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A pharmacokinetic model for percutaneous absorption

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Summary

A linear pharmacokinetic model for percutaneous absorption has been derived. Following topical application, the amount of drug excreted as a function of time is found to depend upon 4 first-order kinetic processes; the physical significance of the rate constants is discussed and their interpretation proposed. The model, applied to previously published data, successfully describes the pattern of behaviour observed for the 3 drugs: testosterone, benzoic acid and hydrocortisone. It is believed that the pharmacokinetic scheme presented is both straightforward in concept and sufficiently sophisticated in design to possibly prove of general applicability for understanding the percutaneous absorption and subsequent fate of a variety of drugs.

Introduction

The percutaneous absorption of a drug from a topically applied vehicle is a complex process. The physicochemical characteristics of the drug and the vehicle and the physiological condition of the skin are many-faceted variables that can significantly affect the penetration and subsequent fate of the chemical agent.

In defining percutaneous absorption, we must include transfer of the drug from the vehicle to the skin, diffusive penetration through the various layers of the integument into the dermis and subsequent removal via the cutaneous vasculature (e.g. Riegelman, 1974). At this point the degree of complexity that may be intro-

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duced into a model for the process must be decided. Most simplistically, first-order rate constants may be assigned to the 3 steps but this immediately introduces several questionable assumptions: for example, (i) that first-order kinetics are appropriate for this situation; (ii) that the different layers of the skin comprise a single diffusional barrier such that drug transport across this region can be adequately described by one rate constant; (iii) that cutaneous metabolism (Wester and Noonan, 1981) can be ignored; and (iv) that there is no formation of an epidermal reservoir of the drug (McKenzie and Stoughton, 1962; Stoughton, 1965; Vickers, 1963; Winkelmann, 1963). Furthermore, if, as is often the case, skin penetration is assessed from measurement of drug levels in the urine, then other pharmacokinetic processes, not confined to the region of skin to which the drug is applied, must be considered.

A model, which could include all these and other variables not mentioned above, would be extremely complex and would find no data of sufficient accuracy to justify its use. In tackling the problem, therefore, we must decide which processes we believe limit the rate and extent of drug absorption from topical applications and focus our attention thereupon. The recent literature has various examples of this type of approach that are either purely theoretical or that combine experimental observations with mathematical interpretation. In the former category, Fox et al. (1979), Hadgraft (1980) and Guy and Hadgraft (1982) have considered simultaneous diffusion and metabolism through the epidermis, and Hadgraft (1979) has proposed a description of the epidermal reservoir. In the latter class, recent illustrations include that of Yu et al. (1979a, b), who proposed a physical model evaluation of the transport and bioconversion of a topical pro-drug, a study with methotrexate by Wallace and Barnett (1978), and the work of Naito and Tsai (1981) on the pharmacokinetics of indomethacin percutaneous absorption from ointment bases.

We present a novel pharmacokinetic model for percutaneous absorption and show that the interpretation may be applied to and is consistent with previously published experimental data (Anjo et al., 1980). The penetration charactersitics are described by 4 first-order rate constants and, while this approach considerably simplifies the mathematics involved, we demonstrate the physical significance of the kinetic processes by relating the parameters to known physicochemical constants and accepted skin properties.

Model

The pharmacokinetic model is schematically illustrated in Fig. 1; both a classical compartmental representation and a scheme designed to indicate the physical significance of the 4 contributory first-order rate constants are shown.

We designate the fourth compartment to represent drug in the urine. The kinetic constant k_4 therefore describes the removal process of drug once it has penetrated to the dermal vasculature. No attempt is made to differentiate between drug in the cutaneous capillaries and drug in the general circulation. Such a refinement introduces complications not justified by the precision with which experimental data may be obtained. In this model, therefore, k_4 is identical to the elimination rate constant

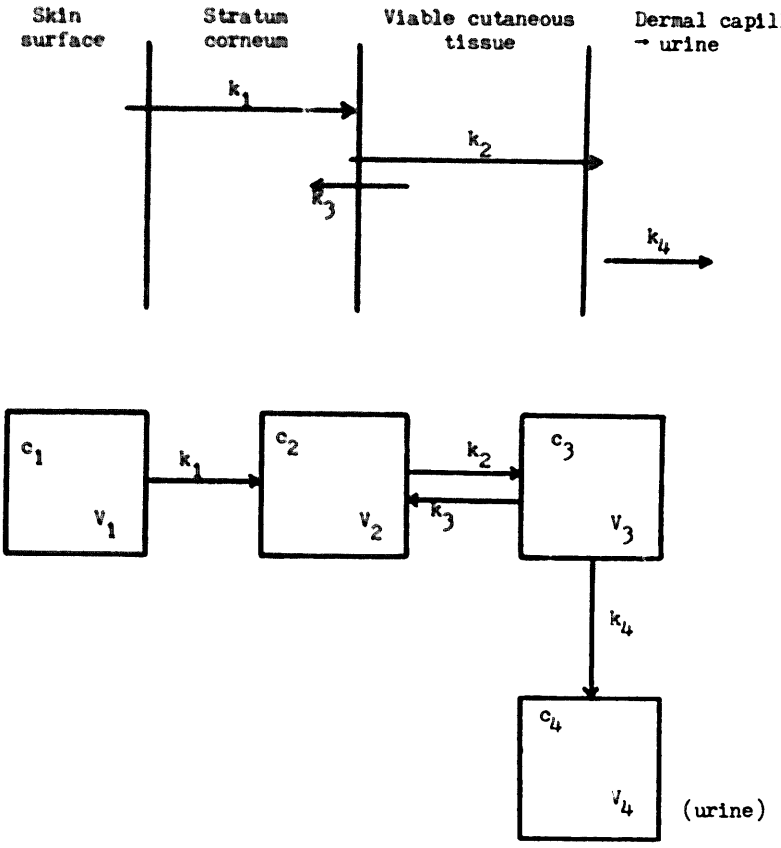

Fig. 1. Diagrammatic representation of the pharmacokinetic model.

determined, for example, following intravenous administration of the compound.

The absorption phase of the drug is characterized by k_1. In this description, we consider that the value of k_1, is limited by the diffusion of drug across the stratum corneum and hence k_1 reflects the rate of this process. It follows that a numerical estimate for k_1 will be given by the ratio D_s/h_s^2 were D_s is the drug diffusion coefficient in the stratum corneum of thickness h_s. Experimentally we may expect to estimate k_1 from either: (i) in vitro permeation studies using isolated stratum corneum; or (ii) the disappearance of radioactivity from the skin surface following topical application of labelled drug.

The rate constant k_2 represents movement of drug further into the skin following penetration of the stratum corneum. It describes, therefore, diffusion through the more aqueous in nature viable epidermal and upper dermal tissue. Thus, as for k_1, we may relate k_2 to a diffusion coefficient (D_{vt}) divided by a diffusion path length squared (h_{vt}^2). Because of the inherent skin structure, we can be confident that D_{vt} will exceed D_s in magnitude. It has been suggested that D_{vt} may be approximated by the corresponding solute diffusion coefficient in an aqueous protein gel (Scheuplein, 1967) and hence we should be able to propose reasonable values for k_2.

The significance of the kinetic process described by k_3 is perhaps the least obvious. However, as will become apparent, the role of this rate constant in determining the final pharmacokinetic profile is crucial. Essentially, it is this parameter which reflects the competition for the drug between the hydrophobic stratum corneum and the hydrophilic viable tissue; for a drug that binds tightly to the stratum corneum components or that has a high oil/water partition coefficient, for example, k_3 will be large. It can be seen, therefore, that k_3 is able to account for an epidermal reservoir effect (e.g. Vickers, 1963): the greater the value of k_3 the longer will be the period for which the drug is effectively held up at the stratum corneum-viable tissue interface.

Hence, the 4 rate constants in this model essentially relate to processes taking place at the local skin site to which the drug is applied. This approach is different to that recently adopted by Naito and Tsai (1981) to interpret the percutaneous absorption of indomethacin. However, if the excretion of drug can be shown to be rate-limited by processes occurring within the skin, then the assumptions, which we make in developing the model, are sound. We believe that the results presented below provide much justification for our hypotheses.

Theory

The mathematical derivation required to obtain an expression for the amount of drug excreted in the urine as a function of time is straightforward. Despite the fundamental differences in interpretation between our approach and that of Naito and Tsai (1981), the compartmental nature of the problem produces similar differential equations and solutions that, not unexpectedly, are sums of exponentials.

Using the notation of the compartmental representation in Fig. 1, 4 rate equations can be written:

$$\frac{dc_1}{dt} = -k_1 c_1 \tag{1}$$

$$\frac{dc_2}{dt} = \frac{V_1}{V_2} k_1 c_1 - k_2 c_2 + \frac{V_3}{V_2} k_3 c_3 \tag{2}$$

$$\frac{dc_3}{dt} = \frac{V_2}{V_3} k_2 c_2 - (k_3 + k_4) c_3 \tag{3}$$

$$\frac{dc_4}{dt} = \frac{V_3}{V_4} k_4 c_3 \tag{3}$$

where V_i and c_i are, respectively, the volume of and the drug concentration in compartment i.

To simplify the algebra involved in manipulating these equations to obtain c_4 (i.e. to evaluate the amount of drug in the urine at time t), we first normalize all

concentrations with respect to c_0 the concentration in compartment 1 at $t = 0$. In other words, we define

$$u_i = c_i/c_0 \quad (i = 1, 2, 3, 4) \tag{5}$$

We then solve the equations using the technique of Laplace transformation. Substituting Eqn. 5 into Eqns. 1–4 and taking the Laplace transforms gives the following set of simultaneous equations:

$$s\bar{u}_1 - 1 = -k_1\bar{u}_1 \tag{6}$$

$$s\bar{u}_2 = \frac{V_1}{V_2}k_1\bar{u}_1 - k_2\bar{u}_2 + \frac{V_3}{V_2}k_3\bar{u}_3 \tag{7}$$

$$s\bar{u}_3 = \frac{V_2}{V_3}k_2\bar{u}_2 - (k_3 + k_4)\bar{u}_3 \tag{8}$$

$$s\bar{u}_4 = \frac{V_3}{V_4}k_4\bar{u}_3 \tag{9}$$

By repeated substitution and rearrangement of Eqns. 6–9, $\bar{u}_1$, $\bar{u}_2$ and $\bar{u}_3$ may be eliminated to produce an expression for u_4

$$V_4u_4/V_1 = F\mathcal{L}^{-1}\{k_1k_2k_4/[s(s + k_1)(s + \alpha)(s + \beta)]\} \tag{10}$$

where α and β are the roots of the quadratic

$$s^2 + (k_2 + k_3 + k_4)s + k_2k_4 \tag{11}$$

(and thus $\beta\alpha = k_2k_4$) and F is the fraction of the applied topical dose and metabolites recovered in compartment 4.

The left-hand side of Eqn. 10 represents the ratio (ϕ_t) of the amount of drug that has reached the urine at time t to the amount in compartment 1 at $t = 0$. Inversion of Eqn. 10 is simple and gives

$$\phi_t = Fk_1k_2k_4\left\{1/k_1\alpha\beta - \frac{e^{-k_1t}}{k_1(k_1 - \alpha)(k_1 - \beta)} - \frac{e^{-\alpha t}}{\alpha(\alpha - \beta)(\alpha - k_1)} - \frac{e^{-\beta t}}{\beta(\beta - k_1)(\beta - \alpha)}\right\} \tag{12}$$

which correctly predicts that at infinite time ϕ_t equals F.

Results and Discussion

When the clearance of a drug from the general circulation is by relatively rapid and complete renal excretion, in vivo percutaneous absorption may be measured by quantitation of the penetrant and its metabolites in the urine. In this case, the processes controlling the appearance of drug in the excretion compartment are those occurring at and within the skin site of application and the approach of our new model is appropriate. Anjo et al. (1980) have reported data for 3 drugs that satisfy the above criteria and we now apply the pharmacokinetic model developed in the preceding section to their published results.

The 3 compounds are testosterone, benzoic acid and hydrocortisone which were studied precisely in one subject and demonstrate a reasonable range of penetrability characteristics. The labelled compounds were topically applied in acetone and excretion rates as a function of time were determined by radioactive assay of the urine. In this study, the same measurements were made following parenteral administration of the same dose and thus we have direct access to k_4 values. Furthermore, for the percutaneous absorption experiments, surface disappearence of radioactivity was also followed enabling the rate constants k_1 to be fixed. Percentage recoveries of the initial topical doses were found for testosterone and benzoic acid; for hydrocortisone, we have estimated F to be 0.02, which is in good agreement with literature data (e.g. Feldman and Maibach, 1969).

Presentation of the percutaneous penetration results is generally given in the form of a plot of % dose excreted per hour versus time. By a simple manipulation of Eqn. 12 and input of appropriate values for the rate constants and F, we are able to generate characteristic curves. As stated above, the experimental work provides k_1, k_4 and F for each compound. The applicability of the pharmacokinetic model therefore depends upon our ability to locate values for k_2 and k_3 such that we can; (i) fit the data; and (ii) rationalize the relative magnitude of the kinetic constants in terms of the known properties of the drugs and in terms of the physical interpretations that we have assigned the various processes.

In Figs. 2, 3 and 4, for testosterone, benzoic acid and hydrocortisone, respectively, we compare the reported experimental data with predictions based upon our new model. The parameters, with which the theoretical curves are calculated, are presented in Table 1. Firstly, we see that the fit of the model to the experimental results is reasonably good, particularly for testosterone. No attempt has been made to use an iterative computing technique to find the 'best' k_2 and k_3 values, though such a procedure could become routine if the model were to be used regularly for data analysis. We note that for testosterone we are able to find close correlation between the model and the data. For benzoic acid, the experimental data is more scattered; however, it may be seen that the new model is consistent with the observations over the time period considered. Hydrocortisone involves problems in experimentation because of the very low percentage of the dose absorbed. It is not surprising that in this case the fit is least impressive particularly for the earlier times when a very low % dose excreted per hour is being measured; further, although we have chosen $F = 0.02$ (which is an acceptable literature value), for this set of data we do not know

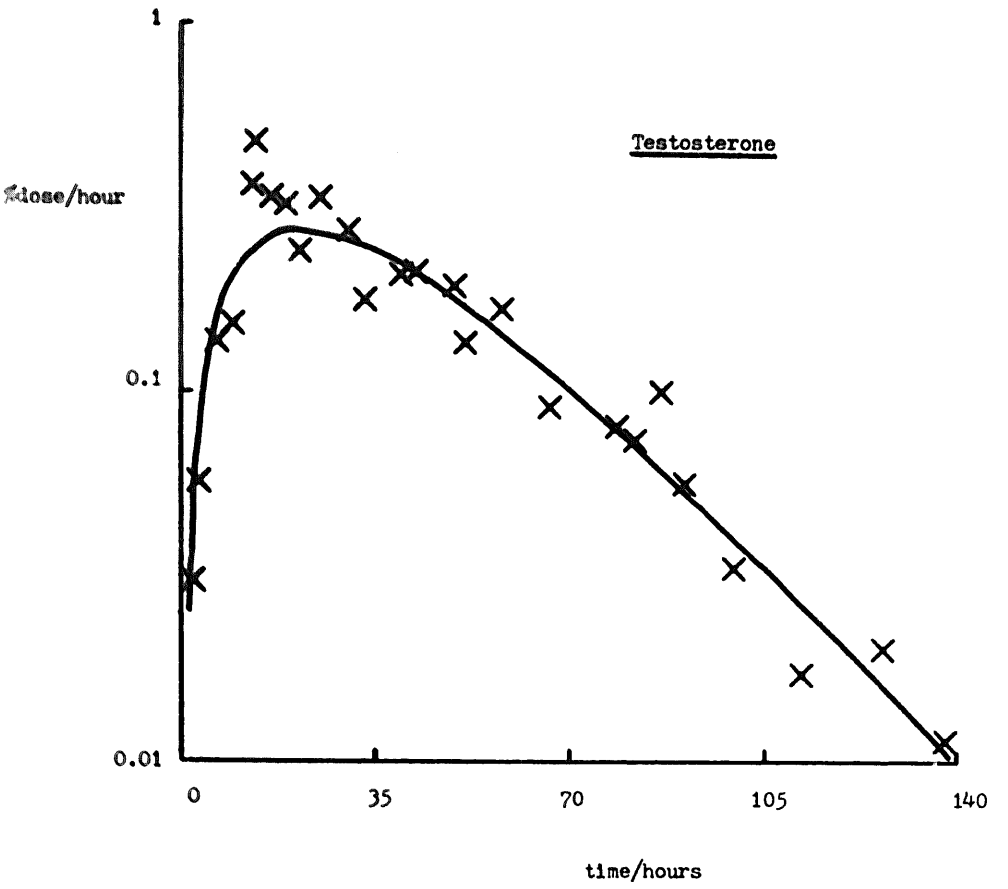

Fig. 2. Testosterone: comparison of experimental results (crosses) with theoretical predictions based upon the model (solid line) using the data in Table 1.

the real F. With these limitations, the fact that our predictions begin to approach the experimental data for hydrocortisone is encouraging and supports both the reasoning behind the model and its potential wide applicability.

Before we may reach this conclusion, however, it is necessary to consider the values of k_2 and k_3 estimated for the 3 drugs in Table 1. Firstly, we find the experimental data best-fit by the same k_2 for testosterone and hydrocortisone; for benzoic acid, a value twice as large is predicted. The assigned significance attached to the k_2 process is the diffusion of drug through the viable epidermis and upper dermal tissue, such that:

$$k_2 \equiv D_{vt}/h_{vt}^2$$

where D_{vt} is the diffusion coefficient and h_{vt} the diffusion path length. Given that h_{vt} will be constant for all 3 drugs, the differences in k_2 must be due to different diffusion coefficients. The results in Table 1 suggest, therefore, that benzoic acid diffuses twice as quickly through the viable skin tissue as the two steroids. Taking

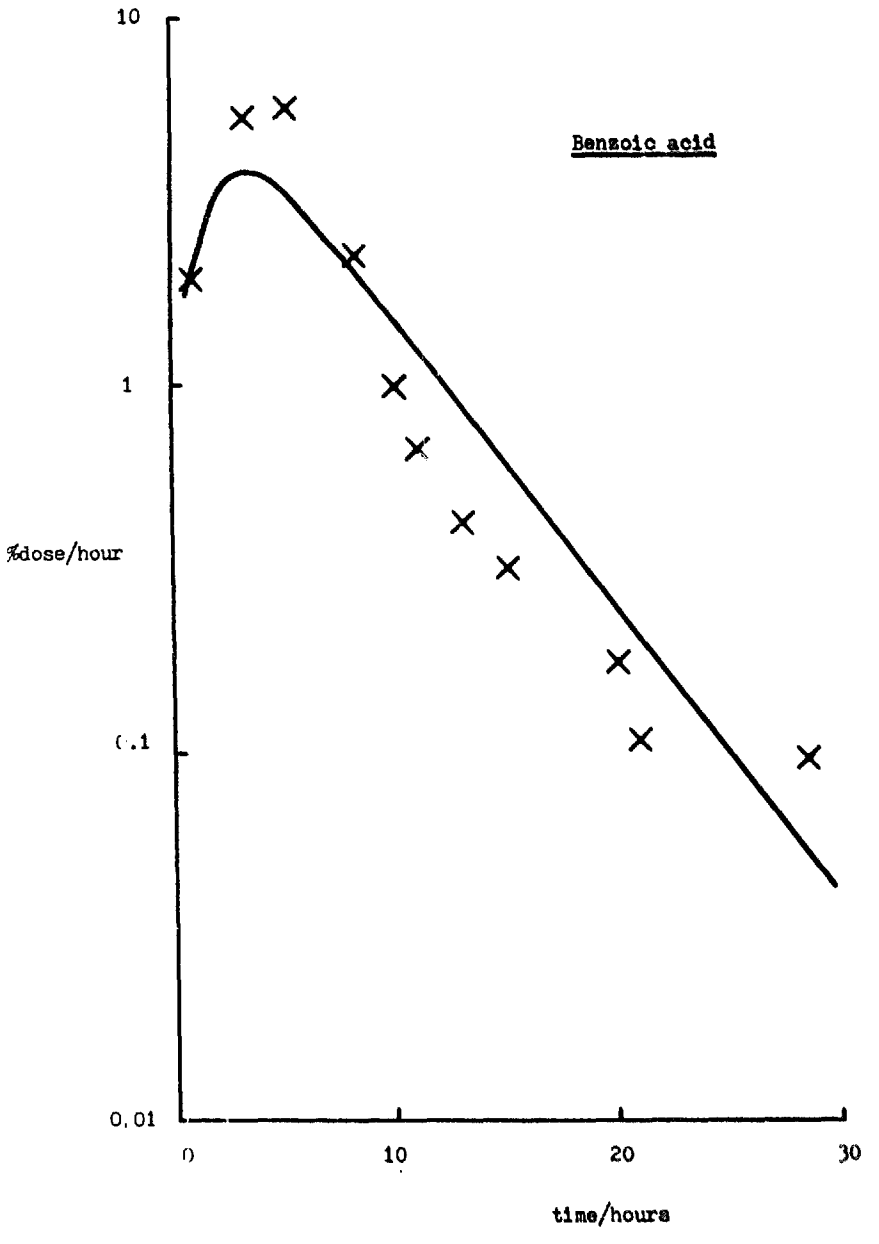

Fig. 3. Benzoic acid: comparison of experimental results (crosses) with theoretical predictions based upon the model (solid line) using the data in Table 1.

into consideration the relative sizes of the molecules, it is acceptable that this is the case and that no distinction between testosterone and hydrocortisone is possible. If h_{vl} is taken to be approximately 150 μm, then we may calculate

D_{vl} (testosterone, hydrocortisone) $= 0.9 \times 10^{-7}$ cm$^2 \cdot$ s^{-1}

D_{vl} (benzoic acid) $= 1.8 \times 10^{-7}$ cm$^2 \cdot$ s^{-1}

The order of magnitude of these results shows that the proposed comparison of this

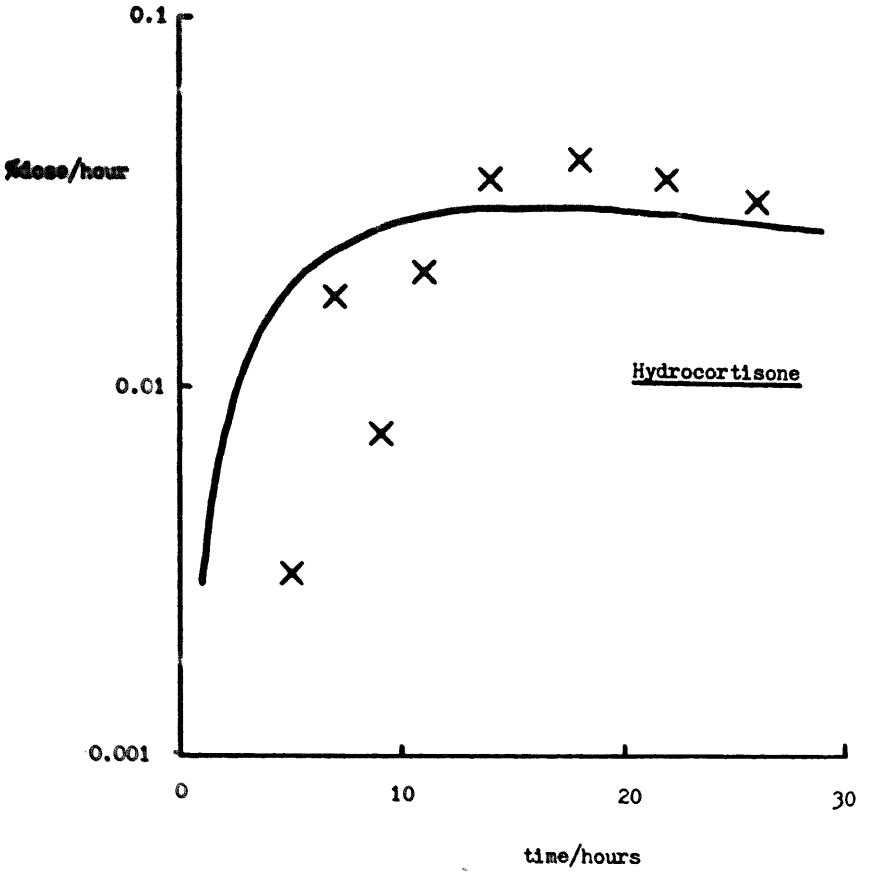

Fig. 4. Hydrocortisone: comparison of experimental results (crosses) with theoretical predictions based upon the model (solid line) using the data in Table 1).

diffusive process to that through an aqueous protein gel is quite reasonable.

We now turn to the k_3 values and observe that they follow the ranking:

testosterone > hydrocortisone > benzoic acid

TABLE 1

PHYSICAL PARAMETERS USED TO EVALUATE THE THEORETICAL CURVES IN FIGS. 2, 3 AND 4

Fig.	Drug	F [a]	$10^5 k_1/s^{-1}$ [a]	$10^5 k_2/s^{-1}$ [b]	$10^5 k_3/s^{-1}$ [b]	$10^5 k_4/s^{-1}$ [a]
2	Testosterone	0.168	1.60	40	75	2.90
3	Benzoic acid	0.36	5.11	80	0.4	16.45
4	Hydrocortisone	0.02	0.602	40	5	4.38

[a] Literature values (Anjo et al., 1980).

[b] Estimated parameters.

with approximately a factor of 10 separating one drug from the next. The interpretation of k_3 is that it relates to the drug's affinity for the hydrophobic stratum corneum over that for the much more aqueous viable tissue. The k_3 parameter may provide information relevant to stratum corneum binding of the drug or to an epidermal reservoir effect. In this context, it is instructive to consider the ratio of the rate constants k_3/k_2—this effective partition coefficient is more sensitive to drug properties in this case than the individual k_3 values:

Testosterone, $10^3 k_3/k_2 = 1875$

Benzoic acid, $10^3 k_3/k_2 = 5$

Hydrocortisone, $10^3 k_3/k_2 = 125$

In terms of k_3/k_2, therefore we have

testosterone > hydrocortisone ≫ benzoic acid

and a clear distinction between the two steroids and benzoic acid. This seems a sensible result: it is unlikely and unproven that benzoic acid binds tightly to the stratum corneum or produces a reservoir effect. The compound has an appreciable water solubility and, as can be seen in Fig. 3, is relatively quickly absorbed following topical application. The steroids, on the other hand, are known to form epidermal reservoirs and, compared to benzoic acid, have very poor aqueous solubilities. That testosterone has a ratio k_3/k_2 an order of magnitude greater than that of hydrocortisone is also consistent with their relative hydrophobicities and expected stratum corneum/viable tissue partition coefficients.

Finally, we summarise our findings. (1) For drugs cleared rapidly and completely from the general circulation, a new pharmacokinetic model has been developed to describe the appearance of a topically applied compound in the excretion compartment as a function of time. (2) First-order kinetics are assumed and the time course of drug behaviour is considered in terms of 4 rate constants. (3) The physical significance of the kinetic processes is proposed: absorption and elimination rate constants are defined and assumed fixed by the experimental data. The two other rate constants, which control penetration through the viable tissue and the competition for the drug between this region and the stratum corneum, are chosen to provide the best-fit to the data. (4) The magnitudes of the floated kinetic parameters are assessed using experimental data for 3 drugs of different skin penetration characteristics. Good correlation between the model and the results is found and the numerical values of the derived rate constants are compatible with the physical interpretations and the bio-physicochemical conditions. (5) We believe the model simple yet adaptable enough to prove of general use for the interpretation of percutaneous absorption data. Further work with compounds of different physical and pharmacokinetic properties is necessary and is proposed to confirm this conclusion.

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