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Transdermal drug delivery to neonates

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Summary

A pharmacokinetic model has been formulated to assess the potential of transdermal drug delivery to preterm infants. The permeability of the skin in these infants is high and this route of administration may prove a suitable means of delivering many drugs. Theoretical equations show how the rate of drug delivery influences the plasma levels of the topically applied drugs.

Introduction

The stratum corneum of preterm infants is not well developed and, as such, provides little barrier to the ingress of substances (Harpin and Rutter, 1983). This enhanced skin permeability may be used to advantage in certain circumstances in the administration of drugs that act systemically. By using this route it is possible to circumvent some of the normal difficulties encountered when oral and i.v. administration are used in neonatal therapy. Oral administration is hampered by the unpredictable absorption of drugs from the gut (Jones and Ballie, 1979) and i.v. administration is complicated by the need to have an infusion access line, the dead volume of which is large relative to the small volume of drug required in such infants. There are also problems due to the incompatibility of some drugs with the

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i.v. fluids. Thus transdermal drug delivery would appear to be an attractive method of administering drugs to the neonate.

In order to assess the feasibility of such an administration technique we have formulated a pharmacokinetic model to describe the absorption process. The model is a straightforward linear representation based on a previous analysis which was successfully used to predict the percutaneous absorption of benzoic acid, hydrocortisone and testosterone across adult human skin (Guy et al., 1982). The rate constants in the model may be related to the physicochemical properties of the diffusing drug. Thus this type of approach may be used predictively to assess the potential of neonatal transdermal drug delivery.

Theory

Fig. 1 shows an idealized model of the absorption processes involved and the associated classical pharmacokinetic compartments. k_0 (mass per unit area per unit time) describes the zero-order release from the delivery device (of thickness l_d) which is essentially placed directly in contact with the viable epidermis there being no effective stratum corneum in the neonate. k_2 describes the diffusion of the drug through the viable epidermis which can be considered to have the permeability characteristics of an aqueous protein gel (Scheuplein, 1967). The ratio $k_3/(k_0/l_dc)$ is an 'effective partition coefficient'; it describes the relative affinity of the drug between the viable epidermis and the delivery device. k_4 is the normal elimination rate constant for the drug, it cannot be estimated. It is a parameter, like the volume of distribution which must either be known or measured by separate experiment. k_4 is the rate at which the drug disappears from the circulation and appears in the urine.

k_0 may be determined by measuring the in vitro release characteristics of the device or by an assessment of the physicochemical properties of the drug compared with the release properties of the polymer used in the delivery system. k_2 represents the diffusion of the drug through the viable epidermis and a numerical value for k_2

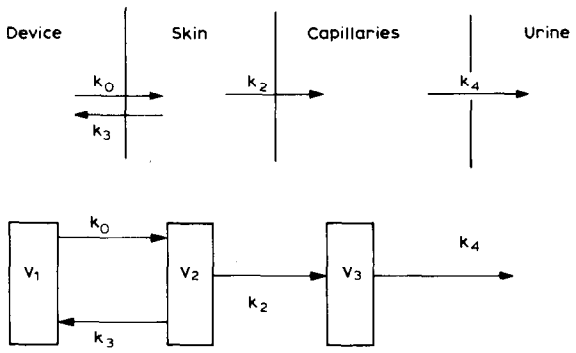

Fig. 1. Schematic representation of the kinetic model.

will be given by D_{ve}/l_{ve}^2 where D_{ve} is the diffusion coefficient of the drug through the viable epidermis of thickness l_{ve}. V_1 is the volume of the applied delivery system, V_2 is the volume of the viable epidermis and V_3 the volume of distribution.

The rate equations describing the concentrations in the different compartments may be written:

$$\frac{dc_1}{dt} = \frac{-k_0}{l_d} + \frac{V_2}{V_1} \cdot k_3 c_2 \tag{1}$$

$$\frac{dc_2}{dt} = \frac{V_1}{V_2} \cdot \frac{k_0}{l_d} - (k_2 + k_3)c_2 \tag{2}$$

$$\frac{dc_3}{dt} = \frac{V_2}{V_3} \cdot k_2 c_2 - k_4 c_3 \tag{3}$$

$$\frac{dc_4}{dt} = \frac{V_3}{V_4} \cdot k_4 c_3 \tag{4}$$

In order to simplify the solution of these simultaneous equations, the concentrations are normalized with respect to the concentration in compartment 1 at $t = 0$, i.e.

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

The equations are then solved by the use of Laplace transforms

$$s\bar{u}_1 - 1 = \frac{-k_0}{l_d c_0 s} + \frac{V_2}{V_1} \cdot k_3 \bar{u}_2 \tag{6}$$

$$s\bar{u}_2 = \frac{V_1}{V_2} \cdot \frac{k_0}{l_d c_0 s} - (k_2 + k_3)\bar{u}_2 \tag{7}$$

$$s\bar{u}_3 = \frac{V_2}{V_3} \cdot k_2 \bar{u}_2 - k_4 \bar{u}_3 \tag{8}$$

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

By repeated substitution it is possible to obtain a value for u_3, the normalized concentration of drug in the plasma.

$$\bar{u}_3 = \frac{V_1}{l_d V_3} \cdot \frac{k_2 k_0}{c_0 s(s + k_4)(s + (k_2 + k_3))} \tag{10}$$

Inverting Eqn. 10 gives an expression for the concentration of drug in the plasma:

$$c_3 = \frac{A k_0 k_2}{V_3 k_4 (k_2 + k_3)} \left(1 + \frac{k_4 \exp(-(k_2 + k_3)t) - (k_2 + k_3)\exp(-k_4 t)}{(k_2 + k_3 - k_4)}\right) \tag{11}$$

where A is the area of the device in contact with the skin. The expression assumes that k_0 is invariant during the period of application.

Results and Discussion

Initial experiments indicate that percutaneous penetration from aqueous gels containing theophylline sodium glycinate produce therapeutic levels of theophylline in the plasma of preterm infants (Evans et al., 1984). The blood concentrations, however, are not well controlled and initially it would be instructive to use theophylline as a model compound to explore the usefulness of Eqn. 12 in predicting blood levels following transdermal delivery.

Estimates from the different rate constants in Eqn. 12 have to be considered. The transderm-nitro (Ciba Pharmaceuticals) delivery system designed to release glyceryl trinitrate releases the active constituent at a rate of 35.8 $\mu g \cdot cm^{-2} \cdot h^{-1}$ (Chien et al., 1983). Thus a zero-order release rate of 50 $\mu g \cdot cm^{-2} \cdot h^{-1}$ would be a reasonable initial delivery rate to investigate for theophylline. k_2 describes the diffusion of the theophylline across the viable epidermis. We have previously shown that the diffusional barrier in this region resembles that of an aqueous protein gel (Guy et al., 1982) and we can estimate k_2 from previous data using the following relationship (Guy et al., 1985a)

$$k_2^u = k_2^{BA}\left(\frac{MW^{BA}}{MW^u}\right)^{1/3}$$

where k_2^u is the unknown rate constant, k_2^{BA} is the known value for benzoic acid (Guy et al., 1982), and MW^{BA} and MW^u are, respectively, the molecular weights of the benzoic acid and the unknown. This equation is an approximation based on the Stokes-Einstein relationship and approximating the molecular radius by assuming it to be proportional to the cube root of the molecular weight (Flynn et al. 1974). Until a systematic appraisal of diffusion coefficients of penetrants in the viable epidermis has been attempted this is the only feasible approach. In previous work on adult skin where we have analyzed urinary excretion data we have found this equation adequate (Guy et al., 1985b).

With the correct design of transdermal system, the affinity of the device for the drug compared to the skin should be negligible and a small value of k_3 is thus chosen ($k_3 = 1 \times 10^{-4}$ h^{-1}). The effect of varying k_3 will be shown later.

k_4 is the elimination rate constant of theophylline in the preterm infant and V_3 its volume of distribution. A value of 0.025 h^{-1} has been assigned to k_4 and 0.65 $l \cdot kg^{-1}$ to V_3 (Simons et al., 1981). Fig. 2 shows the predicted plasma levels generated using these data for a 2.5 kg preterm infant and a transdermal delivery system of 2.5 cm^2 in area. Fig. 2 shows that the rise to constant plasma levels is not rapid and that a loading dose may be required to produce a rapid effect. This is a result of the slow elimination rate constant for this particular drug. However, the

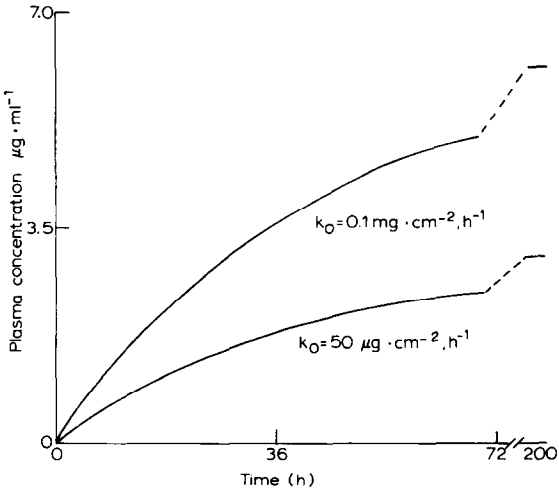

Fig. 2. The plasma concentration–time profile for theophylline delivered transdermally to a 2.5 kg preterm infant. $k_2 = 2.55\ h^{-1}$; $k_3 = 1 \times 10^{-4}\ h^{-1}$; $k_4 = 0.025\ h^{-1}$. The effect of varying k_0 is shown.

levels attained are approximately 3 $\mu g \cdot ml^{-1}$ which is just below the therapeutic level required (4–12 $\mu g \cdot ml^{-1}$). By increasing the delivery rate to 0.1 $mg \cdot cm^{-2} \cdot h^{-1}$, therapeutic levels are achieved as can be seen in Fig. 2. The problems of the slow elimination rate may be seen by comparing the curves in Fig. 2 and Fig. 3. In Fig. 3 the same rate constants have been used except that k_4 has been increased by an order of magnitude. In this case the peak levels are attained after about 20 h as compared with 150 h but the peak levels are also down by an order of magnitude. Thus in any transdermal system account has to be taken of the elimination rate constant of the drug. If the plasma half-life is long then the formulation will require a design such that a loading dose is administered which is maintained by a zero-order rate controlling system.

Fig. 4 shows the effect of increasing k_3. As k_3 increases the drug has more affinity for the device, i.e. it partitions unfavourably into the viable epidermis. For

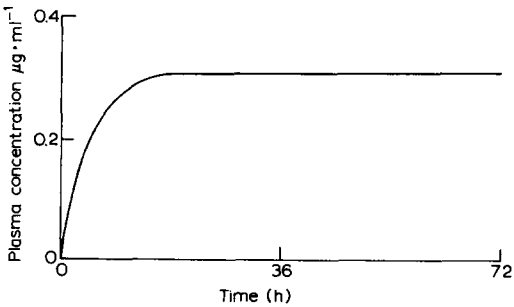

Fig. 3. The plasma concentration–time profile for theophylline delivered transdermally to a 2.5 kg preterm infant. $k_2 = 2.55\ h^{-1}$; $k_3 = 1 \times 10^{-4}\ h^{-1}$; $k_4 = 0.25\ h^{-1}$.

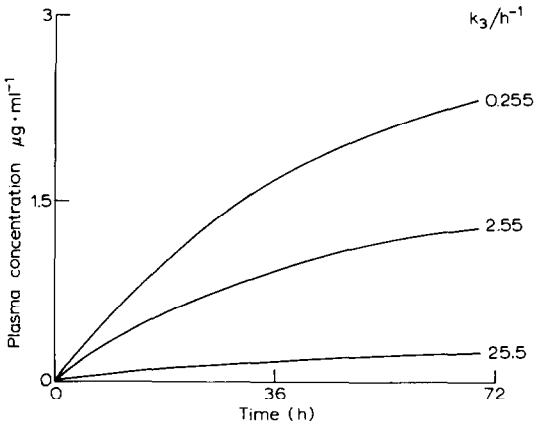

Fig. 4. The plasma concentration time profile for theophylline delivered transdermally to a 2.5 kg preterm infant. $k_0 = 50\ \mu g \cdot cm^{-2} \cdot h^{-1}$; $k_4 = 0.025\ h^{-1}$.

comparison the theophylline values have been maintained and Fig. 4 shows the effect of changing k_3. Even though a transdermal device has been designed to deliver a drug at a constant rate the degree of partitioning between the device and the skin is an important factor in determining the speed at which steady drug levels are reached in the plasma.

It seems feasible that there are several groups of compounds which could be administered with advantage to neonates by a transdermal route. In order to identify these it is necessary to have a complete appraisal of their physicochemical properties and their elimination rate constant and volume of distribution. If these are known it is possible to predict the rates of drug delivery required to maintain steady plasma levels following transdermal application. The modelling approach will also highlight difficulties involved in the time to reach steady levels as dictated either by poor partitioning from the delivery device or from small elimination rate constants.

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