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In vitro permeation of several drugs through the human nail plate: relationship between physicochemical properties and nail permeability of drugs

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Abstract

The objectives of the present study are to clarify the relationship between the physicochemical properties and the nail permeability of drugs through human nail plates. Homologous *p*-hydroxybenzoic acid esters were used to investigate the relationship between the octanol/water partition coefficient and the permeability coefficient of several drugs. The nail permeability was found to be independent of the lipophilicity of a penetrating drug. However, the nail permeability of several model drugs was found to markedly decrease as their molecular weights increased. The nail permeability of an ionic drug was found to be significantly lower than that of a non-ionic drug, and the nail permeability of these drugs markedly decreased as their molecular weights increased. The permeation of a model drug, 5-fluorouracil (5-FU), through healthy nail plates was also determined and compared with that through nail plates with fungal infections. The drug permeation through a nail plate decreased with an increase in nail plate thickness. Nail plates with fungal infections exhibited approximately the same 5-FU permeation as healthy nail plates. We suggest that the permeability of a drug is mainly influenced by its molecular weight and permeability through nails with fungal infection can be estimated from data on healthy nail permeability. © 2004 Elsevier B.V. All rights reserved.

Keywords: Nail; Nail permeation; Fungal nail plate; Onychomycosis; Antifungal agents

1. Introduction

Onychomycosis has been treated mainly with oral antifungal medication (Piepponen et al., 1992; Villars and Jones, 1992). This oral therapy, however, sometimes has severe systemic side effects, which interrupt treatment (Wilson and Plunkett, 1962). On the other hand, it is well known that topical treatment is not widely used in onychomycosis therapy. The anticipated low levels of nail penetration and permeation during topical antifungal drug exposure are very significant factors in onychomycosis therapy. Only a few drug permeation studies have been performed on the human nail plate and, as a consequence, the mechanisms behind healthy and fungal nail permeation have yet to be confirmed. Walters et al. (1983) have suggested that the nail plate be-

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haves like a hydrophilic gel membrane and that there is an additional lipophilic route, as revealed by an in vitro penetration study of homologous alcohols through the human nail plate. Mertin and Lippold (1997) also suggested that the nail plate behaves like a hydrophilic gel membrane and that the dissociation of a penetrating drug leads to a reduction in the penetration rate, as revealed by an in vitro penetration study of homologous nicotinic acid esters, benzoic acid and pyridine through the human nail plate and bovine hoof membrane. Since they used healthy nails from dead men and women for the in vitro permeation study, they were probably not able to carry out many permeation studies using human nail plates. We have developed a modified side-by-side diffusion cell using nail tip pieces from healthy volunteers in order to investigate the nail penetration mechanism and enhancing system. From the results we obtained using our in vitro technique, we suggest that drug diffusion in the upper layer of the human nail plate is the main barrier to nail permeation and that the full-thickness nail

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plate behaves like a hydrophilic gel membrane (Kobayashi et al., 1999). In addition, we found that *N*-acetyl-L-cysteine and 2-mercaptoethanol are able to enhance drug permeation through the human nail plate (Kobayashi et al., 1998). However, it is very difficult to evaluate antifungal drug permeation, because of the very low nail permeability involved.

In order to clarify the nail permeation mechanism of drugs through human nail plate, we studied the relationship between the physicochemical properties and the healthy nail permeability of several drugs. To observe the effect of octanol/water partition coefficients on nail permeability coefficients, homologous *p*-hydroxybenzoic acid esters were used as model drugs. The effects of the molecular weight and drug dissociation on nail permeability were also investigated in a nail permeation study using several model drugs. We investigated the relationship between the flux of a model drug, 5-fluorouracil (5-FU), and the healthy or fungal nail plate thickness.

2. Experimental

2.1. Materials

Antipyrine, 5-FU, *p*-hydroxybenzoic acid esters (methyl ester, MP; ethyl ester, EP; propyl ester, PP; butyl ester, BP; amyl ester, AP; hexyl ester, HP) and sodium nicotinate were obtained from Tokyo Kasei Kogyo Co. (Tokyo, Japan). Aminopyrine, barbital sodium, benzoic acid, ethanol, procaine hydrochloride, pyridine and sodium benzoate were obtained from Wako Pure Chemical Industries (Osaka, Japan). Deuterium oxide was obtained from Merck Co. (Darmstadt, Germany). Isoproterenol hydrochloride, lidocaine, lidocaine hydrochloride and mexiletin hydrochloride were obtained from Sigma Chemical Co. (St. Louis, MO, USA). Croconazole hydrochloride was supplied by Shionogi & Co. (Osaka, Japan). Isosorbide dinitrate was supplied by Toko Pharmaceutical Ind. Co. (Tokyo). All other reagents were obtained from commercial sources.

2.2. Preparation of the nail plate

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Healthy nail tip pieces were obtained from the fingers and toes of healthy volunteers (15 males and 5 females; mean age 25 years, range 20–45) using nail clippers. Nail pieces, which had been allowed to grow for at least one month, were used in this permeation study. Fungal nail plates were supplied from Saiseikai Central Hospital (Tokyo) and Saitama Medical Center (Saitama Medical School, Saitama, Japan). The thickness of the healthy and fungal nail pieces was measured with a micrometer (Mitutoyo Corp., Japan) equipped with pointed metal attachments. Healthy nail plates, having a thickness of about 400 μ m (350–450 μ m), were used to evaluate the effect of the octanol/water partition coefficient, molecular weight and dissociation of the penetrant on the nail permeability. Both fungal and healthy nail plates were used to make a comparison between the different drug permeabilities. After healthy and fungal nail pieces were hydrated for a day, they were used to evaluate drug permeability.

2.3. Determination of solubilities and octanol/water partition coefficients

The drug suspensions were mixed with a magnetic stirrer at 37 °C. After 12 and 24 h, each suspension was subjected to filtration (Ekicrodisc 3; German Sciences Japan, Ltd., Tokyo). The filtrate was immediately diluted with methanol or acetonitrile to obtain samples for analysis. No difference in drug solubility was observed between 12 and 24 h. The octanol/water partition coefficient of the drugs (K_{ow}) was defined as the solubility ratio in octanol/water at 37 °C. A few of the values were taken from the literature (Morimoto et al., 1992).

2.4. Permeation studies

A piece of nail plate was sandwiched between two adapters made of polypropylene with an O-shaped ring (effective diffusion area $0.049 \,\mathrm{cm}^2$) and mounted in a side-by-side diffusion cell (1.5-2.5 ml) with a water jacket connected to a water bath at 37 °C (Kobayashi et al., 1998). The dorsal nail plate side was filled with a drug suspension or solution (almost all drugs were applied as suspensions, but for drugs with a high solubility, the dorsal nail plate side was filled with drug solution. The maximum flux was evaluated from the flux obtained with the applied concentration and drug solubility. In both cases, the drug concentration in the dorsal nail plate side was almost constant throughout the nail permeation studies) and the ventral nail plate side was filled with distilled water. No preservative was added because the receiver solution was clear even at the end of the experiment. Drug permeation was measured by sampling the solution on the ventral nail plate side at pre-determined times. The experimental period was 5-17 days, because of the low degree of nail permeability of the drugs used.

2.5. Analytical methods

Deuterium oxide was quantified from the intensity of the O–D stretching vibrational band at 2512 cm^{-1} with an infrared spectrophotometer (260-30, Hitachi, Tokyo) (Hatanaka et al., 1993). Ethanol was measured by GC as described previously (Kobayashi et al., 1997). Other drugs were determined by HPLC. Sample solutions were injected into an HPLC consisting of a pump system (LC-10A, Shimadzu Seisakusho, Kyoto, Japan), an UV detector (SPD-10A, Shimadzu), a chromatopack (C-R5A, Shimadzu), a system controller (SCL-10A, Shimadzu), an auto injector (SIL-10A, Shimadzu), and a reverse-phase column (Inertsil ODS 250 mm × 4.6 mm i.d., GL Sciences Inc., Tokyo). The mobile phase, which consisted

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of methanol/0.1% phosphoric acid or acetonitrile/0.1% phosphoric acid mixtures, with or without ion-pair chromatography reagents (sodium 1-hexanesulfonate or sodium dodecylsulfate), was pumped at flow rate ranging from 1 to 1.5 ml/min. No other peak apart from the drug and internal standard was observed on the HPLC recording. It was clear that the permeating drugs were stable and no material leached from the nail plates during the permeation studies.

3. Results and discussion

3.1. Influence of the octanol/water partition coefficient on the permeability coefficient

The steady-state permeation of drugs through the solution-diffusion membrane is characterized by Fick's law:

$$J = \frac{D_{\rm m} K_{\rm m} C_{\rm V}}{h} \tag{1}$$

in which *J* is the steady-state flux, K_m is the membrane/donor vehicle partition coefficient of the drug, D_m is the diffusion coefficient of the drug in the membrane, C_V is the concentration in the donor solvent and *h* is the membrane thickness. The permeability coefficient (*P*) can be characterized as follows:

$$P = \frac{D_{\rm m} K_{\rm m}}{h}.$$
 (2)

To predict the skin permeability of drugs, Potts and Guy (1992) carried out their analysis using a mathematical model based on permeant size (molecular volume (MV) or molecular weight (MW)) and octanol/water partition coefficient ($K_{\rm ow}$). The functional dependence of $D_{\rm m}$ on MW is exponential and it can be characterized by:

$$D_{\rm m} = D^0 \exp(-\beta \,\mathrm{MW}) \tag{3}$$

where D^0 represents the diffusivity of a hypothetical molecule having zero molecular weight and β is a constant. The relationship between K_m and K_{ow} is better expressed as:

$$K_{\rm m} = [K_{\rm ow}]^f \tag{4}$$

where the coefficient, f, accounts for the difference between the partitioning domain presented by octanol and that presented by the membrane lipids. A combination of Eqs. (2), (3) and (4) yields Eq. (5):

$$\log P = \log(D^0/h) + f \log K_{\rm ow} - \beta' \,\mathrm{MW}$$
(5)

where $\beta' = \beta/2.303$.

The effect of the octanol/water partition coefficient on the permeability coefficient of each drug was investigated. Fig. 1 shows a typical permeation profile of one of the model drugs, *p*-hydroxybenzoic acid methyl ester, through the healthy human nail plate. Steady-state fluxes of homologous *p*-hydroxybenzoic acid esters can be observed from 4.5 to 6.5 days allowing calculation of the nail permeability coefficients.

Table 1 shows the physicochemical parameters and nail permeability coefficients of homologous p-hydroxybenzoic acid esters used as model drugs in this investigation. The molecular weights of homologous p-hydroxybenzoic acid esters covered a narrow range from 152.12 to 222.28. The logarithm values of the octanol/water partition coefficients varied widely from 1.53 to 4.25.

Fig. 2 shows the relationship between the octanol/water partition coefficient and the permeability coefficient of *p*-hydroxybenzoic acid esters. The permeability of *p*-hydroxybenzoic acid esters did not increase with an increase in lipophilicity. If a nail plate behaves as a lipid partition membrane, the slope (*f*) should be clearly greater than 0; but it was nearly zero (f = -0.160). Multiple regression analysis was carried out to clarify which parameters (molecular weight or octanol/water partition coefficient) contribute to the permeability of *p*-hydroxybenzoic acid



Fig. 1. Typical permeation profile of *p*-hydroxybenzoic acid methyl esters through the healthy human nail plate. Each value represents the mean \pm S.E. (n = 4).

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Table 1 Physicochemical parameters and nail permeability coefficients ($h = 400 \,\mu\text{m}$) of *p*-hydroxybenzoic acid esters

| Drug | MW | $\log K_{\rm ow}{}^{\rm a}$ | P^{b} |
|--|--------|-----------------------------|-----------------|
| <i>p</i> -Hydroxybenzoic acid methyl ester (MP) | 152.15 | 1.53 | 3.68 ± 0.08 |
| <i>p</i> -Hydroxybenzoic acid ethyl ester (EP) | 166.18 | 2.23 | 2.43 ± 0.48 |
| <i>p</i> -Hydroxybenzoic acid propyl ester (PP) | 180.20 | 2.75 | 2.01 ± 0.35 |
| <i>p</i> -Hydroxybenzoic acid butyl ester (BP) | 194.23 | 3.13 | 2.38 ± 0.32 |
| <i>p</i> -Hydroxybenzoic acid amyl ester (AP) | 208.25 | 3.65 | 2.24 ± 0.39 |
| <i>p</i> -Hydroxybenzoic acid hexyl ester (HP) | 222.28 | 4.25 | 1.24 ± 0.32 |

Each value represents mean \pm S.E. (n = 4).

^a K_{ow} : octanol/water partition coefficient.

^b *P*: permeability coefficient ($\times 10^7$ cm/s).

esters. It was suggested that the molecular weight makes a greater contribution to the permeability coefficient than the octanol/water partition coefficient. The *F*-values of the molecular weight or octanol/water partition coefficient were 1.9399 or 0.1058, respectively.

From our findings, it was evident that nail plates behave as a hydrophilic gel membrane rather than a lipophilic partition membrane. Although this suggestion agreed with the investigations of Walters et al. (1983) and Mertin and Lippold (1997), an additional lipophilic route suggested by Walters et al. (1985) could not be found in the human nail plate. It has been reported that lipids are present in the dorsal and ventral plates, but only at very low levels in the intermediate plate which forms the main nail body (Jarrett and Spearman, 1966; Kobayashi et al., 1999). In addition, the lipid content



Fig. 2. Relationship between the permeability coefficient (*P*) and the octanol/water partition coefficient (K_{ow}) of *p*-hydroxybenzoic acid esters. Each value represents the mean \pm S.E. (*n* = 4). The abbreviations attached to the closed circle (\bullet) represent the model drugs in Table 1.

in the human nail plate has been found to be much lower than in the stratum corneum of skin (Walters and Flynn, 1983). Thus, there does not appear to be an additional lipophilic route in the human nail plate.

3.2. Influence of the molecular weight and dissociation on the permeability coefficient

Nail permeability was found to be independent of the lipophilicity of the drug used. From the findings in this early study, the coefficient, f, in Eq. (5) can be assumed to equal zero. Thus, substitution of f = 0 in Eq. (5) gives a simple model as follows:

$$\log P = \log\left(\frac{D^0}{h}\right) - \beta' \,\mathrm{MW}.\tag{6}$$

We investigated the nail permeability of several model drugs having various molecular weights. Because the influence of drug dissociation on the nail permeability is not clearly understood, the nail permeability of non-ionic and ionic drugs was evaluated separately.

Table 2 summarizes the pK_a , pH of the donor solution, molecular weight and permeability coefficient of the model drugs used in this investigation. All the model drugs were in the non-ionic form in the donor solution. The molecular weight of the model drugs ranged from 20 to 240. The nail permeability of drugs having a molecular weight of above 240 could not be determined, because of the low nail permeability. The nail permeation data of *p*-hydroxybenzoic acid esters ($pK_a = 8.4$, donor pH = 3.8–5.8) were added to this investigation because they exist in non-ionic form in the donor solution.

According to Eq. (6), Fig. 3 shows the relationship between the permeability coefficient and the molecular weight of each non-ionic drug. The logarithm of the nail permeability coefficient decreased as the molecular weight of the penetrating drug increased. A linear relationship (r = -0.860, P < 0.01) existed between the permeability coefficient and the molecular weight of the model drug, the slope (β') and the intercept $(\log(D^0/h))$ being 0.00856

Table 2 Physicochemical parameters and nail permeability coefficients ($h = 400 \,\mu\text{m}$) of non-ionic model drugs

| Drug | pK _a | pH ^a | MW | $P_{\rm non}{}^{\rm b}$ |
|----------------------|-----------------|-----------------|-------|-------------------------|
| Deuterium oxide | _ | 7.81 | 20.0 | 45.52 ± 4.30 |
| Ethanol | _ | 7.43 | 46.1 | 19.81 ± 2.21 |
| Pyridine | 5.19 | 7.35 | 79.1 | 6.36 ± 0.40 |
| Benzoic acid | 4.19 | 3.21 | 122.1 | 12.84 ± 0.05 |
| 5-Fluorouracil | 8.0, 13.0 | 4.65 | 130.1 | 2.08 ± 0.13 |
| Antipyrine | 1.50 | 6.37 | 188.2 | 0.53 ± 0.07 |
| Aminopyrine | 5.00 | 8.44 | 232.3 | 0.09 ± 0.02 |
| Lidocaine | 7.92 | 10.21 | 234.3 | 0.39 ± 0.14 |
| Isosorbide dinitrate | - | 5.72 | 236.1 | 1.51 ± 0.29 |

Each value represents mean \pm S.E. (5-FU, n = 30; other drugs, n = 3-4). ^a The pH in the donor solution.

^b P_{non} : permeability coefficient (×10⁷ cm/s) of non-ionic drugs.

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Fig. 3. Relationship between the permeability coefficient (*P*) and the molecular weight (MW) of non-ionic and ionic drugs. Each value represents the mean \pm S.E. (5-FU, n = 30; other drugs, n = 3-6). The dotted line represents the 95% confidence interval of the regression line. The closed circle (\bullet) represents the non-ionic drugs in Table 2. The open square (\Box) represents the ionic drugs in Table 3.

and -5.260, respectively. This finding suggests that nail permeability depends on the molecular weight of the penetrating drug, i.e. the drug diffusivity in the nail plate. The nail permeability of non-ionic drugs (P_{non}) can be predicted approximately from the linear regression (log $P_{non} = -0.00856 \,\text{MW} - 5.260$) and molecular weight of each drug.

Table 3 summarizes the pK_a , pH of the donor solution, molecular weight and permeability coefficient of the other model drugs. The model drugs existed in ionic form in the donor solution. The molecular weights of the ionic drugs used in this investigation ranged from 120 to 312.

Fig. 3 shows the relationship between the permeability coefficient and the molecular weight of the ionic drug. The logarithm of the nail permeability coefficient decreased as

Table 3

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Physicochemical parameters and nail permeability coefficients ($h = 400 \,\mu\text{m}$) of ionic model drugs

| Drug | pK_a | pH ^a | MW ^b | $P_{\rm ion}^{\rm c}$ |
|-----------------------------|--------|-----------------|-----------------|-----------------------|
| Sodium benzoate | 4.19 | 8.12 | 121.1 | 0.910 ± 0.136 |
| Sodium nicotinate | 4.85 | 7.21 | 122.1 | 0.606 ± 0.204 |
| Barbital sodium | 7.91 | 10.29 | 183.2 | 0.135 ± 0.016 |
| Mexiletin hydrochloride | 9.0 | 4.87 | 179.3 | 0.202 ± 0.057 |
| Isoproterenol hydrochloride | 8.57 | 4.06 | 211.2 | 0.084 ± 0.013 |
| Lidocaine hydrochloride | 7.86 | 4.33 | 235.3 | 0.031 ± 0.003 |
| Procaine hydrochloride | 8.8 | 5.27 | 237.3 | 0.110 ± 0.016 |
| Croconazole hydrochloride | 6.0 | 1.96 | 311.8 | 0.017 ± 0.009 |

Each value represents mean \pm S.E. (n = 4-6).

^a The pH in the donor solution.

^b The molecular weight with an ionic form of the drug.

^c P_{ion} : permeability coefficient (×10⁷ cm/s) of ionic drugs.

the molecular weight of the penetrating ionic drug increased. A linear relationship (r = -0.966, P < 0.01) also existed between the permeability and the molecular weight of the ionic drug; the slope (β') and intercept $(\log(D^0/h))$ were 0.01030 and -5.907, respectively. The nail permeability of ionic drugs (Pion) can also be predicted from the linear regression (log $P_{ion} = -0.01030$ MW - 5.907) and molecular weight of the ionic form. Multiple regression analysis was carried out to clarify which parameters (molecular weight or degree of dissociation) contribute to the permeability of model drugs. The degree of dissociation of the model drugs was calculated from the pK_a and pH in the donor solution. It was found that the molecular weight makes a greater contribution to the permeability coefficient of model drugs than the degree of dissociation. The F-values of the molecular weight or degree of dissociation were 10.9254 or 0.8599, respectively.

The permeability coefficient $(12.84 \times 10^{-7} \text{ cm/s})$ of the non-ionic form of benzoic acid, which is an acidic drug, was about 10 times higher than that $(0.91 \times 10^{-7} \text{ cm/s})$ of its ionic form. The permeability coefficient $(39.31 \times 10^{-9} \text{ cm/s})$ of the non-ionic form of lidocaine, which is a basic drug, was also about 10 times higher than that $(3.10 \times 10^{-9} \text{ cm/s})$ of its ionic form. In addition, the regression lines, which show the relationship between the permeability coefficient and the molecular weight of the non-ionic and ionic drugs, were parallel to each other. Furthermore, the regression line of the non-ionic form was about 10 times higher in position than that of the ionic form, as shown in Fig. 3. These results make it clear that dissociation leads to a reduction in nail permeability, irrespective of the charge on the drug. It is thought that the decrease in the permeability of ionic drugs is caused by a small increase (about 100) in the apparent molecular weight due to ion hydration.

In the investigation of Walters et al. (1983), they concluded that there was little or no dependence of human nail permeability on the dissociation of miconazole. However, Mertin and Lippold (1997) contradicted this conclusion because they found that the dissociation of benzoic acid and pyridine leads to a reduction in their penetration rate through bovine hoof membrane. They concluded that the decreased permeation caused by dissociation, is due to the Donnan effect or electrostatic repulsion between the keratin membrane and the diffusing molecule. The conclusions that we drew from our investigation using human nail plate agree with those of the latter researchers. The former researchers used citrate/phosphate buffer solution to evaluate the effect of miconazole dissociation on nail permeability. Their buffer solution has a high ionic strength and is composed of compounds exhibiting different ionic forms (mono-, di- and tri-ionic forms) with changing pH, compared with that (constant ionic strength, $\mu = 0.158$) used in the investigation of the latter group. The diffusion coefficient of the tri-ionic forms for citrate or phosphate is lower than that of the di-, mono-, and non-ionic forms (Southard et al., 1991). It seems that the decrease in permeability due to dissociation could

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