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Parabolic structure-activity relationships: a simple pharmacokinetic model

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Several models have been proposed for the parabolic relationship that many drugs show between pharmacological response and lipophilicity. Hansch and coworkers (Penniston et al 1969; Hansch & Clayton 1973) have proposed that the parabolic relationship arises from the passive diffusion of the drug through alternating aqueous and lipid phases and produced computer simulations to substantiate this argument. McFarland (1970) also considered a system comprising alternating aqueous and lipid phases and using probability arguments derived a bilinear equation to describe the relationship between pharmacological response and lipophilicity. Kubinyi (1976, 1977) has extended McFarland's work and reported that the bilinear model explains most of the data in the literature better than Hansch's quadratic model.

Since an in vivo biological system is much more complicated than a series of alternating aqueous and lipid phases, these models must be viewed as empirical rather than fundamental. Consequently we will use the term 'parabolic' to describe the situation in which, amongst a group of compounds with varying lipophilicity one compound elicits the largest pharmacological response (per unit dose). The term is not meant to imply quadratic in the sense of Hansch.

All of the approaches that have been proposed so far have as their basis the postulate that pharmacological response is determined by the ability of the drug to reach its receptor site. While this postulate is undoubtedly correct, the contribution of the drug's pharmacokinetics to its concentration at the receptor site has been neglected. Thus all of the proposed models are closed in that the drug accumulates at the receptor site. It was the purpose of the present study to investigate, in the most elementary fashion, the impact of pharmacokinetics on structure-activity relationships.

Closed model

The simplest example of alternating aqueous and lipid phases consists of an aqueous-lipid-aqueous sequence as shown in Fig. 1. The aqueous to lipid rate constant is k_1 and the lipid to aqueous rate constant is k_2. Assuming that the volumes of the three compartments are equal, the rate equations governing the drug concentration in the three compartments are

$$\frac{dC_1}{dt} = -k_1C_1 + k_2C_2 \quad (1)$$

$$\frac{dC_2}{dt} = k_1C_1 - 2k_2C_2 + k_1C_3$$

$$\frac{dC_3}{dt} = k_2C_2 - k_1C_3$$

* Correspondence.

Introducing a reduced time, $\tau = k_2 t$, and dimensionless concentrations, $C_1' = C_1/C_1(0)$, $C_2' = C_2/C_1(0)$ and $C_3' = C_3/C_1(0)$ where $C_1(0)$ is the concentration of drug in compartment 1 at time zero, equations (1) become

$$\frac{dC_1'}{d\tau} = -PC_1' + C_2' \qquad (2)$$

$$\frac{dC_2'}{d\tau} = PC_1' - 2C_2' + PC_3'$$

$$\frac{dC_3'}{d\tau} = C_2' - PC_3'$$

where $P = k_1/k_2$ represents the drug's lipophilicity. If the drug is introduced as a bolus into compartment 1 the solution for C_3', the proposed receptor site, is

$$C_3'(\tau) = \frac{[2 + Pe^{-(P+2)\tau} - (P+2)e^{-P\tau}]}{2(P+2)} \qquad (3)$$

This equation has been extensively studied by Cooper et al (1981) and they found that for any fixed value of τ there is a value of P for which $C_3'(\tau)$ is maximal. The results of these studies are summarized in Fig. 2 which shows the relationship between optimal lipophilicity, P_{opt}, and sampling time, τ. It can be seen that as the sampling time becomes longer the optimal lipophilicity decreases. When the variables are transformed back into their original units it becomes apparent that for each combination of τ and P_{opt} there is an infinite set of values for k_1, k_2 and t which satisfy the relationships $P_{opt} = k_1/k_2$ and $\tau = k_2 t$.

There are two problems associated with this model. Firstly the sampling time is arbitrary and consequently so is the optimal lipophilicity. Secondly, the model is closed in that the ultimate concentration in compartment 3 decreases monotonically as a function of P, viz

$$C_3'(\infty) = \frac{1}{P+2} \qquad (4)$$

If the drug equilibrates with the receptor site in a time much shorter than that required for distribution equilibrium with other tissues and for drug elimination, then the closed model, under the pseudo steady-state hypothesis, is a good representation of the in vivo situation: otherwise it is not.

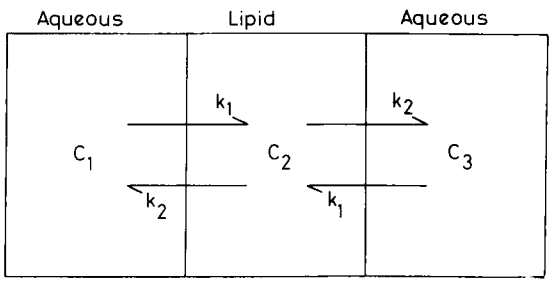

FIG. 1. Three compartment closed model of alternating aqueous-lipid phases.

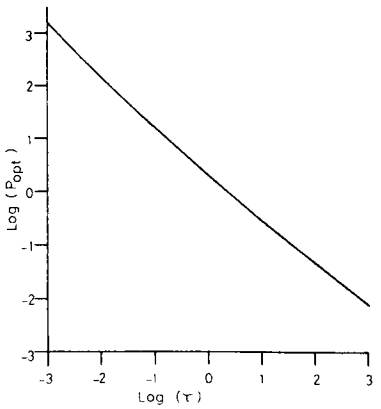

FIG. 2. Optimal lipophilicity, P_{opt}, as a function of sampling time, τ, for a three compartment closed model.

Open model

The previous model can be made open by the inclusion of an exit rate constant, k, from compartment 1 as shown in Fig. 3. Although the model is not mammalian in the sense of usual pharmacokinetic models, it is the simplest open model which shows parabolic behaviour. The equations for this model are

$$\frac{dC_1'}{d\tau} = PC_1' + C'_2 - k'C_1' \qquad (5)$$

$$\frac{dC_2'}{d\tau} = PC_1' - 2C_2' + PC_3'$$

$$\frac{dC_3'}{d\tau} = C_2' - PC_3'$$

where $k' = k/k_2$. The solution for C_3 is

$$C_3' = P\left[\frac{e^{\lambda_1\tau}}{(\lambda_1-\lambda_2)(\lambda_1-\lambda_3)} + \frac{e^{\lambda_2\tau}}{(\lambda_2-\lambda_1)(\lambda_2-\lambda_3)} + \frac{e^{\lambda_3\tau}}{(\lambda_3-\lambda_1)(\lambda_3-\lambda_2)}\right] \qquad (6)$$

Where λ_i are the roots of the cubic equation

$$\lambda^3 + (2P + k' + 2)\lambda^2 + (P^2 + 2P + k'P + 2k')\lambda + k'P = O \qquad (7)$$

Simulations using equation (6) for $k' = 1$ and various values of P demonstrate that there is an optimal value for P for which the peak concentration is maximal (see Fig. 4). If the peak concentration is equated to peak response this means that there is a parabolic relationship between response and lipophilicity.

Further simulations confirmed this finding. The effect of lipophilicity on peak concentration in compartment

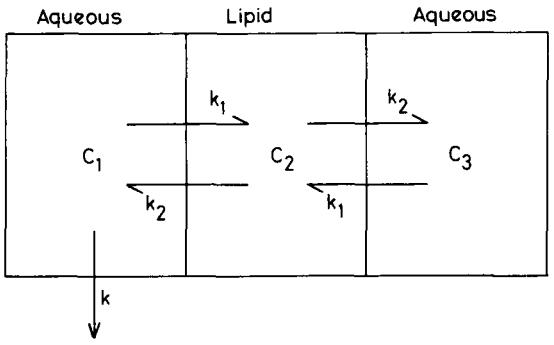

FIG. 3. Three compartment open model.

3, for several values of k′, is shown in Fig. 5. The bilinear nature of the curves is evident. It can be seen that as k increases the optimal lipophilicity also increases at the expense of the peak concentration, which decreases. This behaviour is summarized in Fig. 6. As with the closed model there is an infinite set of values of the variables k_1, k_2 and k, satisfying the relationships $P_{opt} = k_1/k_2$ and $k' = k/k_2$, corresponding to any given combination of k′ and P_{opt}.

Discussion

Two variations of the open model were studied. Firstly elimination from compartment 3 was considered and secondly a restraint was placed on the rate constants, k_1 and k_2. There is some evidence (Lippold & Schneider 1975; Van de Waterbeemd et al 1980) that, far from increasing to infinity, these rate constants reach limiting values. One possible explanation is that, when the rate of transfer between the two phases becomes so rapid, the rate limiting step becomes not the transfer, but diffusion to the interface. Consequently we tried imposing the following restrictions on the rate constants (similar constraints were used by Van de Waterbeemd et al 1980)

$$k_1 = \frac{a\,P}{b+P} \qquad (8)$$

$$k_2 = \frac{a}{b+P}$$

where a and b are constants. These two variations on the basic model produced quantitative changes but the parabolic behaviour was still retained. Unlike previously, when the constraints of equation (8) are applied, to each combination of k′ and P_{opt} there corresponds only one set of values for the variables k_1, k_2 and k.

It was not the purpose of the present study to produce

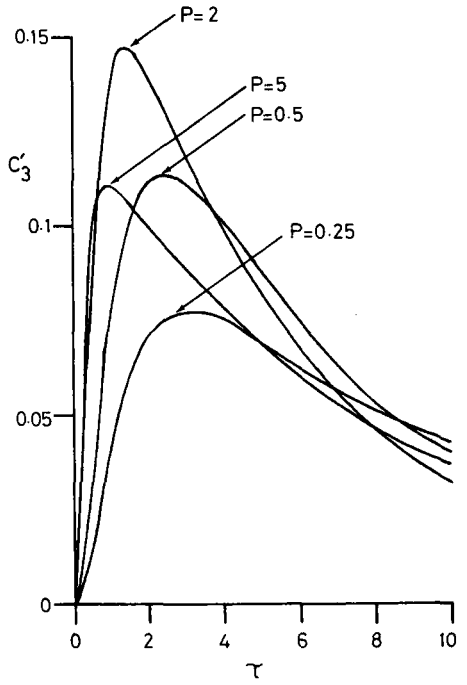

FIG. 4. Effect of lipophilicity, P, on the concentration (C_3)-time (τ) profile in compartment 3 of a three-compartment open model. The elimination rate constant, k′, is equal to 1.

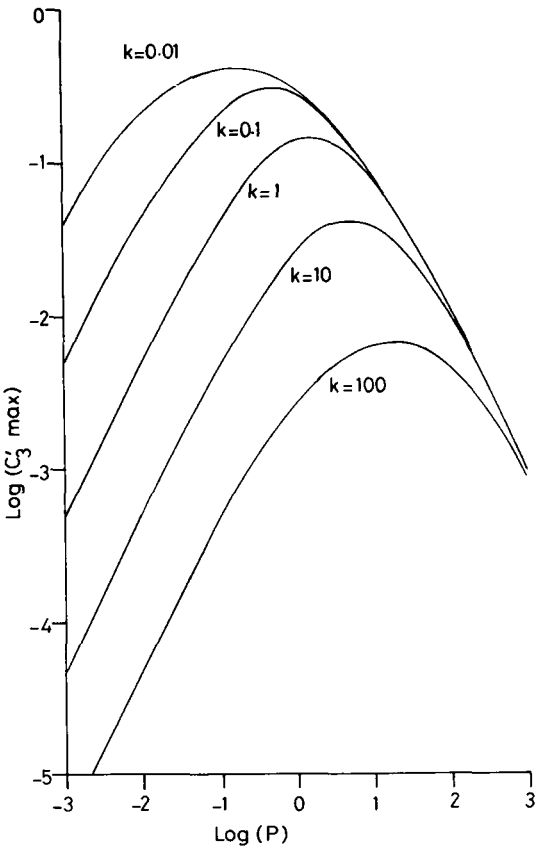

FIG. 5. Effect of lipophilicity, P, on peak concentration in compartment 3 (C_3' max) of a three-compartment open model as a function of elimination rate constant, k′.

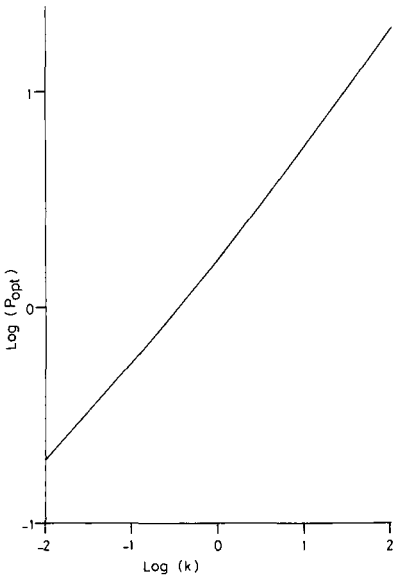

FIG. 6. Optimal lipophilicity, P_{opt}, as a function of elimination rate constant, k′, for a three-compartment open model.

a definitive model which would relate molecular structure to pharmacological activity. Instead we raise several issues which, we feel, have been treated inadequately. The validity of the model herein described and that of previous models is not established by the fact that they predict parabolic structure-activity relationships. In order to define a structurally valid in vivo model detailed pharmacokinetic experiments are needed: preferably on a homologous group of compounds. From the results of these experiments it would be possible to define the effect of structure, perhaps in the guise of a parameter such as lipophilicity, on fundamental pharmacokinetic parameters such as clearance and volume of distribution. However it would then be necessary to separate the effect of structure on a drug's pharmacokinetics and its pharmacological response. Pharmacological activity is related to the drug concentration at the receptor site whereas most pharmacokinetic studies are restricted to measurements of drug concentration in blood or plasma. Consequently it is often difficult to relate the pharmacokinetics of a drug to its pharmacodynamics. In the simplest situation pharmacological response is directly related to blood or plasma concentration. However, if the receptor site is in a tissue which does not rapidly equilibrate with blood it may not be possible to separate structural effects associated with pharmacokinetics from those associated with pharmacological response.

At the present time detailed experiments such as those described above do not exist. Consequently we have not elaborated on the simple model discussed in this paper but we believe it to be a more realistic representation of the in vivo situation than previously described closed models.

Since the paper was submitted a comprehensive review of the existing literature on structure-pharmacokinetic relationships has appeared (Seydel & Schaper 1982).

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