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Short Communication

A theoretical justification for the superposition principle

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Westlake (1971) has developed an empirical model-independent superposition principle by which one can predict the multiple-dose plasma levels of a drug as a function of time and dose number, as well as carry out dosage regimen calculations from single-dose plasma level data. The equation obtained from the application of this empirical superposition method to linear systems, and discussions on its suitability have been given by Gibaldi and Perrier (1975) and Wagner (1975). However, a theoretical justification for the method has not been provided.

In this report a theoretical justification for the method is presented, using the two-compartment open model with first-order absorption, distribution and elimination rates. A similar justification can also be applied to any linear system.

The multiple-dosing equation for the model is:

$$C_n(t) = A\left(\frac{1 - e^{-n\alpha\tau}}{1 - e^{-\alpha\tau}}\right)e^{-\alpha t} + L\left(\frac{1 - e^{-nk_a\tau}}{1 - e^{-k_a\tau}}\right)e^{-k_a t} + B\left(\frac{1 - e^{-n\beta\tau}}{1 - e^{-\beta\tau}}\right)e^{-\beta t} \quad (1)$$

where $C_n(t)$ is the drug level in plasma at time t during the nth dosing interval, τ is dosing interval and A, B, L, α, β and k_a are constants. The definitions of these constants can be found in the textbooks (Gibaldi and Perrier, 1975; Wagner, 1975).

When n = 1, Eqn. 1 simplifies to Eqn. 2

$$C_1(t) = A\,e^{-\alpha t} + L\,e^{-k_a t} + B\,e^{-\beta t} \quad (2)$$

in which $C_1(t)$ is the drug concentration at time t following administration of the first dose. It is assumed that:

$$C_n(t) = C_1(t) + x \quad (3)$$

Substituting for $C_n(t)$ and $C_1(t)$ from Eqns. 1 and 2 into Eqn. 3 and subsequent solution for x will result in Eqn. 4.

$$x = A\,e^{-\alpha t}\left[\frac{1 - e^{-(n-1)\alpha\tau}}{1 - e^{-\alpha\tau}}\right]e^{-\alpha\tau} + Le^{-k_a t}\left[\frac{1 - e^{(n-1)k_a\tau}}{1 - e^{-k_a\tau}}\right]e^{-k_a\tau}$$

$$+ B\,e^{-\beta t}\left[\frac{1 - e^{-(n-1)\beta\tau}}{1 - e^{-\beta\tau}}\right]e^{-\beta\tau} \tag{4}$$

Substitution of x from Eqn.4 into Eqn. 3 yields:

$$C_n(t) = C_1(t) + B\,e^{-\beta t}\left[\frac{1 - e^{-(n-1)\beta\tau}}{1 - e^{-\beta\tau}}\right]e^{-\beta\tau}$$

$$+ A\,e^{-\alpha t}\left[\frac{1 - e^{-(n-1)\alpha\tau}}{1 - e^{-\alpha\tau}}\right]e^{-\alpha\tau} + L\,e^{-k_a t}\left[\frac{1 - e^{-(n-1)k_a\tau}}{1 - e^{-k_a\tau}}\right]e^{-k_a\tau} \tag{5}$$

Since, by definition $\alpha > \beta$ and usually $k_a > \beta$, and τ is a time at post-absorptive, post-distributive phase, therefore the values of $e^{-\alpha\tau}$ and $e^{-k_a\tau}$ approach zero. Thus, the values of the third and fourth terms on the right-hand side of Eqn. 5 are negligible and Eqn. 5 reduces to Eqn. 6.

$$C_n(t) = C_1(t) + B\,e^{-\beta t}\left[\frac{1 - e^{-(n-1)\beta\tau}}{1 - e^{-\beta\tau}}\right]e^{-\beta\tau} \tag{6}$$

Eqn. 6 is identical to the one obtained from the application of the empirical superposition principle to the linear systems (Gibaldi and Perrier, 1975; Wagner, 1975).

In the cases where the conditions mentioned above are not met, the value of $C_n(t)$ calculated from Eqn. 6 may not be accurate.

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