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Effect of absorption and elimination rates on the maintenance time of therapeutic drug levels. Derivation of an equation for this time and its applications *

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Comparisons between different formulations of a drug are usually made in terms of bioavailability. There are variations between definitions of bioavailability but broadly speaking all are concerned with comparing the area under the drug plasma concentration–time curve following ingestion of a formulation of the drug with that obtained following ingestion of the drug under standard conditions. Thus, the American Pharmaceutical Association (1972) defines bioavailability as 'a term used to indicate a measurement of both the relative amount of an administered drug that reaches the general circulation and the rate at which this occurs'.

The preferred standard condition is that of an intravenous injection of the same drug dose. In this latter case the comparison is justified by the fact that the areas under the curves represent integrals the ratio of which are equal to the fraction of dose absorbed, F. The ratio of areas is therefore a true measure of bioavailability. However, although such a ratio is a useful commentary on the absorption properties of a drug formulation it may have little to do with the relative therapeutic effect of different formulations. Two formulations of the same drug may display the same areas under the curve, and yet one of them may show a plasma concentration–time curve characterized by a narrow, high peak and the other a low, broad peak. The first formulation may show drug levels above some minimum response level, albeit for a short time, while the second formulation may never reach this level.

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The incorporation of a rate term, as in the definition above, or of the time for occurrence of the peak concentration (Chodos and Disanto, 1973) makes the comparison of formulations more valid from a therapeutic standpoint. However, it still remains a fairly arbitrary indicator of therapeutic effect. The earlier the time of peak concentration the sharper the shape of the plasma concentration–time curve, but what is of real interest is the time at which some minimum effective level of concentration is reached and for how long this minimum level is maintained. The calculation of such times, and the effects of various factors upon them, is discussed below for the case of an open one-compartment system.

For a one-compartment model with first-order absorption of a fraction F of a dose D of a drug, the concentration in the compartment at any given time t is

$$C = \frac{k_a FD}{V(K_{el} - k_a)}(e^{-k_a t} - e^{-K_{el} t}) \tag{1}$$

where V is the apparent volume of distribution, and k_a and K_{el} the first-order rate constants for absorption and elimination, respectively. This equation shows the normal behaviour of such a bi-exponential function: the concentration is zero at time zero, rises to a maximum and thereafter declines. If the concentration ever reaches a therapeutic level C_{ther} then, unless this is the maximum of the curve, it will be reached on both upward and downward limbs of the curve, at times t_1 and t_2.

The first such time can be approximated to by expanding the exponential terms in Eqn. 1 to the first two powers, i.e.

$$C_{ther} = \frac{k_a FD}{V(K_{el} - k_a)}\left[1 - k_a t_1 + \tfrac{1}{2}(k_a t_1)^2 - 1 + K_{el} t_1 - \tfrac{1}{2}(K_{el} t_1)^2\right] \tag{2}$$

and solving for t_1

$$t_1 = \frac{1}{k_a + K_{el}} \pm \frac{1}{k_a + K_{el}} \sqrt{1 - \frac{2C_{ther} \cdot V \cdot (k_a + K_{el})}{k_a \cdot F \cdot D}} \tag{3}$$

It can be seen by inspection that a similar solution will be obtained for t_2 and patently the values for t_1 and t_2 are given by use of the positive and negative roots of Eqn. 3, respectively. The time of maintenance of the therapeutic level is then given by

$$\Delta t = t_2 - t_1 = \frac{2}{k_a + K_{el}} \sqrt{1 - \frac{2C_{ther} \cdot V(k_a + K_{el})}{k_a \cdot F \cdot D}} \tag{4}$$

Expressing k_a in terms of K_{el}, i.e.

$$k_a = nK_{el} \tag{5}$$

then gives

$$\Delta t = \frac{2}{(n+1)K_{el}} \sqrt{1 - \frac{2C_{ther} \cdot V(n+1)}{n \cdot F \cdot D}} \tag{6}$$

For a given drug C_{ther}, V is constant. Provided that there is no capacity-limited elimination, K_{el} is also constant. Possible variables in Eqn. 6 are therefore D, F and n. In all cases therapeutic levels will be reached providing that

$$n \cdot F \cdot D \geqslant 2\, C_{ther} \cdot V(n+1) \tag{7}$$

As the dose D is increased, and assuming that the fraction of drug absorbed and the absorption rate constant are not capacity-affected, the maximum value of Δt is given by

$$\Delta t_{D \to \infty} = \frac{2}{(n+1)K_{el}} \tag{8}$$

This is shown in Fig. 1 for two cases: that of $K_{el} = 0.1\ h^{-1}$ and $K_{el} = 0.3\ h^{-1}$. The value of n assumed is 1, so that the limiting values of Δt are 10 h and 3.33 h, respectively. As would be expected, the shorter the half-life of the drug the smaller the dose required to give a maximum duration of action.

The effect of varying n in Eqn. 6 is more complex than that of varying D. From Eqn. 6, Δt is real providing

$$n \geqslant \frac{2C_{ther} \cdot V}{F \cdot D - 2C_{ther} \cdot V} \tag{9}$$

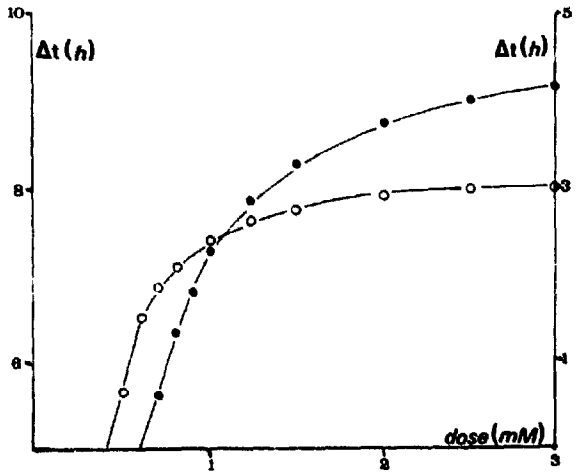

Fig. 1. Limiting effect of dose on duration of therapeutic action (see Eqn. 8). $C_{ther} = 0.01\ \mu M/ml$, V = 12 l, n = 1. ● (left hand ordinate) $K_{el} = 0.1\ h^{-1}$. ○ (right hand ordinate) $K_{el} = 0.3\ h^{-1}$.

and if $F \cdot D$ is constant, this gives a lower limit for useful values of n. An upper limit for n is given by an analogous equation incorporating a toxic concentration level, C_{tox}, i.e.

$$\frac{2C_{tox} \cdot V}{F \cdot D - 2C_{tox} \cdot V} \geqslant n \tag{10}$$

From Eqn. 6, as n increases Δt increases to a maximum value and then declines. This situation is shown in Fig. 2 (curve A). In order to remove any dependence on a

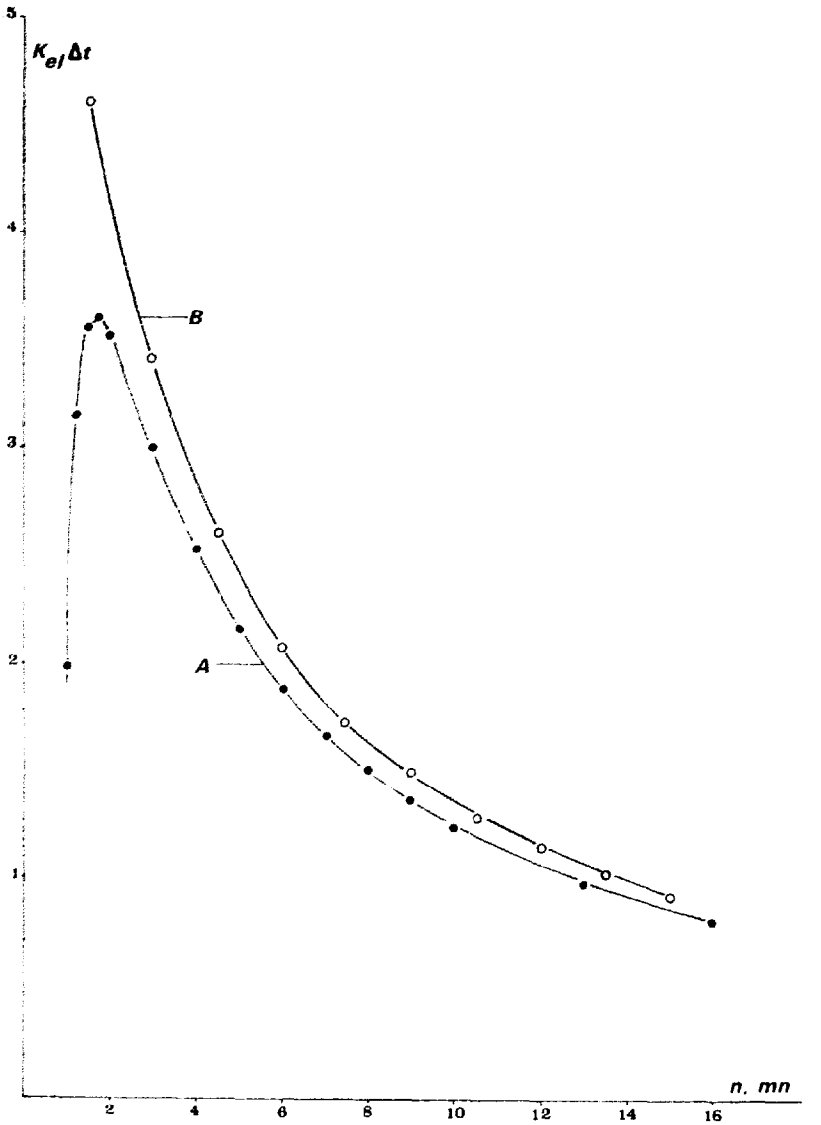

Fig. 2. Effect of increasing absorption rate on the duration of therapeutic effect. Curve A, no change in fractional absorption occurring; curve B, fractional absorption changing as a function of absorption rate. Values of C_{ther}, V as in Fig 1. $F \cdot D$ and d (see text) taken as 0.5 mM ($F = 0.5$, $D = 1$ mM) and 0.24, respectively. The abscissa shows n (curve A) or mn (curve B) where $m = 1.5$.

specific value of K_{el}, time has been replaced by relative time, a dimensionless quantity given by $K_{el} \cdot \Delta t$. It is possible to generalize the result even further by using the dimensionless ratio $C_{ther} \cdot V/F \cdot D$ (= d) instead of the dose D. Fig. 2 shows that the maximum time of therapeutic action is reached at low ratios of absorption to elimination rate constants and that an increase in the absorption rate thereafter leads initially to a rather rapid decline in the time for duration of action.

The value of n giving the maximum time for therapeutic action is obtained by differentiating Eqn. 6 with respect to n and equating to zero. This gives

$$n_{max\,\Delta t} = \frac{3C_{ther} \cdot V + \sqrt{C_{ther} \cdot V \cdot (C_{ther} \cdot V + 4F \cdot D)}}{2(F \cdot D - 2C_{ther} \cdot V)} \tag{11}$$

which can be written more conveniently as

$$n_{max\,\Delta t} = \frac{3d + \sqrt{d(d+4)}}{2(1-2d)} \tag{12}$$

where d is defined above. Results from the use of this expression are shown in Fig. 3. At low doses a high value of the absorption rate constant (large n) is needed to get sufficient drug into the system rapidly enough for the therapeutic concentration to be reached at all. As the dose moves to higher levels the requirement for n to be large no longer holds. Under these conditions, as is the case in Fig. 2, it can be seen that the longest durations of action occur at low ratios of absorption to elimination rate constants.

The fraction of dose absorbed, F, has an effect on the therapeutic maintenance time which, from Eqn. 6, is similar to that of the dose D. However, since F has a maximum value of 1 the effect is limited. For a sparingly soluble drug it has been argued (Macheras and Rosen, 1980) that an m-fold increase in the absorption rate constant modifies the fraction absorbed according to

$$F' = \frac{mF}{(m-1)F + 1}$$

where F′ is the new fractional absorption. Eqn. 6 now becomes

$$\Delta t = \frac{2}{(mn+1)K_{el}} \sqrt{1 - \frac{2C_{ther}V(mn+1)([m-1]F+1)}{m^2 \cdot n \cdot F \cdot D}} \tag{13}$$

The solution of this equation for values of m and n giving the maximum time for duration of action is obviously more complex than that for Eqn. 6. However, it is comparatively simple to calculate values for Δt for given values of the quantities in the rest of Eqn. 13 and this has been done to give curve B in Fig. 2. Here, for the values of C_{ther}, V, F, D and n used in the generation of curve A, a value of m = 1.5 has been taken to form curve B. The abscissa then represents mn. As would be

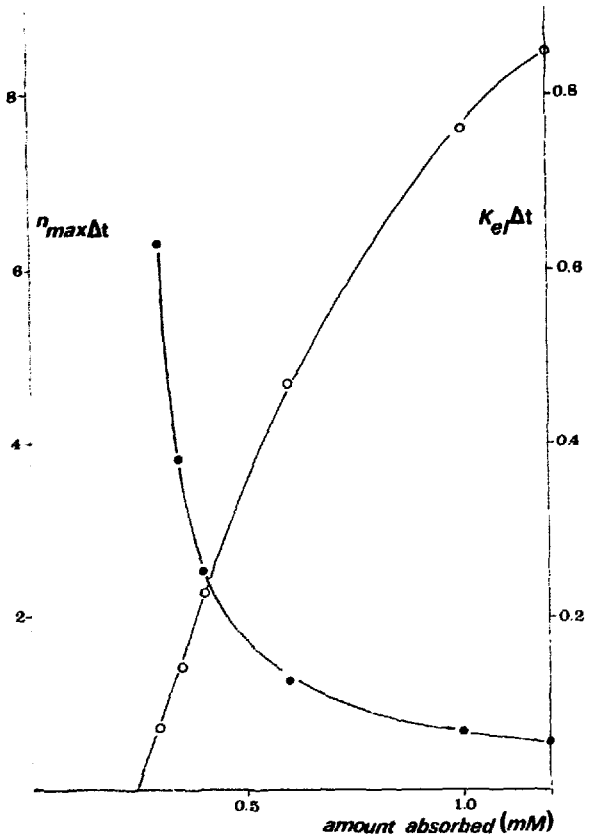

Fig. 3. Values of the ratio of absorption to elimination rate constants giving the maximum duration of action ($n_{max\,\Delta t}$) of a drug as a function of relative drug dose (d), ●. The relative duration of action ($K_{el}\Delta t$) is also shown, ○.

expected, the chief effect of taking the possibility of an increased fractional absorbance into account is to increase the duration of action overall. It should also be noted that such an increase is subject to a much more rapid fall-off as n increases than is the case when the fractional absorption is invariant. A complete analysis would of course involve a three-dimensional graphical display showing the simultaneous effect of changing m and n on Δt.

It is generally accepted that for a protein-bound drug only the free drug is available for therapeutic action. If the free concentration is at the level required for therapeutic effect then this free concentration, C_f, is produced by a total concentration C_T where C_T and C_f are related by the normal hyperbolic binding equation. In considering the duration of action, C_T now replaces C_{ther} in Eqn. 6. The net result of protein binding is therefore to increase the dose needed to produce a given duration of therapeutic effect by a factor of C_T/C_f. Normally the relationship between C_T and C_f is linear, but we have shown previously (Macheras and Rosen, 1980) that doses may be such that an increase in n leads to non-linearity of response. In such circumstances the effect on the maintenance time of therapeutic (or toxic) levels may be pronounced.

Consideration of the duration of action of a drug formulation as outlined above may form a more rational basis for formulation changes than that of availability. The equations obtained for duration of action can be used to find the most efficacious absorption rate and as a guard against reaching toxic levels of drug.

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