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Metabolism and excretion of diethylpropion in man under acidic urine conditions

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After oral administration, diethylpropion is rapidly and extensively metabolized in man by *N*-de-ethylation and stereoselective carbonyl reduction. The unchanged drug excreted in acidic urine represents about 2% of the dose, while the total metabolites determined account for some 85%. The excretion curves indicate that the probable contribution of the parent compound to the observed activity is small. The major metabolites, together representing about 70% of the dose, are *N*-ethylaminopropiophenone, (+)-*N*-diethylnorpseudoephedrine, (+)-*N*-ethylnorpseudoephedrine, (−)-norephedrine and (−)-norpseudoephedrine. The other stereoisomers of the three amino-alcohols, and aminopropiophenone, are present in minor amounts.

Diethylpropion (Amfepramone D.C.I.) (I, Fig. 1), an anorectic agent (e.g. Boissier, 1962; Eiden, 1970) is completely absorbed from the human gastrointestinal tract and excreted exclusively *via* the renal pathway (Schreiber, Bozian & others, 1965). It undergoes extensive metabolism, the main metabolic routes being *N*-dealkylation, keto reduction and deamination, with *para*-hydroxylation occurring only to a small extent (Schreiber, Min & others, 1968). However, because the pooled urine samples were made alkaline (pH 12) and extracted over 24 h, some qualitative and quantitative aspects of these studies are questionable, since diethylpropion (I) and its amino-ketone metabolites (II and III) are unstable under alkaline conditions (Hossie, 1970). Consequently, some of the "metabolites" detected by Schreiber & others (1968) are probably artifacts.

Hossie (1970) showed that the two major metabolic pathways are *N*-dealkylation (compounds II, III, V and VI account for some 60% of the dose) and reduction (compounds IV, V and VI account for about 40% of the dose). No *N*-oxides or glucuronides could be detected.

The amino-ketones contain one asymmetric carbon atom, but after metabolic reduction a second asymmetric centre is created; little is known of the stereochemistry of the derived amino-alcohols IV, V and VI excreted by man. Hossie (1970) showed that the ratio VI threo: VI erythro compound was approximatively 3:1, but g.l.c. conditions did not give a suitable separation of the diastereoisomers to allow full quantitative assessment. Banci, Cartoni & others (1971) found IV to be present only in the threo form, the V erythro form to be possibly present with V threo form, and VI to be composed of more threo than erythro forms.

We have investigated in man the quantitative aspects of the excretion of I and its metabolites II to VI, and the stereochemical characteristics of the excreted amino-alcohols IV, V and VI.

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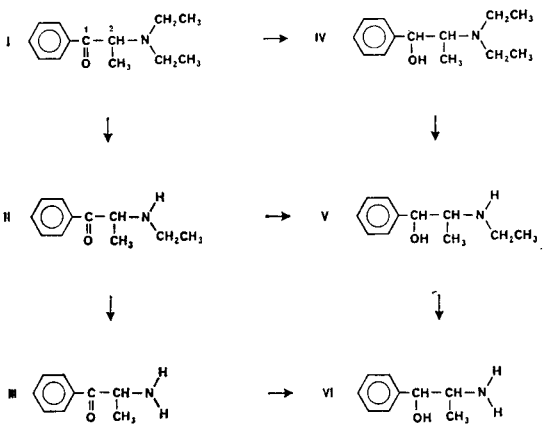

FIG. 1. Investigated routes and metabolites in the metabolism of diethylpropion (I).

METHODS

General methods

The subjects were four healthy males, aged 23 to 30, from Pakistan, Canada, England and Switzerland. They had not taken any drug for several days before diethylpropion administration, and refrained from smoking and drinking alcohol during the trials.

Ammonium chloride (enteric coated tablets), given in suitable regimens (10–15 g over 48 h), was used to induce and maintain a constant acidic urine (pH 5·0 $\pm$ 0·3). The fluid intake was as usual. The trials began in the morning after a light breakfast, and the drug (25 mg diethylpropion hydrochloride) was administered as an aqueous solution (200 ml). Urine samples were collected at various times over 30 h.

Analytical methods

Each urine sample was analysed for compounds IV, V, VI (aliquots A), I, II and III (aliquots B) as described by Testa & Beckett (1972). Throughout the trials, 6 to 8 samples (samples C) were then analysed for the threo and erythro forms of amino-alcohols IV, V and VI. The samples excreted between 2 and 8 h were then pooled and analysed as sample D for the enantiomeric proportions of the diastereoisomers of IV, V and VI.

RESULTS AND DISCUSSION

Acidic urine minimizes tubular reabsorption of amines, thus avoiding further metabolism, allowing the maximum possible recovery of a basic drug and a good evaluation of the rates of metabolism. Under these conditions, the excretion rates of the drug and its basic metabolites are proportional to their plasma concentrations (Beckett, 1966; Beckett, Salmon & Mitchard, 1969; Khan, 1972; Beckett & Khan, to be published).

The total recovery of diethylpropion and its metabolites (Table 1), accounted for about 85% of the dose; the rest ($\approx$15%) probably represents deaminated metabolites. Typical excretion curves are presented as semi-log plots in Fig. 2a and b. These curves show that the excretion of the compounds investigated is practically complete within 30 h.

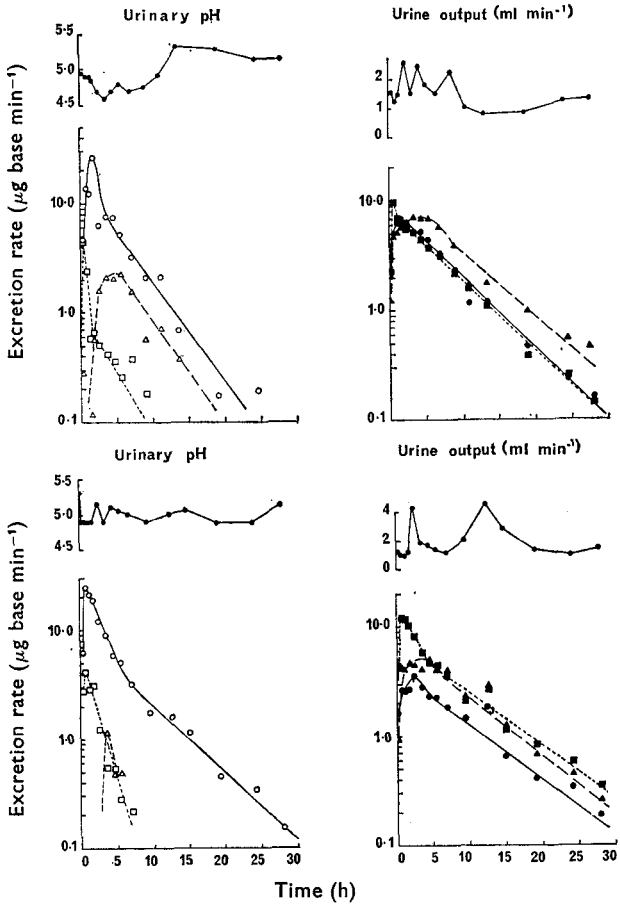

FIG. 2. Excretion of diethylpropion and its basic metabolites under acidic urine conditions after an oral dose of 25 mg of the hydrochloride.
Key: I □ - - - □. II ○——○. III △ - - - △. IV ■ - - - ■. V ●——●. VI ▲ - - - ▲
Fig. 2a: subject 2. Fig. 2b: subject 4.

Table 1. *Recovery in man of diethylpropion and its basic metabolites excreted under acidic urine conditions.*

	Recoveries of compounds I to VI, expressed as percentages of dose[1)2)]				Mean values of recovery in the 4 subjects
	subj. 1	subj. 2	subj. 3	subj. 4	
Compounds recovered[3)]					
I	1·1	1·8	1·9	2·4	1·8
II	30·4	23·7	22·4	29·6	26·5
III	1·4	6·1	2·0	0·8	2·6
IV	11·1	14·4	16·6	21·0	15·8
V	14·6	17·4	12·9	11·4	14·1
VI	25·7	28·7	28·3	22·2	26·2
Total of dealkylated products (II, III, V, VI)	72·1	75·9	65·6	64·0	69·4
Total of reduced products (IV, V, VI)	51·4	60·5	57·8	54·6	56·1
Total recovery	84·3	92·1	84·1	87·4	87·0

1) Oral dose of 25 mg diethylpropion hydrochloride in aqueous solution.
2) The percentage of dose is calculated from the total excreted amount of each compound, expressed in molar units.
3) I: diethylpropion; II: *N*-ethylaminopropiophenone; III: aminopropiophenone; IV: *N*-diethylnorephedrine; V: *N*-ethylnorephedrine; VI: norephedrine.

The percentages of the threo and erythro forms of the amino-alcohols IV, V and VI were constant within experimental error when measured at various time intervals after drug administration to the four subjects. Average values were therefore calculated for each trial, and used together with the percentages of enantiomers determined using sample D to obtain the average percentages of the four stereoisomers of each amino-alcohol IV, V and VI (Table 2). The small amount of the erythro form of IV precluded the determination of its enantiomeric percentage. Probable racemization of I, II and III during the extraction procedure, precluded any attempt to determine the percentages of the enantiomers.

The observed intersubject variations were small under the standardized conditions used (e.g. time of administration, acidic urine). The total recoveries, the percentages of compounds I to VI (Table 1), and the stereoisomeric percentages of the amino-alcohols IV, V and VI (Table 2) remained fairly constant for all subjects. The results indicate that despite the different ethnic backgrounds of the subjects, *N*-dealkylation, keto reduction and the stereochemistry of these processes show only slight intersubject variations for diethylpropion and its metabolites.

Table 2. *Stereochemistry of amino-alcohols IV, V and VI excreted in man as diethylpropion metabolites under conditions of acidic urine.*

Compounds[1]		Percentages of stereoisomers of each amino-alcohol[2], as recovered in the urine of 4 subjects				Mean values of percentages in the 4 subjects
		subj. 1	subj. 2	subj. 3	subj. 4	
IV	erythro[3]	4	2	2	2	2
	(+)-threo	86	80	80	75	80
	(—)-threo	10	18	18	23	18
V	(+)-erythro	8	7	5	7	7
	(—)-erythro	21	17	14	10	15
	(+)-threo	51	56	66	59	58
	(—)-threo	20	20	15	24	20
VI	(+)-erythro	1	6	3	1	3
	(—)-erythro	42	41	39	33	39
	(+)-threo	9	11	10	19	12
	(—)-threo	48	42	48	47	46

1) Absolute configurations: (+)-erythro: (1*S*; 2*R*); (—)-erythro: (1*R*; 2*S*); (+)-threo: (1*S*; 2*S*); (—)-threo: (1*R*; 2*R*).
2) The sum of the 4 stereoisomers of each amino-alcohol is considered as 100%.
3) The amounts of IV erythro recovered are too small to allow the estimation of its enantiomeric percentage.

Combining the mean values of Tables 1 and 2 allows the calculation of the proportions of the various stereoisomers of the diethylpropion metabolites excreted (Table 3); five compounds are major metabolites, i.e. II, and the (+)-IV threo, (+)-V threo, (—)-VI erythro and (—)-VI threo forms.

The low recovery of unchanged diethylpropion, together with a low peak level and a short observed half-life, are strong evidence that this drug, because of immediate and extensive metabolism, contributes very little to the total activity observed. Its pharmacological properties, and more specificially its anorectic activity, is caused by a very complex mixture of metabolites whose proportions are time-dependent, and whose own activities are expected to show large qualitative and quantitative differences.

Table 3. *Mean recoveries, for four subjects under acidic urine conditions, of diethylpropion and its basic metabolites, expressed as percentages of dose (ranges in brackets).*

Major compounds excreted		Minor compounds excreted	
II	26·5% (22·4–30·4)	I	1·8% (1·1–2·4)
(+)-IV threo	12·7% (9·6–15·8)	III	2·6% (1·4–6·1)
(+)-V threo	8·2% (6·7–9·7)	IV erythro	0·3% (0·3–0·4)
(—)-VI erythro	10·2% (7·4–11·8)	(—)-IV threo	2·8% (1·1–4·8)
(—)-VI threo	12·1% (10·4–13·6)	(+)-V erythro	1·0% (0·7–1·2)
		(—)-V erythro	2·1% (1·1–3·1)
		(—)-V threo	2·8% (1·9–3·5)
		(+)-VI erythro	0·8% (0·2–1·7)
		(+)-VI threo	3·1% (2·3–4·2)

Thus compounds II, III, (+)- and (—)-VI threo have a central locomotor stimulatory action in mice, whereas (+)- and (—)-VI erythro are inactive (van der Schoot, Ariëns & others, 1962; Fairchild & Alles, 1967). The central stimulant activity of *Catha edulis* ("khat") is considered to reside in the (+)-VI threo form (Alles, Fairchild & Jensen, 1961). The compounds (±)-IV (probably erythro), and (±)-V (probably erythro) have diverse pharmacological activities (Curtis, 1928; Chen, Wu & Henriksen, 1929); the (—)-VI erythro form has anorectic activity (Abdallah, 1968).

In the consideration of the importance of stereochemistry on the activities of the amino-alcohol metabolites IV, V and VI, we make use of the four ephedrine stereoisomeric analogues (i.e. *N*-ethyl of V changed to *N*-methyl) whose pharmacological and anorectic activities have been extensively studied (e.g. review by Patil, Lapidus & Tye, 1970). Thus the erythro diastereoisomers (i.e. (+)- and (—)-ephedrine) are more potent as central nervous stimulants than the threo diastereoisomers [i.e. (+)- and (—)-pseudoephedrine (Lanciault & Wolf, 1965)]. The 1*R* configuration [(—)-erythro and (—)-threo] seems to enhance a direct stimulatory activity, whereas the 1*S* configuration [(+)-erythro and (+)-threo)] is associated with an indirect action; the configuration at carbon 2 significantly influences activity only when carbon 1 has the *R* configuration (Patil, Tye & Lapidus, 1965; Patil, Lapidus & Tye, 1967). The anorectic activity of the ephedrine stereoisomers in mice decreases in the order: (—)-ephedrine, (+)-ephedrine, (+)-pseudoephedrine and (—)-pseudoephedrine (Abdallah, 1968).

Therefore the five major metabolites of diethylpropion (see Table 3) are likely to account for almost the whole of the activity of the drug, with probably the major contributions coming from II, and the (—)-VI erythro and (+)-IV threo forms. The latter is likely to have pronounced cns effects because of its very much greater lipid solubility relative to all other amino-alcohols excreted (Taylor, 1972).

Known or suspected interspecies differences occur in the metabolism of diethylpropion [e.g. no carbonyl reduction in the rabbit (Banci & others, 1971)]. Consequently, there will be major differences in the relative concentrations of the above active metabolites when diethylpropion is administered to different species. In the absence of appropriate metabolic studies, extrapolation to man of pharmacological data in animals or isolated organs is at best misleading.

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