J. Pharm. Pharmacol. 1997, 49: 955–959
Received May 16, 1997
Accepted June 10, 1997

Effects of Penetration Enhancers on the In-vitro Percutaneous Absorption of Progesterone

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Abstract

Because progesterone seems suitable for treatment of premenstrual syndrome, the influence of penetration enhancers such as propylene glycol, urea and laurocapram (Azone) on the percutaneous absorption of progesterone from carbopol hydroalcoholic gels and from poly(ethylene glycol) ointments has been investigated.

Skin experiments were performed using excized abdominal rat and porcine skin. Addition of 10% laurocapram was found to be the most efficient enhancer for progesterone from carbopol hydroalcoholic gels, for both rat and porcine skin; the next most efficient enhancer was urea in poly(ethylene glycol) bases. This enhanced the diffusion rates 2·5 fold, compared with pure poly(ethylene glycol) alone.

The results show that hydroalcoholic gels and poly(ethylene glycol) ointments are both suitable vehicles for progesterone and that premenstrual syndrome might be treated effectively by use of hydroalcoholic gels containing 10% laurocapram.

Topically applied progesterone seems suitable for treatment of premenstrual syndrome, PMS (Dennerstein et al 1985; Smith & Schiff 1989; Lewis et al 1995). The results of new studies suggest that progesterone level is related to the severity of distressing symptoms in PMS patients (Wang et al 1996). PMS might be defined as a combination of physical and behavioural symptoms which occur during the luteal phase of the menstrual cycle and are absent during the follicular phase. Because PMS is, therefore, a cyclic disorder, an underlying endocrine dysfunction has been assumed.

Oral administration requires large doses, an appropriate vehicle, and an increased surface area (micronization) to achieve reasonable blood levels. The pharmacokinetic profile of orally administered progesterone is one of rapid absorption and short life (Sitruk-Ware et al 1987; Norman et al 1991).

Knepp et al (1988) showed that progesterone can be absorbed transdermally from a novel liposome-based drug-delivery patch consisting of a moulded agarose matrix, and that unlike progesterone taken orally is not subject to interception by the liver. Artini et al (1995) compared the absorption and efficacy of progesterone administered intramuscularly, and vaginally as a cream. Serum progesterone levels were compared with those in the control of the not-supplemented group and were found to be more steady with progesterone vaginal cream than after intramuscular injection. Therefore vaginal cream is better for bioavailability; it appears to be a more accepted and a more suitable method for progesterone support. This study indicates the suitability of transdermal application of progesterone.

The composition and biophysical structure of the stratum corneum of different species might play an important role in barrier properties and responses to vehicles. Furthermore, enhanced permeation in different species might vary depending on the effects of alcohol on skin components and the relative abundance of these components. Lipid composition varies between species. Despite many investigations the influence of the composition and structure of the stratum corneum on permeation remains unclear (Pershing et al 1990; Potts et al 1991; Knutson et al 1993). Excized animal skin, e.g. rodent skin, is used in studies on percutaneous absorption of drugs, possibly because of its ready availability, although it differs significantly from human skin (Chowhan & Pritchard 1978). Wester & Maibach (1985) demonstrated that porcine skin and human skin give comparable results for the percutaneous absorption of haloprogin, *N*-acetylcysteine, testosterone, cortisone, caffeine and butter yellow.

Because permeation of vaginally administered progesterone was highest from poly(ethylene glycol)-based suppositories (Price et al 1983; Safwat et al 1991), it should be investigated whether poly(ethylene glycol) ointment is a suitable vehicle for dermal use also. The aim of the current study was to examine the influence of some penetration enhancers on the in-vitro permeation of progesterone through abdominal rat skin and pig-ear skin. Carbopol gels containing 60% ethanol and 10% propylene glycol as co-solvents were used to obtain a vehicle in which the drug is well distributed and which is easily spreadable; 3% progesterone was incorporated into all formulations. The permeation characteristics of the gels and poly(ethylene glycol) ointments were evaluated using Franz diffusion cells.

Materials and Methods

Materials

Progesterone was supplied by Sigma (St Louis, MO), urea by Merck (Darmstadt, Germany) and Carbopol 940 by Goodrich (UK). Laurocapram (Azone) was synthesized according the method of Bodde (1989). Triethanolamine was in accordance with the specifications in the Pharmacopoea Austriaca (ÖAB 1990); propylene glycol, poly(ethylene glycol) 400 and poly(ethylene glycol) 4000 were in accordance with the spe-

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Table 1. Compositions of the progesterone–hydroalcoholic gels.

Progesterone	Carbopol 940	Triethanolamine –water (1 : 1) 50%	Propyleneglycol	Ethanol 60% (w/w)	Laurocapram
3·0	1·0	3·0	–	93·0	–
3·0	1·0	3·0	10·0	83·0	–
3·0	1·0	3·0	10·0	78·0	5·0
3·0	1·0	3·0	10·0	73·0	10·0

Table 2. Composition (%) of the poly(ethylene glycol) ointments.

Progesterone	Unguentum Polyethylenglycoli	Laurocapram	Urea
3·0	97·0	–	–
3·0	92·0	–	5·0
3·0	92·0	5·0	–
3·0	87·0	10·0	–

cifications in the Pharmacopoea Europaea (1990); Unguentum Polyethylenglycoli conformed to the preparation of the Pharmacopoea Austriaca (ÖAB 1990) and consisted of poly(ethylene glycol) 400 and poly(ethylene glycol) 4000 in the mass ratio 60 : 40 (w/w).

Centricon-3 was purchased from Amicon Grace Company (Danvers, USA). All materials were of reagent grade.

Formulations

The composition of the progesterone hydroalcoholic gels, poly(ethylene glycol) ointments used in this study, are shown in Tables 1 and 2. Gels were prepared by dispersing the total mass of Carbopol 940, specified in Table 1, in approximately 10 g water and neutralizing with triethanolamine (carbopol concentrate). After 30 min the progesterone solution in ethanol–water was added to the mixture. For gels containing propylene glycol and laurocapram, progesterone was suspended in the gel and then ethanol was added. The resulting suspension was manufactured with the neutralized carbopol concentrate.

Unguentum Polyethylenglycoli (ÖAB 1990) was prepared according to the Pharmacopoea Austriaca. Poly(ethylene glycol) 400 and poly(ethylene glycol) 4000 were melted together on a water bath (65°C) and then stirred as they cooled to room temperature. The resulting product was a white odourless ointment.

Progesterone and an equal amount of melted Unguentum Polyethylenglycoli were prepared as a concentrate and then mixed with the remaining Unguentum Polyethylenglycoli. If penetration enhancers were included, progesterone was dissolved in laurocapram or in urea-poly(ethylene glycol) 400 and then stirred together with the rest of ointment.

Skin membrane preparation

The abdominal hair of female rats, 250–300 g, was shaved with hand-held razors. The rats were then anaesthetized with ether, killed by cervical dislocation, and the abdominal skin was surgically removed from the animals and adhering subcutaneous fat was carefully removed. Porcine skin was prepared from the ears of female pigs; these were shaved with a hand-held razor. Full-thickness skin was obtained by carefully removing the subcutaneous fat with a dermatome.

Permeation studies

Franz diffusion cells with a diffusion area of 0·785 cm^2 (LG-1083-PC; Erweka) were used in these studies. The excized skins were placed with the stratum corneum facing the donor compartment and the dermis side facing the receptor. In all experiments 1·5 g of the formulations (Tables 1 and 2) were placed on the skin surface in the donor compartment which was sealed from the atmosphere with plastic film (parafilm). The geometry of the cell required the application of a larger amount of formulation, as is usual in-vivo. The receptor compartment was filled with propylene glycol–water, 40 : 60 (w/w). During the experiments, the solution in the receptor side was maintained at 37 ± 1°C and stirred at 500 rev min^{-1} with teflon-coated magnetic stirring bars. After application of the sample on the donor side, samples were collected from the receptor side at designated time intervals and replaced with a fresh receptor.

Determination of dependence of progesterone solubility on various enhancers

An excess amount of the powdered drug was added to 2 mL each of water, water–ethanol, water–ethanol–propylene glycol, water–ethanol–propylene glycol–5% laurocapram and water–ethanol–propylene glycol–10% laurocapram. The suspensions were covered with parafilm and stirred for 24 h at 25°C for equilibration. All experiments were performed in quadruplicate.

Analytical methods

Procedure for the solubility experiments. Samples were filtered through a membrane filter (Minisart, RC 4; 0·22 μm), diluted, and assayed by HPLC. To remove disturbing poly(ethylene glycol) 400, the filtrates were sucked through C_{18} cartridges (Analytichem, Bond-Elut C-18) previously conditioned with methanol (5 mL). The loaded cartridges were washed with distilled water (3 × 4 mL) and eluted with methanol (1 mL). The resulting purified sample (20 μL) was analysed by HPLC (Perkin-Elmer, Series 2).

Procedure for hydroalcoholic gels. Assays of progesterone in the hydroalcoholic gels and in the acceptor phase during permeation experiments were performed by a previously reported HPLC method (Valenta & Schmatzberger-Wagerer 1995). At the beginning of the experiments, when progesterone concentrations were sometimes below the detection limit, precolumn concentration was performed by solid-phase extraction (Valenta & Janout 1994).

Procedure for formulations containing poly(ethylene glycol). The retention times of the inactive excipients poly(ethylene glycol) 4000 and poly(ethylene glycol) 400 were such that the

Table 3. Solubility of progesterone at 25°C, and the effect of different enhancers on the solubility.

Ingredients	Solubility ($\mu g\,mL^{-1}$)	Solubility improvement
Water	11·9 ± 1·2	1
Ethanol/water (60 : 40, w/w)	84·9 ± 2·4	7·1
Ethanol/water/propylene glycol (60 : 30 : 10, v/v)	181·7 ± 25·3	15·2
Ethanol/water/propylene glycol/laurocapram (60 : 25 : 10 : 5, v/v)	258·4 ± 58·2	21·7
Ethanol/water/propylene glycol/laurocapram (60 : 20 : 10 : 10, v/v)	393·8 ± 66·5	33·1
Poly(ethylene glycol) 400/water (40 : 60; w/w)	210 ± 18*	17·6

Values are means ± s.d. of results from four separate HPLC analyses of the same sample. *Data obtained from the literature (Toddywala et al 1991).

compound peaks interfered with those of progesterone in the HPLC method. Purification and concentration were achieved by ultrafiltering the sample solution through an anisotropic membrane (part of the centricon-3) with a 3000 MW cut-off. The receptor phase (1·5 mL) was therefore centrifuged through centricon-3 (2500 *g*; 60 min) to remove the poly(ethylene glycol) 4000. The filtrate was sucked through a C_{18} cartridge previously conditioned with methanol (5 mL). To purify the sample from the lower molecular weight poly(ethylene glycol) 400, the cartridges were washed with distilled water (3 × 4 mL). After elution of progesterone with methanol (1 mL) the eluate (20 μL) was analysed by HPLC.

Results and Discussion

Diffusion studies to evaluate the in-vitro permeation of progesterone from hydroalcoholic gels and Unguentum Polyethylenglycoli (with and without enhancers) proved to be an appropriate means of screening the formulations for the relative availability of the drug.

Ethanol and propylene glycol improved the solubility of progesterone. In combination they have a synergistic effect, as is shown in Table 3.

A mixture of 5% v/v laurocapram in water–ethanol–propylene glycol, 30 : 60 : 10 (v/v) increased the solubility of progesterone 21·7-fold compared with water alone, and by 1·4-fold compared with the mixture without laurocapram. Adding 10% laurocapram increased the solubility 33-fold compared with water alone, and more than 2-fold compared with the solvent mixture alone.

The compositions of four carbopol hydroalcoholic gels and five poly(ethylene glycol) ointments are listed in Tables 1 and 2. The inclusion of the selected enhancers was shown to have a significant effect on the permeation of progesterone, but to a variable extent. In the absence of enhancers, progesterone permeated at a higher rate from carbopol hydroalcoholic gels (31·2 $\mu g\,cm^{-2}\,g^{-1}$ in 24 h) than from poly(ethylene glycol) ointments (27·8 $\mu g\,cm^{-2}\,g^{-1}$ in 24 h) (Table 4).

Propylene glycol (Barry 1987; Barry & Bennett 1987; Huth et al 1996) and laurocapram (Phillips & Michniak 1995a, b; Diez-Sales et al 1996; Hadgraft 1996; Harrison et al 1996; Szolarplatzer et al 1996) were selected as penetration enancers compatible with carbopol gels. Propylene glycol alone increased the permeation through rat skin from 31·2 $\mu g\,cm^{-2}\,g^{-1}$ (without propylene glycol) to 66·15 $\mu g\,cm^{-2}\,g^{-1}$ (Table 4). A small increase compared with the control value was measured for porcine skin (Table 5). Further addition of 5% laurocapram reduced the rate of release of progesterone from 45·64 $\mu g\,cm^{-2}\,g^{-1}$ to 39·6 $\mu g\,cm^{-2}\,g^{-1}$. Combinations of propylene glycol with 10% laurocapram were necessary to obtain the highest enhancement of progesterone permeation; this was true both for rat skin, for which the permeation was 174·2 $\mu g\,cm^{-2}\,g^{-1}$ after 24 h (Fig. 1), and for porcine skin, permeation 78·97 $\mu g\,cm^{-2}\,g^{-1}$ after 24 h (Fig. 2). Comparison of the results obtained using rat and porcine skin showed they were rather similar (Figs 1 and 2), although lower with porcine skin (Table 5). These data are in accordance with those from other investigations (Cleary 1984).

In addition to urea, laurocapram was tested in combination with the poly(ethylene glycol) vehicle. The incorporation of 5% laurocapram in the ointments reduced permeation 1·8-fold, compared with the pure poly(ethylene glycol) ointment. 10% laurocapram was necessary to enhance the permeation from poly(ethylene glycol) vehicle 5·5-fold compared with pure poly(ethylene glycol) ointment (Table 4). The optimum laur-

Table 4. Effect of different enhancers on the amount of progesterone released from hydroalcoholic gels and poly(ethylene glycol) ointments through excized rat skin.

Composition	Permeation ($\mu g\,cm^{-2}\,g^{-1}$) of applied material		
	1 h	7 h	24 h
Carbopol gel	15·4 ± 4·25	28·3 ± 11·0	31·2 ± 12·6
10% Propylene glycol	33·1 ± 13·26	41·2 ± 27·5	66·15 ± 13·5
10% Propylene glycol + 5% laurocapram	7·95 ± 6·2	26·5 ± 22·2	45·3 ± 7·2
10% Propylene glycol + 10% laurocapram	24·2 ± 19·1	105·0 ± 21·2	174·2 ± 65·0
Unguentum Polyethylenglycoli	6·25 ± 4·1	21·0 ± 7·8	27·8 ± 1·0
5% Urea	18·75 ± 9·9	33·4 ± 8·44	69·5 ± 5·9
5% Laurocapram	3·12 ± 3·5	11·5 ± 3·35	15·5 ± 1·68
10% Laurocapram	29·37 ± 5·0	79·9 ± 22·2	153·4 ± 13·2

Table 5. Effect of the enhancers on the amount of progesterone released from hydroalcoholic gels through excized porcine skin.

Composition	Permeation ($\mu g\,cm^{-2}\,g^{-1}$) of applied material		
	1 h	7 h	24 h
Carbopol gel	5·29 ± 1·76	25·3 ± 25·1	45·64 ± 34·1
10% Propylene glycol	17·8 ± 1·27	29·5 ± 11·7	55·18 ± 18·3
10% Propylene glycol + 5% laurocapram	20·44 ± 0·1	34·3 ± 8·5	39·6 ± 11·1
10% Propylene glycol + 10% laurocapram	41·9 ± 8·2	60·7 ± 13·3	78·9 ± 29·7

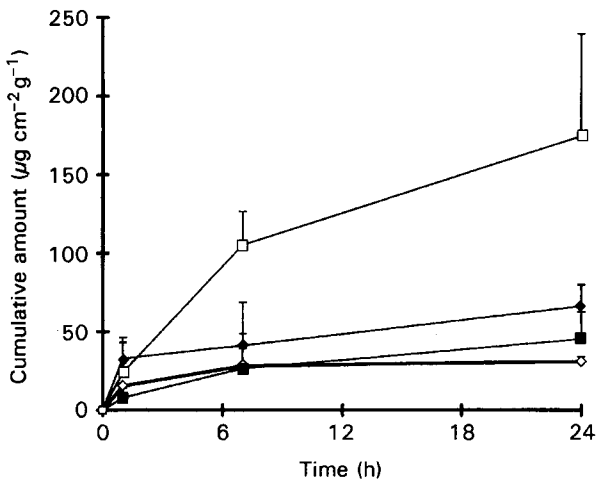

FIG. 1. Effect of propylene glycol and laurocapram on the percutaneous absorption of progesterone from carbopol hydroalcoholic gels through excized rat skin. △ Control, ▲ with 10% propylene glycol, ■ with 10% propylene glycol and 5% laurocapram, □ with 10% propylene glycol and 10% laurocapram. The data incorporate the standard deviations of results from three experiments.

ocapram concentration depended on the physicochemical properties of the active drug and the formulation. Using human skin Wotton et al (1985) observed the inhibiting effect of the presence of 1% laurocapram in poly(ethylene glycol) 400. We confirmed this negative effect from the semi-solid vehicle poly(ethylene glycol) 400 plus poly(ethylene glycol) 4000 (Unguentum Polyethylenglycoli) in the presence of 5% laurocapram for both rat and porcine skin, but if 10% laurocapram was added the progesterone permeation was clearly enhanced. The addition of 5% urea improved the permeation 2·5-fold after 24 h (Fig. 3). Though infinite-dose conditions predominate, the lag times in the experimental curves are not evident. The reason for this is not clear.

There is contradictory data in the literature: on the one hand, it is confirmed by experimental data (Diez-Sales et al 1996) that laurocapram should not enhance the permeability of the most lipophilic compounds (log $P_{O/W} > 3$) whereas the permeability of the highly lipophilic compound anthracene (log $P_{O/W} = 4{\cdot}5$) is, on the other hand, reported to be enhanced by laurocapram (Stoughton & McClure 1983). In accordance with these data we found that permeation of progesterone (log $P_{O/W} = 3{\cdot}76$; Johnson et al 1995) from hydroalcoholic gels and from poly(ethylene glycol) vehicles is clearly enhanced by addition of 10% laurocapram. This trend is confirmed if porcine skin is used.

It is known that the concentration of laurocapram required to produce optimum enhancement varies from one drug to another. In our investigations the incorporation of 10% laurocapram enhanced the permeation of progesterone 5–6 fold, compared with permeation from the gel without any additive.

From poly(ethylene glycol) vehicles the ranking order of the most effective enhancers after 24 h was observed to be 10% laurocapram > 5% urea.

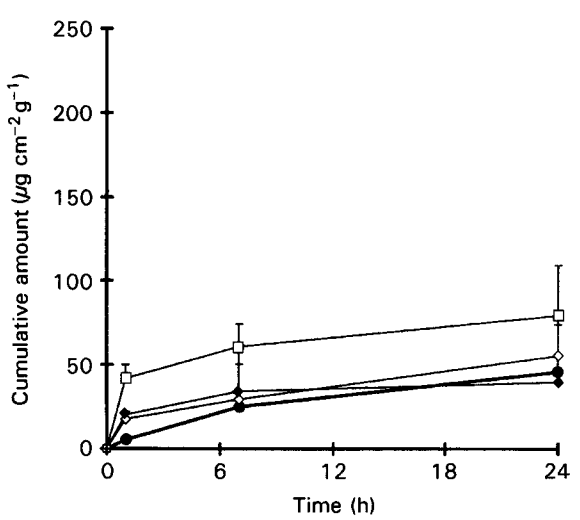

FIG. 2. Effect of propylene glycol and laurocapram on the percutaneous absorption of progesterone from carbopol hydroalcoholic gels through excized porcine skin. ■ Control, ◇ with 10% propylene glycol, ◆ with 10% propylene glycol and 5% laurocapram, □ with 10% propylene glycol and 10% laurocapram. The data incorporate the standard deviations of results from three experiments.

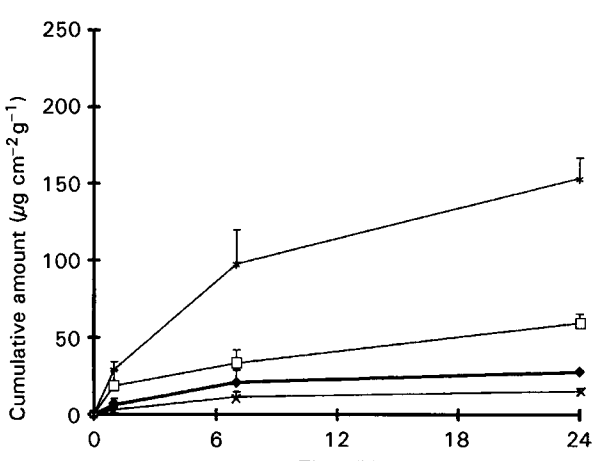

FIG. 3. Effect of urea and laurocapram on the percutaneous absorption of progesterone from poly(ethylene glycol) ointments through excized rat skin. ◆ Control, □ with 5% urea, × with 5% laurocapram, * with 10% laurocapram. The data incorporate the standard deviations of results from three experiments.

We manufactured the formulations as described, rather than adding laurocapram to the finished product, because it is reported (Stoughton & McClure 1983) that the activity of laurocapram was lost if it was simply mixed with an existing formulation.

In conclusion, hydroalcoholic gels and poly(ethylene glycol) ointments are both suitable vehicles for progesterone because of their high permeation through rat and porcine skin. However, permeation through animal skin is not always equivalent to that through human skin and so investigations should be performed with human skin. If the results are confirmed, we would recommend treatment of PMS by use of hydroalcoholic gels containing 10% laurocapram, which gave the highest permeation within the group of hydroalcoholic gels, although the permeation of progesterone from poly(ethylene glycol) ointments with addition of 10% laurocapram is approximately equivalent. The application of hydroalcoholic gels has the advantage of their being readily spreadable on large surfaces compared with poly(ethylene glycol) preparations, which are viscous, tough and osmotically active vehicles.

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