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Penetration of the human nail plate: the effects of vehicle pH on the permeation of miconazole

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In order to assess the relative permeability of the nail plate to ionized and unionized drugs the permeation of miconazole at varying pH has been followed as a function of time. The pH was adjusted from 3·1 to 8·2 to obtain between 5 and 100% dissociation of the drug. No significant difference in the rate of permeation was demonstrated. The data suggests that the ionic form of miconazole dissolves as easily in the nail plate as the free base and, therefore, topical bioavailability can be enhanced by decreasing the formulation pH thereby increasing drug solubility.

Previous studies on the physicochemical properties of the human nail plate have indicated a marked difference between the permeability characteristics of this tissue and that of the epidermis (Walters et al 1983). Whereas the stratum corneum behaves as a lipid barrier to the permeation of low molecular weight chemicals (Scheuplein 1965; Durrheim et al 1980) the nail plate exhibits behaviour similar to that of a hydrogel of high ionic strength. Furthermore chemicals, such as dimethylsulphoxide, which have been shown to be remarkably effective as enhancers of skin penetration (Scheuplein & Ross 1970; Astley & Levine 1976) have shown little promise as accelerators of nail plate permeability (Kligman 1965; Walters & Flynn 1981). These differences between two tissues of such intimately related origins cannot be attributed to any obvious differences in morphogenesis; rather the inconsistencies appear to be due to differences in the relative amounts of the lipid and protein regimes (Walters et al 1983) and perhaps the physicochemical qualities of each of these phases. Stratum corneum contains at least 10% lipid, most of which is believed to be intercellular, whereas the nail plate contains no more than 1% (Baden et al 1973). The low lipid fraction of the nail is consistent in makeup and amount with lipids derived mostly from the residual cell membranes. In its normal state the nail also contains less water than the stratum corneum, about 10% moisture by actual estimate (Baden et al 1973). Permeation data for the homologous nonelectrolytes, the n-alkanols, indicate the relative importance of the various regimes of the nail plate in determining its barrier properties and show the nail to be a far different membrane than the stratum corneum. In this communication further evidence of unique behaviour of the nail plate membrane is presented. Specifically the permeation of a weak electrolyte, miconazole, does not appear to be influenced by its degree of ionization.

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Method

Tritiated miconazole (1-[2,4-dichloro-β-(2,4-dichlorobenzyloxy)phenethyl]imidazole) was supplied by Ortho Pharmaceutical Corporation. The radiolabelled chemical was diluted with 0·9% NaCl before use. Details of the diffusion cell and permeation procedures have been given elsewhere (Walters et al 1981). The permeation of [^{3}H]miconazole through hydrated nail plate was followed as a function of pH of the bathing medium at 37 °C. The pH was adjusted from 3·1 to 8·2, with citrate/phosphate buffer, to obtain between 5 and 100% dissociation. During these experiments [^{14}C]ethanol (New England Nuclear) was the internal reference.

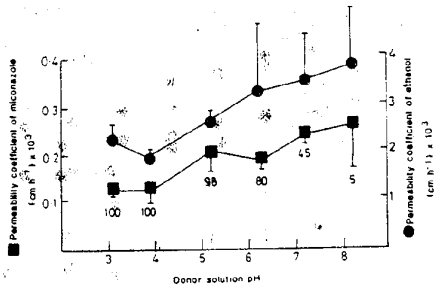

FIG. 1. pH-permeation profile for miconazole and ethanol data are mean ± s.d. ($n = 5$). Figures beneath the miconazole curve are % dissociations.

Results and discussion

The effect of pH on the permeability coefficients of miconazole and ethanol are shown in Fig. 1. It is expected that the permeability of a weak electrolyte should vary as a function of pH, providing the membrane behaves as a lipoidal structure. It has been demonstrated, for example, that organic ions can permeate the stratum corneum, but the rate of permeation is only a fraction of that of the undissociated form

(Arita et al 1970; Wallace & Barnett 1978; Dyer et al 1981). The low permeation rates of dissociated compounds through skin are assumed to be due to a relative inability of ions to partition into the lipid phases of the horny layer. The lack of importance of lipid phases as a medium of transport across the nail, as suggested previously (Walters et al 1983), is reflected in the ability of both the dissociated and the undissociated species of miconazole to permeate at near equivalent rates (Fig. 1). Miconazole is a weak base with a pK_a of 6·65 and, therefore, the more acidic the medium the greater is the degree of ionization. Yet the flux of miconazole, through different nail plates, is invariant at low pH where ionization is near complete. Moreover, the permeability coefficients of the reference compound, ethanol, follow the same pattern as a function of pH. The ratio, $P_{miconazole}/P_{ethanol}$ is essentially invariant. Thus the ionic form of miconazole dissolves as easily in the nail plate as the free base. Since there is little or no dependency of permeability on pH, these data suggest that the overriding aspect in increasing topical bioavailability of miconazole, for the treatment of onychomycoses, is increasing the solubility of the drug in a formulation, which can be done by decreasing the pH.

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