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The metabolism and urinary excretion in man of phentermine, and the influence of *N*-methyl and *p*-chloro-substitution*

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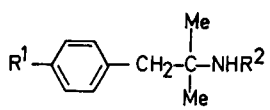
The urinary excretion of phentermine, mephentermine and chlorphentermine was examined after oral administration of phentermine and chlorphentermine hydrochlorides and mephentermine sulphate to man under normal and acidic conditions of urinary pH. The rate of excretion of both phentermine and mephentermine fluctuated with changes in urine pH, a more acidic pH causing a faster rate of excretion; changes in urine flow rate had only a slight effect. The rate of excretion of chlorphentermine was affected by changes in pH and urinary flow rates. Phentermine and mephentermine were recovered almost quantitatively within 24 h from subjects under acidic urine control; only about 35% chlorphentermine was recovered under similar conditions.

Mephentermine (Ib) is the *N*-methyl, and chlorophentermine (Ic) the *p*-chloroderivative of phentermine (Ia).



(I)

Ia $R^1 = R^2 = H$ Ib $R^1 = H$ $R^2 = Me$ Ic $R^1 = Cl$ $R^2 = H$

The metabolism of mephentermine in man does not appear to have been reported hitherto. The urinary excretion of unchanged chlorphentermine after oral administration was reported to be about 70% for rats and about 25% for mice (Opitz & Weischer, 1966, 1967; Dubnick, Towne & others, 1968); only about 5% of a dose of phentermine was similarly recovered. Lower recoveries of chlorphentermine with increase in dose were recorded from rats and man but no correlation with urine volume was noted. *N*-Demethylation and *p*-hydroxylation of mephentermine was effected by dogs, rabbits and rats given the drug intraperitoneally (Walkenstein, Chumakow & Seifter, 1955). One third of the dose was in the faeces but little unchanged drug was recovered from the urine, and then only in the first hour after administration. The urinary excretion of phentermine, mephentermine and chlorphentermine by man after the drug had been taken by mouth is now reported.

MATERIALS AND METHODS

Dosage regimens for oral administration of phentermine, mephentermine and chlorphentermine

Male subjects (age 25–45), under normal (pH about 5–8), or acidic urine control were given, on separate widely spaced occasions, an oral dose of 12·45 mg of phen-

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termine hydrochloride, 14·11 mg of mephentermine sulphate or 6·0 to 72 mg of chlorphentermine hydrochloride, in 60–80 ml aqueous solutions. Also, two subjects under acidic urine control were given 72 mg of chlorphentermine hydrochloride whilst drinking water at a rate of 700 ml/h.

Collection and examination of urine

The general procedure adopted for diet and the collection of urine was similar to that previously described by Beckett & Rowland (1965a). The induction and maintenance of an acidic urine (pH $\geqslant$ 5·0) was as described by Beckett & Brookes (1967). Urine samples were analysed by gas-liquid (g.l.c.) and thin-layer (t.l.c.) chromatography. Preparative t.l.c. was used to obtain samples suitable for infrared spectroscopy of phentermine excreted in the urine after oral administration of mephentermine sulphate.

The amount of the metabolite, phentermine, excreted was calculated as a percentage of the dose of mephentermine sulphate administered.

Gas-liquid chromatography

The ethereal extracts of urine were analysed using a Perkin Elmer F11 gas chromatograph with a flame ionization detector and a stainless steel column (3 ft $\times$ $\frac{1}{8}$ inch), packed with 10% KOH, 10% Apiezon L and acid washed, DMCS treated Chromosorb G (80–100 mesh) (column A). The analysis was run isothermally at 160° and using a nitrogen flow rate of 30 ml/min, the column condition and gas pressures being made optimum. A second column (B) also used has been described earlier (Beckett & Brookes, 1967).

Aletamine hydrochloride (10 μg base/ml in water), used as internal standard was added to urine at the start of the extraction procedure. Calibration curves for the amines were prepared as for amphetamine (Beckett & Rowland, 1965a). In addition, some of the ether extracts of urine were treated with acetone, acetic and propionic anhydrides, and examined by g.l.c. as described earlier (Beckett & Brookes, 1967). Several control urines from smokers and non-smokers were similarly examined because nicotine in smokers' urine interferes with the methyl orange assay procedure for the structurally similar amphetamine (Beckett, Rowland & Triggs, 1965). Phentermine, chlorphentermine and mephentermine were added (1 μg/ml) to urines at pH 4 and 9, stored at 4° and the solutions assayed periodically for two weeks.

Thin-layer chromatography

Glass plates, 20 $\times$ 20 cm coated with silica gel G (Merck) 0·25 mm thick, prepared according to Stahl, Schröter & others (1956) and dried at 90–100° for 30 min were spotted with ethereal extracts described above, together with authentic samples of phentermine, mephentermine and chlorphentermine and developed at room temperature (22–24°) with (*a*) ethanol (96%)–ammonium hydroxide (25%) (80:20); (*b*) methanol–chloroform–ammonium hydroxide (90:10:0·3); (*c*) methanol–chloroform (50:50). Mephentermine was visualized (red spot) by Dragendorff's spray (Stahl, 1962), and chlorphentermine and phentermine (pink spots) by freshly diazotized *p*-nitroaniline (Wickström & Salvesen, 1952).

Preparative t.l.c. was carried out under identical conditions using solvent system (*a*). Those sections of the plates containing the extracted phentermine and mephentermine, and the authentic samples, were scraped off and added to separate 5 ml portions of

20% w/v aqueous sodium hydroxide, well mixed and the drug content completely extracted with 3 × 2·5 ml of diethyl ether, the extracts being examined with a Unicam SP 100 infra-red spectrophotometer.

RESULTS

Identity of the metabolite of mephentermine

Analysis by g.l.c. of ethereal extracts of urines from subjects taking mephentermine sulphate gave one peak identical in retention time with that of authentic mephentermine and another with that of authentic phentermine. Identical retention times of the propionyl and acetyl derivatives of both amines and of the corresponding authentic samples (Table 1) confirmed the analysis. No acetone derivative was obtained for phentermine (or chlorphentermine) because of the steric hindrance of the second α-methyl group.

Table 1. *Retention times of phentermine, mephentermine and chlorphentermine and some derivatives on g.l.c. columns.*

Column	Compound		Retention time (min)
A	Phentermine		3·2
	Mephentermine		5·2
	Chlorphentermine		9·0
B	Acetyl derivative	Phentermine	4·4
Temp. 165°		Mephentermine	3·6
		Chlorphentermine	14·6
B	Propionyl derivative	Phentermine	12·3
Temp. 140°		Mephentermine	10·1
		Chlorphentermine	41·2

T.l.c. in systems (*a*)–(*c*) gave R_F values (0·53, 0·38 and 0·26 respectively) that were identical for the metabolite and for phentermine. Preparative t.l.c. gave an oil with an infrared spectrum identical with that of phentermine.

Quantitative analysis of phentermine, mephentermine and chlorphentermine

Analysis by g.l.c. gave linear calibration curves for all drugs. No interfering peaks occurred from control urines. The drugs in acidic and alkaline urines were stable for at least two weeks at 4°.

Urinary excretion

Phentermine. About 70–80% was excreted in 24 h from subjects under acidic urine control (Table 2). The excretion rate reached a maximum 2–3 h after drug administration, and then fell exponentially, e.g. see Fig. 1.

(*b*) *Mephentermine.* The excretion rate of mephentermine and its metabolite, phentermine, varied with urine pH in a manner similar to that seen with amphetamine and methylamphetamine (Beckett & Rowland, 1965a,b) and was only slightly influenced by urine output (Fig. 2A). With a normal urine pH, subjects excreted about 30–40% mephentermine and about 7–12% phentermine over 24 h (Table 2). In subjects with acidic urine, the excretion rate was much higher and rate fluctuations were almost abolished (Fig. 2A); about 70% of mephentermine and phentermine was excreted in 24 h and there was negligible inter-subject variation (Table 2). The

Table 2. *Urinary excretion of mephentermine, phentermine or chlorphentermine after oral administration to subjects with normal (pH 5–8) urine or acidic (pH ≯5) urine control* (24 h collection).

		Mephentermine sulphate (14·11 mg) % excreted			Phentermine HCl (12·45 mg) % excreted	Chlorphentermine hydrochloride		
Urine condition	Subject	As mephentermine	As phentermine	Total	As phentermine	Subject	Dose (mg)	% excreted as chlorphentermine
	I	60·8	7·2	68·0	74·0	III	72	16·7
	II	56·3	12·1	68·4		V	72	23·6
	III (1)	59·2	13·0	72·2	73·9	III	24	45·5
Acidic	III (2)	61·8	8·8	70·6		I	12	30·0
	IV				78·9	IV	12	38·6
	V (1)				71·7	V (1)	12	32·0
	V (2)				83·6	V (2)	12	39·2
						V	6	39·4
	VI	35·0	11·5	46·5				
Normal	III	28·9	7·0	35·9				
	V	41·1	8·1	49·2				

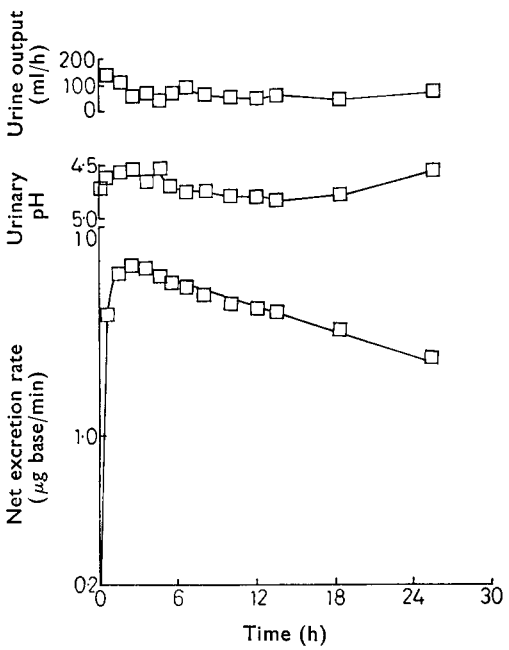

FIG. 1. Urinary excretion of phentermine with corresponding urinary pH and urine output after oral administration of 12·45 mg of phentermine hydrochloride in aqueous solution to subject III under acidic urine control.

excretion rate of mephentermine reached a maximum about 2–3 h after drug administration and then fell exponentially (Fig. 2B), while the excretion rate of phentermine reached a maximum after about 7 h.

(*c*) *Chlorphentermine.* The excretion rate was influenced by urine pH but primarily by rate of urine flow when the urine was kept acidic (Fig. 3) except when using the lowest dose (6 mg), and then the excretion rate of the drug reached a

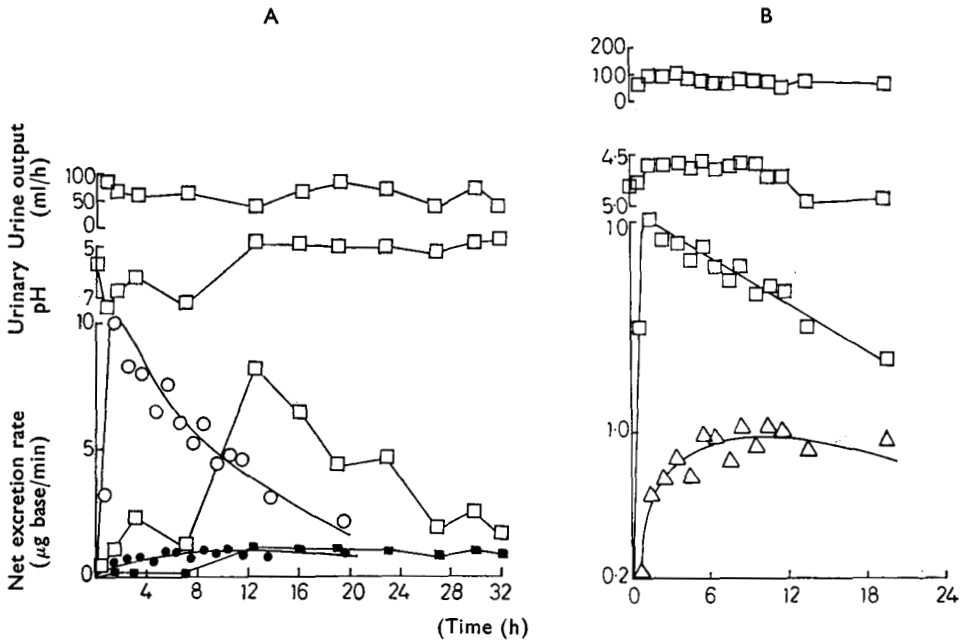

FIG. 2. A. Urinary excretion of mephentermine and its metabolite phentermine after oral administration of 14·11 mg of mephentermine sulphate with no urinary pH control (a) and acidic urine control (b). Acidic urine control: —○— mephentermine, —●— phentermine. No urinary pH control: —□— mephentermine, —■—phentermine.

B. Urinary excretion of mephentermine —□— and its metabolite phentermine —△—, with corresponding urinary pH and urine output after oral administration of 14·11 mg mephentermine sulphate in aqueous solution to subject III under acidic urine control.

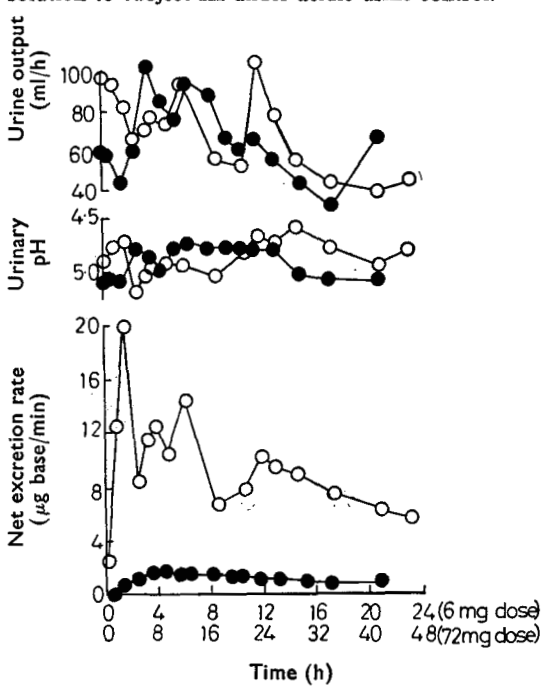

FIG. 3. Urinary excretion of chlorphentermine with corresponding urinary pH and urine output after oral administration of 6 mg (●) or 72 mg (○) of chlorphentermine hydrochloride in aqueous solution to a subject (V) under acidic urine control.

maximum 3–5 h after administration and fell exponentially. With doses of 24 mg of chlorphentermine hydrochloride or less, 24 h urine excretion accounted for about 35% drug, but this was only about 20% after doses of 72 mg (Table 2); water-loading with accompanying diuresis (about 500 ml/h) caused about double this amount of drug to be excreted unchanged.

DISCUSSION

The dealkylation of mephentermine in man to yield its major metabolite, phentermine, parallels that observed by Walkenstein & others (1955) with animals. The pH-dependent fluctuations in excretion rates of phentermine and mephentermine were expected since the pK_a values of phentermine and mephentermine are 9·84 and 10·11 respectively, so, like amphetamine and methylamphetamine (Beckett & Rowland, 1965a,b), renal tubular reabsorption of these drugs would be faster at an alkaline than at an acidic pH. Thus, the greater excretion of phentermine and mephentermine that we found when compared with the findings of Walkenstein & others (1955) and of Opitz & Weischer (1966), is because of pH control of urine. The high excretion of mephentermine and phentermine after oral administration indicates that their absorption from the gut is complete.

Our findings that the 24 h urinary excretion of phentermine and mephentermine after oral administration with acidic urine control is similar (70–80% of dose), while that of chlorphentermine is half this amount, are reflected in the elimination half lives of 7–8 h for phentermine and mephentermine and 14 h for chlorphentermine. The urinary excretion of both amphetamine and methylamphetamine in the same subjects as those used in the present work, was about 65% (Beckett & Rowland, 1965a,b; Brookes, 1968). Thus, the introduction of an α-methyl group into amphetamine has made the resulting compounds less susceptible to metabolism, most probably by steric hindrance. The ratio of drug to metabolite for both mephentermine and methylamphetamine was approximately the same, indicating that the *N*-dealkylation mechanism was not affected by the introduction of the α-methyl group into methylamphetamine. Because the excretion of mephentermine is the same as phentermine, we conclude that the *N*-methyl group has not rendered the former more susceptible to metabolism, a conclusion substantiated by drug excretion after methylamphetamine and amphetamine administration. *p*-Substitution of halogen in the molecule significantly changes the urinary excretion pattern of phentermine, not only by reducing the rate of excretion under acidic urine conditions but also by making the halogen-substituted drug susceptible to fluctuations in urine flow rate. Furthermore, compared with phentermine, there is a marked delay before chlorphentermine is excreted in the urine and reaches its maximum rate. Similar effects of such halogen substitution also occur (*a*) in the introduction of *m*-CF_3 and *p*-Cl into amphetamine to give norfenfluramine (Beckett & Brookes, 1967) and *p*-chloroamphetamine (Beckett & Salmon, to be published) respectively, and (*b*) in the introduction of *p*-Cl and *p*-Br into the pheniramine molecule to give chlorpheniramine and brompheniramine (Beckett & Wilkinson, 1965; Kabasaklian, Taggart & Townley, 1968).

In the buccal absorption test (Beckett & Triggs, 1967; Brookes, 1968), the lipid solubilities of phentermine, mephentermine, amphetamine and methylamphetamine were virtually identical, while chlorphentermine, chloramphetamine and norfenfluramine were significantly more lipid soluble, even at an acidic pH. Hence the

reduced urinary excretion, and concomitant increase in elimination half life of chlorphentermine, and probably also chloramphetamine, is the result of the greater lipid solubility of the chloro-substituted compounds which enhances their renal tubular reabsorption and redistribution in the body.

Since the completion of this work, Jun & Triggs (1970) have reported an average elimination half life for chlorphentermine in man, of 41 h, after monitoring whole blood concentrations, and suggest that the drug also undergoes multi-compartment distribution.

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