International Journal of Pharmaceutics, 32 (1986) 159–163
Elsevier

IJP 01078

Interpretation and prediction of the kinetics of transdermal drug delivery: oestradiol, hyoscine and timolol

Richard H. Guy [1] and Jonathan Hadgraft [2]

[1] *Departments of Pharmacy and Pharmaceutical Chemistry, University of California at San Francisco, San Francisco, CA 94143 (U.S.A.) and*

[2] *The Welsh School of Pharmacy, University of Wales Institute of Science and Technology, Cardiff CF1 3XF, Wales (U.K.)*

(Received February 6th, 1986)
(Accepted April 5th, 1986)

Key words: transdermal drug delivery – oestradiol – hyoscine – timolol

Summary

A kinetic model has been used to predict the plasma concentration vs time profiles for oestradiol, hyoscine and timolol following transdermal drug delivery. Rate constants describing a drug's passage across the stratum corneum and viable epidermis are calculated from simple physicochemical parameters. When used in conjunction with the in vitro release characteristics of the topical formulation (simple vehicle or sophisticated delivery system), and with knowledge of the drug's systemic clearance, the kinetic values permit simulation of the expected plasma level profile. The theoretical predictions are consistent with published human in vivo data for each of the three compounds. This kinetic approach may be useful, therefore, in the evaluation of feasible candidates for transdermal drug delivery.

Introduction

There has been increasing interest in transdermal drug delivery over the past 5 years (Guy and Hadgraft, 1985a). This activity has been catalyzed by the advantageous delivery of nitroglycerin via the skin (Good, 1983; Karim, 1983a and b; Imhof et al., 1984; Wolff et al., 1985). The topical administration of a variety of compounds has now been investigated and data have been published on hyoscine (Price et al., 1981; Chandrasekaran et al., 1978; Chandrasekaran, 1983; Muir and Metcalfe, 1983), nitroglycerin (Good, 1983; Karim, 1983a and b; Imhof et al., 1984; Wolff et al., 1985), clonidine (Arndts and Arndts, 1984; Weber et al., 1984; Lawson, 1985), nicotine (Rose et al., 1985), timolol (Vlasses et al., 1985) and oestradiol (Laufer et al., 1983; Schenkel et al., 1985). Recently, plasma levels in man of oestradiol (Schenkel et al., 1985), hyoscine (Muir and Metcalfe, 1983) and timolol (Vlasses et al., 1985) following transdermal delivery have been determined and reported, expanding the previous database which had been established with nitroglycerin (Good, 1983) and clonidine (Arndts and Arndts, 1984). In previous communications (Guy and Hadgraft, 1985b and c), we have modelled the transdermal delivery of these latter two drugs with a kinetic approach in which the rate constants are determined by the physicochemical properties of the drug. If this approach is valid, we should be able to predict the plasma

Correspondence: J. Hadgraft, The Welsh School of Pharmacy, University of Wales Institute of Science and Technology, Cardiff CF1 3XF, Wales, U.K.

levels of other drugs which are delivered topically provided certain basic physical chemical information is available. In this communication we adopt this technique to calculate the plasma concentration vs time profiles expected for oestradiol, hyoscine and timolol following transdermal delivery and then compare these results with the recently published data.

Interpretation

The model (Guy and Hadgraft, 1985a, b, c and d) is shown schematically in Fig. 1. Delivery from the applied formulation is controlled by the input function k_i. In the case of a membrane-moderated delivery system such as that used to administer clonidine, k_i is the sum of a zero-order rate (k_0), as determined by the membrane permeability to drug diffusing from the reservoir, plus a first-order component (k_1) describing release of the drug from the adhesive immediately adjacent to the skin (Guy and Hadgraft, 1985b and c). The in vivo oestradiol and hyoscine results have been obtained subsequent to the topical application of precisely such systems (Schenkel et al., 1985; Muir and Metcalfe, 1983). The zero-order components of the release behaviour have been characterized; the first-order portions have been assumed, for the purpose of this analysis, to be identical to that of the hyoscine device (Chandrasekaran et al., 1978). The published timolol data, on the other hand, was obtained after application of the drug in a simple gel base (Vlasses et al., 1985). Hence, in the interpretation discussed in this communication, we assume no zero-order component of k_i and that timolol is released to the skin in a first-order fashion alone. The simplicity of the vehicle almost certainly ensures that this rate is faster than the transfer of drug across the skin. In a previous publication (Guy and Hadgraft, 1985b), we analyzed the transcutaneous input kinetics of nitroglycerin from Nitrobid ointment and employed a first-order rate constant corresponding to a half-life for release of 0.5 h. Faster kinetics do not affect the plasma concentration–time course because the percutaneous absorption process becomes, as stated above, completely rate-determining. In this paper, we again employ a release half-life of 0.5 h to characterize the timolol vehicle; we will also show that faster release kinetics do not significantly affect the predicted plasma concentration time course.

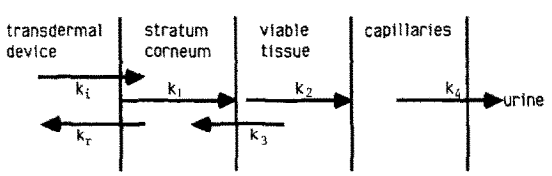

Fig. 1. Schematic representation of the kinetic model.

The model depicted in Figure 1 has been described in previous publications (Guy and Hadgraft, 1985a, b, c and d) and the equations necessary to calculate systemic drug concentrations after transdermal delivery have been developed and solved. As discussed above, input kinetics from the device are described by k_0 and k_1 or by k_1 alone. The significance of the remaining kinetic parameters and the determination of their values are as follows.

k_r reflects the fact that there will be competition for the drug between the device and the skin at the system–stratum corneum interface. An optimally designed delivery vehicle will minimize k_r and facilitate the unidirectional movement of drug from the applied phase into the body. For the calculations reported below, we have assigned, therefore, a very small value to k_r.

k_1 and k_2 characterize, respectively, drug diffusion across the stratum corneum and viable epidermis. These rate constants are proportional to the corresponding diffusion coefficients in these tissue layers and are, to a first approximation, inversely related to the cube-root of the drug molecular weight. Their values are assessed from previously determined k_1 and k_2 parameters for benzoic acid and an appropriate correction for molecular size (Guy et al., 1985).

k_3 modulates the rate at which the permeating drug partitions between the lipophilic stratum corneum and the much more aqueous in

nature viable epidermis. The greater the magnitude of k_3, therefore, the slower the partitioning step. The ratio k_3/k_2 reflects, as a result, an "effective stratum corneum–viable tissue partition coefficient" for the drug. Previous work has shown that k_3 can be reliably estimated from k_2 and the octanol/water partition coefficient (K) of the drug via the empirical relationship $k_3/k_2 = K/5$ (Guy et al., 1985).

k_4 describes the systemic elimination kinetics of the drug from the body and is derived directly from the published biological half-life. This rate constant cannot be predicted but must be evaluated experimentally following parenteral administration of the drug in vivo.

Results and Discussion

The physicochemical and pharmacokinetic information and the derived rate constants for oestradiol, hyoscine and timolol are collected in Table 1. Table 1 also contains three additional parameters essential for the kinetic analysis.

(a) The volumes of distribution (V_d) of the three drugs. For oestradiol and timolol, these values were available in the literature (Kutsky, 1973; Gilman et al., 1985); for hyoscine V_d was inferred from i.v. infusion data (Chandrasekaran et al., 1978).

(b) The surface areas (A) of the transdermal devices used in the oestradiol and hyoscine studies (Schenkel et al., 1985; Muir and Metcalfe, 1983).

(c) The amount of drug (M) present either in the adhesive of the patch (in the case of oestradiol and hyoscine (Schenkel et al., 1985; Muir and Metcalfe, 1983)) or administered in the topical vehicle (in the case of timolol (Vlasses et al., 1985)).

Using this complete compilation and the predictive equations of the model (Guy and Hadgraft, 1985b and c), simulations have been performed with the input kinetics associated with the vehicles used in the recent in vivo studies (and which have been discussed above). The results are shown in Figs. 2, 3 and 4 for oestradiol, hyoscine and timolol, respectively. Included on these graphs are the recently published human in vivo data (Schenkel et al., 1985; Muir and Metcalfe, 1983; Vlasses et al., 1985). The agreement between theo-

TABLE 1

PHYSICOCHEMICAL AND PHARMACOKINETIC DATA AND THE DERIVED RATE CONSTANTS FOR OESTRADIOL, HYOSCINE AND TIMOLOL

	Oestradiol	Hyoscine	Timolol
molecular weight (D_a)	272.4	303.4	316.4
log K	2.49 [a]	1.24 [b]	1.91 [b]
half-life (h)	0.05 [c]	1.12 [d]	4.1 [d]
V_d (litres)	4.81 [c]	70 [d]	164 [d]
A (cm^2)	20	2.5	–
M (mg)	0.1	0.15	60
k^0 ($\mu g/cm^2/h$)	0.21	3.8	–
k^l (h^{-1})	1.3	1.3	1.3
k_r (h^{-1})	10^{-4}	10^{-4}	10^{-4}
k_1 (h^{-1})	0.141	0.136	0.134
k_2 (h^{-1})	2.22	2.14	2.11
k_3 (h^{-1})	137	7.44	34.3
k_4 (h^{-1})	13.9	0.619	0.169

[a] C. Hansch, personal communication.
[b] Hansch and Leo (1979).
[c] Kutsky (1973).
[d] Gilman et al. (1985).

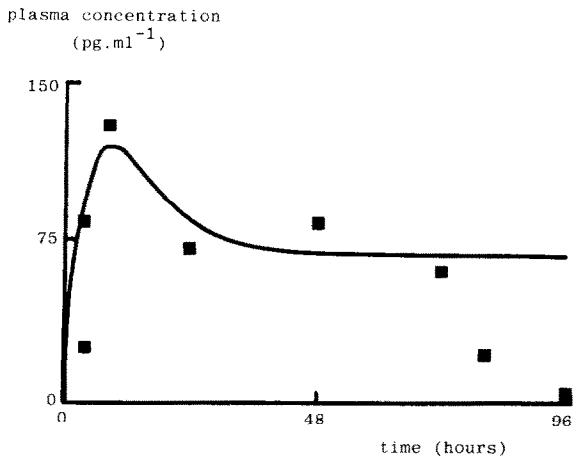

Fig. 2. Predicted and experimental (■) plasma concentration–time course for oestradiol. The predicted profile includes a baseline oestradiol in the plasma of 8 pg·ml^{-1}.

retical prediction and experiment is good. Two predicted curves are included for timolol (Fig. 4); the simulation, which is slightly higher at earlier

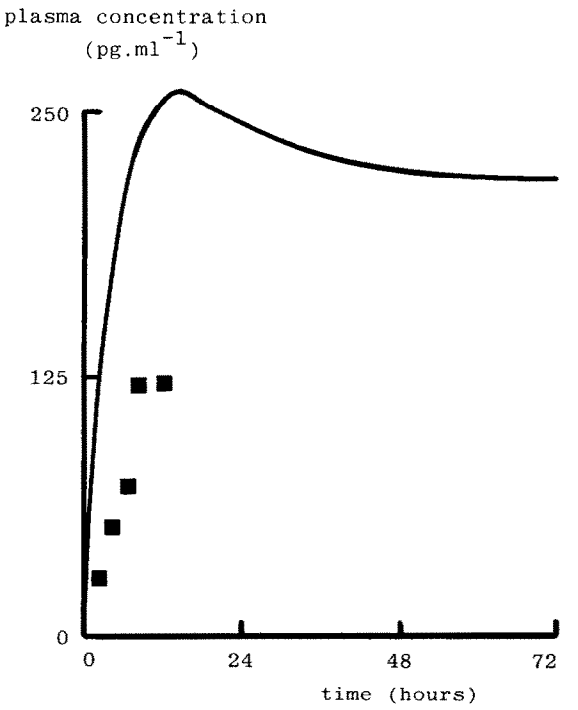

Fig. 3. Predicted and experimental (■) plasma concentration–time course for scopolamine.

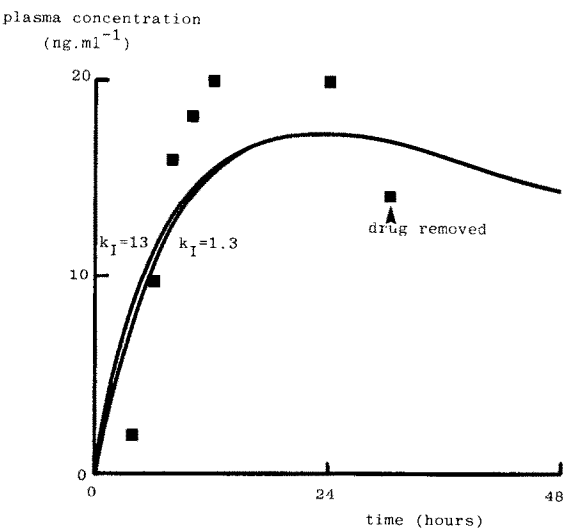

Fig. 4. Predicted and experimental (■) plasma concentration–time course for timolol. In the experimental data the patch was removed at 30 h. The theoretical profiles show two first-order input rates corresponding to $k_I = 1.3$ h^{-1} and 13 h^{-1}.

times, has used a first-order input kinetic constant (k_I) of 13 h^{-1}, i.e. a value 10 times higher than that quoted in Table 1. It is clear, therefore, that the stratum corneum, rather than the delivery system, is controlling the systemic access of this drug.

For oestradiol and hyoscine, the mass balance relationship at steady-state

$$A \cdot k_0 = V_d \cdot k_4 \cdot C_{ss}$$

may be used to evaluate the hypothetical plateau drug concentration (C_{ss}) in plasma which should result from the zero-order input. Substitution of the appropriate values from Table 1 into this equation gives C_{ss} levels for oestradiol and hyoscine, respectively, of approximately 62 and 219 pg/ml. The limited in vivo data suggest that this prediction is reasonable for oestradiol (Schenkel et al., 1985). The oestradiol system is designed to deliver drug for 3 days after which time there is insufficient ethanol in the reservoir to solubilize the remaining drug. For this reason the theoretical and experimental results diverge after 72 h. For

hyoscine, though, no firm conclusion can be drawn because plasma concentrations were measured for only 12 h after transdermal application (Muir and Metcalfe, 1983), a period insufficient for steady-state to have been established.

Overall, the results support the contention that the kinetic model can adequately simulate in vivo transdermal drug delivery data for the three compounds considered. Successful utilization of the approach, furthermore, has already been demonstrated for nitroglycerin and clonidine (Guy and Hadgraft, 1985b and c). It may be suggested, therefore, that the technique has potential to be uased as a powerful screening tool in the feasibility assessment of transdermal drug delivery candidates.

Acknowledgements

Financial support was received from NIH (GM-33395) and Vick International. R.H.G. is the recipient of a Special Emphasis Research Career Award from the National Institute of Occupational Safety and Health (K01-0H-00017).

References

Arndts, D., and Arndts, K., Pharmacokinetics and pharmacodynamics of transdermally administered clonidine. Euro. J. Clin. Pharmacol., 26 (1984) 79–85.

Chandrasekaran, S.K., Bayne, W. and Shaw, J.E., Pharmacokinetics of drug permeation through human skin. J. Pharm. Sci., 67 (1978) 1370–1374.

Chandrasekaran, S.K., Controlled release of scopolamine for prophylaxis of motion sickness. Drug Dev. Ind. Pharm., 9 (1983) 627–646.

Gilman, A.G., Goodman, L.S. and Gilman, A., The Pharmacological Basis of Therapeutics, 7th Edn., Macmillan, New York, 1985, pp. 1663–1733.

Good, W.R., Transderm–nitro controlled delivery of nitroglycerin via the transdermal route. Drug Dev. Ind. Pharm., 9 (1983) 647–670.

Guy, R.H., Hadgraft, J. and Maibach, H.I., Percutaneous absorption in man: a kinetic approach. Toxicol. Appl. Pharmacol., 78 (1985) 123–129.

Guy, R.H. and Hadgraft, J., Transdermal drug delivery: the ground rules are emerging. Pharm. Int., 6 (1985a) 112–116.

Guy, R.H. and Hadgraft, J., Kinetic analysis of transdermal nitroglycerin delivery. Pharm. Res., 2 (1985b) 206–211.

Guy, R.H. and Hadgraft, J., Pharmacokinetic interpretation of the plasma levels of clonidine following transdermal delivery. J. Pharm. Sci., 74 (1985c) 1016–1018.

Guy, R.H. and Hadgraft, J., The prediction of plasma levels of drugs following transdermal application. J. Controlled Release, 1 (1985d) 177–182.

Hansch, C. and Leo, A.J., Substituent Constants for Correlation Analysis in Chemistry and Biology, Wiley-Interscience, New York, 1979.

Imhof, P.R., Vuillemin, T., Gerardin, A., Racine, A., Muller, P. and Follath, F., Studies of the bioavailability of nitroglycerin from a transdermal therapeutic system (Nitroderm-TTS). Eur. J. Clin. Pharmacol., 27 (1984) 7–12.

Karim, A., Transdermal absorption: a unique opportunity for constant delivery of nitroglycerin. Drug Dev. Ind. Pharm., 9 (1983a) 671–689.

Karim, A., Transdermal absorption of nitroglycerin from microsealed drug delivery (MDD) system. Angiology, 34 (1983b) 11–21.

Kutsky, R.J., Handbook of Vitamins and Hormones, Van Nostrand Reinhold, New York, 1973.

Laufer, L.R., DeFazio, J.L., Lu, J.K.H., Meldrum, D.R., Eggena, P., Sanbhi, M.R., Hershman, J.M. and Judd, H.L., Estrogen replacement therapy by transdermal estradiol administration. Am. J. Obstet. Gynecol., 146 (1983) 533–540.

Lawson, A.A.H., Clinical and pharmacological studies with transdermal clonidine. In L.F. Prescott and W.S. Nimmo (Eds.), Rate Control in Drug Therapy, Churchill Livingstone, Edinburgh, 1985, pp. 215–219.

Muir, C. and Metcalfe, R., A comparison of plasma levels of hyoscine after oral and transdermal administration. J. Pharm. Biomed. Anal., 1 (1983) 363–367.

Price, N.M., Schmitt, L.G., McGuire, J., Shaw, J.E. and Trobough, G., Transdermal scopolamine in the treatment of motion sickness at sea. Clin. Pharmacol. Ther., 29 (1981) 414–419.

Rose, J.E., Herskovic, J.E., Trilling, Y. and Jarvik, M., Transdermal nicotine reduces cigarette craving and nicotine preference. Clin. Pharmacol. Ther., 38 (1985) 450–456.

Schenkel, L., Balestra, J., Scmitt, L. and Shaw, J., Transdermal oestrogen substitution in the menopause. In L.F. Prescott and W.S. Nimmo (Eds.), Rate Control in Drug Therapy, Churchill Livingstone, Edinburgh, 1985, pp. 294–303.

Vlasses, P.H., Ribeiro, L.G.T., Rotmensch, H.H., Bondi, J.V., Loper, A.E., Hichens, M., Dunlay, M.C. and Ferguson, R.K., Initial evaluation of transdermal timolol: serum concentrations and β-blockade. J. Cardiovasc. Pharmacol., 7 (1985) 245–250.

Weber, M.A., Drayer, J.I.M., Brewer, D.D. and Lipson, J.L., Transdermal continuous antihypertensive therapy. Lancet, 1 (1984) 9–11.

Wolff, M., Cordes, G. and Luckow, V., In vitro and in vivo-release of nitroglycerin from a new transdermal therapeutic system. Pharm. Res., 2 (1985) 23–29.