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Urinary excretion kinetics of methylamphetamine in man

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The urinary excretion of methylamphetamine and its metabolite, amphetamine, was studied after oral administration of (+)- and (−)-methylamphetamine hydrochloride to three male subjects. Fluctuations in the excretion rate of both amines occurred and were associated with changes in urinary pH. The fluctuations were abolished when the urine was maintained either acid or alkaline, by administration of ammonium chloride and sodium bicarbonate respectively. The total amount of both amines excreted was lower under alkaline than acid urine conditions. *N*-Demethylation of methylamphetamine was small, but greater for the (+)- than the (−)-isomer.

SIGNIFICANT amounts of methylamphetamine are reported to be excreted in urine in man. After oral administration of (−)-methylamphetamine, Richter (1938) recovered 56% in 48 hr, while Utena, Ezoe & Kato (1955) gave values of 70–90% recovery for the (+)-isomer. The analytical procedures were non-specific and would not differentiate between methylamphetamine and its *N*-demethylation product amphetamine, so that the observed results were probably higher than the true values. Cartoni & de Stefano (1963), using a specific method of assay, reported 50% of the drug was excreted unchanged and 17% as amphetamine.

The urinary excretion of amphetamine (pK_a 9·77, Leffler, Spencer & Burger, 1951; 9·93, Lewis, 1954) is influenced by urinary pH (Beckett & Rowland, 1964; Asatoor, Galman, Johnson & Milne, 1965). Since methylamphetamine has a similar pK_a value of 9·87 (Leffler & others, 1951) the effect of urinary pH on the excretion of methylamphetamine has been examined. Preliminary findings have been reported elsewhere (Beckett & Rowland, 1965b).

Experimental

URINE EXCRETION TRIAL

Three male subjects were given an oral dose of 11·0 mg methylamphetamine base in the form of 13·7 mg hydrochloride in water (50–100 ml). When the urinary pH was not controlled, the (+)- and (−)-isomers were given on separate occasions. In acid and alkaline urine trials, only (+)-methylamphetamine was administered.

The regimen of administration of drug, times of urination, measurement of urinary pH and dosage for ammonium chloride and sodium bicarbonate was as described for amphetamine (Beckett & Rowland, 1965c).

Any subjective effects experienced by the subjects were noted.

Plasma study. Blood was collected 1½ hr after an oral dose of 11·0 mg (+)-methylamphetamine had been given to three subjects.

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DETERMINATION OF METHYLAMPHETAMINE AND AMPHETAMINE IN URINE AND PLASMA

Methylamphetamine and amphetamine were determined by gas-chromatography as previously reported, and in a number of experiments amphetamine was further identified as its acetone derivative (Beckett & Rowland, 1965a). Methylamphetamine (0·1–10 μg/ml urine; 1 μg/ml plasma) and amphetamine (0·1–10 μg/ml urine) were added to the urine or plasma of subjects who had not received any drug. These solutions and others in which no drug had been added were analysed. Methylamphetamine (1 μg/ml) was added to acid and alkaline urine and stored at 4°. The methylamphetamine content was determined daily for 4 days.

Results

Linear calibration curves for both amine components in urine within the range 0·1–10 μg/ml were obtained. The presence of methylamphetamine interfered with the determination of amphetamine, to the extent of 1% of the methylamphetamine peak at the t_R value for amphetamine, and any appropriate correction was made. No substance which interferes with the determination of the amines was found in the urine or plasma of subjects who had not taken methylamphetamine. Methylamphetamine was stable for at least 4 days in acid or alkaline urine stored at 4°.

URINARY EXCRETION

pH of urine not controlled. The results are shown in Table 1. The excretion rate of methylamphetamine and amphetamine varied with urinary pH but not with urine output (Fig. 1). The urinary pH fluctuated within the range 5·2–7·6, whether or not the drug was given.

TABLE 1. URINARY EXCRETION OF METHYLAMPHETAMINE AFTER ORAL ADMINISTRATION OF 13·7 MG (+)- AND (−)-METHYLAMPHETAMINE HYDROCHLORIDE. URINARY pH NOT CONTROLLED

Subject	Isomer	% of the methylamphetamine dose excreted					
		As methylamphetamine			As amphetamine*		
		16 hr	24 hr	48 hr	16 hr	24 hr	48 hr
M.R. ..	(+)	14·0	22·1	26·7	1·7	3·8	6·0
	(−)	17·3	27·3	38·3	0·8	1·7	3·1
N.B. ..	(+)	15·3	21·3	28·9	2·5	4·5	9·2
	(−)	15·1	25·8	43·5	0·5	1·4	4·0
E.J.T. ..	(+)	31·5	42·7	54·9	5·2	6·5	9·6
	(−)	30·6	48·5	67·5	1·0	2·0	3·6

* Calculated as the equivalent amount of methylamphetamine

Urinary pH alkaline. The amount of methylamphetamine excreted in 16 hr in alkaline urine (pH 8·0 ± 0·2) was 0·6 to 2·0% (mean 1·5%) of the dose administered; negligible amounts of its metabolite amphetamine were excreted. Urine collected in the period 40–48 hr after drug administration, by which time the urine had become acid (pH 5·5–6·0) (sodium

bicarbonate administration was discontinued at the 14th hr), yielded significant amounts of methylamphetamine (4·3%) and its metabolite amphetamine (2·6%) (Fig. 2).

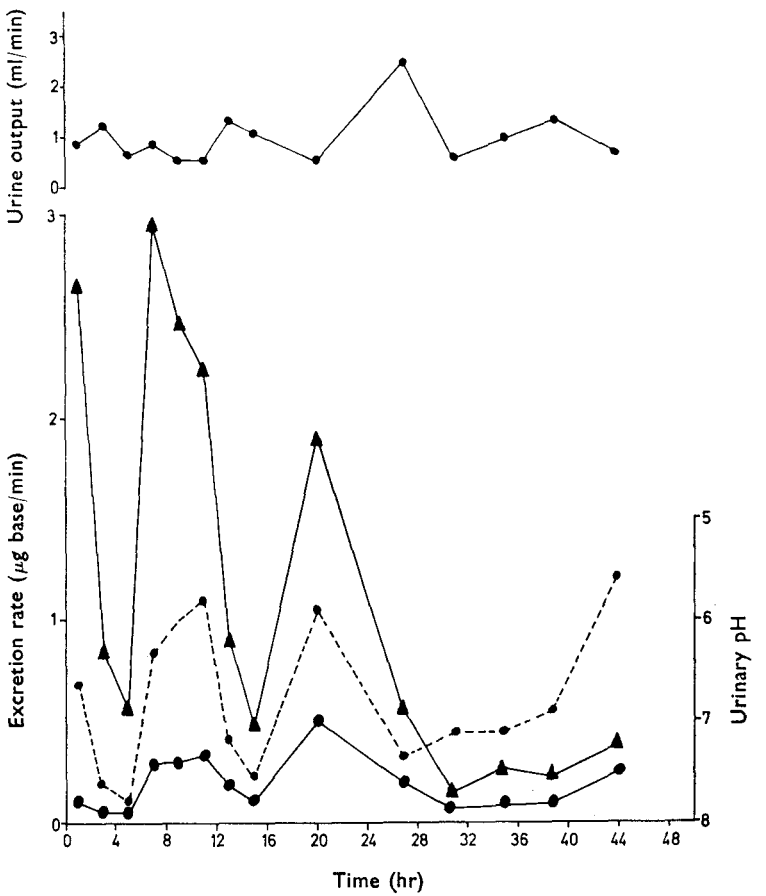

FIG. 1. The influence of urinary pH and urine output on the urinary excretion of methylamphetamine (and its metabolite) in man, after oral administration of 11·0 mg (+)-methylamphetamine. Subject M. R. - - -●- - - = Urinary pH. —▲— = Methylamphetamine. —●— = Amphetamine. (Similar patterns were obtained in other subjects).

Urinary pH acid. Table 2 gives the 16 hr urinary excretion of unchanged methylamphetamine (mean 63%) and amphetamine (mean 6·6%), as a percentage of the dose administered, after oral administration of (+)-methylamphetamine to subjects whose urine was maintained acid. Under these constant acidic conditions, the observed fluctuations in the excretion rate of methylamphetamine and amphetamine were abolished (see Fig. 1). Also, changes in urine output had little effect on the

excretion of either of these amines. The excretion rate of methylamphetamine reached a maximum about 2½ hr after administration of the drug and then fell exponentially (Fig. 3). Amphetamine excretion rate reached a maximum 5–7 hr after administration of methylamphetamine.

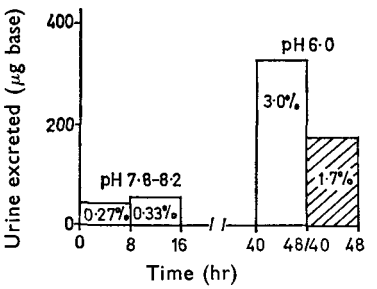

FIG. 2. Urinary excretion of methylamphetamine and its metabolite amphetamine, after a single oral dose of 13·7 mg (+)-methylamphetamine hydrochloride under alkaline and normal urinary pH conditions. Methylamphetamine unshaded, amphetamine shaded. Subject M.R.

PLASMA LEVELS

Not more than 0·03 μg/ml methylamphetamine could be detected in the plasma after an oral dose of 11 mg (+)-methylamphetamine.

TABLE 2. URINARY EXCRETION OF METHYLAMPHETAMINE AND AMPHETAMINE AFTER ORAL ADMINISTRATION OF 13·7 MG (+)-METHYLAMPHETAMINE HYDROCHLORIDE; URINE MAINTAINED ACIDIC THROUGHOUT THE TRIAL

	% of the methylamphetamine dose excreted						Biological half-life, hr	
	As methylamphetamine			As amphetamine		Urinary pH		
Subject	16 hr	24 hr	Total	16 hr	24 hr		Methylamphetamine	Amphetamine*
M.R.	63·2	—	70·6	7·0	—	5·0 ± 0·2	4·3	5·0
N.B.	57·4 (15 hr)	58·2 (19 hr)	61·0	6·5 (15 hr)	7·6 (19 hr)	5·1 ± 0·2	4·0	4·75
E.J.T.	69·4	75·5	77·5	5·8	7·2	4·95 ± 0·2	4·6	4·90

* Beckett & Rowland (1965c)

CLINICAL EFFECTS

Central nervous stimulation and dryness of the mouth were more pronounced after the administration of (+)-methylamphetamine when the urine was maintained alkaline than when the urinary pH was not controlled or the urine maintained at an acid pH. No effects were observed with the (−)-isomer.

Discussion

The marked fluctuations in the excretion of methylamphetamine and its metabolite amphetamine may be explained by non-ionic diffusion of bases in the kidney (Milne, Scribner & Crawford, 1958; Weiner & Mudge, 1964). This is indicated by the following evidence.

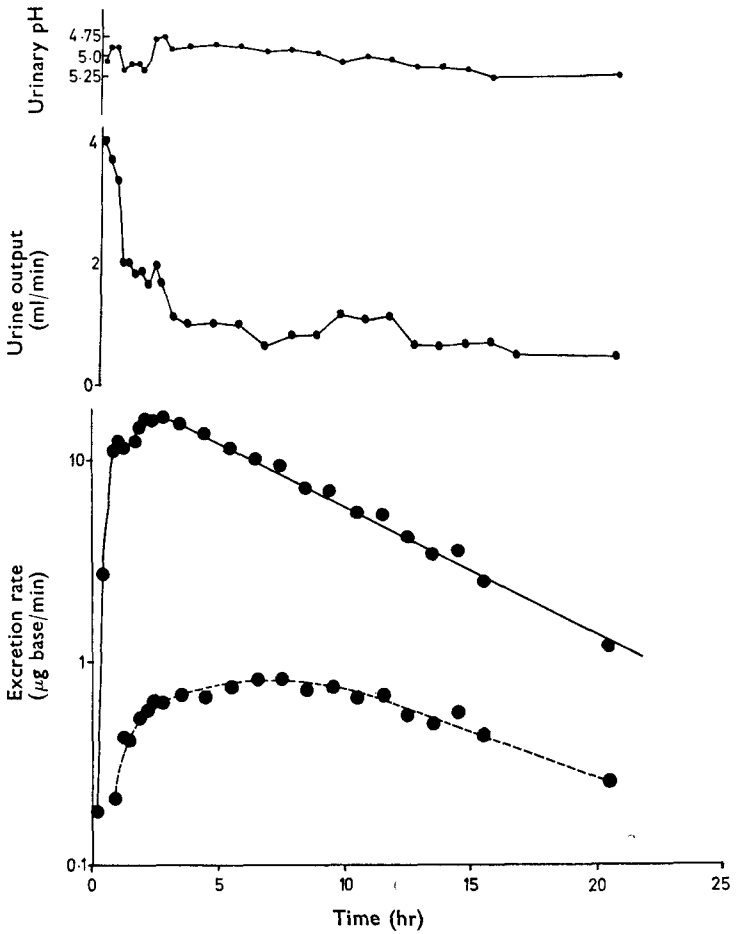

FIG. 3. Urinary excretion of methylamphetamine and amphetamine, urinary pH and urine output after oral administration of 11·0 mg (+)-methylamphetamine; urine maintained acidic throughout the trial. —●— = Methylamphetamine. - - -●- - - = Amphetamine. Subject E. J. T.

(*a*) Fluctuations in the excretion rate of these amines appear to depend upon urinary pH changes.

(*b*) There is a forty fold increase in the 16 hr excretion of methylamphetamine in acid urine over that found in alkaline urine.

(*c*) The excretion patterns of (+)- and (−)-methylamphetamine are similar.

(*d*) Under alkaline urine conditions, subjective effects were more prolonged indicating reabsorption and longer retention of the drug in the body; when sodium bicarbonate treatment was stopped at the 14th hr, significant amounts of methylamphetamine were excreted 40–48 hr after a dose of the drug. Even though there is only 0·5% unionised drug in

alkaline urine, reabsorption of methylamphetamine from the kidney is almost 100%.

When the urine is maintained at an acid pH, excretion of unchanged drug is the major route of elimination of methylamphetamine from the body. The total expected excretion of this drug (Table 2), calculated by the same procedure as for amphetamine (Beckett & Rowland, 1965c), indicates that excretion of unchanged drug is essentially complete within 24 hr of the dose. Under such conditions the biological half-lives of (+)-methylamphetamine and (+)-amphetamine are similar (Table 2). This result could be explained by a passive excretion process predominating, or by assuming that the rate constants for secretion of these bases into the kidney tubules are similar (Weiner & Mudge, 1964).

Under normal conditions, most of the methylamphetamine is excreted unchanged, and only a small amount of *N*-demethylation occurs, we suggest therefore that the pharmacological activity of the drug probably resides in the unchanged molecule. Some degree of stereospecific *N*-demethylation of methylamphetamine is indicated by the difference in the amounts of amphetamine excreted after administration of each isomer (+) or (−) of methylamphetamine; this cannot be attributed to differences in the metabolism and excretion of (+)- and (−)-amphetamine (Beckett & Rowland, 1965c). Since methylamphetamine is relatively stable and yet only low plasma levels were found, it is concluded that the drug is concentrated extravascularly.

The clinical implications of these results are the same as for amphetamine (Beckett, Rowland & Turner, 1965). These present findings further illustrate the need to record urinary pH changes when studying the urinary excretion of bases.

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