i\tau}}{\lambda_i}\right)\right\}$$

$$\mathrm{AUMC_{ss}}|_0^\tau = \sum_{i=1}^{n}\left\{\frac{C_i^0}{\lambda_i^2} - \tau\frac{C_i^0 e^{-\lambda_i\tau}}{\lambda_i(1-e^{-\lambda_i\tau})}\right\}$$

$$\mathrm{AUMC_{ss}}|_0^\tau = \mathrm{AUMC_{IV}}|_0^\infty - \tau\,\mathrm{AUC_{ss}}|_\tau^\infty$$

$$\mathrm{AUMC_{IV}}|_0^\infty = \mathrm{AUMC_{ss}}|_0^\tau + \tau\,\mathrm{AUC_{ss}}|_\tau^\infty \qquad \text{(Eq. 3)}$$

By analogy, it can be shown that for multiple infusions:

$$\mathrm{AUMC_{IV}}|_0^\infty = \mathrm{AUMC_{ss}}|_0^\tau - \frac{\mathrm{T}}{2}\mathrm{AUC_{ss}}|_0^\tau + \tau\,\mathrm{AUC_{ss}}|_\tau^\infty \qquad \text{(Eq. 4)}$$

where T is the duration of the infusion

V_{ss} can be determined by appropriate substitution of corrected area values, Eqs. 1, 3, and 4, into Eq. 2. If pharmacokinetic profiling is carried out during the last dose, then samples can be obtained until drug concentration is negligible, allowing $\mathrm{AUC_{ss}}|_\tau^\infty$ to be estimated by area analysis. Otherwise, when the concentration–time curve can only be characterized over a dosing interval, it is necessary to calculate an extrapolated area from the apparent terminal elimination rate. Although $\mathrm{AUC_{ss}}|_\tau^\infty$ may be numerically small, it should not be neglected as the product of $\mathrm{AUC_{ss}}|_\tau^\infty$ and τ will often contribute significantly to $\mathrm{AUMC_{IV}}|_0^\infty$.

It is recognized that in these situations, and often for the steady-state situation in general, mean residence time will be very closely approximated from the ratio of total AUMC to total AUC over a dosing interval with extrapolation to infinity. However, our method does offer an alternative and a more exact mathematical approach to estimating the apparent volume of distribution at steady-state during multiple dosing. We have applied this approach in our present pharmacokinetic studies (7, 8).

While this communication was under review, Bauer and Gibaldi (9) proposed the use of reverse superimposition to determine V_{ss} during multiple dosing. Unlike our analysis which assumes that steady state has been achieved, their method can be applied at any time during therapy. It should be noted, however, that the single-dose curve derived from data obtained during a dosing interval is dependent on the accuracy of the trough level for the previous dose. Therefore, both methods are likely to prove useful in the analysis of multiple-dose data but, as pointed out by Bauer and Gibaldi, are subject to computational errors.

(1) L. Z. Benet and R. L. Galeazzi, *J. Pharm. Sci.*, **68**, 1071 (1979).
(2) D. S. Riggs, "The Mathematical Approach to Physiological Problems," Williams and Wilkens, Baltimore, Md., 1963, chaps 7 and 8.
(3) J. G. Wagner, *J. Pharmacokinet. Biopharm.*, **4**, 443 (1976).
(4) D. Perrier and M. Mayersohn, *J. Pharm. Sci.*, **71**, 372 (1982).
(5) A. B. Straughn, *J. Pharm. Sci.*, **71**, 597 (1982).

0022-3549/84/0200-0281$01.00/0

(6) J. H. ... Schwartz, and M. I. Surks, *J. Clin. Endocrinol. Me* ...1975).
(7) D. J. Swa... P. Reitberg, I. L. Smith, P. B. Wels, and J. J. Schentag, *J. Pharmacokinet. Biopharm*, in press (1984).
(8) D. P. Reitberg, T. J. Cumbo, I. L. Smith, and J. J. Schentag, *Clin. Pharmacol. Ther.*, in press (1984).
(9) L. A. Bauer and M. Gibaldi, *J. Pharm. Sci.*, **72**, 978 (1983).

*Ian L. Smith**x
Jerome J. Schentag‡
*The Clinical Pharmacokinetics Laboratory
Millard Fillmore Hospital
Buffalo, NY 14209
‡Division of Clinical Pharmacy Science
Department of Pharmaceutics
State University of New York at Buffalo
School of Pharmacy
Amherst, NY 14260

Received November 22, 1982.
Accepted for Publication November 16, 1983.

Transdermal Administration of (15*S*)-15-Methyl Prostaglandin $F_{2\alpha}$ Methyl Ester to Rhesus Monkeys

Keyphrases □ Drug delivery systems—controlled-release transdermal administration, prostaglandins, rhesus monkeys □ Prostaglandins—transdermal delivery system, controlled release

To the Editor:

Drug formulation technology has advanced dramatically in recent years. Controlled-release delivery systems offer a number of distinct advantages in therapeutics, one being the potential for designing delivery systems that release therapeutic agents at preselected rates such that in a given situation blood concentration of a drug can be maintained at the desired level for an extended period of time. This ability to control the rate of drug delivery aids in separating the beneficial effects of a drug from the undesirable side effects. Such delivery systems are particularly useful for drugs with short biological half-lives and/or narrow therapeutic indices. Transdermal delivery systems are one of the most exciting applications of controlled-release technology. We report here our preliminary experiments, which demonstrate that (15*S*)-15-methyl prostaglandin $F_{2\alpha}$ methyl ester (carboprost methyl) is readily absorbed when administered transdermally to rhesus monkeys using a polymeric controlled-release delivery system.

The transdermal delivery system consisted of laminated polymeric membranes with a surface area of 40 cm^2. Carboprost methyl was at a concentration of 16% (w/w) in the inner drug-bearing membrane. This membrane was covered with a rate-controlling membrane which allowed a steady-state release rate of 480 μg/h. Double-sided adhesive tape was applied to the periphery of the transdermal patches for attachment to the skin.

The transdermal patches were placed on the shaved chests of four third-trimester pregnant rhesus monkeys. The animals were anesthetized with ketamine hydrochloride[1], and uterine motility was recorded using a fluid-filled polyethylene catheter[2] inserted transabdominally which was attached to a polygraph[3] using a P-23 Dc transducer[4] (1). Peripheral blood samples were collected from the femoral vein and immediately placed in tubes containing heparin. The plasma was harvested and frozen at −20°C for subsequent determination of (15*S*)-15-methyl prostaglandin $F_{2\alpha}$ by radioimmunoassay (2).

The skin was hydrated prior to applying the transdermal delivery system in three animals: a hot towel compress was used on two animals and the skin was irrigated with water on the third animal. To evaluate the rate of drug absorption without prior hydration, the transdermal patch was applied to one animal immediately after shaving the skin.

Drug absorption was more rapid in those animals whose skin had been hydrated. A plasma prostaglandin concentration of ~1200 pg/mL was attained by 0.5 h after application of the transdermal delivery system in the water irrigated animal. In one animal in which a hot towel compress was used the plasma concentration of prostaglandin was ~2200 pg/mL by 0.5 h. The plasma prostaglandin concentration in the second animal similarly pretreated was ~1100 pg/mL by 1 h and 2300 pg/mL by 3 h. Thus, absorption of the drug was slightly slower in this animal even though the skin had been hydrated in a similar manner. When no attempt was made to hydrate the skin, prostaglandin was not detectable in the blood of the fourth monkey until 3 h after the transdermal delivery system had been applied. At this time the concentration was only 100 pg/mL. Thereafter there was a gradual increase in plasma concentration of prostaglandin to 490 pg/mL at 5 h when the delivery system was removed.

All four animals had an increase in the frequency and amplitude of uterine contractions following application of the transdermal delivery systems. In all cases uterine motility increased gradually without any evidence of a rapid onset of prostaglandin effects. The uterine motility tracing from one of these animals is shown in Fig. 1. The mean time to the initiation of stimulated uterine motility was 90 min (range = 45–150 min). The onset of increased uterine activity was temporally related to the increase in prostaglandin detected in the blood in three of the four animals. In one of the animals the rapid increase in blood prostaglandin (2200 pg/mL at 0.5 h) was not reflected in an immediate increase in uterine motility.

These preliminary results clearly demonstrate that carboprost methyl is readily absorbed transdermally in the rhesus monkey when administered using a polymeric controlled-release delivery system. This was particularly true when the skin was hydrated prior to application of the transdermal patch. It is known that hydration of the skin causes the stratum corneum to swell (3). Thus, the normally tight, dense packing of the cells in this layer is loosened. Presumably, this would facilitate movement of prostaglandin through the stratum corneum into the deeper epidermal and dermal layers. However, it is evident that prostaglandin can be absorbed when no effort is made to hydrate the skin, albeit, at a much slower initial rate.

Transdermal delivery systems are finding more and

[1] Vetalor, Parke-Davis and Co.

[2] PE60, Clay Adams.
[3] Grass.
[4] Strathan.

0022-3549/84/0200-0282$01.00/0