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Short Communications

Some considerations concerning the effect of an increased rate of oral absorption on drug levels of protein-bound drugs

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The absorption of an oral formulation of a drug from the gastrointestinal tract is controlled by 3 major steps: the disintegration of the formulation, the dissolution of the active component and the transfer of the dissolved drug across the gut wall. While the disintegration step is subject to a great deal of control on the part of the manufacturer the other two steps are more often related to the nature of the drug. Most usually the actual absorption stage is rate-limiting for the process as a whole, and little can be done to bring about significant alteration in it. In the case of sparingly soluble drugs, the rate of dissolution can become rate-limiting overall. In this case it is often possible to cause meaningful changes in rate by alterations in particle size, choice of excipient etc.

It is well known that if all other factors are kept constant then the effect of increasing absorption rate is to increase the peak blood level achieved and to decrease the time at which it occurs (Kaplan, 1973). However, the actual extents of these changes are less well appreciated, and we have seen no comment on how other factors may influence them. The purpose of the present communication is to show how changes in the absorption rate affect free drug levels in blood when the drug is subject to protein binding.

Consider the simple one-compartment system shown in scheme 1.

$$\begin{matrix}\text{dose D} \\ \text{fraction f absorbed}\end{matrix} \xrightarrow{k_a} \begin{matrix}\text{conc C} \\ \text{vol. V}\end{matrix} \xrightarrow{K} \text{eliminated drug} \qquad \text{(scheme 1)}$$

The concentration C varies with time according to

$$C = \frac{k_a f D}{V(K - k_a)} (e^{-k_a t} - e^{-Kt}) \qquad (1)$$

The peak concentration is reached after a time given by

$$t_{max} = \frac{1}{k_a - K} \ln \frac{k_a}{K} \qquad (2)$$

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and is itself given by

$$C_{max} = \frac{fD}{V} e^{-Kt_{max}} \quad (3)$$

Substituting Eqn. 2 in Eqn. 3 gives

$$C_{max} = \frac{fD}{V} \left(\frac{K}{k_a}\right)^{(K/k_a - K)} \quad (4)$$

which can be written more conveniently as

$$C_{max} = \frac{fD\phi^{(\phi/1-\phi)}}{V} \quad (5)$$

where $\phi = K/k_a$.

Assume initially that the dose is completely absorbed (f = 1) and that the same dose is given in formulations which give rise to different absorption rates. If there is no restriction on the elimination rate (i.e. K is constant for all values of C) then C_{max} can be readily calculated for various values of ϕ. The values of C_{max} so obtained are in terms of D/V and are perhaps best expressed as a percentage of the same dose given intravenously. This is shown in Table 1 (column 2) for values of ϕ encompassing a 10-fold variation in k_a.

It is more usual, in the case of a sparingly soluble drug, that not all the dose is absorbed. If this is the case then the paths leading to non-absorption can be expressed, to a first approximation, by a composite first-order rate constant, k_n. The fraction absorbed

TABLE 1

EFFECT OF INCREASING RATES OF ABSORPTION ON PLASMA LEVELS OF FREE DRUG IN THE PRESENCE OF PROTEIN BINDING AND ASSUMING A CONCENTRATION OF BINDING PROTEIN OF 4.5 g% IN A VOLUME OF DISTRIBUTION OF 3 LITRES

ϕ	Peak concentration of free drug as a % of the maximum total concentration when the same dose is given intravenously					
	No binding		Drug bound with association constant 10^5 l · mol^{-1}			
	f = 1	f = 0.6 *	1 mM dose		2 mM dose	
			f = 1	f = 0.6 *	f = 1	f = 0.6 *
0.5	50.0	30.0	1.00	0.53	1.48	0.64
0.25	63.0	47.2	1.38	0.93	2.44	1.33
0.1	77.4	68.3	1.89	1.55	4.42	3.01
0.05	85.4	80.1	2.22	1.99	6.34	4.98

* Assumed fraction absorbed at lowest absorption rate constant considered.

is then given by

$$f = \frac{k_a}{k_a + k_n} \tag{6}$$

and as k_a increases this fraction also increases if k_n remains constant. An n-fold increase in absorption rate then leads to a new value of the fraction absorbed, f', given by

$$f' = \frac{nf}{(n-1)f + 1} \tag{7}$$

Suppose that under a given set of conditions 60% of a drug dose is absorbed (f = 0.6). If all else remains constant while the absorption rate is doubled, then according to Eqn. 7, 75% of the dose will be absorbed (f' = 0.75); while a 3-fold increase in absorption rate gives f' = 0.82. Therefore an increase in rate of absorption may increase the peak level of the drug both because of the increase vis-a-vis elimination and because it leads to a greater fraction absorbed. In Table 1 the third column shows how the latter effect influences C_{max}. The lowest value of absorption rate constant considered in the table occurs when $\phi = 0.5$, and we have based our calculations on the quite arbitrary value of f = 0.6 for the fraction of dose absorbed at this rate.

Effect of protein binding

It has been suggested that in the case of dicoumarol, binding to plasma protein facilitates the absorption process (Brodie, 1966). In general this is unlikely to be a serious contributor to the absorption rate since the concentration gradient of drug across the gut wall into the blood stream will in any case be high and the difference made to the gradient by association of some of the drug with plasma protein will be of negligible significance.

The total concentration of drug reaching the blood under different conditions of absorption rate will be as outlined above, but the concentration of free drug will be different and the difference will depend on the association constant of the drug, the protein concentration, the volume of distribution and the drug dose. As an example we have calculated the free drug for doses of 1 mM and 2 mM given an association constant of 10^5 l mol^{-1}, a volume of distribution of 3 litres and a protein concentration of 4.5 g%. Values are shown in Table 1 (columns 4–7) for the two cases of complete absorption and absorption with f = 0.6 at the lowest absorption rate.

As can be seen from Table 1, the effect of increasing the absorption rate is much more marked for a protein-bound drug than for a drug which is entirely in the free form.

If all the dose is always completely absorbed the increasing rate causes a 170% increase in peak level if the drug is unbound, and 220% and 430% increases for 1 mM and 2 mM doses respectively, under the conditions stated. These increases are further accentuated if the drug is incompletely absorbed.

Expressed, as in Table 1, as a percentage of the initial total concentration reached by the same drug given intravenously, the values of per cent free drug obtained are independent of the volume of distribution. They do, however, depend on the total amount of protein available for binding. If binding to albumin of interstitial fluid is considered as well as plasma albumin the total albumin available is almost doubled. The increase in free

drug shown in, say, column 5 of Table 1 as ϕ changes from 0.5 to 0.05 is then 335% rather than 375%. Conversely, any tendency towards hypoalbuminaemia causes the increase to be greater than 375%, as will the presence of endogenous or exogenous binding inhibitors.

The outbreak of phenytoin intoxication seen in Australia a decade ago (Tyrer et al., 1970) could have had its origins in the sort of phenomenon outlined above. Patients on phenytoin in a calcium sulphate formulation were changed to the same dose of phenytoin in a lactose formulation, causing signs of intoxication to appear in some instances. Changes in the excipients of phenytoin capsules can cause changes in dissolution rate of 10-fold and more (Bastami and Groves, 1978). Phenytoin is incompletely absorbed, and in the presence of calcium may form an insoiuble complex (Bochner et al., 1972). However, Bochner et al. calculated that only 25% of the dose is affected in this way, whereas the blood levels measured by these authors show a 4-fold increase in total phenytoin between calcium and lactose formulations. It would thus seem more likely that a change in the rate of absorption of phenytoin and a consequent increase in free drug was the cause of the effects noted.

REFERENCES

Bastami, S.M. and Groves, M.J., Some factors influencing the in vitro release of phenytoin from formulations. Int. J. Pharm., 1 (1978) 151–164.

Bochner, F., Hooper, W.D., Tyrer, J.H. and Eadie, M.J., Factors involved in an outbreak of phenytoin intoxication. J. Neurol. Sci., 16 (1972) 481–487.

Brodie, B.B., Pharmacological and clinical implications of drug transport. In P. Desgrez and P.M. De Traverse (Eds.), Transport Function of Plasma Proteins, Elsevier, New York, 1966, pp. 137–145.

Kaplan, S.A., Biopharmaceutics in the preformulation stages of drug development. In J. Swarbrick (Ed.), Dosage Form Design and Bioavailability, Lea and Febiger, Philadelphia, 1973, pp. 1–30.

Tyrer, J.P., Eadie, M.J., Sutherland, J.M. and Hooper, W.D., Outbreak of anticonvulsant intoxication in an Australian city. Br. Med. J., 2 (1970) 271–273.