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Evaluation of the percutaneous absorption and metabolism of some aminopropiophenones

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The absorption of diethylpropion (DEP I), dimethylpropion (DMP I) and some of their basic metabolites into and passage through the skin was investigated and a comparison of their metabolism following oral and percutaneous administration made. High percentages (60–80%) of DEP I and its metabolites and a small percentage of DMP I and its metabolites were taken up into the skin in less than 2 min—the remaining percentages of the compounds were absorbed into the skin by a first order process. The rate of appearance of the compounds in the blood, which reflects their rate of passage through the skin, did not correlate with their rate of absorption into the skin. More metabolism occurred with all the compounds after their oral administration than after their percutaneous application.

A review on transdermal drug absorption (Wester & Noonan 1980) has indicated that skin enzymes may possess metabolic activities comparable with those of the liver; thus, topically applied drugs may be considerably metabolized, especially when the drug forms a reservoir in the skin. The metabolism of corticosteroids, which are known to form substantial reservoirs (McKenzie & Stoughton 1962), has been reported (Berliner 1972; Hay & Hodgins 1973). However, after percutaneous administration of (−)-methylephedrine, (−)-ephedrine, (±)-norephedrine and (−)-ethylephedrine, the recovery of metabolites from urine was lower than after oral administration (Beckett et al 1972). This suggests that skin metabolism in this case was of less importance than normal first pass metabolism.

In the present study the absorption of diethylpropion, dimethylpropion and their metabolites into and passage through the skin was investigated, and a comparison of their skin metabolism with their first pass metabolism involving the liver and gut wall was made.

METHODS

Gas liquid chromatographic analysis (GLC)

A Perkin Elmer FII gas chromatograph with flame ionization detector was used for the determination of all the compounds. Conditions were as follows: N_2 flow 1·25 $cm^3 s^{-1}$, H_2 pressure 135 kPa and air pressure 110 kPa; injection block temperature 250 °C.

Free bases of dimethylpropion (DMP I) and its metabolites monomethylpropion (DMP II), methylephedrine (DMP IV), and diethylpropion (DEP I) and its metabolites ethylaminopropiophenone (DEP II), diethylnorephedrine (DEP IV) were extracted from samples (4–6 ml of urine or aqueous solution) into 100 µl of chloroform (single step extraction) after addition of alkali and shaking in a test-tube for 2·25 min on a Fison whirlimixer. The test-tubes were then centrifuged to separate the two immiscible phases. When DMP II was not present, 1–2 µl of the chloroform layer was injected directly onto a column (1 m) containing Chromosorb G (AW DMCS, 100–120 mesh) coated with 2% Carbowax 20M and 10% Apiezon L. When DMP II was present, it was acetylated, before injection on the column, by adding 50 µl of acetic anhydride to the chloroform layer and leaving overnight. For DMP I, II and IV, ethylephedrine hydrochloride was used as internal marker and the column temperature was 195 °C. For DEP, I, II and IV, dimethylamphetamine hydrochloride was used as internal marker and the column temperature was 180 °C.

Two other metabolites of DMP I, ephedrine (DMP V) and norephedrine (DMP VI) were extracted from the samples (5–8 ml urine or aqueous solution) with 4 × 3 ml of treated diethyl ether (Hollingsbee 1977; Rahman 1977), after addition of alkali. Then 2–5 µl of the diethyl ether layer was injected onto a column (1 m) containing Chromosorb G (AW DMCS, 80–100 mesh) coated with 5% Carbowax 6000 and 5% KOH, with nikethamide as internal marker and a column temperature of 165 °C.

Determination of drug loss from solutions applied on the skin

Hydrochlorides of DMP I, II, IV, V, VI and DEP I, II, IV in water were made alkaline and extracted with ether. After evaporation of the solvent, solu-

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tions were made containing approximately 1% of each base in 2% glycerol in absolute ethanol; exact concentrations were determined by GLC. Each solution (100 μl) was separately applied on different days onto the surface of a circular area of skin (2·5 cm diam.) as follows:

First the area of skin to be used was wiped with absolute ethanol, then a sticking plaster 'washer' (internal diam. 2·5 cm) with adhesive on both sides was applied to the skin on the inner aspect of the forearm of a volunteer. The above 'free base' solution was then applied (2 min) under a stream of cold air to the area of skin within the 'washer' using a 100 μl glass SGE syringe. The solvent thus evaporated leaving the drug in glycerol on the skin surface.

A circular piece of polythene was stretched in the centre so that a circular section (2·5 cm diam.) was raised about 2 mm, giving a hat-like appearance. This was attached to the adhesive 'washer' so that only the 'brim of the hat' was touching the washer on the skin.

Finally a square piece of 'adhesive plaster' with a hole (2·5 cm diam.) cut out of its centre was placed on top of the formed polythene leaving the central portion uncovered.

All three parts of this 'occlusive' patch were removed at certain times after drug application (i.e. 2, 5, 30, 45 or 60 min) and the drug remaining on the skin and the patch material was wiped off with pieces of cotton wool soaked in 0·1 M hydrochloric acid. Organic bases were then extracted from the pieces of cotton wool (extractability about 95%) and analysed by GLC as described above. The amount of drug lost from the surface of the skin either by absorption into the skin and the patch material or by evaporation was then calculated.

Determination of drug loss from solutions applied on a glass surface

The procedure described under 'determination of drug loss from solutions applied on the skin' was repeated, applying the drug solutions on glass plates. These were maintained at 37 °C. The amount of drug lost from the surface after certain times (30, 60, 120 and 180 min) either by absorption into the patch material or by evaporation, was then calculated. The term evaporation is used hereafter to define any process of drug loss other than absorption into the skin.

Urinary excretion studies

The urinary excretion rates and the cumulative urinary excretion of DMP I, DMP II, DMP IV, DEP I and their metabolites were determined after their oral and percutaneous administration. In all the trials, a 'low fat diet' was followed by the subject who also took ammonium chloride sustained release pellets (potency–579 mg g^{-1}), starting 24 h before the trials according to need (about 5–8 g over 48 h) to ensure an acidic urine flow (pH 4·8–5·0) throughout the trials. Urine was collected at 0·5 h intervals for 4 h, then at 1 h intervals for up to 14 h and then as convenient i.e. at 2–3 h intervals for up to 24 h. All the samples were analysed by GLC.

For oral administration the drugs were in aqueous solution. Table 1 shows the doses administered in each trial calculated as mg of base.

For percutaneous administration 100 μl of a 2·5–5% solution of each free base in 2% glycerol in absolute ethanol was used; the exact concentrations were determined by GLC. The preparation and application of each solution was carried out as described previously. The exact amounts applied were 3·98 and 3·06 mg for the two trials with DEP I and 2·73, 2·52 and 4·96 mg for the trials with DMP I, DMP II and DMP IV, respectively. The 'occlusive patches' were removed after 24 h and the amount of any drug or metabolite(s) remaining on the surface of the skin and the patch material were determined.

RESULTS AND DISCUSSION

Figs 1 and 2 show graphical representations of the results obtained after application of DMP I, II, IV and DEP I, II, IV onto the skin (in-vivo trials) and onto glass plates (in-vitro trials). The results are the mean values of duplicate determinations. The in-

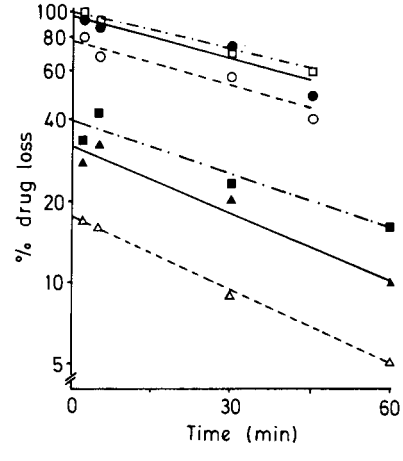


FIG. 1. Profiles of drug loss from the surface of the skin after the application onto the skin of dimethylpropion (DMP I), diethylpropion (DEP I) and their metabolites. —●— DMP I, – –○– – DMP II, –·–□–·– DMP IV, —▲— DEP I, – –△– – DEP II, –·–■–·– DEP IV.

Table 1. Comparison of urinary excretion of DMP I, DEP I, DMP II, DMP IV and their metabolites in 24 h after percutaneous and oral administration of these drugs to one subject under conditions of acidic urinary pH.

Drug admin.	Route	Dose** in mg	Parent drug Tmax*1	Parent drug % Recovery	% Recovery of metabolites			Total % recovery	R p/m*2
					DEP II	DEP IV	Total		
DEP I	Oral	21·2	1·2 h	N/M*3	36·3	35·6	71·9	71·9	
	Oral	21·2	1·5 h	N/M*3	25·2	29·7	54·9	54·9	
	Oral	21·2	1·0 h	8·5	31·5	24·8	56·3	64·8	0·15
	Oral	4·3	1·2 h	7·0	26·0	25·0	51·0	58·0	0·14
	Skin	3·9	4·5 h	9·2	20 4	16·3	36·7	45·9	0·25
	Skin	3·0	4·2 h	14·7	19·1	13·4	32·5	47·2	0·45
					DMP II	DMP IV			
DMP I	Oral	41·5	0·5 h	25·4	5·7	47·2	52·9	78·3	0·48
	Oral	41·5	0·5 h	21·4	10·2	51·9	62·1	83·5	0·35
	Oral	4·2	0·5 h	19·8	6·0	58·0	64·0	83·8	0·31
	Skin	2·1	6·7 h	37·4	N/D*4	39·4	39·4	76·8	0·95
					DMP V	DMP VI			
DMP II	Oral	24·6	1·0 h	35·0	48·0	4·0	52·0	87·0	0·67
	Oral	24·6	1·0 h	37·0	48·0	5·0	53·0	90·0	0·70
	Oral	24·6	1·0 h	52·0	38·0	8·0	46·0	98·0	1·13
	Skin	1·6	2·5 h	32·7	18·0	N/D*4	18·0	50·7	1·81
					DMP V	DMP VI			
DMP IV	Oral	29·9	1·8 h	82·3	13·7	N/D*4	13·7	96·0	6·01
	Skin	4·1	2·5 h	102·0	N/D*4	N/D*4	—	102·0	

** The percutaneous dose is the actual dose of drug calculated to be absorbed into the skin.
*1 Tmax = time of maximum urinary excretion rate.
*2 R p/m = ratio of percentage recoveries of parent drug to metabolites.
*3 N/M = not measured.
*4 N/D = not detected.

vivo results for DEP I, II, IV and DMP IV are the mean values obtained in two trials on subject SM, while those for DMP II and DMP I are the mean values of five and six trials, respectively, on the same subject. The straight line graphs in Figs 1 and 2 indicate that first order processes of drug loss by absorption or evaporation begin at least 2 min after application of each drug on the skin surface or 30 min after their application on the glass surface.

The Bo values shown in Table 2 indicate that in less than 2 min after the application of the drugs onto the skin: (i) much more DEP I and its metabolites are taken up into the skin compared with DMP I and its metabolites, (ii) less of the amino alcohols DMP IV and DEP IV are taken up into the skin compared with their corresponding ketones, and (iii) much more of the monoalkylamino ketones, i.e. DEP II and DMP II are taken up into the skin compared with their corresponding dialkylamino ketones, i.e. DEP I and DMP I. Also the K_1 values shown in Table 2 indicate that, when the first order process of absorption begins, DEP I and its metabolites are

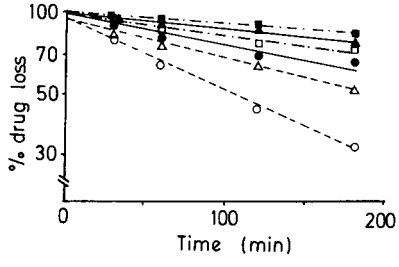


FIG. 2. Profiles of drug loss from the surface of the glass after the application onto glass plates of dimethylpropion (DMP I), diethylpropion (DEP I) and their metabolites. —●— DMP I, - -○- - DMP II, -·-□-·- DMP IV, —△— DEP I, - -△- - DEP II, -·-■-·- DEP IV.

Table 2. Pharmacokinetic parameters of dimethylpropion (DMP I), monomethylpropion (DMP II), methylephedrine (DMP IV), diethylpropion (DEP I), 2-ethylaminopropiophenone (DEP II) and diethylnorephedrine (DEP IV), calculated from the results in Figs 1 and 2.

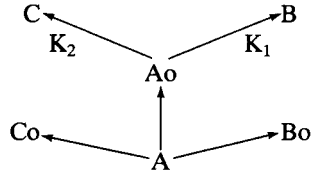
Drug	Ao	Co	Bo	K	K_1	K_2
DMP I	94·6	0·0	5·4	0·0111	0·0084	0·0027
DMP II	76·1	5·4	18·3	0·0122	0·0072	0·0050
DMP IV	100·0	0·0	0·0	0·0110	0·0091	0·0019
DEP I	31·8	0·0	68·2	0·0187	0·0175	0·0012
DEP II	11·3	6·3	82·4	0·0210	0·0177	0·0033
DEP IV	38·5	0·0	61·5	0·0145	0·0136	0·0009

Ao = y-intercepts of the lines in Fig. 1, i.e. % of drug lost from the surface of the skin by first order processes.
Co = 100 minus the y-intercepts of the lines in Fig. 2, i.e. % drug lost from the glass surface by non-first order processes.
Bo = 100 − Ao − Co, i.e. % of drug absorbed into the skin by a non-first order process.
K and K_2 = Slopes of the lines in Figs 1 and 2 respectively, i.e. rate constants of loss of drug from the surfaces of the skin and the glass plate, respectively.
$K_1 = K - K_2$, i.e. rate constants of absorption of drug into the skin.

absorbed into the skin at a much faster rate than DMP I and its metabolites.

Urinary excretion data obtained after oral or percutaneous administration of DEP I, DMP I, II and IV are shown in Table 1. After percutaneous application less than 1% of the drugs was detected on the surface of the skin and the patch material after 24 h. Therefore, the actual amount of drug absorbed into the skin was calculated as follows:

The whole process of absorption and evaporation of these drugs after their application onto the skin is illustrated in Scheme I.



Scheme I

Where A = amount of drug applied to the skin, B = amount of drug absorbed into the skin by a first order process, C = amount of drug lost by evaporation from the skin by a first order process; Ao, Bo, Co, K_1 and K_2 are as defined in Table 2.

For this kind of system (parallel drug loss) the equations 1, 2 and 3 apply (Notari 1980) at infinite time.

$$K = K_1 + K_2 \quad (1)$$

$$B_\infty/C_\infty = K_1/K_2 \quad (2)$$

$$Ao = B_\infty + C_\infty \quad (3)$$

From equations 1, 2, and 3, equation 4 can be derived:

$$B_\infty = [(K - K_2)/K]\,Ao \quad (4)$$

B_∞ is the percentage of drug which would be absorbed into the skin till infinity by a first order process; C_∞ is the percentage of drug which would be lost from the surface of the skin till infinity by a first order process of evaporation; K is as defined in Table 2. The total percentage of drug which would be absorbed into the skin, by a first or non-first order process, till infinity was calculated using equation 5:

$$B_{total} = B_\infty + Bo \quad (5)$$

The B_{total} values for DMP I, II, IV and DEP I were calculated to be: DMP I, 77·0%; DMP II, 63·4%; DMP IV, 82·7%; DEP I, 98·0%. These values were used to calculate the actual amounts of the drugs absorbed into the skin after percutaneous application and they are listed under dose in mg in Table 1.

From the R p/m values (the ratio of percentage recoveries of parent drug to metabolites) shown in Table 1, it is evident that more metabolism occurred with all four compounds after their oral administration than after their percutaneous administration. This indicates that if any skin metabolism occurred, this was much less than first pass metabolism involving the liver and/or the intestinal wall. A comparison of the urinary excretion data obtained following oral and buccal administration of DEP I and DMP I also suggested that these drugs undergo substantial first pass metabolism involving the liver and possibly the gut wall (Markantonis 1982).

With all four drugs studied, the time of their maximum urinary excretion rates (T max) was longer when the skin route was used (see Table 1 and one example Fig. 3). Probably a large proportion of the drug applied was held in the skin and then released slowly to the blood and subsequently excreted in the urine. The time of the peak urinary excretion rates following percutaneous administration increased in the order: DMP II < DMP IV < DEP I < DMP I. DEP I has a longer Tmax than DMP II and DMP IV although it is absorbed into the skin at a much faster

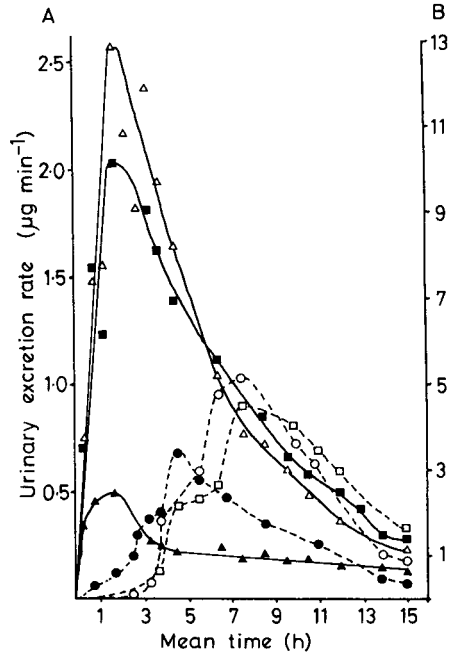


FIG. 3. Urinary excretion rates of DEP I and its metabolites following (B) oral administration of DEP I hydrochloride (25 mg) in solution and (A) percutaneous application of DEP I base (3·9 mg). Oral route: △—△ DEP II, ▲—▲ DEP I, ■—■ DEP IV; Percutaneous route: ○- - -○ DEP II, ●- - -● DEP I, □- - -□ DEP IV.

rate than either of the other two compounds. Therefore, the rate of appearance of DEP I in the blood, which reflects its rate of passage *through* the skin, does not correlate with its rate of absorption *into* the skin. This is due to factors such as (i) reversible binding of drug to skin tissue, (ii) sideways diffusion of drug into the hydrated stratum corneum in preference to penetration of the lipid barrier layer (especially with very non-lipid soluble drugs), (iii) the percentage of drug unionized at pH 7·4 (i.e. pH of blood) and (iv) the lipid/water solubility of drug.

Twenty-four hours after application of DEP I onto the skin, small quantities (less than 1%) of its metabolites DEP II and DEP IV were detected on the skin surface within the patch area. With DMP I, II and IV no metabolites were detected on the skin surface after 24 h. Because DEP I is the most highly metabolized of the four drugs and because of its fast absorption into, but relatively slow passage through, the skin it is probable that some metabolism of this compound occurs in the skin.

The maximum urinary excretion rates of the metabolites obtained after percutaneous administration of the four drugs were much lower, in relation to their doses than those obtained following oral administration (see example Fig. 3). This is a result of both the avoidance of first pass metabolism involving the liver and possibly the gut wall (lower percentages of metabolites were formed) and the slow release of the drugs from the skin into the blood.

The maximum urinary excretion rates of the parent drugs obtained after oral and percutaneous administration did not, in relation to their doses, differ as much as those of their metabolites. This is because the slow release of the drugs from the skin into the blood is compensated for by the higher percentages of those drugs being delivered into the blood by avoidance of first pass metabolism.

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