Amphetamine Blood and Urine Levels in Man

Keyphrases ☐ Amphetamine—blood, urine levels ☐ Urinary excretion—unchanged amphetamine ☐ Distribution volume—amphetamine

Sir:

During the last few years several attempts have been made to determine the pharmacokinetics of amphetamine in man (1, 2). Such information is useful as such but it is also necessary before one can evaluate the influence of dosage design, especially prolonged-release formulations, on the absorption and availability of this drug. From the start attention has been directed toward urinary studies since they are convenient, concentration effected by the kidneys results in measurable levels of unchanged drug, and at the time, no method was available which could determine the very low levels expected in the blood. Because of this last difficulty radioactive amphetamine has been administered and blood levels determined but these were total radioactivity rather than unchanged drug (3, 4). Unfortunately the convenience of urinary studies was shown by Beckett and Rowland to be negated, to some extent, by the fact that excretion of this amine is highly sensitive to urinary pH, kidney reabsorption increasing from more alkaline urine (2). As urinary pH fluctuates throughout the day it is therefore necessary to maintain a constant (acidic) urinary pH for excretion studies to be meaningful (2, 5). Recently a relationship between urinary pH and the extent of amphetamine reabsorption from the kidney tubule has been calculated by Beckett *et al.* and used, together with the analog computer, to predict urinary and body levels of amphetamine when there is no urinary pH control (6, 7).

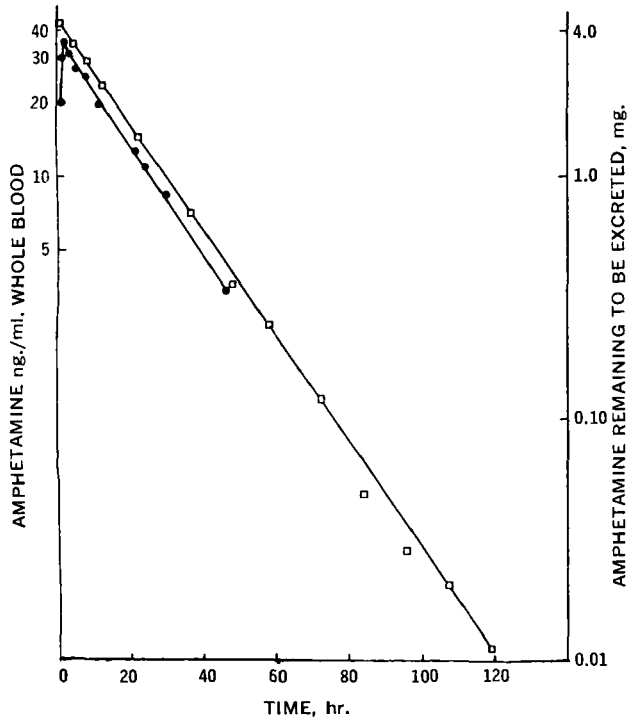

Figure 1—*Blood and urine levels of amphetamine (in mole equivalent terms expressed as sulfate) following oral administration of 10 mg. (+)-amphetamine sulfate (Subject A). Key: ●, whole blood; □, urine.*

Obviously neither the acidic urine studies nor computational methods are convenient in frequent or large-scale clinical studies. In order to overcome this problem a specific method for the determination of amphetamine in whole blood (and urine) has been developed (8). The results of preliminary work using this method are now reported. In this study three male subjects each ingested 10 mg. dextroamphetamine sulfate in 50–100 ml. of water. Blood samples were drawn over the next 48 hr. while urine was collected, usually at 12-hr. intervals, for 6 days and volume and urinary pH recorded. Samples were then assayed for unchanged drug. Figure 1 illustrates the general pattern observed in these subjects and Table I contains some pertinent pharmacokinetic data. All subjects gave peak blood levels around 2 hr. after which they declined exponentially over the next 48 hr. with a half-life around 12 hr. Mean total urinary recovery of unchanged amphetamine was 45% of the ingested dose, which is higher than the 32% previously found (2). This is probably due to the generally acidic urine noted in the present study or a slower metabolic rate constant in this group and only slightly the result of the extended period of urine collections. Especially of interest was the finding that the urinary kinetic data gave a monoexponential decay for at least seven half-lives, with a value corresponding to that in the blood (Table I). Accordingly there is no discernible additional phase subsequent to the terminal blood samples. Also, because urinary pH values did not vary to a great extent, due to the 12-hr. collection interval, large fluctuations in the excretion rate of this drug were not observed. Proportionality between blood and urine data allows an estimate of 120 ml./min. for the apparent renal clearance of amphetamine. Further interpretation of this awaits plasma protein-binding studies, distribution measurements of this drug between red blood cells and plasma, and clearance determinations under various urinary pH conditions. The mean apparent volume of distribution, based on area determination, was 270 l., confirming the earlier prediction of high extravascular concentration of this drug.

For a large number of patients 5 mg. dextroamphetamine sulfate is a therapeutic dose whose effects usually wear off within 4 hr. A half-life of 12 hr. for this drug would then indicate that a second dose at 4 hr. should be more than sufficient to maintain the desired effect for a further 8 hr., provided the minimum therapeutic blood level does not change with time. This accords with the recommended regimen of a dose to be taken morning and midday, which allows the stimulant effect of this amine to subside by the time the patient retires at night (9). Prolonged-release amphetamine preparations are also available and for these the initial and maintenance doses should be approximately equal when a 12-hr. therapeutic level is desired.[1] Too much drug in

[1] For prolonged release products, as an approximation, the ratio of maintenance to initial dose is given by $0.693 \cdot h / t_{1/2}$, h being the number of hours desired to maintain a therapeutic level (10).

Table I—Some Parameters Defining the Pharmacokinetics of Amphetamine in Man

Subject	Weight, kg.	Half-life, hr. Blood	Half-life, hr. Urine	% Dose Excreted Unchanged	Vol. of Distribution, l.	Renal Clearance, ml./min.
A	66	12.5	13.5	42	275	103
B	71	11.0	12	46	250	115
C	63	13.0	13.5	48	290	139

the initial or maintenance dose can obviously lead to the patient still being stimulated at night, in which case they would offer no advantage over the readily adjustable uncoated tablet dosage regimen.

Simple tablets or capsules of amphetamine are probably absorbed within 4 hr. after administration, whereas this may take up to 12 hr. with prolonged-release dosage forms (5). Extensive samples are therefore required during this period so that the absorption kinetics can be adequately defined. This is readily achieved using blood studies but, for reasons discussed above, meaningful urinary excretion studies are inconvenient especially in extensive clinical evaluations. Consequently it is recommended that blood studies be carried out and that excretion data be used mainly to confirm the half-life of amphetamine beyond levels which are conveniently measured in the blood. Similar arguments hold for other basic drugs which behave in an analogous manner to amphetamine. At present a more complete pharmacokinetic study of amphetamine is being conducted in man.

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Books

Biological Oxidations. Edited by THOMAS P. SINGER, Interscience Publishers, A Division of John Wiley and Sons, 605 Third Avenue, New York, N.Y. 10016, 1968. ix + 722 pp. 15 × 22.5 cm. Price $19.75.

Due to the wealth of information that is available today in many different research areas, it is probably true that multiauthored books will increasingly become the standard method of publication. Two difficulties arise with this type of book: (*a*) one tardy contribution delays publication of the whole book and (*b*) there may be considerable overlap of subject matter in the several related chapters. There was, in fact, a long delay in the submission of certain chapters for this book, but the editor has avoided the frequent pitfall of unnecessary overlap of discussion in the various chapters.

The organization of the book is excellent; it fulfills the goal of allowing the nonexpert to gain an overview of this important field. The book is divided into two parts. The first third of the book is devoted to the gross processes in biological oxidations whereas the last two thirds of the volume is devoted to the enzyme and coenzymes involved in the biological oxidations. Many, but not all chapters contain a summary or concluding remarks. There is an abundance of structural formulas, tables, and graphs which allow one to visualize easily the reactions or inspect the experimental data. Mechanisms of the catalytic reactions are emphasized and usually speculations are clearly distinguishable from rather firmly established mechanisms. Limited information concerning the importance of enzyme inhibitors as a tool to study reaction mechanism is described.

In reviewing this book, it becomes abundantly clear that the term "mechanism" is used differently in the various chapters. In some cases mechanism means the sequence of reactions that occur; in other cases it means a detailed description of the reaction of the substrate and/or the coenzyme but, in few cases, is there invoked a detailed mechanistic role for the enzyme. These statements are not meant as a criticism but rather a description of the present state of knowledge. Thus, for those who would study this book an appreciation of the elegant research in a difficult field will be developed and a recognition of future areas of research will be apparent.

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The Biochemistry of Foreign Compounds. By DENNIS V. PARKE, Pergamon Press Inc., 44-01 21st St., Long Island City, NY 11101, 1968. ix + 269 pp. 14.5 × 22 cm. Price $10.00.

This is Volume 5 of the International Series of Monographs in Pure and Applied Biology, Biochemistry Division. The book is divided into two sections, Biochemical Mechanisms and Applications. In general, the book is well written but gives only a telescoped view of