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SHORT COMMUNICATION

A method for the evaluation of some oral prolonged-release forms of dexamphetamine in man, using urinary excretion data

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ALTHOUGH urinary excretion studies (Campbell, Nelson & Chapman, 1959; Chapman, Shenoy & Campbell, 1959; Shenoy, Chapman & Campbell, 1959) have been used as a technique to evaluate prolonged-release dosage forms of amphetamine, the significance of the results is in doubt because of the use of non-specific assay methods and the failure to control urinary pH. The use of radioactive material has indicated the similarity between a dose of 5 mg amphetamine three times a day and a 15 mg prolonged release preparation (Rosen, Tannenbaum, Ellison, Free & Crosley, 1965).

Since the urinary excretion of amphetamine is pH-dependent (Beckett & Rowland, 1964; Asatoor, Galman, Johnson & Milne, 1965) excretion rates will reflect drug levels in the plasma only when the renal reabsorption of the drug is negligible (i.e. when the urinary pH is $5{\cdot}0 \pm 0{\cdot}5$). Only under such conditions can the patterns of absorption of the drug from conventional and prolonged-release forms be compared in a meaningful fashion. It should be possible to evaluate the results of changing a drug formulation by the study of drug excretion in a few subjects.

This preliminary communication reports the results obtained with various pellet-type preparations, using a specific and sensitive assay for unchanged amphetamine (Beckett & Rowland, 1965a), and using subjects whose urine was rendered acidic.

EXPERIMENTAL

Trial conditions. Male subjects, 22–26 years, were used. An acidic urine was induced and maintained by ammonium chloride. The regimen was 8 g ammonium chloride (0·5 g enteric coated tablets) taken on the day before the trial (2 g every 4 hr), then 2 g at 1 hr before the dose and 1 g every 4 hr thereafter. Breakfast of tea or coffee and toast was taken 1 hr before the dose of dexamphetamine. Urine was collected at 15 or 30 min intervals for the first 3 or 4 hr, then hourly for 16 hr, followed by a 24 hr sample. For the prolonged-release forms further samples were taken at 2 or 4 hr intervals or both.

Dosage forms. (1) "Free Capsule"—consisting of sugar pellets, coated with dexamphetamine sulphate and contained in a gelatin capsule. (2) "Fast Capsule"—as in (1) except that the pellets were further coated with a thin lipid film designed to delay the release of the drug. (3) "Slow Capsule"—as in (2) but with a thicker lipid coating on the pellets. (4)

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"Free Pellets"—as in (1) but without the gelatin capsule. (5) Preparation A—was a product consisting of a mixture of pellets, contained in a gelatin capsule: (20% of the pellets as in (1); 30% as in (2); 10% as in (3) and the remainder with lipid coatings of intermediate thicknesses). Dose: 15 mg dexamphetamine sulphate. (6) Preparation B—was a commercial product consisting of drug pellets, each coated with a material forming a dialysing membrane, contained in a gelatin capsule. In this instance the pellets were claimed to be identical. Dose: 15 mg dexamphetamine sulphate (product also contained 60 mg amylobarbitone).

Regimens. (A) To establish the individual release properties of the pellet groups used in Preparation A, the excretion of dexamphetamine was compared after 15 mg doses in each of the forms (1), (2) and (3). These trials also served to indicate the efficiency with which dexamphetamine is absorbed in different parts of the alimentary tract.

(B) The dexamphetamine pattern of excretion after a single 15 mg dose given in form (1) was compared with those obtained after administration of each of the prolonged-release products A and B.

(C) A divided dose regimen of 5 mg doses in form (1) given at 0, 4 and 8 hr was investigated. The pattern of excretion after this regimen was also compared with those for the prolonged-release products A and B.

(D) The possibility of a dose-effect in the elimination of dexamphetamine was examined by comparing dexamphetamine excretion after a single 5 mg dose in form (1) with its excretion after a single 15 mg dose in the same form.

(E) The effect of the gelatin capsule on the absorption of the dexamphetamine was examined by comparing the excretion of the drug after a 15 mg dose in form (1) with its excretion after the same dose in form (4). A 15 mg dose of dexamphetamine in aqueous solution was also given, as a further control, in one subject.

Each of the above regimens was investigated in three subjects, but only one subject received the solution.

Determination of amphetamine. Amphetamine, in urine, was determined by the gas-liquid chromatographic method described by Beckett & Rowland (1965a).

Calculations. In the post-absorptive phase, under acidic urine conditions, the elimination of dexamphetamine declines exponentially. The biological half-life ($t_{\frac{1}{2}}$) and the amount of drug excreted at infinite time were calculated by standard methods (Beckett & Rowland, 1965b). The percentage of the dose absorbed at various times was calculated using the equation derived by Wagner & Nelson (1964), for urinary excretion data.

RESULTS AND DISCUSSION

The effect produced on the net absorption rate of dexamphetamine, by varying the thickness of the lipid coating on the pellets was reflected in the patterns of excretion obtained with forms (1), (2) and (3). A peak excretion rate of dexamphetamine was established after about 3 hr with form (1), 5–6 hr with form (2), and 11–14 hr with form (3). The results

indicated that dexamphetamine is absorbed throughout a substantial portion of the alimentary tract.

The capsule delays the time for complete absorption of the dexamphetamine from "free" forms by $1\frac{1}{2}$ to 2 hr. The absorption rates calculated in the subjects given a 15 mg dose in solution or "free pellet" forms were similar to those obtained by Beckett & Rowland (1965b) using aqueous solutions of amphetamine.

Fig. 1 shows typical patterns of dexamphetamine excretion obtained with various dosage forms and regimens in subject J.F.T. Similar curves were obtained for the other subjects. Both preparations A and B (see curves IV and V in Fig. 1) eliminated the marked "peaking" effect produced by the single 15 mg "free capsule" form (see curve I, Fig. 1), and the "staircase" effect produced by the 5 mg "free capsule" form given three times a day (see curve II, Fig. 1).

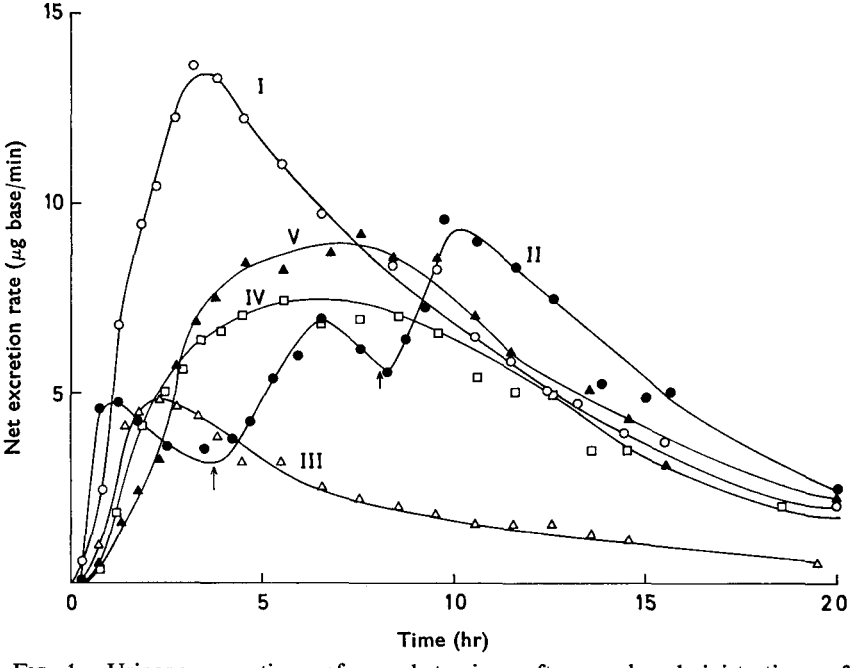

FIG. 1. Urinary excretion of amphetamine after oral administration of dexamphetamine sulphate in different dosage forms and regimens. Subject: J.F.T. Acidic urine control. Curve I —○— 15 mg "Free Capsule". Curve II —●— 3 × 5 mg "Free Capsule" at 4 hr intervals (↑) (first dose given as "Free Pellets"). Curve III —△— 5 mg "Free Capsule". Curve IV —□— 15 mg Prolonged-release Preparation A. Curve V —▲— 15 mg Prolonged-release Preparation B.

A comparison of curves IV and V in Fig. 1 shows that appreciable excretion rate levels of dexamphetamine were established slightly more rapidly with preparation A than with preparation B. This is due to the presence of a portion of the dose, in preparation A in the "free" form. The pattern produced by preparation B showed excellent reproducibility

from subject to subject, whereas that of Preparation A was variable, suggesting a slightly more erratic drug release.

In one subject (G.T.T.), following preparation A, there were further small excretion peaks at 14 and 24 hr after dosage).

Provided that ammonium chloride does not interfere with drug release and absorption, curves IV and V in Fig.1 indicate that preparations A and B were capable of prolonging the absorption of dexamphetamine and of producing reasonably sustained release of the drug for 7 to 8 hr.

In general, no marked inter-or intra-subject variations in the elimination of dexamphetamine were found when a 15 mg "free" dose was given on several occasions. This suggests that it is not necessary to use large numbers of subjects when evaluating dosage forms of the drug by the present method.

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