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Percutaneous absorption: multidose pharmacokinetics

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Summary

A linear pharmacokinetic model has been derived previously to analyze percutaneous absorption data. The model, which contains four first-order rate constants, has been extended to assess the effects of repeated topical dosing. It has been shown in previously published data that the amount of hydrocortisone excreted is dependent on the dosage regimen adopted. The model successfully describes the excretion pattern of hydrocortisone over a two-week period in which the drug was applied daily. Good correlation has also been established for the percutaneous penetration of malathion following repeated dosing. The patterns of the excretion profile for these two substances are different due to the difference in their physicochemical properties. These properties are reflected in the four first-order rate constants in the pharmacokinetic model.

Introduction

In a previous publication (Guy et al., 1982) we have presented a pharmacokinetic model in which the urinary excretion data of 3 compounds, hydrocortisone, testosterone and benzoic acid, were predicted and compared with existing published data. The correlation between the in vivo data and the predicted profile was good. The model employed a linear pharmacokinetic analysis with four first-order rate

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constants, as depicted in Fig. 1. The four rate constants may be ascribed to the physicochemical parameters of the penetrant molecule and accepted properties of the stratum corneum and viable epidermis.

The model presented previously describes the absorption and distribution of a single application of the drug. Clinically it would be more desirable to be able to predict the absorption of drugs after multidosing and in this paper we have addressed this problem using our pharmacokinetic model. In order to test the validity of our approach we have compared our theoretical model with in vivo data for hydrocortisone (Wester et al., 1980) and malathion (Wester et al., 1983).

Little systematic data is available on the effects of the chronic administration of topical drugs. However, in the case of both hydrocortisone (Wester et al., 1980) and salicylic acid (Roberts and Horlock, 1978), there was an increase in the amount of drug absorbed with repeated daily skin application. In the past this increase has been attributed to changes in the barrier function of the skin. We show in this paper that increased absorption as a function of time may be, in part, attributable to the physicochemical properties of the penetrant.

Theory

The pharmacokinetic scheme depicted in Fig. 1 has been described in detail (Guy et al., 1982) and the solution for the fourth (urine) compartment is given by:

$$\phi_t = Fk_1k_2k_4\left\{1/k_1\alpha\beta - \frac{e^{-k_1t}}{k_1(k_1-\alpha)(k_1-\beta)} - \frac{e^{-\alpha t}}{\alpha(\alpha-\beta)(\alpha-k_1)} - \frac{e^{-\beta t}}{\beta(\beta-k_1)(\beta-\alpha)}\right\} \quad (1)$$

where ϕ_t is the ratio of the amount of drug that has reached the urine at time t to the

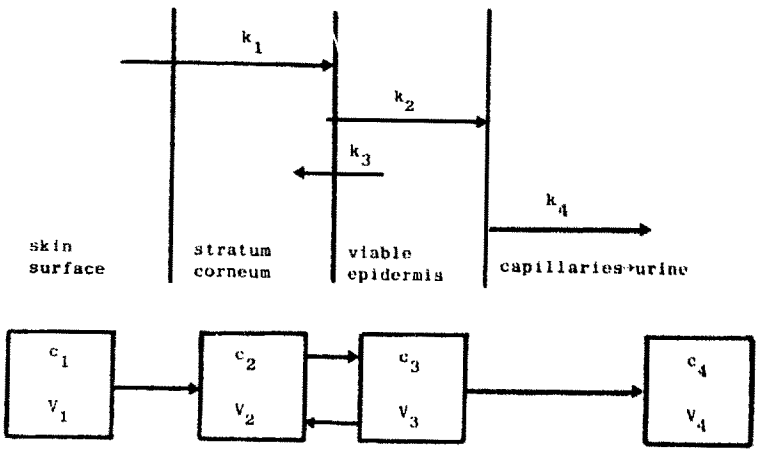

Fig. 1. Schematic representation of the pharmacokinetic model.

amount in compartment 1 at $t = 0$. F is the fraction of the applied topical dose plus metabolites recovered in the fourth compartment, α and β are the roots of the quadratic equation

$$s^2 + (k_2 + k_3 + k_4)s + k_2k_4 = 0$$

and k_1 through k_4 are the first-order rate constants depicted in Fig. 1.

It is possible to calculate the cumulative amounts of drug appearing in the urine following multidosing by summation of eq. 1. For example, if a labelled drug is applied at time $t = 0$ the fractional amount of drug appearing in day 1 will be ϕ_1^* where the superscript denotes the drug is labelled and the subscript is the time period, i.e. ϕ_1^* is calculated using Eq. 1 with $t = 24$ h. If unlabelled drug is applied at the same dose at the end of day 1, on day 2, the fractional amount of this second dose appearing in the urine is ϕ_2^c (where c indicates that the drug is unlabelled). Furthermore, labelled drug applied on day 1 will continue to be excreted on day 2 and subsequent days. The amount of this dose excreted on day 2 may be represented as $\phi_2^* - \phi_1^*$. The total drug excreted in the second 24-h period is thus $\phi_2^c + (\phi_2^* - \phi_1^*)$. It is thus possible to assess the level of drug excretion at different times and to express the fraction of the labelled drug excreted in any time period during a dosing regimen.

Results and Discussion

In vivo multiple dosing data for two compounds, malathion and hydrocortisone, have been obtained (Wester et al., 1980, 1983). Malathion is a compound which is known to penetrate the stratum corneum rapidly and we would thus expect a fairly fast value for k_1, the rate constant which describes diffusion through the stratum corneum. We have estimated that k_1 should be comparable to that for benzoic acid given in our previous publication (Guy et al., 1982) and a value of 5×10^{-5} s^{-1} has been ascribed to k_1. k_2 reflects the diffusion of malathion through the viable epidermis and a value of 5×10^{-4} s^{-1} has been taken to be representative. This value has been estimated by considering the values given by Guy et al. (1982) and by taking into account the relative molecular size of the diffusants.

Again k_3 is estimated from the value for benzoic acid. Both compounds are known not to form reservoirs in the skin and a value of 5×10^{-6} s^{-1} has been taken as typical for this type of compound. k_4, the elimination rate constant, has been measured in vivo (Feldmann and Maibach, 1974) and a value of 6×10^{-5} s^{-1} is representative.

With a knowledge of these rate constants and an F value of 0.04 (Wester et al., 1983), it is possible to calculate the cumulative fraction of a radiolabelled dose which appears in the urine following topical administration. The fractions eliminated over a 14-day period are shown in Fig. 2. In this representation, radiolabelled malathion was given on day 0 and day 7. At each intervening 24-h period 'cold' malathion was administered. The profiles show that, for this compound, the radiolabelled dose is

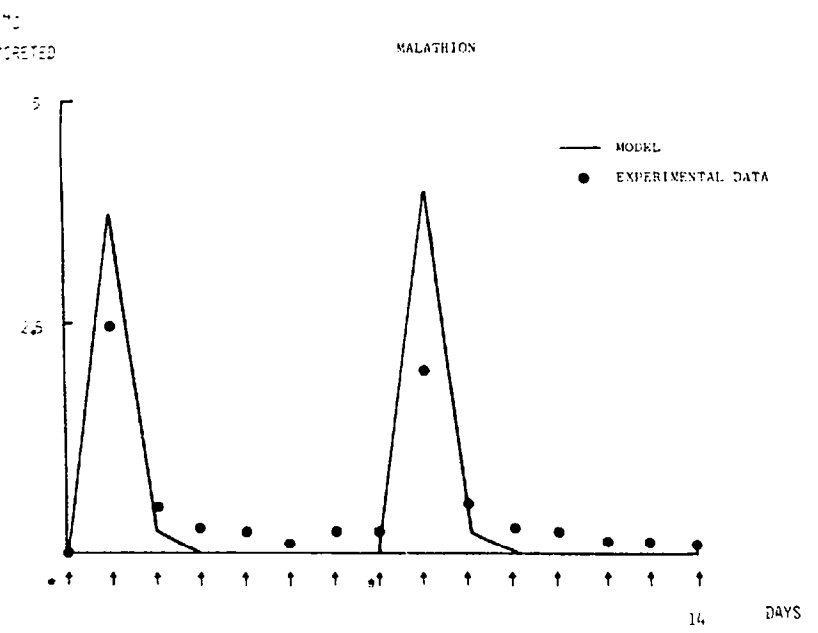

Fig. 2. Percutaneous absorption of [^{14}C]malathion. ↑ represents malathion application and *↑ represents [^{14}C]malathion application. ● represents experimental points from Wester et al. (1983). The solid line is the theoretical curve predicted by the pharmacokinetic model.

absorbed rapidly and also eliminated rapidly. By day 2 only a small fraction of the radiolabelled dose is excreted. Fig. 2 also shows in vivo data produced by Wester et al. (1983). There is very good agreement between the theoretical levels predicted by the pharmacokinetic model and the in vivo results. The major difference is the small amount of malathion appearing in the urine, in vivo, on days 3–7 and 10–14 which is not predicted. This may be attributable to reversible binding of the malathion which is not accounted for in the mathematical model. Allowance for this could be made but would complicate the model considerably. In view of the small fraction of material involved such a complication would not be justified.

Contrasting results are found when multiple topical administration of hydrocortisone is considered. The required parameters for this compound have been previously discussed (Guy et al., 1982): $k_1 = 6.02 \times 10^{-6}\ s^{-1}$; $k_2 = 4 \times 10^{-4}\ s^{-1}$; $k_3 = 5 \times 10^{-5}\ s^{-1}$; $k_4 = 4.38 \times 10^{-5}\ s^{-1}$; $F = 0.02$.

Using these rate constants the time course for urinary excretion may be predicted and is given in Fig. 3. In vivo data obtained by Wester et al. (1980) are also shown in Fig. 3. Agreement between the theoretical predictions and the in vivo data are again good. However, in Fig. 3 it is seen that the profiles following day 0 administration and day 7 administration are different. The peak levels of radioactivity are a factor of 3 different and the subsequent decays following the peaks are also different.

The difference in behaviour compared to malathion may be attributed to the different physicochemical characteristics of the two compounds. Malathion has a fast absorption and elimination rate constant but more significantly the ratio k_3/k_2 is an order of magnitude smaller than hydrocortisone. This ratio reflects the relative

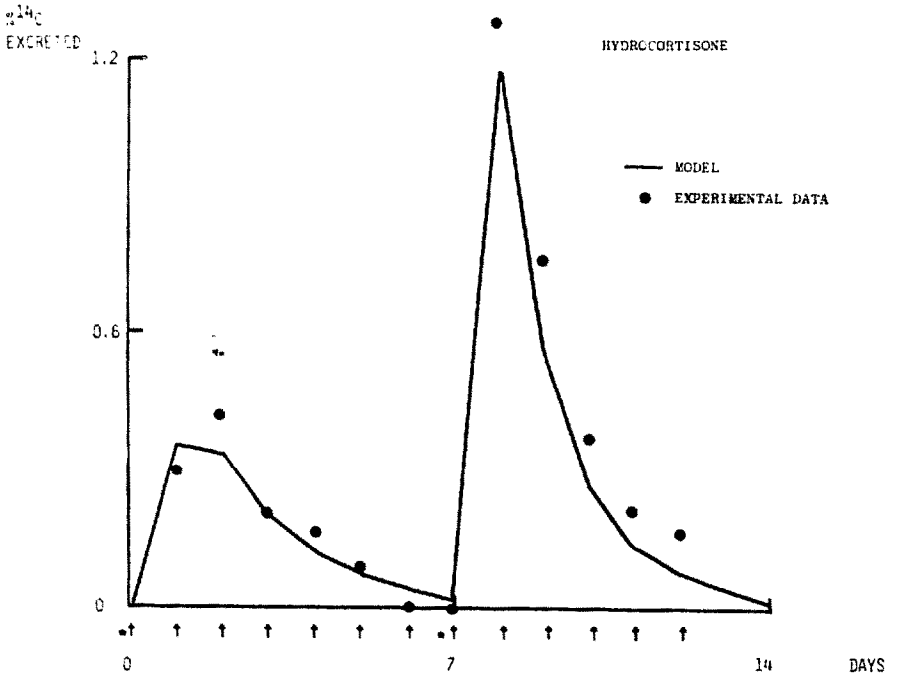

Fig. 3. Percutaneous absorption of [^{14}C]-hydrocortisone. ↑ represents hydrocortisone application and *↑ represents [^{14}C]hydrocortisone application. ● represents experimental points from Wester et al. (1980). The solid line is the theoretical curve predicted by the pharmacokinetic model.

affinity of the drug for the stratum corneum compared with the viable epidermis. For compounds which form reservoirs in the skin this value would be expected to be large and in these cases transport out of the stratum corneum is hindered.

Alternatively, the difference in profiles may be described in terms of a relative binding capacity of the drug for components of the skin. In the case of hydrocortisone, binding sites have to be filled and it is the filling of these, reflected by the large k_3 value, which reduces the radioactivity peak on day 1. By day 7 all the sites have been filled, i.e. steady-state conditions prevail, and the peak level is much higher.

These predictions have significance clinically in the optimization of dosage regimens. By considering the physicochemical properties of the diffusant it is possible to predict the time course of absorption following post-topical administration after multidosing. In certain circumstances it may prove therapeutically more desirable to administer high concentrations of drug early in treatment followed by a lower dosage preparation. It may also be possible, using this type of analysis, to minimize side-effects following long-term therapy by optimizing and modulating the dosing. Future developments in topical administration will undoubtedly encompass the use of more potent drugs for which a pharmacokinetic analysis based on fundamental physicochemical principles will be useful both pharmaceutically and toxicologically.

Acknowledgements

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