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The microbial degradation of topically applied drugs

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Summary

The surface of the skin supports a range of microorganisms capable of metabolizing some topically applied drugs. In order to ascertain the significance of this degradation we have established a mathematical model to predict the influence of this biotransformation on the plasma levels of the drug. The model is a linear kinetic representation of the process of skin absorption and the rate constants are predicted from a physicochemical consideration of the properties of the drug. The results of the simulations show that microbial degradation of the drug can be significant, particularly if the topical formulation is a thin film. If a transdermal device is used the theoretical calculations show that enzymatic degradation of the active substance is likely to be clinically less significant.

Introduction

A wide range of microorganisms can be found on healthy skin, the most common commensal being *Staphylococcus epidermidis*. This organism and others have been shown to be capable of metabolizing drugs which may be applied topically. These include steroid esters such as betamethasone-17-valerate (Brookes et al., 1982) and

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nitroglycerin (GTN) (Denyer et al., 1984). Thus drugs intended for both local and systemic action may be degraded before they reach their target site. In order to establish the significance of this metabolic degradation we have formulated a mathematical model, the basis of which is a pharmacokinetic analysis which has been developed previously (Guy et al., 1983). The rate constants in the model have physical significance and can be related to the physicochemical properties of the penetrant.

If microbial decomposition of a topical drug can occur, the efficacy of transdermal therapy can be questioned. Although this route of drug administration has many advantages, it is possible that much of the drug could be metabolized before it even reaches the plasma. In previous publications we have addressed this problem by considering cutaneous metabolism within the skin (Guy and Hadgraft, 1984) and in this paper we consider the effects that surface microbial metabolism may have.

The model

A schematic representation of the pharmacokinetic model is presented in Fig. 1. The rate constants have the following significance.

Thin film application

The drug will be degraded in the film at a rate determined by k_b. This may be approximated by a first-order rate constant which will be a function of both the drug and microorganism. The remaining drug will diffuse across the stratum corneum at a rate given by k_1. In previous work we have shown that this rate constant is related to the molecular weight (m) of the penetrant according to Eqn. 1.

$$k_1(h^{-1}) = 0.184 \times \left(\frac{122}{m}\right)^{0.3} \quad (1)$$

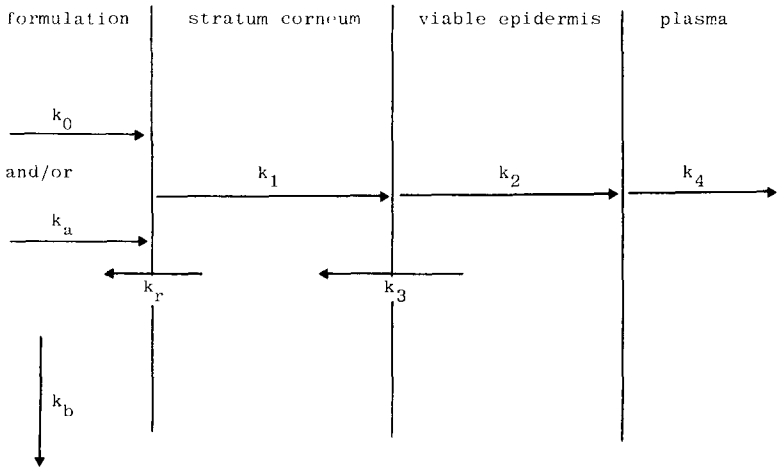

Fig. 1. Schematic representation of the rate processes involved in skin penetration.

The drug then diffuses deeper into the skin tissues where it experiences the viable epidermis which has similar diffusional characteristics to an aqueous protein gel (Scheuplein, 1967). k_2 describes the diffusional resistance and may also be related to the molecular weight of the drug (Eqn. 2).

$$k_2(h^{-1}) = 2.9 \times \left(\frac{122}{m}\right)^{0.3} \tag{2}$$

If the drug is very lipophilic or binds strongly to components of the stratum corneum, it will have difficulty 'partitioning' into the viable tissue. In order to produce this effect in the model, a backward rate constant, k_3 is included. The ratio k_3/k_2 may be regarded as an 'effective partition coefficient' and empirically we have shown (Guy and Hadgraft, 1985a) that this may be related to the octanol–water partition coefficient (K_{oct}).

$$K_{eff} = \frac{k_3}{k_2} = \frac{k_{oct}}{5} \tag{3}$$

Thus if the molecular weight and the octanol–water partition coefficient of the drug are known, the rate constants k_1 through k_3 can be calculated.

k_4 cannot be predicted; it is the elimination rate constant of the drug from the plasma as determined in normal pharmacokinetic analysis.

Transdermal delivery system

In Fig. 1 there are three other rate constants which are used to describe the delivery of the drug to the skin surface from a transdermal device. In general the device will deliver drug with zero-order kinetics (k_0) during its application time. The devices have a layer of adhesive which contain a priming dose of the drug. This releases the drug with first-order kinetics as described by k_a. It is also possible that the drug will not partition favourably into the skin. A backward rate constant, k_r, is included to allow for this possibility. For most transdermal applications, the device and adhesive should have been designed such that the value of k_r is minimal. In all our theoretical calculations we have assumed this and have accordingly used a value for k_r of 1×10^{-4} h^{-1}.

In order to assess the significance of metabolism at the skin surface we consider the effect of k_b on the levels of drug found in the plasma. This is achieved by solving the linear differential equations which can be written for the kinetic scheme in Fig. 1.

For thin film application these are:

$$\frac{dc_1}{dt} = -(k_1 + k_b) \cdot c_1 \tag{4}$$

$$\frac{dc_2}{dt} = \frac{V_1}{V_2} \cdot k_1 c_1 - k_2 c_2 + \frac{V_3}{V_2} \cdot k_3 c_3 \tag{5}$$

$$\frac{dc_3}{dt} = \frac{V_2}{V_3} \cdot k_2 c_2 - (k_3 + k_4) \cdot c_3 \tag{6}$$

$$\frac{dc_4}{dt} = \frac{V_3}{V_4} \cdot k_4 c_3 \tag{7}$$

where V_i refer to the volumes of the different regions in Fig. 1. E.g. V_3 refers to the volume of distribution of drug in the plasma. Solving the differential equations for this region:

$$c_3 = \frac{M_\infty}{V_3} \cdot k_1 k_2 \cdot \left\{ \frac{e^{-(k_1+k_b)t}}{(k_1 + k_b - \alpha)(k_1 + k_b - \beta)} + \frac{e^{-\alpha t}}{(\alpha - \beta)(\alpha - (k_1 + k_b))} + \frac{e^{-\beta t}}{(\beta - (k_1 + k_b))(\beta - \alpha)} \right\} \tag{8}$$

where M_∞ is the total dose applied and α and β are the roots of the quadratic equation:

$$s^2 + (k_2 + k_3 + k_4)s + k_2 k_4 = 0 \tag{9}$$

The equations for transdermal delivery are more complex. Since the device keeps the drug reservoir away from the skin surface and hence away from the micro-organisms, we make the approximation that the zero-order kinetics to the skin surface are little affected by the microorganisms. This means that the contribution to the concentration of drug in the plasma, given by the zero-order input, is (Guy and Hadgraft, 1985a):

$$c_3^0 = \frac{A k_0 k_1 k_2}{V_3} \cdot \left\{ \frac{1}{\alpha\beta\epsilon} - \frac{e^{-\alpha t}}{\alpha(\alpha - \beta)(\alpha - \epsilon)} - \frac{e^{-\beta t}}{\beta(\beta - \alpha)(\beta - \epsilon)} - \frac{e^{-\epsilon t}}{\epsilon(\epsilon - \alpha)(\epsilon - \beta)} \right\} \tag{10}$$

where $\epsilon = k_1 + k_r$

The adhesive layer which is in immediate contact with the skin surface, and hence the microorganisms, will have its drug content depleted with rate constant, k_b. Eqn. 8 is modified to compensate for this and becomes:

$$c_3^a = \frac{M_\infty}{V_3} \cdot k_1 k_2 k_a \cdot \left\{ \frac{e^{-\alpha t}}{(\beta - \alpha)(\alpha - \omega)(\alpha - \mu)} + \frac{e^{-\beta t}}{(\alpha - \beta)(\beta - \omega)(\beta - \mu)} + \frac{e^{-\omega t}}{(\alpha - \omega)(\omega - \beta)(\omega - \mu)} + \frac{e^{-\mu t}}{(\alpha - \mu)(\mu - \beta)(\omega - \mu)} \right\} \tag{11}$$

where ω and μ are the roots of the quadratic:

$$s^2 + (k_a + k_r + k_1 + k_b)s + k_a(k_1 + k_b) = 0 \quad (12)$$

The amount of drug in the plasma may then be obtained by taking the sum of Eqns. 10 and 11.

Results and Discussion

It is now possible to use Eqns. 8, 10 and 11 to predict the possible effect of microbial degradation. We have previously shown the utility of such equations for predicting the transdermal delivery of nitroglycerin (Guy and Hadgraft, 1985b) and have used this compound as a typical example of a drug that can be delivered transdermally. It is also known to be metabolized by microorganisms that exist on the skin surface (Denyer et al., 1984). The appropriate rate constants are summarized in Table 1.

A detailed description of the metabolism of nitroglycerin by skin flora has not been reported but it is possible to estimate some appropriate half-lives for the breakdown. Using the data of Denyer et al. (1984), it appears that the half-lives lie in the range 8–24 h depending on the species of *Staphylococci.* In order to investigate the effect of metabolism using the pharmacokinetic model we have chosen a wide range of half-lives to cover the possibility of faster metabolism. k_b values have been chosen such that half-lives ranging from 2 to 24 h are represented.

For the application of a thin film of nitroglycerin, as may be experienced in the application of an ointment formulation the plasma levels are given in Fig. 2. The effect of k_b is pronounced. The curves correspond to an applied dose of 10 mg, and for comparison, we can set the effective plasma levels to be 0.1 $ng \cdot ml^{-1}$. If no microbial metabolism occurs, drug levels in excess of 0.1 $ng \cdot ml^{-1}$ occur from 1 to 11 h following topical application. The plasma levels achieved when microbial

TABLE 1

KINETIC CONSTANTS FOR NITROGLYCERIN

k_0 ($\mu g \cdot cm^{-2} h^{-1}$)	36
k_a (h^{-1})	1.3
k_b (h^{-1})	variable
k_r (h^{-1})	10^{-4}
k_1 (h^{-1})	0.15
k_2 (h^{-1})	2.36
k_3 (h^{-1})	53
k_4 (h^{-1})	18.2
A (cm^2)	10
V_3 (litres)	231
M_∞ (mg)	2

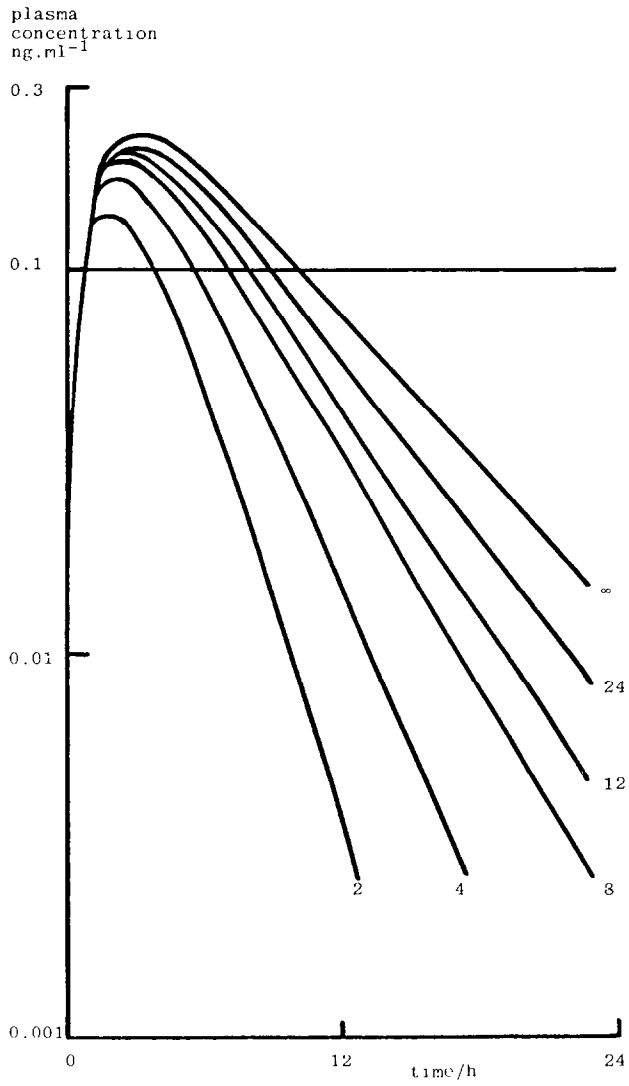

Fig. 2. Theoretical plasma concentration–time profiles for topically applied nitroglycerin as a thin film. The effect of changing the metabolism is shown; the numbers against the curves represent the half-life (h) of microbial degradation.

degradation occurs with a half-life of 8 h reduce effective therapy to between 1 and 7 h. For faster metabolism the effective times become shorter. It should also be noted that the peak levels attained are reduced and the area under the curve is considerably reduced in the presence of microbial biotransformation of the drug.

A similar but not so pronounced effect is seen in the case of transdermal delivery with zero-order input. Fig. 3 shows the theoretical plasma profiles and the effect of metabolism. For a half-life of degradation of 8 h, the plasma levels are slightly

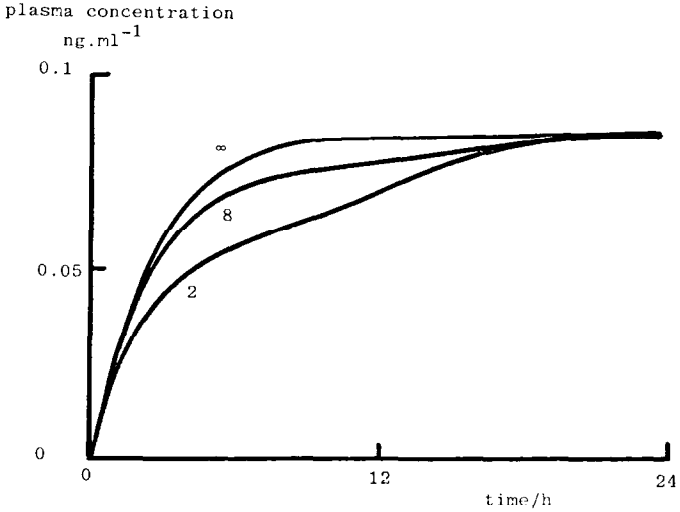

Fig. 3. Transdermal drug delivery of nitroglycerin from a zero-order release device containing an adhesive priming dose of 2 mg. The effect of microbial degradation on the plasma concentration–time profile is shown for various half-lives of metabolism. These are shown, in hours, against the curves.

reduced and it takes longer to achieve steady drug levels. The curve corresponding to a half-life of 2 h shows considerable reduction in the plasma levels. If the degree of degradation is known, this loss in drug concentration can be compensated by increasing the priming dose of the drug in the adhesive. This is demonstrated in Figs.

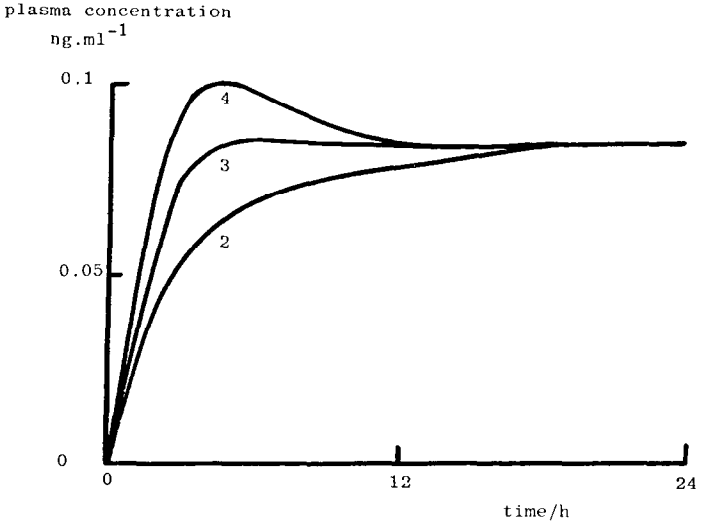

Fig. 4. The effect of increasing the priming dose in a zero-order delivery system, shown in mg, on the plasma concentrations of nitroglycerin. A fixed half-life for degradation of 8 h has been used.

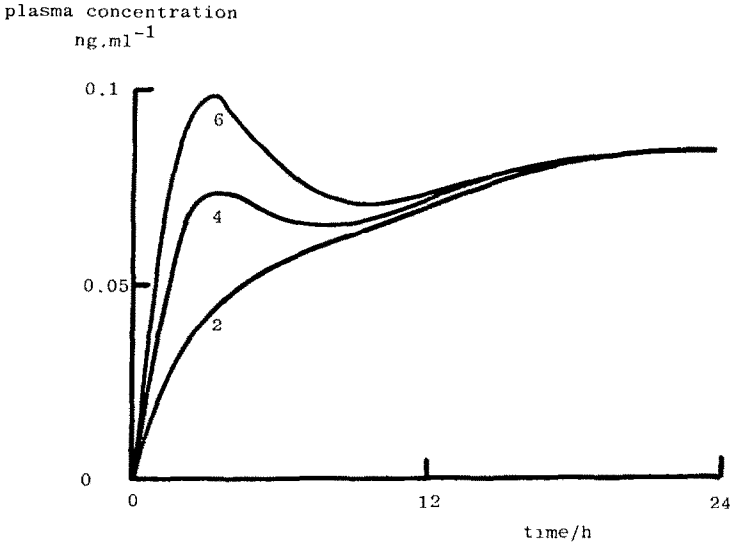

Fig. 5. The effect of increasing the priming dose in a zero-order delivery system, shown in mg, on the plasma concentrations of nitroglycerin. A fixed half-life for degradation of 2 h has been used.

4 and 5. Acceptable plasma levels can be established by increasing the adhesive dose; if too large a dose is used, some overshoot can occur.

The profiles generated by this mathematical approach show how plasma levels can be affected by microbial metabolism of the drug. In some circumstances the effect can be compensated by increasing the adhesive dose, and the degree to which this should be increased can be calculated. Degradation of topically applied drugs can be a problem and Wester and Noonan (1980) have identified the problem of cutaneous metabolism, with particular reference to nitroglycerin. From the data in the literature we cannot distinguish between drug metabolism occurring in the skin or on the skin surface. More work needs to be conducted in both areas in order to identify the kinetic parameters of metabolism. When these are precisely known it will be possible to use the equations derived above to optimize the transdermal delivery of drugs. If microbial metabolism is suspected, the potential for micro-organisms to survive in the presence of various formulations becomes an important issue.

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