International Journal of Pharmaceutics, 67 (1991) 97–100
Elsevier

IJP 02214

Influence of oleic acid and other permeation promoters on transdermal delivery of dihydroergotamine through rabbit skin

Esmail M. Niazy

College of Pharmacy, King Saud University, Riyadh (Saudi Arabia)

(Received 23 February 1990)
(Modified version received 11 May 1990)
(Accepted 3 June 1990)

Key words: Oleic acid; Percutaneous absorption; Penetration enhancer; Dihydroergotamine

Summary

Dihydroergotamine (DHE) has recently been suggested as a potential candidate for transdermal administration. In an attempt to increase transdermal delivery of the drug, different enhancers including oleic acid, lauric acid, procaine hydrochloride and urea, were evaluated in vitro, utilizing improved Franz diffusion cells. Oleic acid was found to be the most effective enhancer tested, increasing the percutaneous absorption of DHE by 208-fold. It was found that procaine hydrochloride and lauric acid enhanced transdermal delivery of DHE by 2- and 3-fold, respectively. On the other hand, the formulation containing 6.0% urea did not show any significant difference from the control. The sizable enhancement observed with oleic acid in this study warrants in vivo experimentation with DHE/oleic acid formulations in the future.

Introduction

Transdermal drug delivery, as a route for systemic drug administration, has become a subject of considerable interest (Dasta and Geraets, 1982; Shaw, 1984; Good et al., 1985; Vlasses et al., 1985; Dietz et al., 1986; Wellstein et al., 1986; Plezia et al., 1986; Findlay et al., 1987; Nishihata et al., 1988; Banerjee and Ritschel, 1989; Mahjour et al., 1989). Currently it is one of the advancing areas in drug development research.

In a recent investigation we have shown that dihydroergotamine (DHE), which is used in treating migraine, is a good candidate for transdermal administration (Niazy et al., 1989).

Penetration promoters, enhancers or accelerants are thought to interact with some component of skin causing the stratum corneum to swell and/or leach out some of the structural components and thus increase drug penetration through the barrier membrane (Elfbaum and Laden, 1968; Barry, 1983; Hadgraft, 1984). However, the mechanism of those promoters is not fully understood. The literature on penetration enhancers was recently reviewed (Woodford and Barry, 1987).

The purpose of this investigation is to study the effect of various penetration accelerants such as oleic acid (OA), lauric acid (LA), urea and procaine hydrochloride on enhancing the transdermal delivery of DHE upon addition to the drug-vehicle formulation. Oleic acid and lauric acid have been

Correspondence: E.M. Niazy, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia.

reported to increase permeation of various polar and non-polar compounds through the skin (Cooper, 1984; Aungst et al., 1986. In previous studies urea has been found to enhance transdermal delivery of phenylbutazone (Tsai and Naito, 1985) and piroxicam (Tsai et al., 1985) through rabbit skin. Procaine hydrochloride has been recently shown to increase transport of acyclovir across rat skin (Saidaum, 1988). Therefore, these agents were selected as possible penetration enhancers for the transdermal formulation of DHE.

Materials and Methods

Materials

Dihydroergotamine mesylate (Sandoz Pharmaceuticals, E. Hanover, NJ, U.S.A.), propylene glycol (Fisher Scientific Co., Fair Lawn, NJ, U.S.A.), oleic acid (Hopkin and Williams, Ltd, Essex, U.K.), lauric acid (Fluka AG, Buchs, Switzerland), urea (Riedel-De-Haen AG, Seelze-Hanover, F.R.G.), procaine hydrochloride (Philip Harris Ltd, Birmingham, U.K.), propyl hydroxy-4-benzoate (E. Merck AG, Darmstadt, F.R.G.), sodium chloride, glycine and hydrochloric acid (BDH Chemicals Ltd, Poole, U.K.) were used without further purification. Methanol (E. Merck AG, Darmstadt, F.R.G.) and acetonitrile (BDH Chemicals Ltd, Poole, U.K.) were HPLC grade.

In vitro diffusion studies

In vitro drug diffusion studies were conducted utilizing improved Franz diffusion cells (Crown Glass Company, Somerville, NJ, U.S.A.). Rabbit skin obtained from the dorsal area was used as a barrier membrane. Preparation of rabbit skin and the in vitro permeation technique were described in details in our previous studies (Niazy et al., 1989, 1990).

To investigate the enhancing effect of OA on percutaneous absorption of DHE and to find out the optimal concentration which produces the maximum enhancing effect, several experiments were performed using different concentrations of OA which were prepared by adding OA to propylene glycol solution containing 16.0 mg/ml of the drug to obtain a final formulation containing 2.0, 6.0 and 10% (v/v) OA. The effects of other additives including LA, procaine hydrochloride and urea on permeation of DHE through the skin were also studied by preparing formulations containing 6.0% (w/v) of each in propylene glycol/DHE solution (16.0 mg/ml). 1 ml of each tested formulation was applied to the epidermal surface, which was sufficient to cover the exposed surface area of the skin (3.14 cm^2). One cell was used as reference where 1.0 ml of propylene glycol containing 16.0 mg DHE was applied to the skin. Drug concentrations in the receptor compartment were determined, after withdrawing 2.0 ml samples at 3, 6, 9, 12 and 24 h post-application, using an HPLC assay method previously developed in our laboratory (Niazy et al., 1988).

Statistical analysis

Statistical analysis was performed by using Student's *t*-test.

Results and Discussion

The cumulative amounts of DHE transported across the rabbit skin during the 24 h at different time intervals from propylene glycol formulations containing various concentrations of OA are shown in Table 1. The total amount of DHE that penetrated the skin during the 24 h period from the formulations containing 0.0, 2.0, 6.0 and 10.0% OA were 7.3, 6.1, 1510.9 and 366.0 μg respectively. The total amount of DHE absorbed from propylene glycol base containing 2.0% OA was almost the same as that delivered from the formu-

TABLE 1

Cumulative amount of DHE penetrated through the skin from propylene glycol base using oleic acid as enhancer

Time (h)	Control: (no. O.A.)	2% O.A.	6% O.A.	10% O.A.
3	0.3 ± 0.02	0.2 ± 0.03	8.4 ± 4.85	0.2 ± 0.03
6	0.6 ± 0.05	0.6 ± 0.09	147.1 ± 11.72	0.7 ± 0.18
9	0.9 ± 0.06	1.0 ± 0.10	660.2 ± 22.26	17.1 ± 1.70
12	1.6 ± 0.14	1.4 ± 0.11	866.6 ± 55.13	121.9 ± 9.35
24	7.3 ± 1.80	6.1 ± 1.52	1510.9 ± 157.20	366.0 ± 20.97

Values in μg, mean of 3 cells ± S.E.

lation containing 0.0% OA (control) with no significant difference ($P > 0.05$). It can be seen from Table 1 that the penetration of DHE was markedly increased from the formulations containing 6.0 and 10.0% OA. Table 1 also illustrates a marked reduction in the lag time for permeation of DHE from the formulation containing 6.0% OA. The extent of enhancement, based upon 24 h permeation was 208-fold with 6.0% OA. Further increase of OA up to to 10.0%, decreased the extent of enhancement to about 50.5-fold. A similar enhancing effect for OA was previously reported by Cooper (1984) for the transport of salicylic acid. Mirejovsky and Takruri (1986) reported that 5.0% OA enhanced transdermal delivery of hydrocortisone by about 40-fold. On the other hand, Aungst et al. (1986) showed that the permeation of naloxone was increased by 22-fold in the presence of 10.0% OA. These two reports seem to be in agreement with our results. The penetration enhancement effect of OA may be due to interaction of OA-propylene glycol system with the skin leading to structural changes and thus disrupting the stratum corneum lipid structure (Golden et al., 1987; Goodman and Barry, 1988). In addition it is possible that OA exerts its enhancing effect on the permeation of DHE through rabbit skin by ion pair formation. Similar enhancement mechanism for OA had been reported by Green et al. (1988) for the transdermal delivery of naphazoline.

Table 2 summarizes the permeation data of DHE from propylene glycol base in the presence of other additives. The cumulative amount of DHE that penetrated in the skin during 24 h period from the formulations containing 6.0% (w/v) LA, procaine hydrochloride and urea were 21.9, 13.4 and 5.2 μg, respectively. It can be seen that LA enhanced transdermal delivery of DHE by 3 times compared to the control (7.3 μg). However, the extent of enhancement observed with LA was much less than that obtained with 6.0% OA. This result may be attributed to the low concentration of LA (6%) in the formulation. A previous study (Aungst et al., 1986) has indicated that maximum flux of naloxone was observed using 20.0% LA. Moreover, Green et al. (1988) reported that OA appears to be a better enhancer than LA due to the capability of OA to disrupt the ordered array of straight chain skin lipids. The total amount of DHE delivered from propylene glycol base containing 6.0% (w/v) urea (5.2 μg) was almost the same as that observed from the control (7.3 μg) with no significant difference ($P > 0.05$). The same result was observed by Aungst et al. (1986) who pointed out that the urea had no effect on naloxone flux. The cumulative amount of DHE permeated from the formulation containing 6.0% (w/v) procaine hydrochloride after 24 h was almost twice that delivered by the control after the same time period. Recently, Saidaum (1988) showed that the presence of 5.0% (w/w) procaine hydrochloride increased acyclovir penetration through rat skin by 7-fold. The mechanism involved in the enhancement process was not clear. However, the positive results obtained warrant future experimentation in this area.

TABLE 2

Cumulative amount of DHE penetrated through the skin from propylene glycol base using various enhancers

Time (h)	Control	Lauric acid (6%)	Procaine hydrochloride (6%).	Urea (6%)
3	0.3 ± 0.02	0.3 ± 0.01	0.2 ± 0.05	0.2 ± 0.07
6	0.6 ± 0.05	0.6 ± 0.09	0.6 ± 0.13	0.5 ± 0.03
9	0.9 ± 0.06	1.2 ± 0.19	1.3 ± 0.34	1.0 ± 0.25
12	1.6 ± 0.14	2.7 ± 0.46	2.5 ± 0.73	2.1 ± 0.63
24	7.3 ± 1.80	21.9 ± 3.84	13.4 ± 1.69	5.2 ± 0.77

Values in μg, mean of 4 cells ± S.E.

In conclusion, this investigation provides useful information about penetration enhancers, which could be utilized in the development of clinically acceptable transdermal therapeutic systems for DHE in the future. Additional studies are currently underway to investigate various transdermal formulations of DHE in vivo.

Acknowledgements

The author would like to thank Mr Abubakr El-Gorashi for valuable contribution and Mr K. Abbas for typing the manuscript.

References

Aungst, B., Rogers, N. and Shefter, E., Enhancement of naloxone penetration through human skin in vitro using fatty acids, fatty alcohols, surfactants, sulfoxides and amides. *Int. J Pharm.*, 33 (1986) 225–234.

Banerjee, P. and Ritschel, W., Transdermal permeation of vasopressin. II. Influence of Azone on in vitro and in vivo permeation. *Int. J. Pharm.*, 49 (1989) 199–204.

Barry, B., Properties that influence percutaneous absorption. In. Swarbrick, J. (Ed.), *Dermatological Formulation: Percutaneous Absorption*, Dekker, New York, 1983, pp. 127–233.

Cooper, E., Increased skin permeability for lipophilic molecules. *J. Pharm. Sci.*, 73 (1984) 1153–1156.

Dasta, J. and Geraets, P., Topical nitroglycerin: a new twist to an old standby. *Am. Pharm.*, NS 22 (1982) 29–32.

Dietz, A., Carlson, J. and Beck, C., Effect of transdermal azatadine on reducing histamine-induced wheal area. *Ann. Allergy*, 57 (1986) 38–41.

Elfbaum, S. and Laden, K., The effect of dimethyl sulphoxide on percutaneous absorption. *J. Soc. Cosm. Chem.*, 19 (1968) 119–127, 163–172, 841–847.

Findlay, J., Place, V. and Snyder, P., Transdermal delivery of testosterone. *J. Clin. Endocrinol. Metab.*, 64 (1987) 266–268.

Golden, G., McKie, J. and Potts, R., Role of stratum corneum lipid fluidity in transdermal drug flux. *J. Pharm. Sci.*, 76 (1987) 25–28.

Good, W., Powers, M. and Schenkel, L., A new transdermal delivery system for estradiol. *J. Controlled Release*, 2 (1985) 89–97.

Goodman, M. and Barry, B., Action of penetration enhancers on human skin as assessed by the permeation of model drug 5-fluorouracil and estradiol. I. Infinite dose technique. *J. Invest. Dermatol.*, 91 (1988) 323–327.

Green, P., Guy, R. and Hadgraft, J., In vitro and in vivo enhancement of skin permeation with oleic and lauric acids. *Int. J. Pharm.*, 48 (1988) 103–111.

Hadgraft, J., Penetration enhancers in percutaneous absorption. *Pharm. Int.*, 5 (1984) 252–254.

Mahjour, M., Mauser, B. and Fawzi, M., Skin permeation enhancement effects of linoleic acid and Azone on narcotic analgesics. *Int. J. Pharm.*, 56 (1989) 1–11.

Mirejovsky, D. and Takruri, H., Dermal penetration enhancement profile of hexamethylenelauramide and its homologues: in vitro versus in vivo behavior of enhancers in the penetration of hydrocortisone. *J. Pharm. Sci.*, 75 (1986) 1089–1093.

Niazy, E., Molokhia, A. and El-Goraishi, A., Quick and simple determination of dihydroergotamine by high performance liquid chromatography. *Anal. Lett.*, 21 (1988) 1833–1843.

Niazy, E., Molokhia, A. and El-Goraishi, A., Effect of Azone and other penetration enhancers on the percutaneous absorption of dihydroergotamine. *Int. J. Pharm.*, 56 (1989) 181–185.

Niazy, E., Molokhia, A. and El-Goraishi, A., Effect of vehicle and drug concentration on transdermal delivery of dihydroergotamine using excised animal skin. *Drug Dev. Ind. Pharm.*, 16 (1990) 1697–1715.

Nishihata, T., Kamada, A., Sakai, K., Takahashi, K., Matsumoto, K., Shinozaki, K., Tabata, Y., Keigami, M., Miyagi, T. and Tatsumi, N., Percutaneous absorption of diclofenac in rats and humans: aqueous gel formation. *Int. J. Pharm.*, 46 (1988) 1–7.

Plezia, P., Linford, J., Kramer, H., Lacono, R. and Hameroff, R., Transdermal therapeutic system (fentanyl) for postoperative pain: an efficacy, toxicity and pharmacokinetic trial. *Anesthesiology*, 65 (1986) A 210.

Saidaum, M., In-vitro studies on the percutaneous absorption of acyclovir, Master's Thesis, King Saud University, Riyadh, Saudi Arabia (1988).

Shaw, J., Pharmacokinetics of nitroglycerin and clonidine delivered by transdermal route. *Am. Heart. J.*, 108 (1984) 217–222.

Tsai, Y., Hsu, L. and Naito, S., Percutaneous absorption of piroxicam from ointment bases in rabbits. *Int. J. Pharm.*, 24 (1985) 61–78.

Tsai, Y. and Naito, S. Percutaneous absorption of phenylbutazone from ointment bases in rabbits. *Int. J. Pharm.*, 23 (1985) 315–331.

Vlasses, P., Ribeior, L., Rotmensch, H., Bondi, J. and Loper, A., Initial evaluation of transdermal timolol: Serum concentrations and B-blockade. *J. Cardiovasc. Pharmacol.*, 7 (1985) 245–250.

Wellstein, A., Kuppers, H., Pitschner, H. and Palm, D., Transdermal delivery of bupranolol: Pharmacodynamics and beta-adrenoceptor occupancy. *Eur. J. Clin. Pharmacol.*, 31 (1986) 419–422.

Woodford, R. and Barry, B., Topical penetration enhancers. *Manuf. Chem.*, 85 (1987) 49–51.