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INVESTIGATIVE REPORT

Effect of Pentane-1,5-diol and Propane-1,2-diol on Percutaneous Absorption of Terbinafine

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The aim of this study was to compare pentane-1,5-diol and propane-1,2-diol used as absorption enhancers for cutaneously administered terbinafine. Fresh human skin samples were placed in a continuous flow diffusion cell with a gel containing terbinafine on top of the skin. Receptor fluid samples were analysed using high-performance liquid chromatography. The quantity of gel remaining on the skin surface after completion of each test was weighed and the amount of drug in the skin was analysed. Addition of pentane-1,5-diol or propane-1,2-diol to the gel increased the percutaneous absorption of the drug. The most efficient absorption enhancer in this comparison was 5% pentane-1,5-diol. ***Key words: high-performance liquid chromatography; percutaneous absorption enhancer; pentane-1,5-diol; propane-1,2-diol; terbinafine.***

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Topical administration can be a highly problematic way to deliver a drug due to the complex structure of the skin and its function as a barrier against foreign substances (1). The rate at which a compound migrates through the skin is determined by the molecular weight and lipophilicity of the compound (2), but it can also be affected by different absorption or penetration enhancers. Ideal enhancers should specifically promote the penetration of compounds across the outermost skin barrier without exhibiting irreversible effects on its properties (3, 4). Cutaneous application has several advantages because the formulation, in this case a gel, may be applied directly to the desired site. The side-effects frequently associated with systemic administration are reduced as systemic absorption is low. First-pass liver metabolism is also avoided when topical application is used.

In vitro percutaneous absorption methods are used widely for measuring the absorption of compounds that come into contact with skin (5, 6). When drugs are applied topically, a pharmacologically active agent must be released from its carrier (vehicle) before it can contact the epidermal surface and be available for penetration of the stratum corneum and lower layers of the skin. Various methods and systems have been developed to measure *in vitro* release of the drug from its vehicle and into the skin. This *in vitro* release test is gaining importance as a product performance and quality control test. Data should no longer be obtained simply by measuring receptor fluid levels only for most experiments (5). Absorption should be defined at the end of an experiment as the sum of the amount of compound diffusing into the receptor fluid plus the absorbed material remaining in skin. Skin levels of the drug are determined after removal of unabsorbed material.

Diols or glycols are used mainly as solvents or anti-freeze agents, but some have been utilized as vehicles in pharmaceutical preparations (7–11). Propane-1,2-diol (propylene glycol) is the only diol that is widely used in dermatology (7, 9). It reduces drug-tissue binding and thus promotes permeation of the drug (3, 12). Pentane-1,5-diol (pentylene glycol) is a viscous oily liquid at room temperature, which is miscible with water, methanol, ethanol, acetone, ethyl acetate and ether (8, 10, 11). It is used mainly as a plasticizer in cellulose products and adhesives, in dental composites and in brake fluid compositions and widely used as a preservative for grain (8). However, pentane-1,5-diol is also an effective solvent, enhancer, water-binding substance, antimicrobial agent (7, 13) and preservative, and may therefore replace several ingredients in a skin composition. Pentane-1,5-diol, has been shown to be cosmetically acceptable and presents little risk for toxicity or skin and eye irritation compared with other diols.

Terbinafine is an allylamine, which has a broad antimycotic effect and is used, for example, in the treatment of fungal foot and nail infections (14). Terbinafine is a highly lipophilic substance with a tendency to concentrate in the skin, nails and fatty tissue (15). The mechanism of action of terbinafine is the inhibition of the enzyme squalene epoxidase, which is involved in the biosynthesis of ergosterol in the fungal cell membrane. Previous studies have shown that terbinafine penetrates the stratum corneum rapidly. In comparison with other similar preparations, the substance remains in the skin for a long time after treatment, possibly because terbinafine is bound to a slow-release reservoir, such as fat in the subcutis (16). The aim of this *in vitro* study was to

monitor whether pentane-1,5-diol and/or propane-1,2-diol increase the percutaneous absorption of the active substance, terbinafine.

MATERIALS AND METHODS

The gels (hydrogels) contained 1.5% Chremophor RH40 INCI and water and were adjusted to pH 6. The gels used in this study were developed by Natumin Pharma AB, Huskvarna, Sweden. They contained 1% terbinafine (Novartis Pharma AG, Basel, Switzerland) and pentane-1,5-diol or propane-1,2-diol (BASF AG, Ludwigshafen, Germany). The following gels were used: gel containing 1% terbinafine only, gel containing 1% terbinafine together with 5% or 20% pentane-1,5-diol and gel containing 1% terbinafine together with 5% or 20% propane-1,2-diol.

Fresh human skin was obtained using a dermatome during surgery for breast reconstruction. The study procedure was approved by the ethics committee of the Medical Faculty University of Göteborg and all patients gave their informed consent prior to entry into the study. The skin pieces were approximately 3 × 6 cm in area and the thickness of the epidermal/dermal skin sample was 300–400 μm. The skin was stored in cold Eagles Minimal Essential Medium (MEM) (Sigma-Aldrich Co., Ayrshire, UK) containing L-glutamine (Sigma-Aldrich Co.) and gentamicin (Department of Microbiology, Sahlgrenska University Hospital, Gothenburg, Sweden) for a maximum of one hour after being surgically removed until the start of the experiment. The thickness of the skin samples were measured using the Dermascan ultrasound equipment (Cortex Technology, Hadsund, Denmark).

One square centimetre of the skin piece was placed in a continuous flow diffusion cell (Laboratory Glass Apparatus Inc., Berkley, USA) with the stratum corneum upper-most. A 50 mg quantity of the test gel was applied on the top of each skin sample. Ethanol (Kemetyl AB, Haninge, Sweden)/phosphate buffered saline (PBS) (Department of Microbiology, Sahlgrenska University Hospital, Göteborg, Sweden) (30:70) was degassed in an ultrasound bath (Branson 2200, Hayward, USA) before being used as receptor fluid. The fluid was pumped through the cell at a flow rate of 2 ml/h. Fractional sampling was started immediately and continued for 60 h and one fraction was sampled every 30 min. Four cells were run in parallel. The test gel that was not absorbed was removed carefully and weighed. The proportion of the test substance that diffused through the skin was analysed using the high-performance liquid chromatography (HPLC) method described below. The test substance absorbed into the skin was extracted using 0.5 ml ethanol and shaken for 10 min. The supernatant was decanted and the procedure was repeated three times. The supernatants were pooled and evaporated with nitrogen gas (AGA Gas, Sundbyberg, Sweden) at 37ºC, dissolved in 0.5 ml mobile phase fluid, filtered through a 0.45 μm syringe filter (Cameo Teflon, Sorbent AB, Göteborg, Sweden) and analysed using HPLC. All experiments were repeated five times.

All samples were analysed by HPLC with absorbance detection (Spectra System UV1000 detector, Detector and Autosampler Spectra System, San Jose, USA) at a wavelength of 242 nm. The mobile phase fluid, methanol (LiChrosolv, Merck, VWR, Stockholm, Sweden)/water (Distilled Super q, Department of Microbiology, Sahlgrenska University Hospital, Göteborg, Sweden) (95:5), was filtered through a 0.22 μm membrane filter (GV membrane filters, Millipore, Billerica, USA) and degassed before use. The pump (LC-10AD, Shimadzu, Kyoto, Japan) was set at 0.4 ml/min. An autosampler (Spectra System AS3000, Detector and Autosampler Spectra System) with a 50 μl loop was used when injecting the sample that was analysed on a Genesis C18 column (Genesis C18, 4 μm, 150 × 3 mm, Sorbent AB, Göteborg, Sweden).

RESULTS

The results for percutaneous absorption of terbinafine in a hydrogel alone and in combination with pentane-1,5-diol or propane-1,2-diol as enhancers are shown in Fig. 1. The amount of terbinafine absorbed into the skin is shown in Table I. For all samples terbinafine was found in the receptor fluid within 5 h.

As shown in Table I, the amount of terbinafine in the receptor fluid was approximately the same for both percentages of pentane-1,5-diol compared with the result from the control gel, which is 10% of that value. When analysing the amount extracted from the skin at the end of the experiment there was about five times more terbinafine in the skin when 5% pentane-1,5-diol was used as enhancer compared with 20% pentane-1,5-diol and the control. For terbinafine left on the skin, the control and 5% pentane-1,5-diol gave similar values and the amount for 20% pentane-1,5-diol was five times greater. The profile in Fig. 1 for 5% pentane-1,5-diol describes a fast penetration through the skin at first that rapidly declines after a peak at approximately 15 h. After this time-point most of the terbinafine is absorbed into the skin. This profile also matches the control curve (Fig. 1), but with a much higher maximum value. The profile of the curve for 20% pentane-1,5-diol shows continuing penetration of terbinafine into the receptor fluid and thus an even release over time. These results indicate that the most efficient absorption enhancer in this comparison is 5% pentane-1,5-diol.

Table I shows quite small differences between the two percentages of propane-1,2-diol. There was seven times more terbinafine in the receptor fluid than in the control gel and twice as much was found in the skin. A slightly

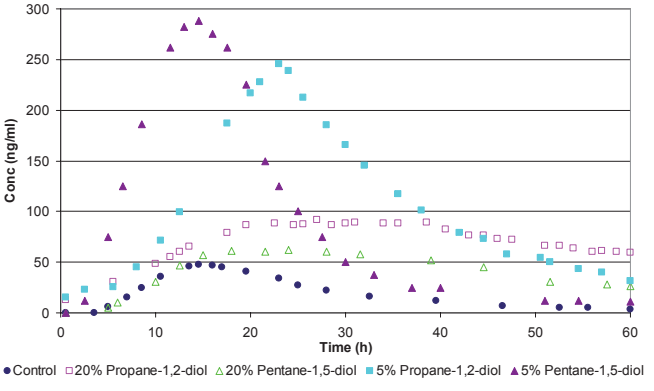

Fig. 1. Percutaneous absorption of terbinafine from a gel formulation containing 1% terbinafine, with the addition of different enhancers. The results are the calculated mean of five samples from the receptor fluid analysed using high-performance liquid chromatography.

Table I. *Percutaneous absorption of gel containing 1% terbinafine in the presence of different enhancers. Results are shown for percutaneous absorption in the skin, passage through the skin (receptor fluid) and non-absorbed terbinafine gel. All results are mean values of five samples*

Enhancer	Terbinafine absorbed in skin (%)	Terbinafine in receptor fluid (%)	Non-absorbed gel (μg)
Control (no enhancer)	8.3	0.35	11.0
20% propane-1,2-diol	21.2	2.1	19.3
20% pentane-1,5-diol	11.1	3.4	76.0
5% propane-1,2-diol	19.4	2.5	34.3
5% pentane-1,5-diol	52.0	2.8	14.0

larger amount of gel remained on the skin surface for the 5% propane-1,2-diol, about three times more than for the control gel. The amount left on the skin for 20% propane-1,2-diol was almost twice the amount for the control gel. These data are interesting in comparison with the curves for 5% and 20% propane-1,2-diol. Although the results in Table I are similar, the profiles in the above-mentioned figures is quite different. The higher percentage of propane-1,2-diol appears to have more of a depot effect, whereas the lower amount of the diol releases a larger amount of terbinafine into the receptor fluid at the beginning and then almost stops.

Fig. 1, which describes the results from the gel with 5% propane-1,2-diol, shows a similar profile as the curves for the control and for 5% pentane-1,5-diol, but the maximum is reached more than 5 h later, although it is almost as high as for 5% pentane-1,5-diol. When the percentage of enhancer is increased to 20% propane-1,2-diol the curve agrees with the result for 20% pentane-1,5-diol, but the terbinafine is found in the receptor fluid from the start of the experiment and reaches its peak later. The curves for 5% added enhancer show a profile that is more desirable in this case than those for 20% added enhancer because the active substance should be absorbed into the skin and not pass through it. It is also favourable if the absorption starts as soon as possible, as is the case for 5% pentane-1,5-diol.

DISCUSSION

Both pentane-1,5-diol and propane-1,2-diol increased the percutaneous absorption of terbinafine into the receptor fluid and into the skin. Percutaneous absorption into the receptor fluid was higher with pentane-1,5-diol than with propane-1,2-diol and highest with 20% pentane-1,5-diol. With 5% of each of the diols the uptake increased quickly to high levels; however, the uptake then also decreased quickly; faster with 5% pentane-1,5-diol than with 5% propane-1,2-diol. When the concentration of the diols was increased to 20% the percutaneous absorption of terbinafine into the receptor fluid was, in total, approximately the same as or slightly higher than for the lower percentages. However, the increase was continued for a much longer time than with 5% of the diols and the area under the curve was higher for 5% of the diols compared with the curves for 20% of the diols.

The highest amount of terbinafine absorbed into the skin was seen when 5% pentane-1,5-diol was used as enhancer; which concurs with previously published results (1). The amount was much higher compared with 20% pentane-1,5-diol and both 5% and 20% of propane-1,2-diol as well as the control substance. The amount of gel left on the skin was lowest when 5% pentane-1,5-diol was used as enhancer. In this case the formulation will appear less greasy compared with the gels with 20% pentane-1,5-diol and 5% and 20% propane-1,2-diol.

The aim was for the substance to penetrate and absorb into the skin, without causing systemic effects. The combination of too high a concentration of pentane-1,5-diol with a lipophilic substance such as terbinafine may result in percutaneous penetration rather than percutaneous absorption. With a lower amount of pentane-1,5-diol the terbinafine can interact with the enhancer as well as the lipophilic regions of the skin, which results in a high amount of drug absorbed and a slower and less efficient transportation of active substance through the skin. Propane-1,2-diol is a less lipophilic substance and, as such, is less suitable as an enhancer in this particular case.

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Conflict of interest: Jan Faergemann has a patent on the use of pentane-1,5-diol as an enhancer. He also has a commercial interest in the development of products with this compound.

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