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Delivery of triamcinolone acetonide through human epidermis: Effect of Actiderm, a new hydrocolloid dermatological patch

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Summary

The penetration of triamcinolone acetonide (TACA) through human epidermis following the evaporation of a finite dose of a hydroalcoholic tincture correlates positively with the applied volume and the penetrated amount of ethanol. The incorporation of salicylic acid into such a tincture extends the lag time and linear region of the TACA penetration curve. Covering with Actiderm following evaporation of a hydroalcoholic vehicle increases 2–3-fold the TACA flux with respect to uncovered skin or to occlusion with Saran Wrap. Solubility and partition coefficient determinations indicate similar thermodynamic activities for the drug in the three tinctures tested; however, diffusion experiments under in vivo mimic conditions show a higher TACA flux for the vehicle composed of isopropyl palmitate and ethanol. This phenomenon probably arises from different kinetics of the diffusion process in circumstances mimicking the in vivo conditions where vehicle components evaporate.

Introduction

It is accepted that the prevention of water loss from the stratum corneum and the subsequent increased water content in the skin enhances the transdermal flux of most drug molecules. It seems that water affects both intercellular lipid and intracellular keratin structures and thus facilitates the penetration of hydrophilic and lipophilic molecules (Barry, 1987). Occlusion, which is a practical way of inducing such conditions, potentiates reservoir formation and promotes skin penetration of corticosteroids, without exception (Barry, 1983). In clinical practice, occlusive films such as Saran Wrap have been employed, however, their use is limited by their side effects of skin maceration and bacterial proliferation (Aly et al., 1978).

Actiderm, a dermatological patch (comprised of a powder mixture of pectin, gelatin and sodium carboxymethylcellulose dispersed in a pressure-sensitive adhesive), has the ability to enhance the blanching effect of topical corticosteroids (Marriott and Martin, 1988), including triamcinolone acetonide (TACA). Because of the hydrocolloids it contains, surface skin moisture is absorbed into the bulk of the adhesive mass thereby preventing over-hydration, skin maceration and bacterial proliferation (Lilly and Lawrence, 1988). Actiderm possesses other advantages including ease of ap-

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plication and good adhesive properties (Queen et al., 1988).

The aims of the present work were to identify factors of importance to the delivery of the drug from these preparations and to attempt to quantify the effect of Actiderm on TACA delivery through human epidermis with respect to unoccluded and conventionally occluded skin.

Material and Methods

Skin preparation

All fat was removed from frozen abdominal cadaver skin with a scalpel. The skin was then immersed for 45 s in water maintained at 60 °C. The heat-treated skin was placed, stratum corneum side uppermost, on paper towels and the epidermis was eased gently away from the underlying dermis using the tip of a gloved finger. The prepared epidermis was floated out on 0.002% aqueous NaN_3 solution and left for 24 h, at room temperature, prior to diffusion experiments.

Preparation of radio-labelled tinctures

A volume of 300 μl (300 μCi) of [^{3}H]TACA alcoholic solution (Amersham TRK 485, 66.5 mCi/mg) was freeze-dried and redissolved in an appropriate volume of tincture (2 or 0.5 ml for infinite and finite dose experiments, respectively). For the determination of ethanol penetration, [^{14}C]ethanol (Amersham 1.13 mCi/mg) was incorporated into Tincture A.

Diffusion experiments

An automated diffusion apparatus (Akhter et al., 1984) was used. The hydrated epidermis was cut into pieces (approx. 1 × 1 cm) and mounted in stainless-steel diffusion cells where the skin area interposed between the donor and the acceptor was 0.126 cm^2 (0.4 cm diameter). The acceptor solution consisted of 0.002% NaN_3 solution perfusing through the compartment at a constant rate of 2 ml/h. The temperature in the diffusion cells was 32 °C. Perfusate samples were collected at 3-h intervals (6 ml), mixed with 14 ml of liquid scintillation fluid (Scintran, BDH) and their radioactivities were measured. The perfusion was run for 3 h prior to the application of the labelled preparation; this first fraction was used as blank.

TABLE 1

Effect of the experimental conditions on the flux of triamcinolone acetonide through human epidermis at 32 °C from tincture A

No. [a]	Experimental conditions	n [b]	Flux (μg cm^{-2} h^{-1})	SE (%) [c]
1	Donor volume, 150 μl; donor chamber hermetically sealed	3	0.967	17.7
2	Donor volume, 140 μl; unsealed	7	0.260	8.9
3	Donor volume, 10 μl; unsealed	5	0.014	13

[a] Reference number; [b] Number of runs; [c] Standard error of the mean; t-test levels of significance for the pairs 1,2 and 2,3: $p < 0.001$.

Three types of experiments were performed:

(1) Infinite dose experiments; in these experiments (Table 1, no. 1) 150 μl of Tincture A (0.15 μCi/μl) was pipetted onto the skin and the donor compartment was hermetically sealed. Under such conditions, a true steady-state diffusion profile was obtained.

(2) Diffusion under unsealed conditions; in order to determine the effect of the applied volume under unsealed conditions, different volumes of radio-labelled Tincture A (Table 1, nos. 2 and 3) were pipetted onto the skin and allowed to evaporate during the experiment.

(3) Finite dose, in-vivo-mimicking diffusion; for studying effects of Actiderm patch or Saran Wrap, 20 μl of labelled preparation (0.6 μCi/μl) was pipetted onto the skin and allowed to evaporate completely. Discs of the occlusive film (0.4 cm in diameter prepared by cork borer) were then gently pushed against the skin using an applicator. Control experiments were run without occlusion (Table 2). Skin samples from the same cadaver were used for comparison between treatments.

TABLE 2

The effect of occlusion on the penetration of triamcinolone acetonide through human epidermis at 32 °C determined from 20 µl evaporated tinctures

No. [a]	Experimental conditions	Skin code	n [b]	Flux ($\mu g\ cm^{-2}\ h^{-1}$)	SE [c] (%)
4	Tincture A unoccluded	D	7	0.018	8.4
5	With Actiderm	D	8	0.037	8.0
6	Tincture A with Actiderm	E	6	0.018	11
7	Occluded with Saran Wrap	E	6	0.018	15
8	Tincture B unoccluded	G	7	0.033	7.2
9	With Actiderm	G	6	0.116	11.9
10	Tincture B with Actiderm	H	7	0.030	15.5
11	Occluded with Saran Wrap	H	7	0.010	6.9
12	Tincture C unoccluded	I	4	0.082	31.2
13	With Actiderm	I	5	0.015	14.8

[a] Reference number; [b] Number of runs; [c] Standard error of the mean; t-test levels of significance for the pairs 4,5, 8,9 and 10,11: $p < 0.001$.

Solubility determinations

TACA (300 mg) was added to 10 ml of each tincture (in four replicates). The vials were shaken in a thermostatted water bath for 48 h at 32 °C. A 1 ml volume of supernatant from each vial (filtered through a 0.2 µm Millipore membrane) was diluted (×100) in acetonitrile; 10-µl samples were directly injected into a reverse-phase HPLC column (C_8, 10 × 2 mm) with the detector set at 240 nm. The mobile phase consisted of acetonitrile/water (1 : 1) at a flow rate of 1 ml/min. Under these conditions, the retention time of TACA was 3.3 min.

Determinations of stratum corneum-vehicle partition coefficient

The method of Barry and Bennett (1987) was employed using stratum corneum from four different sources. Weighed discs (2.5 cm) of dried stratum corneum were placed in vials containing 1 ml of radio-labelled TACA tincture and shaken in a thermostatted water bath at 32 °C for 24 h. The samples were blotted on a filter paper, weighed and dissolved in 2 ml Soluene-350 in glass scintillation vials. Liquid scintillation fluid (14 ml) and glacial acetic acid (150 µl) were added to each vial and the samples stored overnight at room temperature to allow chemiluminescence to subside. The radioactivity was analysed with respect to blanks and standards prepared in vials containing dissolved dry stratum corneum discs. The radioactivity in 100 µl of each vehicle was analysed using blanks and standards prepared in the corresponding tincture. Seven determinations were made for each tincture.

Results and Discussion

Infinite dose experiments

In order to maintain an infinite (non-depleting) amount of donor phase on the skin throughout diffusion experiments with a volatile vehicle it is necessary to seal the donor compartment hermetically. Under such conditions, a prolonged steady flux of TACA was obtained (Fig. 1) which was also the highest TACA flux observed in this study (Table 1, no. 1).

Diffusion under unsealed conditions

When the donor compartment is unsealed the volatile hydroalcoholic vehicle evaporates, leaving the solid drug on the skin surface. Obviously, under such conditions, the time needed for the vehicle to disappear correlates negatively with the amount applied on the skin at time zero. The cumulative penetration curves of TACA following the application of 140 and 10 μl Tincture A are shown in Fig. 2. The application of 140 μl tincture results in an almost 20-fold increase in TACA penetration compared with the lower volume application (Table 1, nos. 2 and 3). It is clear, however, that the delivery of the drug through the skin does not stop following the disappearance of the solvent from the donor compartment as in both cases (10 and 140 μl) the evaporation is completed within the first hour.

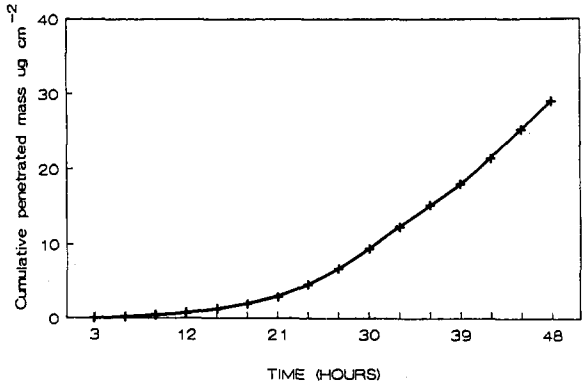

Fig. 1. Cumulative penetrated mass of triamcinolone acetonide through human epidermis at 32° C following the application of 150 μl Tincture A under sealed conditions (example plot).

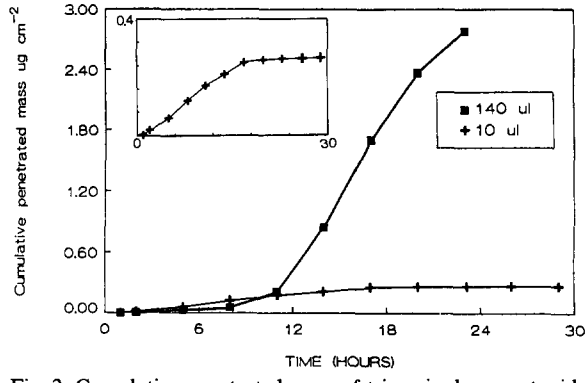

Fig. 2. Cumulative penetrated mass of triamcinolone acetonide through human epidermis at 32° C following the application of 140 or 10 μl Tincture A under unsealed conditions (example plot). Inset: magnification of the lower curve.

Although the steady-state flux of TACA is an order of magnitude higher when a large amount of tincture is applied, the lag time following such application is considerably longer compared to that for a small volume (Fig. 2). In fact, the lag time observed in the case of the small applied amounts of Tincture A is much shorter than one would expect for transepidermal penetration of a corticosteroid. It seems that in this particular situation, where a very small mass of a poor skin penetrant is applied on the skin in a limited amount of a volatile enhancer (ethanol), the flux of TACA arises predominantly from shunt diffusion.

The effect of ethanol

Ethanol is a known penetration enhancer (Ghanem et al., 1987; Yum et al., 1987). Following the application of Tincture A on the skin, the ethanol promptly appears in the perfusate and conceivably plays a significant role in determining the delivery of TACA which follows in the wake of the enhancer (Fig. 3). The decrease in TACA penetration with diminution of the applied volume may also be attributed to the decrease in the effect of ethanol as penetration enhancer. Indeed, when a smaller amount of tincture was applied on the skin the penetrated mass of ethanol decreased significantly (Fig. 4). Other investigators observed an increase in the penetration of neat butyric acid through the skin with rise in the applied volume

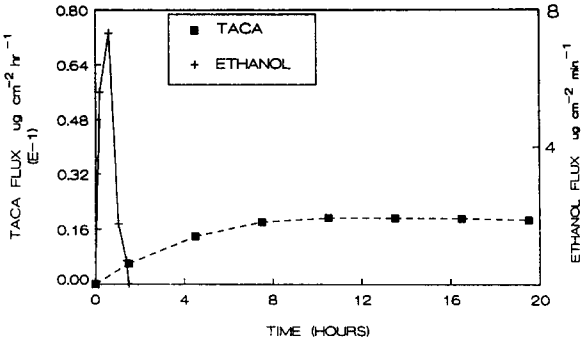

Fig. 3. The flux of [^{14}C]ethanol and [^{3}H]triamcinolone acetonide through human epidermis following the application of 20 μl Tincture A under unsealed conditions (example plot). Note change of flux units.

(Liron and Cohen, 1984), this phenomenon being attributed to the effect of this compound on the skin barrier.

Finite dose, in-vivo-mimicking experiments and the effect of Actiderm

The effects of Actiderm on the transdermal delivery of TACA from the various tinctures with respect to uncovered skin or Saran Wrap occlusion are summarised in Table 2; the respective penetration curves are shown in Fig. 5.

Due to the variability in permeability between skin samples (up to almost 3-fold, see Table 1), each comparison was performed using skin samples from the same donor. For Tincture A, the TACA flux doubled when Actiderm was used with

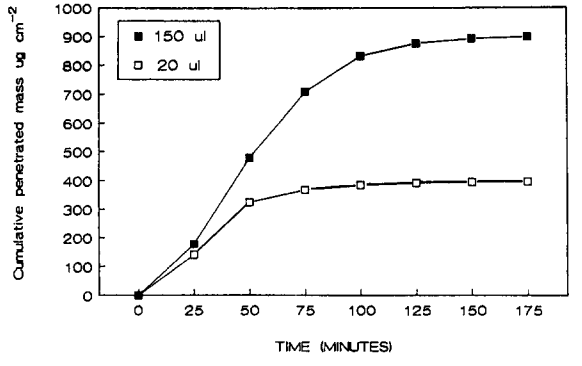

Fig. 4. Cumulative penetrated mass of [^{14}C]ethanol through human epidermis at 32°C following the application of 20 or 150 μl Tincture A under unsealed conditions (example plot).

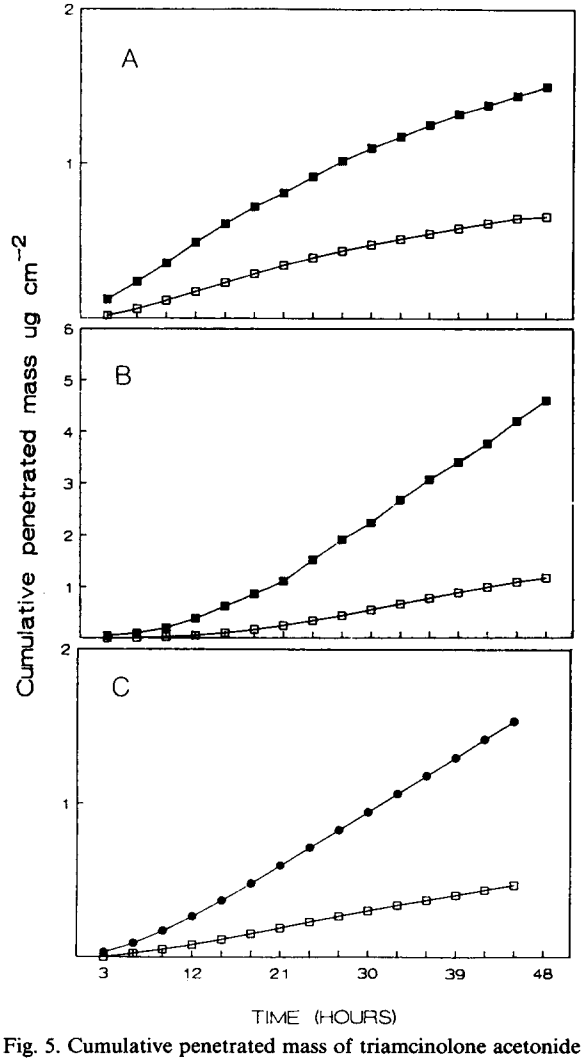

Fig. 5. Cumulative penetrated mass of triamcinolone acetonide through human epidermis following the application of 20 μl tincture (example plots): (A) Tincture A, evaporated (□) and covered with Actiderm (■). (B) Tincture B, evaporated (□) and covered with Actiderm (■). (C) Tincture B evaporated (□) and occluded with Saran Wrap (●).

respect to the uncovered condition (Table 2, nos. 4 and 5). However, no significant increase in the duration of the linear region of flux was observed (Fig. 5A). Also, no effect of Actiderm on TACA delivery from this tincture was found compared to Saran Wrap occlusion (Table 2, nos. 6 and 7).

For Tincture B, however, the use of Actiderm triples the flux of TACA through the skin with respect to uncovered skin (Table 2, nos. 8 and 9;

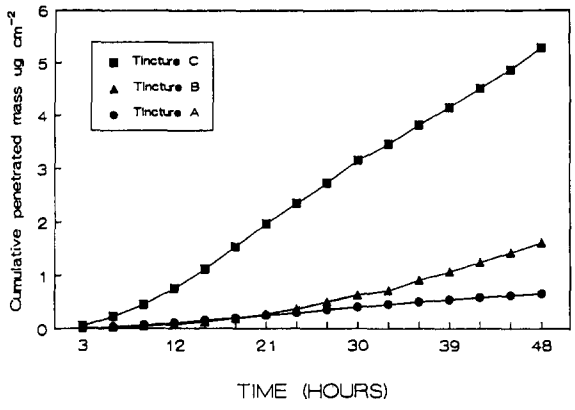

Fig. 6. Cumulative penetrated mass of triamcinolone acetonide through human epidermis at 32° C following the application of 20 μl of Tincture A, B or C under unsealed conditions (example plots).

Fig. 5B) or occlusion with Saran Wrap (Table 2, no. 11; Fig. 5C).

For Tincture C, in contrast to the hydroalcoholic tinctures, a liquid donor phase (isopropyl palmitate) remains on the skin throughout the experiment. When Actiderm is applied on this layer, its hydrocolloid matrix disintegrates into the oil and TACA delivery is drastically reduced (Table 2, nos. 12 and 13). This observation, however does not necessarily represent the in vivo situation in which the amount of oil remaining on the skin is of much less significance as the patient would apply a lower amount of tincture per unit area.

The vehicle effects

Our results obtained for TACA penetration from a finite amount of applied vehicle lie within the same order of magnitude reported for in vitro penetration of TACA delivered from 25 μl ethanolic solution (Ponec and Polano, 1979).

The delivery of TACA from Tincture A, under unsealed conditions, is characterised by a reduced slope of the cumulative penetration curve within the first 24 h (Figs 2, 5A and 6). This reduction cannot be attributed to any significant depletion of TACA from the donor compartment. It seems, therefore, that for this tincture, the amount of penetrant partitioning into the skin prior to the total evaporation of the vehicle determined the resultant flux. In contrast to the delivery of TACA from Tincture A, the penetration profile of the drug delivered from Tincture B is characterised by a considerably longer lag time followed by a prolonged near zero-order delivery, with the cumulative penetration curves steadily increasing (Figs 5B, C and 6). The penetration of the drug is increased here by two enhancers; one acts quickly and disappears at an early stage (ethanol) while the other (salicylic acid) remains in large amounts on the skin throughout the entire penetration process.

Of the three tinctures, Tincture C produces the highest TACA flux through the skin. Whereas the other tinctures evaporate promptly after application, Tincture C leaves an oily donor phase after the evaporation of the ethanol. This donor phase produces a high drug thermodynamic activity as the TACA concentration is near saturation.

Table 3 summarises the vehicle parameters determined for the three tinctures. The saturation solubility and hence the thermodynamic activity of TACA in Tincture A is slightly lower than in the two other tinctures and the stratum corneum-vehicle partition coefficient (K_m) from this preparation is somewhat lower. In general, however, all tinctures produce similar thermodynamic activities for the drug and there are no major differences in TACA partition coefficients, the K_m values being close to unity. This value does not indicate a strong driving force for penetration as reported for corticosteroids in poor solvents, e.g. water (for hydrocortisone, log $K_m = 0.9$; Barry

TABLE 3

The saturation solubilities and stratum corneum-vehicle partition coefficients of triamcinolone acetonide in the various tinctures at 32° C

Tincture	Saturation solubility (% w/v) (±SD)	K_m (±SD)	
		Dry [a]	Wet [b]
A	1.247±0.022	0.74±0.18	0.44±0.10
B	1.645±0.046	1.80±0.24	0.77±0.08
C	1.765±0.007	1.06±0.11	1.11±0.01

[a] Calculated with respect to the dry weight of the stratum corneum.

[b] Calculated with respect to the wet weight of the stratum corneum.

and Bennett, 1987). Practically, however, the solubility of TACA in aqueous preparation is extremely low and such preparations are not suitable for pharmaceutical use.

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