Pharmaceutical Research, Vol. 6, No. 8, 1989

Technical Note

Noncompartmental Analysis for a One-Compartment Model with Equal Absorption and Elimination Rate Constants

Howard Ko,[1] James F. Caputo,[1] and Wade J. Adams[1,2]

Received August 22, 1988; accepted March 6, 1989

KEY WORDS: noncompartmental parameters; one-compartment model; equal absorption and elimination rate constants; multiple dosing.

The analysis of pharmacokinetic data using statistical moment theory, most commonly referred to as noncompartmental or model-independent pharmacokinetic analysis, has been increasingly applied in recent years (1). The only assumptions inherent in this approach are that all dispositional processes may be described by first-order kinetics, with elimination occurring from the central compartment. Benet and Galeazzi (2) presented a method for the calculation of the volume of distribution at steady state, V_{ss}, from bolus intravenous data. Perrier and Mayersohn (3) extended the approach to include other routes of drug administration. In both of these communications (2,3), V_{ss} was estimated from single-dose data. Later, it was shown (4–6) how noncompartmental analysis could be extended to the multiple-dosing situation. However, this work was limited to those cases where concentration versus time curves could be expressed as a sum of exponentials. In this communication, the calculation of noncompartmental pharmacokinetic parameters during multiple dosing is described for a one-compartment model in which the first-order absorption and elimination rate constants are equal.

In the special case of a one-compartment model in which the absorption and elimination rate constants are equal, the concentration versus time dependence, $C(t)$, following single-dose drug administration can be expressed as a gamma function (7),

$$C(t) = \frac{FDk}{V} \cdot t \cdot e^{-kt}$$

where F is the fraction of the dose (D) that reaches the systemic circulation, V is the volume of distribution, and k is the first-order rate constant.

Following single-dose administration, the apparent systemic clearance (CL/F) and mean residence time (MRT) are given by Eq. (1) and Eq. (2), respectively (2,3). In these equations $AUC_1|_0^\infty$ and $AUMC_1|_0^\infty$ are the

$$CL/F = \frac{D}{AUC_1|_0^\infty} \tag{1}$$

$$MRT = \frac{AUMC_1|_0^\infty}{AUC_1|_0^\infty} \tag{2}$$

areas under the concentration versus time curve and first moment curve from time zero to infinity, respectively. The apparent steady-state volume of distribution (V_{ss}/F) can be expressed as the product of the apparent systemic clearance and the mean residence time corrected for the rate of drug input (2,8):

$$V_{ss}/F = \frac{D}{AUC_1|_0^\infty} \cdot \left\{\frac{AUMC_1|_0^\infty}{AUC_1|_0^\infty} - \frac{1}{k}\right\} \tag{3}$$

In the case of multiple-dose drug administration, in which a fixed dose of drug is given at fixed intervals, the apparent systemic clearance, mean residence time, and apparent steady-state volume of distribution can be calculated by equations analogous to the single-dose situation, provided appropriate expressions for the areas under the concentration versus time curve and first moment curve are used in Eqs. (1)–(3) that take into account steady-state conditions. The steady-state concentration versus time dependence during a dosing interval, τ, for a one-compartment model having equal first-order absorption and elimination rate constants was recently derived by Wijnand (9) and is given by

$$C_{ss}(t) = \frac{FDk}{V(1 - e^{-k\tau})} \cdot \left\{t + \frac{\tau e^{-k\tau}}{(1 - e^{-k\tau})}\right\} \cdot e^{-kt}$$

As first shown by Wagner *et al.* (10), the area under the concentration versus time curve at steady state for a dosing interval,

$$AUC_{ss}|_0^\tau = \int_0^\tau C_{ss}(t)dt$$

is equal to $AUC_1|_0^\infty$ following single-dose drug administration. Consequently, $AUC_{ss}|_0^\tau$ can be substituted for $AUC_1|_0^\infty$ in Eqs. (1)–(3) once steady-state conditions have been achieved in a multiple-dose regimen. The area under the first

[1] Drug Metabolism Research, The Upjohn Company, Kalamazoo, Michigan 49008.

[2] To whom correspondence should be addressed.

0724-8741/89/0800-0731$06.00/0

moment curve at steady state for a dosing interval is as follows:

$$\mathrm{AUMC_{ss}}|_0^\tau = \int_0^\tau tC_{ss}(t)dt = \frac{2FD}{Vk^2} - \tau \cdot \left\{\frac{FD}{Vk} \cdot \frac{e^{-k\tau}}{(1-e^{-k\tau})} + \frac{FD\tau}{V} \cdot \frac{e^{-k\tau}}{(1-e^{-k\tau})^2}\right\} \quad (4)$$

The first term in $\mathrm{AUMC_{ss}}|_0^\tau$ is equal to $\mathrm{AUMC_1}|_0^\infty$ following single-dose drug administration, while the second term is equal to the product of τ and the area under the concentration versus time curve from the last dosing interval to infinity as shown below:

$$\mathrm{AUC_{ss}}|_\tau^\infty = \int_\tau^\infty C_{ss}(t)dt = \frac{FD}{Vk} \cdot \frac{e^{-k\tau}}{(1-e^{-k\tau})} + \frac{FD\tau}{V} \cdot \frac{e^{-k\tau}}{(1-e^{-k\tau})^2}$$

As a consequence, Eq. (4) can be rewritten in the following form:

$$\mathrm{AUMC_1}|_0^\infty = \mathrm{AUMC_{ss}}|_0^\tau + \tau \cdot \mathrm{AUC_{ss}}|_\tau^\infty \quad (5)$$

Substitution of this identity into Eqs. (2) and (3) for $\mathrm{AUMC_1}|_0^\infty$ allows the calculation of the apparent systemic clearance, mean residence time, and apparent steady-state volume of distribution under steady-state conditions in a multiple-dose regimen. Thus, for the special case considered here, statistical moment theory gives a result identical to that reported for intravenous drug administration (5,6). As noted by Smith and Schentag (5), although the numerical value of $\mathrm{AUC_{ss}}|_\tau^\infty$ may be numerically small, it should not be neglected, as the product of $\mathrm{AUC_{ss}}|_\tau^\infty$ and τ will often be significant relative to $\mathrm{AUMC_{ss}}|_0^\tau$.

In the case of multiple-dose drug administration in which steady state has not been attained, the apparent systemic clearance, mean residence time, and apparent steady-state volume of distribution can also be calculated provided that appropriate expressions for the areas under the concentration versus time curve and first moment curve are used in Eqs. (1)–(3). The concentration versus time dependence during the nth dosing interval for a one-compartment model having equal first-order absorption and elimination rate constants was recently derived by Wijnand (9) and is given by

$$C_n(t) = \frac{FDk}{V \cdot (1-e^{-k\tau})} \cdot \left\{(1-e^{-nk\tau}) \cdot te^{-kt} + \frac{\tau e^{-k\tau} \cdot [1 + (n-1) \cdot e^{-nk\tau} - ne^{-(n-1)k\tau}]}{(1-e^{-k\tau})} \cdot e^{-kt}\right\}$$

The area under the concentration versus time curve for the nth dosing interval, $\mathrm{AUC_n}|_0^\tau$, is given by the relationship

$$\mathrm{AUC_n}|_0^\tau = \int_0^\tau C_n(t)dt = \frac{FD}{Vk} \cdot \{1 - e^{-nk\tau} - nk\tau\, e^{-nk\tau}\}$$

$$= \mathrm{AUC_1}|_0^\infty \cdot \{1 - (1 + nk\tau) \cdot e^{-nk\tau}\}$$

This expression can be rewritten in a form that can be substituted into Eqs. (1)–(3):

$$\mathrm{AUC_1}|_0^\infty = \mathrm{AUC_n}|_0^\tau / \{1 - (1 + nk\tau) \cdot e^{-nk\tau}\} \quad (6)$$

The area under the first moment curve for the nth dosing interval, $\mathrm{AUMC_n}|_0^\tau$, can be expressed in the form

$$\mathrm{AUMC_n}|_0^\tau = \int_0^\tau tC_n(t)dt = \frac{2FD}{Vk^2} \cdot (1-e^{-nk\tau}) - \frac{FD}{Vk \cdot (1-e^{-k\tau})} \cdot [\tau e^{-k\tau} - \tau e^{-k\tau}e^{-nk\tau} + n\tau e^{-nk\tau} \cdot (1-e^{-k\tau})] + \frac{FD}{V \cdot (1-e^{-k\tau})} \cdot (n\tau^2 e^{-k\tau}e^{-nk\tau} - \tau^2 e^{-k\tau} + \tau^2 e^{-k\tau}e^{-nk\tau}) - \frac{FD}{V \cdot (1-e^{-k\tau})^2} \cdot (\tau^2 e^{-2k\tau} - \tau^2 e^{-2k\tau}e^{-nk\tau})$$

This expression can be rewritten in the form

$$\mathrm{AUMC_1}|_0^\infty = \frac{1}{(1-e^{-nk\tau})} \cdot \left\{\mathrm{AUMC_n}|_0^\tau + \tau \cdot \mathrm{AUC_n}|_\tau^\infty + \frac{n\tau e^{-nk\tau}}{[1 - (1 + nk\tau) \cdot e^{-nk\tau}]} \cdot \mathrm{AUC_n}|_0^\tau\right\} \quad (7)$$

where $\mathrm{AUC_n}|_\tau^\infty$ is equal to

$$\mathrm{AUC_n}|_\tau^\infty = \int_\tau^\infty C_n(t)dt = \frac{FD}{Vk} \cdot \frac{(1-e^{-nk\tau}) \cdot e^{-k\tau}}{(1-e^{-k\tau})} \cdot \left\{1 + \frac{k\tau}{(1-e^{-k\tau})}\right\} - \frac{FD}{V} \cdot \frac{n\tau e^{-k\tau}e^{-nk\tau}}{(1-e^{-k\tau})}$$

In the case that n is an intermediate dose and not the last dose of drug, the following equivalent expression can be substituted for $\mathrm{AUC_n}|_\tau^\infty$ in Eq. (7):

$$\mathrm{AUC_n}|_\tau^\infty = \frac{(1-e^{-nk\tau})e^{-k\tau}}{(1-e^{-k\tau}) \cdot [1 - (1 + nk\tau)e^{-nk\tau}]} \cdot \left\{1 + \frac{k\tau}{(1-e^{-k\tau})} - \frac{nk\tau e^{-nk\tau}}{(1-e^{-nk\tau})}\right\} \cdot \mathrm{AUC_n}|_0^\tau$$

Substitution of Eqs. (6) and (7) into Eqs. (1)–(3) allows the calculation of the apparent systemic clearance, mean residence time, and apparent steady-state volume of distribution.

In conclusion, for the special case of a one-compartment model having equal absorption and elimination rate constants, the systemic clearance, mean residence time, and apparent steady-state volume of distribution can be calculated for the first dose and any subsequent dose in a multiple-dose regimen in which a fixed dose of drug is administered at fixed intervals. However, caution must be exercised when using this method, as it is subject to computational errors as previously noted (4,5).

ACKNOWLEDGMENT

The authors thank Jody E. Katz for typing the manuscript.

REFERENCES

1. M. Gibaldi and D. Perrier. *Pharmacokinetics*, 2nd ed., Marcell Dekker, New York, 1982.
2. L. Z. Benet and R. L. Galeazzi. *J. Pharm. Sci.* 68:1071–1974 (1979).
3. D. Perrier and M. Mayersohn. *J. Pharm. Sci.* 71:372–373 (1982).
4. L. A. Bauer and M. Gibaldi. *J. Pharm. Sci.* 72:978–979 (1983).
5. I. L. Smith and J. J. Schentag. *J. Pharm. Sci.* 73:281–282 (1984).
6. M. Chung, *J. Pharm. Sci.* 73:570–571 (1984).
7. F. H. Dost. *Grundlagen der Pharmakokinetik*, Georg Thieme Verlag, Stuttgart, West Germany, 1968.
8. J. H. Oppenheimer, H. L. Schwartz, and M. I. Surks. *J. Clin. Endocrinol. Metab.* 41:319–324 (1975).
9. H. P. Wijnand. *J. Pharmacokin. Biopharm.* 16:109–128 (1988).
10. J. G. Wagner, J. I. Northam, C. D. Alway, and O. S. Carpenter. *Nature (London)* 207:1301–1302 (1965).