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In-vitro Permeability of the Human Nail and of a Keratin Membrane from Bovine Hooves: Prediction of the Penetration Rate of Antimycotics through the Nail Plate and their Efficacy

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Abstract

In contrast to the partition coefficient octanol/water the molecular size of penetrating drugs has a noticeable influence on the permeability of the human nail plate and a keratin membrane from bovine hooves. The relationship between permeability and molecular weight is founded on well-established theories. The correlation between the permeability of the nail plate and that of the hoof membrane allows a prediction of the nail permeability after determination of the drug penetration through the hoof membrane.

The maximum flux of ten antimycotics (amorolfine, bifonazole, ciclopirox, clotrimazole, econazole, griseofulvin, ketoconazole, naftifine, nystatin and tolnaftate) through the nail plate was predicted on the basis of their penetration rates through the hoof membrane and their water solubilities. An efficacy coefficient against onychomycoses was calculated from the maximum flux and the minimum inhibitory concentration.

Accordingly, amorolfine, ciclopirox, econazole and naftifine are expected to be especially effective against dermatophytes, whereas in the case of an infection with yeasts only, amorolfine and ciclopirox are promising.

The influence of molecular size on permeability was investigated in the present work, after previous studies had shown that drug penetration through the nail plate and a keratin membrane from bovine hooves is independent of the lipophilicity of the diffusing substance (Mertin & Lippold 1997).

Since the penetration of non-electrolytes through biological membranes is similar to that through polymers, the diffusion mechanism has also been transferred (Lieb & Stein 1969). Although there is no consistent theory about the diffusion in polymers, it is assumed that the thermal movement of the polymer chains creates holes which are occupied by the diffusing molecules (Kuminis & Kwei 1968; Lieb & Stein 1969). The penetration rate is limited by the formation frequency and the size distribution of these free volumes. On the other hand, these factors are influenced by the temperature, the nature of the polymer and the interactions of the polymer chains with each other and with the diffusing molecules. Transferred to biological structures, free volumes can be formed by separating lipid bilayers or proteins (Lieb & Stein 1969).

Cohen & Turnbull (1959) deduced an exponential relationship between the molecular volume V_M of the diffusing particle and its diffusion coefficient D from statistical analysis of the fluctuations of the free volume in super cooled liquids:

$$D = D_0 \cdot e^{-\beta \cdot V_M} \quad (1)$$

where D_0 is the diffusion coefficient of a hypothetical molecule with the mole volume of 0 and β is a reciprocal value for the average free volume (Potts & Guy 1993). As the diffusion coefficient through a biological membrane is difficult to determine, it is combined with the partition coefficient barrier/vehicle $PC_{B/V}$ to the permeability coefficient P:

$$P = D_0 \cdot e^{-\beta \cdot V_M} \cdot PC_{B/V} \quad (2)$$

Taking the logarithm leads to:

$$\log P = \log D_0 - \frac{\beta}{2{\cdot}303} V_M + \log PC_{B/V} \quad (3)$$

Since both nail plate and hoof membrane are hydrophilic gel membranes whose $PC_{B/V}$ is approximately unity (Mertin & Lippold 1997), equation 4 follows by combining the constant parameters:

$$\log P = k - \beta' \cdot V_M \quad (4)$$

$$\text{resp. } \log P = k - \beta'' \cdot MW \quad (5)$$

where β'' is similar to β' and contains a factor which reflects the conversion of the molecular volume into the molecular weight (MW).

On the basis of the diffusion of non-electrolytes in polymers, Lieb & Stein deduced an empirical equation which can also be transferred to biological membranes:

$$D = D_0 \cdot MW^{-z} \quad (6)$$

$$\text{resp. } \log D = \log D_0 - z \cdot \log MW \quad (7)$$

If the $PC_{B/V}$ becomes unity, it follows:

$$\log P = k - z \cdot \log MW \quad (8)$$

The parameter z is called mass selectivity coefficient which quantifies the sensitivity of the diffusion coefficient to alterations of the molecular weight of the diffusing compound. It ranges from 1·1 to 3·8 in plastics, from 2·9 to 6·0 in cell membranes and from 0·3 to 0·5 in liquids (Lieb & Stein 1969).

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The higher the value, the higher is the sensitivity to alterations of the molecular weight. The power function of Lieb & Stein (1969) often provides a satisfactory fit to the experimental data, but it is disadvantageous that the exponent z has no physical meaning (Potts & Guy 1993).

However, the single consideration of the molecular volume or weight may lead to the wrong prediction of the diffusion coefficient. Investigations of the penetration of linear and branched paraffins through different polymers show that branching reduces the diffusion to a greater extent than an increase of the molecular volume (Flynn et al 1974). The size as well as the shape of the molecules is important. Due to taking the logarithm of the molecular weight, the equation of Lieb & Stein (Eqn 6) seems to be less sensitive to neglecting the molecular shape than the Cohen-Turnbull correlation (Eqn 1) (Flynn et al 1974).

In this study, the relationship between the permeability of the nail plate or the hoof membrane, respectively, and the molecular weight of the penetrating substance has been investigated to enable the prediction of the nail penetration of potential antimycotics.

Among the nail infections onychomycoses, i.e. infections by fungi, are predominant. As antimycotics, which seem to be suitable for topical application, are expected to have low fluxes due to their slight water solubility, only their penetration through the hoof membrane was studied. The prospective maximum flux (J_{max}) of the antimycotics amorolfine, bifonazole, ciclopirox, clotrimazole, econazole, griseofulvin, ketoconazole, naftifine, nystatin and tolnaftate through the nail plate was calculated from their penetration through the hoof membrane and their water solubility. The efficacy of a topically applied antimycotic is not only influenced by the maximum flux but also by the antifungal potency, which is quantified by the minimum inhibitory concentration (MIC). An efficacy coefficient E is calculated from J_{max} and MIC, which predicts the topical effectiveness of an antimycotic against onychomycoses.

Materials and Methods

Chemicals

Phosphate buffered saline pH 7·4 (Ph. Eur.) and, in the case of the antimycotics, a mixture of phosphate buffer pH 7·4 of a higher buffer capacity with ethanol (resulting ethanol concentration 42% v/v) were used as media. Since the ethanol restrains the dissociation of phosphate, the pH value of the mixture is 8·1. The selection of the model compounds was reduced to water-soluble substances with the exception of the antimycotics.

Paracetamol was obtained from Boehringer Ingelheim (Ingelheim, Germany), phenacetin and bifonazole from Bayer (Leverkusen, Germany), diprophylline from Knoll (Ludwigshafen, Germany), chloramphenicol and clotrimazole from Caesar & Lorentz (Hilden, Germany), iopamidol from Byk Gulden (Konstanz), methyl, ethyl, butyl and hexyl nicotinate were obtained from Aldrich-Chemie (Steinheim, Germany), octyl nicotinate from the Department of Pharmaceutical Chemistry of the University of Düsseldorf, Germany, amorolfine from Hoffmann-La Roche (Basel, Switzerland), ciclopirox olamine and griseofulvin from Cassella-Riedel (Frankfurt, Germany), econazole nitrate from Cilag (Schaffhausen, Switzerland), ketoconazole from Janssen (Beerse, Belgium), naftifine hydrochloride from Sandoz (Nuremberg, Germany) and tolnaftate from Essex (Munich, Germany). HPLC-pure acetonitrile (Acetonitril Chromasolv) and methanol (Methanol Chromasolv) were from Riedel-de Haën (Seelze, Germany).

Penetration studies

The diffusion cells, the preparation of the nails and of the hoof membranes, the penetration studies, the analyses, the determination of the solubilities and the calculation of the permeability coefficient P and of the maximum flux J_{max} have already been described in an earlier publication (Mertin & Lippold 1997). The antimycotics as well as paracetamol, phenacetin and chloramphenicol were presented as saturated solutions in their maximum thermodynamic activity. The setting of the saturation concentrations was guaranteed by suspending and stirring a surplus of the drug at 32°C for 48 h. Due to their very high water solubility, diprophylline and iopamidol were able to be used as non-saturated solutions (hoof membrane: $C = 1000$ mg L^{-1}; nail plate: $C = 20\,000$ mg L^{-1}). With the antimycotics, the donor compartment consisted of the drug suspension in ethanol 42% (v/v), pH 8·1. The penetrating amount per time and area therefore represented the maximum flux. Due to its high solubility in the medium, ciclopirox was an exception: it could be dissolved completely in a concentration of 1000 mg L^{-1}. Since the antimycotic with the least molecular size had a mole mass of 207, homologous nicotinic acid esters served to cover the low molecular weight area which ranged from 140 to 230 in a donor concentration of 1000 mg L^{-1}. Ethanol 42% (v/v), pH 8·1 also served as the acceptor medium.

Determination of the dissociation constants

For the determination of the acid constants of the antimycotics, the potentiometric method of Albert & Serjeant (1984) was performed. Solutions (0·02–0·10 mol) of the antimycotics were used due to their slight solubility. The pH values were recorded with two decimal places after each addition of the titrant at 32±1°C and the pK_a value was determined according to the Henderson-Hasselbalch equation. Since the titrations were carried out in ethanol 42% (v/v), the pH-meter (Digital-pH-Meter 644, Knick, Berlin) with glass electrode (U 402/165, Ingold, Frankfurt) was calibrated with ethanol 42% (v/v) containing 0·001 mol benzoate, salicylate and ammonium buffer solutions. The corresponding pK_a values in ethanol 42% (v/v) are 5·24 (benzoic acid), 3·62 (salicylic acid) (Grunwald & Berkowitz 1951) and 8·78 (ammonium chloride) (Gutbezahl & Grunwald 1953).

Results and Discussion

Permeability and molecular weight

Table 1 shows the molecular weights (MW) and the permeability coefficients of the drugs, calculated from the concentration increase in the acceptor through the nail plate (P_N) and the hoof membrane (P_H). The corresponding data of the homologous nicotinic acid esters (Mertin & Lippold 1997) were included in the analysis. Since the antimycotics were only investigated in ethanol 42% (v/v), pH 8·1, these results were analysed separately from those of the other substances. Figs 1 and 2 show the correlation between the permeability coeffi-

Table 1. Molecular weights (MW) of antimycotics and other drugs and their permeability coefficients through nail plate P_N and hoof membrane P_H.

	MW	P_N (10^{-8} cm^2 s^{-1})	P_H, $P_{H,EtOH}$ resp. 10^{-8} cm^2 s^{-1}
Medium: aqueous phosphate buffer pH 7·4			
Paracetamol	151·2	1·78±0·32	20·97±5·15
Phenacetin	179·2	1·40±0·47	20·78±5·05
Diprophylline	254·3	0·142±0·055	6·14±2·01
Chloramphenicol	323·1	0·182±0·047	9·01±2·61
Iopamidol	777·1	0·010±0·002	1·44±0·34
Medium: ethanol-containing phosphate buffer pH 8·1			
Amorolfine	317·5	n.d.	2·03±0·25
Bifonazole	310·4	n.d.	3·05±037
Ciclopirox	207·3	n.d.	2·13±0·65
Clotrimazole	344·8	n.d.	2·30±0·65
Econazole	381·7	n.d.	3·37±1·20
Griseofulvin	352·8	n.d.	1·00±0·26
Ketoconazole	531·4	n.d.	0·84±0·18
Naftifine	287·4	n.d.	4·08±0·98
Nystatin	926·1	n.d.	0·10±0·02
Tolnaftate	307·4	n.d.	3·44±1·03

Results are presented as means ±s.d., n = 4. n.d., not determined.

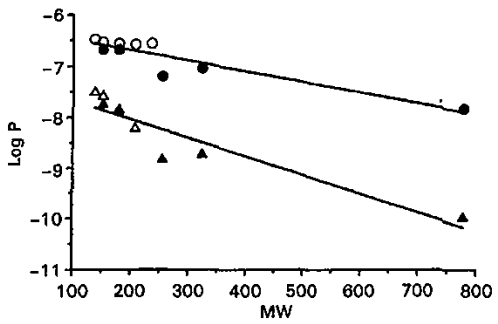

FIG. 1. Relationship between the logarithm of the permeability coefficient P for the nail plate (△, ▲) or the hoof membrane (○, ●) and the molecular weight (n = 3–8, means, s.d. see Fig. 3). Medium: phosphate buffer pH 7·4. P is expressed in cm^2 s^{-1} ○, △ nicotinic acid esters; ●, ▲ remaining substances. Plot according to Cohen & Turnbull (1959) (Eqn 5): log $P_N = -7{\cdot}296 - 0{\cdot}003708$ MW, $r = 0{\cdot}933$ (nail plate) or log $P_H = -6{\cdot}284 - 0{\cdot}002071$ MW, $r = 0{\cdot}920$ (hoof membrane).

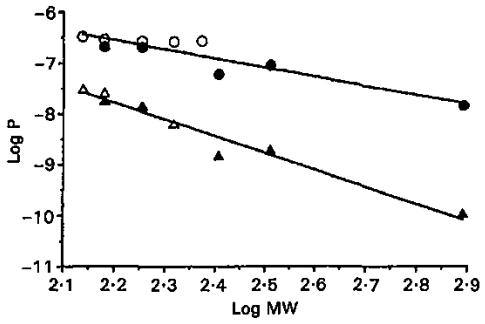

FIG. 2. Relationship between the logarithm of the permeability coefficient P for the nail plate (△, ▲) or hoof membrane (○, ●) and the logarithm of the molecular weight MW (n = 3–8, means, s.d. see Fig. 3). Medium: phosphate buffer pH 7·4. P is expressed in cm^2 s^{-1}. ○, △ nicotinic acid esters; ●, ▲ remaining substances. Plot according to Lieb & Stein (1969) (Eqn 8): log $P_N = -0{\cdot}427 - 3{\cdot}341$ log MW, $r = 0{\cdot}981$ (nail plate) or log $P_H = -2{\cdot}635 - 1{\cdot}782$ log MW, $r = 0{\cdot}924$ (hoof membrane).

cient and the molecular weight according to the theory of Cohen & Turnbull (log P vs MW) and Lieb & Stein (log P vs log MW), respectively, in the aqueous milieu pH 7·4, where the investigated substances were nearly undissociated (Table 1, upper part).

There was a linear relationship with a negative slope between the permeability coefficient and the molecular weight for both the nail plate (generally lower P-values) and the hoof membrane. Although giving of the correlation coefficient r is only permitted for regressions of the second kind (x and y as random variables) (Documenta Geigy 1975), it was nevertheless considered, as it simplifies a judgement of the relationship. The correlation coefficients show that the plot according to Lieb & Stein (Fig. 2) was either equal or slightly superior to the Cohen-Turnbull plot (Fig. 1). The slopes of the nail-plate data and the hoof-membrane data differed in both correlations by a factor of 1·8 to 1·9. This meant that the permeability of the nail plate was about twice as sensitive to a change of the molecular size as that of the hoof membrane. Both results (the lower permeability, but higher slope in the case of the nail plate) could be explained by the denser network of the nail keratin matrix. This demanded that the molecules had to diffuse a longer way due to the greater pore tortuosity and the penetration rate was therefore reduced in general. On the other hand, the penetration rate in the pores was reduced by the increased friction between the diffusing molecules and the gel network, which meant that the radius of the solvated molecule (r_S) became closer to the pore radius of the network (r_P) (Flynn et al 1974). The close-meshed keratin network of the nail plate contains few pores in the order of magnitude of the larger diffusing molecules, which are hindered to a stronger extent than smaller ones. The higher dif-

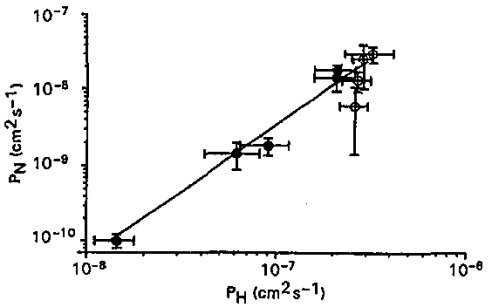

FIG. 3. Relationship between the permeability coefficient of the nail plate P_N and the permeability coefficient of the hoof membrane P_H at 32°C (n = 3–8, means ± s.d.). ○ nicotinic acid esters; ● remaining substances. Log $P_N = 3{\cdot}723 + 1{\cdot}751 \log P_H$, r = 0·971.

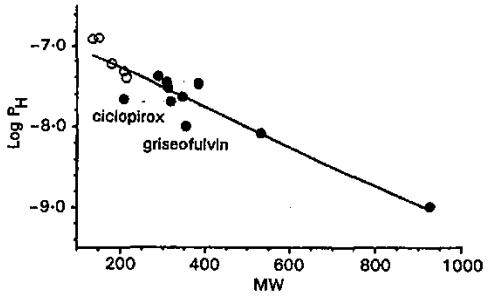

FIG. 4. Relationship between the logarithm of the permeability coefficient of the antimycotics through the hoof membrane P_H and the molecular weight MW (n = 4, means). Medium: ethanol 42% (v/v) pH 8·1. P_H is expressed in cm^2 s^{-1}. ○ nicotinic acid esters; ● antimycotics. Plot according to Cohen & Turnbull (1959) (Eqn 5): log $P_{H,EtOH} = -6{\cdot}795 - 0{\cdot}002427$ MW, r = 0·931.

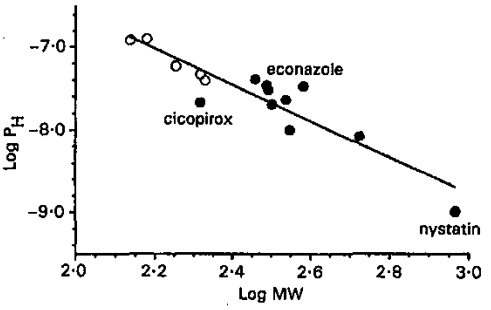

FIG. 5. Relationship between the logarithm of the permeability coefficient of the antimycotics through the hoof membrane P_H and the logarithm of the molecular weight MW (n = 4, means). Medium: ethanol 42% (v/v) pH 8·1. P_H is expressed in cm^2 s^{-1}. ○ nicotinic acid esters; ● antimycotics. Plot according to Lieb & Stein (1969) (Eqn 8): log $P_{H,EtOH} = -2{\cdot}224 - 2{\cdot}181 \log$ MW, r = 0·915.

fusional resistance of the nail keratin cannot only be explained by the lower swelling in the aqueous milieu compared with that of the hoof membrane. With approximately 27% it was only slightly below the corresponding value of the hoof membrane (36%) (Mertin 1995). A distinct difference regarding the structure of the two barriers must be the reason.

The permeabilities of both the nail plate and the hoof membrane derive from the molecular size of the drugs and can be therefore calculated. It is not necessary to have information about partition parameters as in the case of the stratum corneum; correlations using the molar volume instead of the molecular weight showed that this parameter has no advantage (Mertin 1995).

Prediction of the nail permeability

Since nail plates are only available to a certain extent for the preclinical development of topical drugs, it is of interest to calculate the expected permeability coefficient of the nail from a determined value using the hoof membrane model. Although the permeability coefficients of the nail plate and the hoof membrane differ from each other, it has been shown that the bovine hoof membrane may serve as an appropriate model for the nail, because both are hydrophilic gel membranes (Mertin & Lippold 1997). As the logarithm of the permeability coefficient represents the correlating parameter, the nail plate permeability of a drug can be derived directly from a plot of log P of the nail plate (log P_N) vs log P of the hoof membrane (log P_H) after experimental determination of P_H (Fig. 3). The drug permeability of the nail plate evaluated by this procedure should better correspond to the real value than the direct calculation using molecular weight, according to equations 5 and 8, or the parameters in Figs 1 and 2, respectively, since the experimental determination of the penetration through the hoof membrane considers the characteristics of a substance (e.g. interactions with keratin) to a larger extent.

The hoof membrane is therefore a suitable in-vitro model regarding the prediction of the permeability of the nail plate. The result is the following equation (Fig 3):

$$\log P_N = 3{\cdot}723 + 1{\cdot}751 \log P_H \qquad (10)$$

Penetration of the antimycotics and its prediction

The permeability coefficients of the antimycotics through the hoof membrane in the ethanol-containing medium range from $0{\cdot}10 \times 10^{-8}$ to $4{\cdot}08 \times 10^{-8}$ cm^2 s^{-1} (Table 1, lower part and Figs 4 and 5, respectively). The distinct decrease in the penetration rate to one-fourth or one-fifth compared with the pure aqueous milieu was a result of the de-swelling effect of the ethanol. The swelling of the keratin membrane decreased from 36% (m/m) to 27% (m/m) due to replacing water by ethanol 42% (v/v) (Mertin 1995). The correlation according to Cohen & Turnbull (Fig. 4) as well as according to Lieb & Stein (Fig. 5) again showed that there was a clear relationship between the permeability coefficient and the molecular weight. The correlation coefficients were similar to those determined in the pure aqueous milieu, but the Cohen-Turnbull plot seemed to have a slight superiority. For both correlations the regression coefficients of the respective straight lines of the data determined in ethanol 42% (v/v) were higher than in the case of the aqueous solutions: 0·002427 vs 0·002071 (Cohen & Turnbull) and 2·181 vs 1·782 (Lieb & Stein). This was also the consequence of the decrease of the membrane swelling in ethanol with a higher sensitivity of the permeability towards an

Table 2. Physicochemical and antimicrobial properties of the antimycotics.

	$pK_{a,EtOH}$	β_{EtOH}	C_{sw}	$C_{s7.4}$	MIC_D	MIC_Y
Amorolfine	6·6 (water)*	0·0316 (water)	9995	8·8	0·01	0·55
Bifonazole	5·11±0·04	0·0010	0·35	0·13	0·1	0·89
Ciclopirox	8·07±0·05	0·517	8590	1020	2·0	2·0
Clotrimazole	4·74±0·04	0·0004	3·0	2·7	2·3	35
Econazole	5·38±0·04	0·0019	1020	11·5	0·35	100·0
Griseofulvin	no acidic or basic groups		10·4	10·1	3·1	–
Ketoconazole	5·20±0·10	0·0013	10·6	7·9	2·23	25
Naftifine	6·80±0·03	0·0477	8650	2·9	0·55	50
Nystatin	pK_{a1}: about 4·0					
	pK_{a2}: 7·73±0·03	1·00	18·6	18·5	4·5	3
		0·299 (zwitter ion)				
		0·701 (negative)				
Tolnaftate	no acidic or basic groups		0·07	0·11	0·55	–

$pK_{a,EtOH}$: dissociation constant in ethanol 42% (v/v) (n = 6–9, means ± max. deviation). $\beta_{Et\ OH}$: degree of dissociation in ethanol 42% (v/v) at pH 8·1. C_{sw}: water solubility at 32°C (means, n = 2) expressed in mg L^{-1}. $C_{s7.4}$:solubility in phosphate buffer pH 7·4 at 32°C (means, n = 2) expressed in mg L^{-1}. MIC_D, MIC_Y: MIC against dermatophytes or yeasts, respectively, calculated as the geometrical mean of the limits of the highest range given in the literature (Plempel & Stetter 1987; Wilson & Ryley 1990; McEvoy & Litvak 1993) expressed in mg L^{-1}. *Hofmann-La Roche AG (1992). ED, EY: efficacy coefficients against dermatophytes and yeasts, respectively, taking into account the calculated maximum fluxes from water, expressed in cm s^{-1}.

alteration of the molecule size due to the denser structure of the keratin filaments.

Antimycotics, which differ to a larger extent from the regression line, are labelled in the diagrams. Ciclopirox, deviating in both plots, was dissociated at pH 8·1 to about 50% (Table 2) and was inhibited as an anion in its penetration through the negatively charged keratin membrane due to the Donnan equilibrium (Mertin & Lippold 1997). A similar argument can be applied to nystatin, which was present as an anion to 70%. Although griseofulvin had a high affinity towards keratin (ICI-Pharma 1981), its rather low permeability coefficient was probably not due to the sorption phenomenon. It rather represented, as did the deviation of econazole, a normal experimental error.

Since the Cohen-Turnbull correlation led to a better adaptation of the permeability coefficients and was theoretically better sustained than the Lieb-Stein plot, it was used in the following calculations to predict the penetration of the antimycotics through the nail plate. A direct calculation of the nail plate permeability according to Fig. 3 was not possible due to the different substances and media used. Combining the regression equations concerning the permeability of the nail plate in water (Eqn 11) and also the hoof membrane in ethanol 42% (Eqn 12) resulted in equation 13 after transformation:

$$\log P_N = -7{\cdot}296 - 0{\cdot}003708\ MW \quad (11)$$

$$\log P_{H,EtOH} = -6{\cdot}795 - 0{\cdot}002427\ MW \quad (12)$$

$$\log P_N = 1{\cdot}528 \times \log P_{H,EtOH} + 3{\cdot}085 \quad (13)$$

According to equation 13, the permeability coefficients of the antimycotics through the nail plate in an aqueous medium could be derived from the experimental data in ethanol 42% (v/v). Taking the water solubility of the drug C_{sw} (Table 2) into account, the maximum flux through the nail plate was calculated according to equation 14:

$$J_{max} = \frac{P_N}{h_B} \cdot C_{SW} \quad (14)$$

The values were standardized to a barrier thickness of $h_B = 1000\ \mu m$ ($J_{max}(1000\ \mu m)$). As information about the pH value in the nail or its buffer capacity was not available, the water solubility C_{sw} instead of the solubility in phosphate buffer pH 7·4 was used.

While the expected permeability coefficients of the various antimycotics through the nail only differed by a factor of 100, the maximum fluxes ranged from 10^{-8} to 10^{-3} mg cm^{-2} s^{-1} (Table 3) due to the influence of the

Table 3. Permeability coefficients P_N and maximum flux $J_{max}(1000\ \mu m)$ of the antimycotics through the nail plate and their predicted efficacy against dermatophytes E_D and yeasts E_Y, calculated from the experimental data ($P_{H,EtOH}$) according to equations 13, 14 and 15.

	P_N (cm^2 s^{-1})	$J_{max}(1000\ \mu m)$ (mg cm^{-2} s^{-1})	E_D (cm s^{-1})	E_Y (cm s^{-1})
Amorolfine	$2{\cdot}15 \times 10^{-9}$	$2{\cdot}15 \times 10^{-4}$	$2{\cdot}15 \times 10^{-2}$	$3{\cdot}91 \times 10^{-4}$
Bifonazole	$3{\cdot}98 \times 10^{-9}$	$1{\cdot}39 \times 10^{-8}$	$1{\cdot}39 \times 10^{-7}$	$1{\cdot}56 \times 10^{-8}$
Ciclopirox	$2{\cdot}30 \times 10^{-9}$	$1{\cdot}98 \times 10^{-4}$	$9{\cdot}87 \times 10^{-5}$	$9{\cdot}87 \times 10^{-5}$
Clotrimazole	$2{\cdot}59 \times 10^{-9}$	$7{\cdot}77 \times 10^{-8}$	$3{\cdot}38 \times 10^{-8}$	$2{\cdot}22 \times 10^{-9}$
Econazole	$4{\cdot}66 \times 10^{-9}$	$4{\cdot}74 \times 10^{-5}$	$1{\cdot}35 \times 10^{-4}$	$4{\cdot}74 \times 10^{-7}$
Griseofulvin	$7{\cdot}27 \times 10^{-10}$	$7{\cdot}56 \times 10^{-8}$	$2{\cdot}44 \times 10^{-8}$	–
Ketoconazole	$5{\cdot}52 \times 10^{-10}$	$5{\cdot}85 \times 10^{-8}$	$2{\cdot}62 \times 10^{-8}$	$2{\cdot}34 \times 10^{-9}$
Naftifine	$6{\cdot}23 \times 10^{-9}$	$5{\cdot}38 \times 10^{-4}$	$9{\cdot}78 \times 10^{-4}$	$1{\cdot}08 \times 10^{-5}$
Nystatin	$2{\cdot}16 \times 10^{-11}$	$4{\cdot}02 \times 10^{-9}$	$8{\cdot}93 \times 10^{-10}$	$1{\cdot}34 \times 10^{-9}$
Tolnaftate	$4{\cdot}80 \times 10^{-9}$	$3{\cdot}36 \times 10^{-9}$	$6{\cdot}11 \times 10^{-9}$	–

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