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Metabolism, excretion and biological availability of 4′-chloro-2-ethylaminopropiophenone

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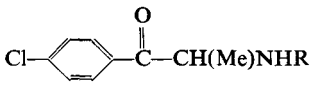
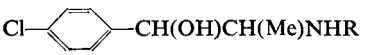
After oral administration of 4′-chloro-2-ethylaminopropiophenone to man, unchanged drug and the de-ethylated, reduced and reduced de-ethylated compounds were found in urine. Comparative urinary excretion studies after the oral administration of 4′-chloro-2-ethyl-aminopropiophenone in a sustained release form and in single or divided doses indicates that, when kidney tubular reabsorption is minimized, the biological availability of a drug can be followed by examining the excretion of either unchanged drug or metabolites formed quickly and directly from the administered drug.

4′-Chloro-2-ethylaminopropiophenone (compound I, Table 1) is currently being investigated as an anorectic agent. It is structurally related to the known anorectic diethylpropion (2-diethylaminopropiophenone) which in man, is excreted both unchanged and in metabolized forms (Schreiber, Min & others, 1968). These authors determined quantitatively the excretion of the metabolites over the period 8–12 h without controlling the pH of the urine or without taking into consideration that α-aminoketone-type compounds could undergo chemical transformation before and during the analysis. Similar α-aminoketones are known to be unstable in alkaline solution (Beckett & Hossie, 1969).

Table 1. *Structures of the compounds investigated*



Aminoketone



Aminoalcohol

Compound	*Structure*	*Chemical Names*
I	ketone R=Et	4′-chloro-2-ethylaminopropiophenone
II	alcohol R=Et	1-(4-chlorophenyl)-1-hydroxy-2-ethylaminopropane
III	ketone R=H	4′-chloro-2-aminopropiophenone
IV	alcohol R=H	1-(4-chlorophenyl)-1-hydroxy-2-aminopropane

The *in vivo* evaluation of the biological availability of amines from sustained release preparations relative to their availability from doses of free drug after administration at a stated interval of time to man, has been evaluated for amphetamine (Beckett & Tucker, 1966), and ephedrine (Beckett & Njikam, unpublished observations) by determining the amount of unchanged drug excreted in urine when kidney tubular reabsorption was minimized.

In the present work the excretion pattern of metabolites as well as unchanged drug, under acidic urinary pH with diuresis, has been used to establish whether the metabolites could be used to indicate biological availability from different drug forms. A further objective was to see whether the determination of drug and metabolite levels would help to explain preliminary unpublished observations that the sustained release preparation of compound I, gave less side effects than the equivalent dose of free drug in single and divided doses.

EXPERIMENTAL

Reagents and apparatus

These have previously been described (Beckett & Hossie, 1969). The sustained release preparation (150 mg of the HCl in Spansule form) was designed to give body levels of drug equivalent to that obtained by three 50 mg doses of the salt given at 4 h intervals.

General method

Two healthy male subjects, who had not taken any drugs for several days previous to the experiment, excepting caffeine (beverages) and nicotine (1 smoker), took the drug orally on an empty stomach as 1 dose of 150 mg, 3 doses of 50 mg every 4 h or as the sustained release capsule. All doses, except the capsule, were taken in 50–100 ml of water. Urine was collected every $\frac{1}{2}$ h for 12 h, except for the single dose (4 h), then hourly until the 16th h and then every 4 h until the 58th h. In all cases the exact time of micturition was noted, the pH of the urine was determined shortly after collection, and the urine was stored at 4°. A "blank" urine sample was collected when the drug was administered and the compounds were quantitatively determined by the method of Beckett & Hossie (1969).

Acidic urine with water loading

Acidic urine was induced and maintained by ammonium chloride or by ammonium chloride and methionine. A typical regimen for ammonium chloride was 1 g (enteric coated) every 3 h and 3 g at bedtime starting the day before the experiment. A typical regimen for methionine and ammonium chloride was 0·5 g of methionine every 2 h and 0·5 g of ammonium chloride every 4 h starting the day before the experiment. To water load, the subjects drank more than their normal intake (approx. 50–100 ml/h) of fluid the evening before the experiment and 300–600 ml of water/h the day of the experiment.

Table 2. *The recovery of 4'-chloro-2-ethylaminopropiophenone and its metabolites in two subjects after administration of 150 mg of the salt as a sustained release capsule (S.R.) or as single or divided doses*

Subject	Dose	Urine	Time	% of compound I excreted as compounds I*	II*	III*	IV*	% Recovered
1	3 × 50**	A.D.	30	22·5	15·1	7·1	4·9	49·6
2	3 × 50**	A.D.	58	17·0	18·4	6·3	6·4	48·1
2	1 × 150	A.D.	58	25·8	15·5	4·2	4·2	49·7
1	S.R.	A.D.	54·8	16·3	18·4	4·6	9·2	48·5
2	S.R.	A.D.	58	17·8	18·0	6·2	7·3	49·3
1	3 × 50**	Uncont.	58	5·9	14·6	2·0	2·7	25·2

A.D.—acidic urine with diuresis; Uncont.—uncontrolled urinary pH and volume;
* calculated as the equivalent amount of compound I;
** 3 doses of 50 mg of the salt given at 4 h intervals.

RESULTS AND DISCUSSION

When the urine is maintained acidic, kidney tubular reabsorption of amines is minimized and the amount of drug recovered in the urine is increased (Beckett & Wilkinson, 1965; Beckett & Rowland, 1965; Beckett, Boyes & Appleton, 1966; Beckett, 1966). When compound I was administered, diuresis as well as acidic pH was required to maintain the smooth excretion profile necessary for the evaluation of the relative performance of the various dosage forms.

The urinary excretion pattern during acid diuresis showed a similar pattern in both subjects, comparable recoveries (Table 2) and maximum excretion of unchanged drug, from a single dose of approximately $1\frac{1}{4}$ h after drug administration (Figs 1A and 2a).

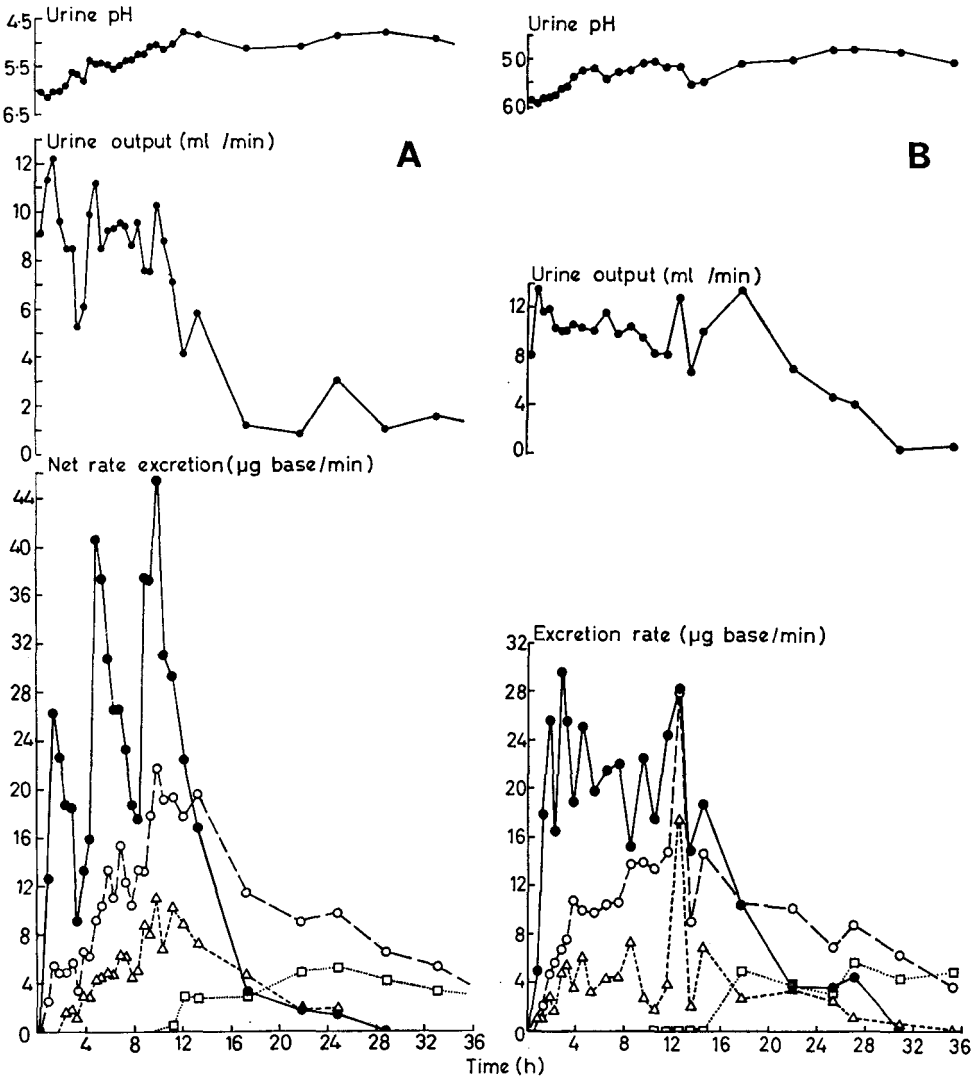


FIG. 1. Urinary excretion of 4′-chloro-2-ethylaminoprophenone (●) and its metabolites, compounds II (○), III (△) and IV (□), after the oral administration of (A) 3 × 50 mg of compound I HCl at 4 h intervals and of (B) a sustained release capsule of compound I HCl (150 mg). Acidic urine and diuresis were maintained. Subject 2.

A semi-log plot of the excretion of unchanged drug during constant urinary pH and flow rate (single 150 mg dose) gave a half-life of approximately 2 h.

The overall percentage excretion of compounds I-IV after the sustained release capsule or after 3 × 50 mg in solution at 4 h intervals was the same (Table 2), thus the drug in the sustained release form was as available for absorption as that in the solution. The "staircase" effect produced by administering 50 mg three times a day (Fig. 1A) was similar to that produced by dexamphetamine (Beckett & Tucker, 1966). The sustained release preparation (Fig. 1B) eliminated both the "staircase" effect (Fig. 1A) and the marked "peaking" effect of the unchanged drug produced by the single 150 mg dose (Fig. 2a). The metabolites do not, however, show these wide fluctuations in the rate of excretion (Figs 1A, B, 2b, c). Instead they show a gradual increase to a maximum and then a slow decrease in the rate of excretion.

Although the unchanged drug excretion rates vary in their profiles for the different dosage forms, those for metabolites II and III are very similar (Fig. 1A, B) for the 3 × 50 mg dose at 4 h intervals and the 150 mg sustained release preparation, but both differ greatly from the profile of compound II and III of the single 150 mg dose of 'free' drug (Fig. 2b, c). Compound IV is not quickly, nor directly, formed from

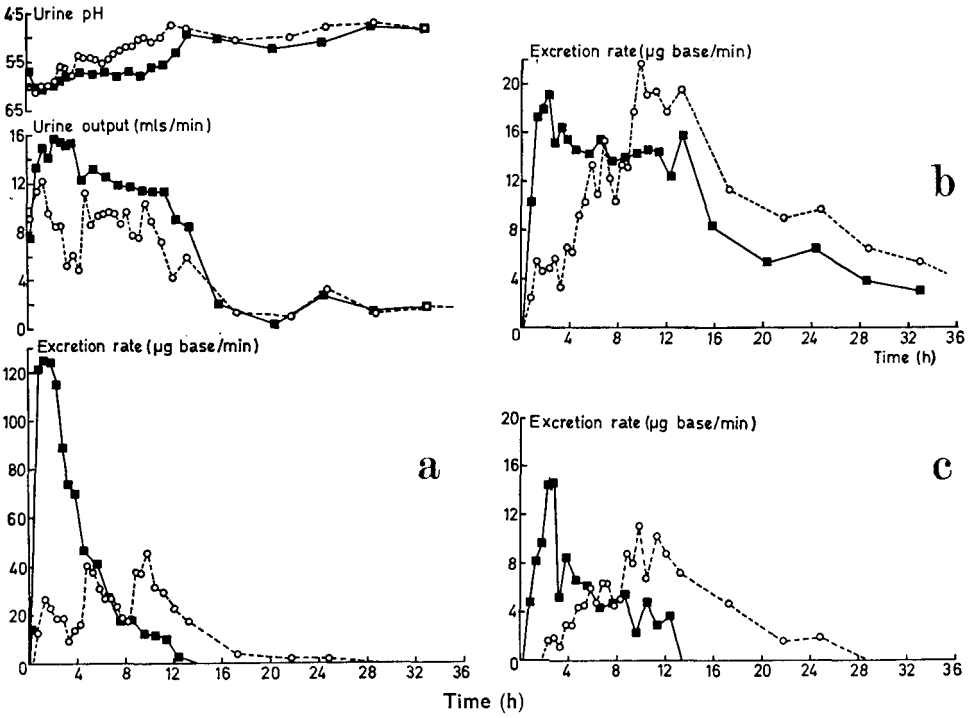


FIG. 2. Comparison of the urinary excretion of (a) unchanged drug, (b) compound II and (c) compound III after the oral administration of 3 × 50 mg of compound I HCl (○) at 4 h intervals and 150 mg of compound I in a single dose (■). Acidic urine and diuresis were maintained. Subject 2.

the parent compound I and is therefore not suitable for comparing the various dosage forms (Fig. 1A, B).

These results suggest that when the excretion of a drug is difficult to measure, it is possible to show the effectiveness of a sustained release formulation by minimizing

tubular reabsorption and by following the excretion of a metabolite which is formed rapidly and directly from the parent compound and comparing the metabolite's excretion profile after single and multiple doses with that after the sustained release product.

In the case of amphetamine, under similar conditions to the present experiment, it has been shown that the amount of amphetamine excreted in the urine is directly related to blood levels (Beckett, Salmon & Mitchard, 1969). If the levels of compounds I–III in blood are similarly related to those in urine, then higher blood levels of compound I is obtained from a single 150 mg dose or 3 × 50 mg doses than from the sustained release preparation. Thus the 150 mg sustained release preparation and the 3 × 50 mg doses at 4 h intervals will give similar blood levels of metabolites, and the former will give a steady level of unchanged drug for 14 to 16 h but eliminate the marked peaks and troughs in the blood levels of unchanged drug exhibited by the latter (Fig. 2b, c). This suggests that the lower constant and sustained blood levels of compound I obtained with the sustained release formulation could account for the observed lack of side effects with this preparation compared with the single 150 mg or 3 × 50 mg dose regimen.

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