THE METABOLISM AND EXCRETION OF 'AMPHETAMINES' IN MAN

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THE 'amphetamines' are a group of drugs, based on β-phenylisopropylamine, which possess a diverse variety of pharmacological properties. They include a broad range of central stimulants, hallucinogens, psychotomimetic and anorexic agents and are widely used in clinical medicine, amphetamine itself being still the therapy of choice in the treatment of narcolepsy.[1]

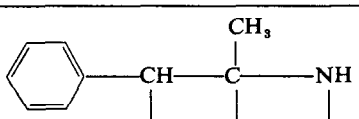
The structure-activity relationships of 'amphetamines' and some related compounds have been discussed by BIEL[2] and some of these compounds in general use are shown in Table 1. It is the purpose of this communication to present an overview of the current situation regarding the excretion and metabolism of certain 'amphetamines' in man.

The metabolism and excretion of amphetamine itself in man had long been a subject of study for many groups of workers[3–10] prior to the development of specific assay procedures based on gas–liquid chromatography,[11–14] and it was early realised that, as expected from the work of MILNE *et al.*[15] and WEINER and MUDGE[16], the excretion was greatly influenced by the urinary pH of the subject[17–20] and unless this factor was controlled, comparison between individuals or the effect of genetic variation, drugs, diet or disease etc. on the excretion and metabolism of 'amphetamines' may only be a reflection of urinary pH.[21–23] Under uncontrolled urinary pH conditions the excretion of unchanged amphetamine averaged 14·5 per cent with a range of 5–30 per cent; concomitant acidification of the urine by administration of ammonium chloride greatly increased the urinary excretion to about 55 per cent of the dose and a much narrower range of intersubject variation was observed.[18] An alkaline urine virtually prevented the excretion of unchanged amphetamine in man.[18] The clinical significance of these findings have been discussed by ROWLAND and BECKETT.[21,43]

Parallel studies on the metabolism of ^{14}C-amphetamine were undertaken by Professor R. T. WILLIAMS, group,[24–26] and these showed that in man, under uncontrolled urinary pH conditions, 4-hydroxylation was a minor route of metabolism accounting for less than 4 per cent of the dose, whereas deamination accounted for 24 per cent.

These results are in good agreement with ELLISON *et al.*[27] and BALTES *et al.*[31], the latter authors using tritiated amphetamine. That changes in urinary pH could actually change the extent by which the amphetamine was metabolised through a given route in man was first shown by BECKETT *et al.*[32]. In this report the deamination route was shown to fall from 17 per cent under fluctuating urine conditions to 5 per cent under controlled acidic conditions. These results were confirmed by DAVIS *et al.*[20] who also showed that 4-hydroxylation of amphetamine was not however greatly influenced by urinary pH variation.

TABLE 1. THE STRUCTURES OF SOME 'AMPHETAMINES' USED IN CLINICAL PRACTICE

Drug					Use
	—	H	H	H	Stimulant, Narcolepsy
Methamphetamine	—	H	H	CH_3	Stimulant
Paradrine	4-OH	H	H	H	Nasal decongestant
Ephedrine	—	OH	H	CH_3	Bronchodilator
Mephentermine	—	H	CH_3	CH_3	Nasal decongestant
Chlorphentermine	4-Cl	H	CH_3	H	Anorexic
Fenfluramine	3-CF_3	H	H	C_2H_5	Anorexic
Methoxyphenamine	2-OCH_3	H	H	CH_3	Bronchodilator
Prenylamine	—	H	H	$(C_6H_5)_2CHCH_2CH_2$	Angina Pectoris
Fenetylline	—	H	H	Aminoethyl theophylline	Psychostimulant, Antidepressant

The work of BECKETT *et al.*[32] is also particularly important in that it showed that under acidic, but not under fluctuating, urinary conditions, the rate of urinary excretion of amphetamine is directly proportional to its plasma concentration.

Other minor metabolites of amphetamine which have been reported to occur in man are formed by β-hydroxylation of either amphetamine or 4-hydroxyamphetamine to yield norephedrine[20,28] or 4-hydroxynorephedrine.[20,28,29] The β-hydroxylation of 4-hydroxyamphetamine had previously been observed in man.[30] 4-Hydroxy-norephedrine is known to have the properties of a false transmitter[29,62] and these β-hydroxylated metabolites may play some role in the development of amphetamine psychosis.[33]

Studies on the excretion of individual stereo-isomers by BECKETT and ROWLAND[34] indicated that stereoselective metabolism occurred, as less of the (+)-isomer was recovered in the subjects' urine. This has been confirmed by GUNNE[35] using a G.L.C. technique which allowed separation of the stereo-isomers. The data obtained from ^{14}C-amphetamine experiments would suggest that stereo-selective deamination may be one of the determining factors[26], although *in vitro* stereo-specific β-hydroxylation is known to occur.[63]

Beckett's group have carried out detailed studies on the influence of molecular modification on the pharmacokinetic characteristics of N-substituted amphetamine in man.[34,36–43] In each case an influence of urinary pH on the excretion of the unchanged drug and its dealkylated metabolite has been observed.

The results of some of these studies are presented in Table 2. Stereo-selective metabolism is emphasised with increasing N-alkyl chain length of up to a C_4 chain, but on increasing the substituent to a *n*-butyl or more bulky group not only is the stereo-selectivity lost but the total drug and metabolite recovered reduced to a much lower level. To some extent these results reflect the partition coefficients of the unionised form of this series of drugs determined using heptane as the organic phase,[54] although far better predictions as to the pharmacokinetic characteristics of these compounds were made possible by the introduction by BECKETT *et al.*[52–54] of the buccal absorption test.

TABLE 2. THE URINARY RECOVERIES (%) OF ENANTIOMORPHS OF *N*-ALKYLAMPHETAMINES TOGETHER WITH THE RECOVERY (%) OF AMPHETAMINE PRODUCED BY METABOLIC DEALKYLATION.

Drug administered	Recovery of compound administered	Recovery of amphetamine	Total recovery	Unaccounted for
(+)-amphetamine	66	←	66	34
(−)-amphetamine	78	←	78	22
(+)-*N*-methylamphetamine	46	7	53	47
(−)-*N*-methylamphetamine	65	3	68	32
(+)-*N*-ethylamphetamine	24	16	40	60
(−)-*N*-ethylamphetamine	73	6	79	21
(+)-*N*-n-propylamphetamine	16	11	27	73
(−)-*N*-n-propylamphetamine	50	15	65	35
(+)-*N*-n-butylamphetamine	2	8	10	90
(−)-*N*-n-butylamphetamine	3	6	9	91
(+)-*N*-benzylamphetamine	traces	3	3+	97
(−)-*N*-benzylamphetamine	traces	4	4+	96
(+)-*N*-*o*-chlorbenzylamphetamine	traces	3	3+	97
(−)-*N*-*o*-chlorbenzylamphetamine	traces	4	4+	96

Subjects maintained under acidic urinary conditions. The data represents the mean urinary recovery. Compiled from references 34, 38, 36, 40, 41, 42.

This test allows compounds to be classified according to their absorption characteristics across the buccal membrane at various pH values, compounds which show the greatest change in buccal absorption with pH being those most sensitive to changes in urinary pH and renal reabsorption. Generally, compounds which are well absorbed at all pH values are well metabolised.[55]

The influence of certain ring substituents on the excretion and metabolism of amphetamine and *N*-ethylamphetamine is indicated in Table 3. Whilst exact comparison is not possible due to lack of pH control, certain trends emerge; thus the introduction of a lipophilic group tends to lower the urinary recovery of the unchanged drug, results which parallel the characteristics of these compounds in the buccal absorption test. When the compound is capable of undergoing *N*-dealkylation

TABLE 3. THE INFLUENCE OF RING AND *N*-SUBSTITUTION ON THE EXCRETION AND METABOLISM OF SOME 'AMPHETAMINES'

Drug	Recovery of drug		or dealkylated metabolite		Reference
	Acid urine	Uncontrolled	Acid urine	Uncontrolled	
(+)-amphetamine	37–61	5–29	—	—	18
(+)-*p*-chloramphetamine	8–23	12	—	—	37
**p*-methoxyamphetamine	—	0·3–15	—	—	44
(±)-*m*-trifluormethyl-amphetamine	24–38	—	—	—	45
**p*-hydroxyamphetamine	—	40–52	—	—	30
(±)-*N*-ethylamphetamine	42–46	12–24	7–13	4–10	36
(±)-*N*-cyanoethyl-amphetamine	5–9	3	34–56	30–50	51
(±)-*N*-ethyl-*m*-trifluormethyl-amphetamine	20–30	5·3	12–23	3·6	45

Figures indicate range of percentage recovery found in urine under urinary conditions indicated after an oral dose.

* Optical isomer not stated.

as in the case of *N*-ethylamphetamine, then the effect of the ring substitution is to increase the importance of this route of metabolism. In the case of 4-hydroxyamphetamine metabolism prior to conjugation is unnecessary and high levels of unchanged drug are excreted as conjugates. Recently, using ^{14}C-4-hydroxyamphetamine SEVER *et al.*[46] have shown that up to 90 per cent of the drug is excreted as a sulphate conjugate in man.

In the case of some *N*-alkylamphetamines studied, only low recoveries of drug and metabolite have been found, which poses the problem as to their metabolic fate. Ring and β-hydroxylation routes have been recognised in man and the extent of these routes in various drugs is indicated in Table 4. *N*-Substitution with a relatively small group, e.g. methyl or chlorpropyl, greatly increases the amount of drug hydroxylated. In the case of drugs with larger substituents the amount of drug metabolised via this route seems to be small, although even in these cases some 4-hydroxyamphetamine is formed.

TABLE 4. THE INFLUENCE OF STRUCTURE ON THE EXCRETION OF RING AND β-HYDROXYLATED DERIVATIVES OF SOME 'AMPHETAMINES' BY MAN

Drug	4-hydroxylation of		nor-ephedrine	*p*-hydroxy-norephedrine	References
	Drug	Amphetamine			
amphetamine	—	3–7	2–3	0·3–0·4	20, 28, 29
N-methylamphetamine	15	1	2–3	1–2	47
N-chlorpropyl-amphetamine	28–33	2–5	—	0·5–5	48
p-hydroxyamphetamine	—	—	—	3–9	30 46
N-(3, 3-diphenylpropyl)-amphetamine	?	+	+	+	49
Fenetylline†	—	5–9	—	—	50

Figures represent the range of percentage recovery from an oral dose.
\+ indicates present but not quantified
† *N*-(aminoethyltheophylline)amphetamine.

It is of interest that β-hydroxylation of an *N*-alkylamphetamine has not been reported; thus whilst methylamphetamine is converted into both norephedrine and 4-hydroxynorephedrine, it is not converted to ephedrine.[47] This suggests that dealkylation is a prerequisite for this metabolic route.

The metabolic oxidation of nitrogen in organic molecules has recently attracted considerable attention[64] and *N*,*N*-dimethylamphetamine has been shown to be extensively converted to the *N*-oxide in man.[65] The extent to which this reaction occurs with amphetamine or its *N*-monosubstituted derivatives remains a matter for conjecture.

The precise mechanism of metabolic oxidation of 'amphetamines' is still unclear. Whilst one would have thought that ring hydroxylation was a typical microsomal reaction, results reported by DINGELL and BASS[56] indicate that this reaction did not proceed in a microsomal system which was able to oxidise other substrates.

Similarly whilst the process of *in vitro* deamination has been known for a long time[57] controversy still exists regarding the mechanism by which this process is mediated.[58–60] Recently a general metabolic scheme for the metabolism of 'amphetamines' has been proposed[61] in which hydroxylation of α-carbon atoms of substituents leads to cleavage of the substituent. In the case of secondary 'amphetamines'

this would lead to two separate 'dealkylated' products due to the presence of two α-carbon atoms in the original molecule. This phenomenon has been recognised in man in the case of the drug Fenetylline.[50]

The alternative *N*-oxidative pathway would lead to the formation of oximes[58–60] by oxidative breakdown of the hydroxylamine. Traces of phenylacetone oxime have been found to be formed in the urine of man receiving amphetamine[42] on treatment of the urine with alkali.

From the foregoing it can be seen that considerable advances have been made in our knowledge regarding the metabolism and excretion of 'amphetamines' in man. However, the gaps which remain must continue to act as a stimulus, as until these are filled the picture inevitably remains fragmentary and extrapolation of experience from one compound to another must be metered with caution.

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