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Short Communications

Estimation of pharmacokinetic parameters in extravascular multiple dose administration in the one-compartment open body model with equal absorption and elimination first-order rate constants

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In the special case of the one-compartment open body model with first-order processes, where the absorption and elimination rate constants are equal ($k_a = k_e = k$) the drug concentration in the body (Cb) is characterized by Eqn. 1 (Dost, 1968; Gibaldi and Perrier, 1975a; Bialer 1980):

$$Cb = \frac{FDkte^{-kt}}{V} \tag{1}$$

where Cb is the drug concentration in the body, D is the dose administered, F is the fraction of the dose absorbed, V is the apparant volume of distribution, t is the time and k is the absorption or elimination rate constant.

Eqn. 1 describes the concentration of the drug in the body after a single dose administration. In this case the general Bateman equation (Eqn. 2) (Dost, 1968) is indeterminable and therefore cannot be used to estimate the relevant pharmacokinetic parameters. (Dost, 1968; Gibaldi and Perrier 1975a; Bialer, 1980). Furthermore, because absorption continues throughout the elimination phase, the terminal slope of log Cb vs t plot is not linear and therefore cannot be used to determine a rate constant or the extrapolated Cb^0 (extrapolated drug concentration in the body at time zero). Obviously, the method of residuals (the 'feathering' technique) cannot be used.

$$Cb = \frac{FDka(e^{-ket} - e^{-kat})}{V(ka - ke)} \tag{2}$$

For this special case with repetitive dosing the drug concentration in the body is described by Eqn. 3:

$$Cb(n) = \frac{FDkt(1 - e^{-nk\tau})}{V(1 - e^{-k\tau})} e^{-kt} \tag{3}$$

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where τ is the dosing interval, n is the number of the administered doses and t is any time from o to τ during a dosing interval. Eqn. 3 may therefore be derived by multiplying the exponential term in Eqn. 1 by the multiple dose accumulation factor, similarly to what is done to Eqn. 2 in the general case of extravascular multiple dose administration (Wagner, 1975; Ritschel, 1980). In this special case no simplified methods such as the ones discussed by Doluisio and Dittert (1969) and Ritschel (1975, 1980) are applicable. This is due to the non-linearity of the terminal slope of the log Cb vs t plot.

At steady-state Eqn. 3 will take the following form:

$$Cb^{ss} = \frac{FDkt\, e^{-kt}}{V(1 - e^{-k\tau})} \tag{4}$$

where Cb^{ss} is the drug concentration at steady-state. The maximum drug concentration in the body in multiple dosing at steady-state (Cb^{ss}_{max}) is described by Eqn. 5.

$$Cb^{ss}_{max} = \frac{FDkt_{max}\, e^{-kt_{max}}}{V(1 - e^{-k\tau})} \tag{5}$$

In the case of a single dose administration as described by Eqn. 1, relationships can be derived for the parameters t_{max} (time of peak drug concentration) and Cb_{max} (peak drug concentration) (Dost, 1968; Gibaldi and Perrier, 1975a).

$$t_{max} = \frac{1}{k} \tag{6}$$

$$Cb_{max} = \frac{FD}{Ve} \tag{7}$$

where e = base of natural logarithms.

By defining t in Eqn. 3 as the time elapsed after the administration of the n^{th} dose we made Eqn. 6 applicable to the multiple dose administration case too. Thus, by substituting Eqn. 6 into Eqns. 3, 4 and 5, the pertinent equations which describe the maximum drug concentration in the body in general and at steady-state can be derived (Eqns. 8 and 9).

$$Cb(n)_{max} = \frac{FD(1 - e^{-nk\tau})}{Ve(1 - e^{-k\tau})} = \frac{Cb_{max}(1 - e^{-nk\tau})}{1 - e^{-k\tau}} \tag{8}$$

$$Cb^{ss}_{max} = \frac{FD}{Ve(1 - e^{-k\tau})} = \frac{Cb_{max}}{1 - e^{-k\tau}} \tag{9}$$

The second term in Eqns. 8 and 9 describes the gneral relationship between the peak drug concentration after single dose and multiple dose administrations (Wagner, 1975; Gibaldi and Perrier, 1975b; Ritschel, 1980; Rowland and Tozer, 1980).

The product of t_{max} and Cb^{ss}_{max} in the repetitive dosing case is equal to AUC/ $e(i - e^{-k\tau})$, as is shown in Eqn. 10, similarly to the single dose administration case (Bialer, 1980):

$$t_{max}Cb_{max} = \frac{FD}{kVe(1 - e^{-k\tau})} = \frac{AUC}{e(1 - e^{-k\tau})} = \frac{\overline{Cb}^{ss} \cdot \tau}{e(1 - e^{-k\tau})} \tag{10}$$

where $\overline{Cb}^{ss}$ is the average steady-state drug concentration and AUC is the area under the curve of Cb vs t from $0 \rightarrow \infty$ in the single dose case or Cb^{ss} vs t from $0 \rightarrow \tau$ in the multiple dose case (Wagner, 1975). From Eqn. 10 the relationship between $\overline{Cb}^{ss}$ and Cb^{ss}_{max} can be derived (Eqn. 11).

$$\overline{Cb}^{ss} = \frac{Cb^{ss}_{max}\, e(1 - e^{-k\tau})}{k\tau} \tag{11}$$

The minimum drug concentration Cb^{ss}_{min} in the body at steady-state is attained at $t = \tau$ and thus the concentration (Cb_{min}) is characterized by Eqn. 12 which is a special case of Eqn. 4 where $t = \tau$.

$$Cb^{ss}_{min} = \frac{FDk\tau\, e^{-k\tau}}{V(1 - e^{-k\tau})} \tag{12}$$

The ratio and the relationship between the maximum and the minimum drug concentration in the body in the multiple dosing at steady state and in general is described in equation 13 and 14.

$$\frac{Cb^{ss}_{max}}{Cb^{ss}_{min}} = \frac{\dfrac{FD}{Ve(1 - e^{-k\tau})}}{\dfrac{FDk\tau\, e^{-k\tau}}{V(1 - e^{-k\tau})}} = \frac{1}{e\, k\tau\, e^{-k\tau}} \tag{13}$$

$$Cb^{ss}_{min} = Cb^{ss}_{max}\, e\, k\tau\, e^{-k\tau} = \frac{\overline{Cb}^{ss} k^2\tau^2\, e^{-k\tau}}{1 - e^{-k\tau}} \tag{14}$$

Relationship between the loading dose and maintenace dose in this special case of equal elimination and absorption rate constants is derived in Eqns. 15 and 16:

$$\frac{FD^*kt\, e^{-kt}}{V} = \frac{FDkt\, e^{-kt}}{V(1 - e^{-k\tau})} \tag{15}$$

$$D^* = \frac{D}{1 - e^{-k\tau}} \tag{16}$$

where D* is the loading dose and D is the maintenance dose.

In this case the ratio between the loading dose and the maintenance dose is equal to the same ratio as in i.v. multiple dosing (Wagner, 1975; Gibaldi and Perrier, 1975b; Notari 1980; Rowland and Tozer, 1980).

In summary, equations have been derived which enable estimation of the oscillations in plasma (body) concentrations during a special case of extravascular multiple dosing. These equations (11 and 12) demonstrate a direct relationship between the maximum, minimum and average drug concentrations in the body.

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