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Use of the analogue computer to predict the distribution and excretion of drugs under conditions of fluctuating urinary pH

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An analogue computer program, incorporating a previously established relation between urinary pH and amphetamine excretion, has been used to predict the quantitative excretion of the drug under normal conditions of fluctuating urinary pH. Under the same conditions, a comparison has been made of computer predicted body levels of amphetamine after administration of the drug in a single solution dose, three divided solution doses, and in various prolonged-release formulations. Advantages of sustained-release preparations are indicated and specifications for a theoretically ideal sustained-release formulation are suggested.

IN a previous paper, Beckett, Boyes & Tucker (1968) described a method for determining a quantitative relation between urinary pH and kidney tubular reabsorption of drugs. A mathematical relation between percentage excretion of amphetamine and urinary pH was established, and it was considered that this relation could be used to predict the excretion of the drug under normal conditions of fluctuating urinary pH.

The ability to predict excretion of a drug will allow an assessment of its behaviour in the general population to be made with increased confidence and precision. Also, the advantages and disadvantages of various pharmaceutical formulations, like "prolonged release" products, with regard to useful availability of drugs, could be better considered. The present paper describes an attempt to make such predictions from the mathematical relation previously established.

Theoretical

The proposed relation between excretion of amphetamine and urinary pH is:

$$\log \% E = -0{\cdot}4383\ pH + 4{\cdot}0384 \quad .. \quad .. \quad 1$$

where % E = percentage amphetamine excreted.

The differential equation describing the body level of amphetamine when the urinary pH is maintained at a constant acidic level ($4{\cdot}7 \pm 0{\cdot}2$) is:

$$\frac{dB}{dt} = ka.A - km.B - ke.B \quad .. \quad .. \quad .. \quad 2$$

(Beckett & others, 1968).

When the urinary pH is fluctuating, the body level of the drug B is designated B*, where:

$$B^* = B + R \quad .. \quad .. \quad .. \quad .. \quad 3$$

(R = amount of drug which has been reabsorbed from the kidney tubules).

On substituting B* for B in equation 2 the term ke.B* represents the rate of presentation of drug to the kidney for excretion at any time.

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Taking equation 1 into account, and multiplying this term (ke.B*) by a factor equivalent to the expected % excretion of the drug, for the pH at a particular time, the result will be the predicted rate of excretion of the drug at that time, i.e.

$$\frac{dB^*}{dt} = ka.A - km.B^* - ke.B^* \times \frac{\%E}{100} \quad .. \quad .. \quad 4$$

$$\frac{dU^*}{dt} = ke.B^* \times \frac{\%E}{100} \quad .. \quad .. \quad .. \quad 5$$

where

$\frac{dU^*}{dt}$ = predicted rate of excretion; % E is calculated from equation 1.

The analogue computer program, shown in Fig. 1, combines equations 1, 4 and 5 to give an output proportional to predicted rate of excretion as a function of time.

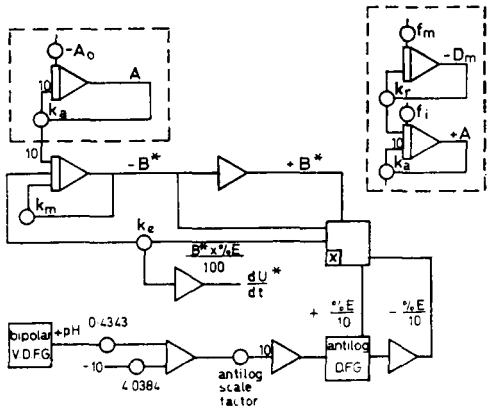

FIG. 1. Analogue computer program for the prediction of amphetamine excretion and body levels, from urinary pH data, after oral administration of the drug in solution and in a sustained-release form. (*Inset*—program for sustained-release.)

Experimental

Apparatus. An analogue computer (Electronic Associates Limited TR-20R) with an X-Y recorder (Advance Electronics Limited), a Perkin Elmer F11 gas chromatograph and a Pye Dynacap pH meter with a screened glass/calomel electrode system.

METHODS

Two male volunteers were given 15 mg oral doses of D(+)-amphetamine sulphate in aqueous solution and urine samples were collected at 30 min intervals for 16 hr; urinary pH was uncontrolled and the pH of each urine sample was accurately measured. The pH measurements for a particular subject, corrected for "lag-time" (Beckett & Tucker, 1968), were programmed on the analogue computer as a function of time. The previously determined values of ka, km and ke for the subject were set on the computer and a plot of $\frac{dU^*}{dt}$ against time was made.

The amphetamine contents of the urine samples were determined by

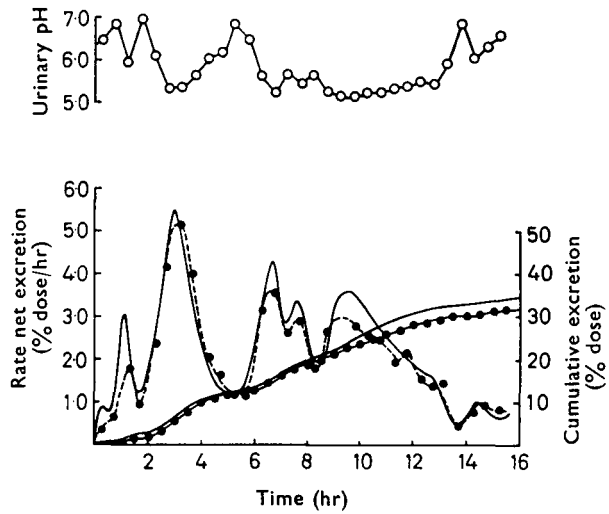

FIG. 2. A comparison of computer predicted and actual rates of excretion and cumulative excretion of amphetamine after oral administration of 15 mg (+)-amphetamine sulphate in solution (subject 1). Continuous lines: computer predictions. - - ● - - Experimental data. —○— Urinary pH.

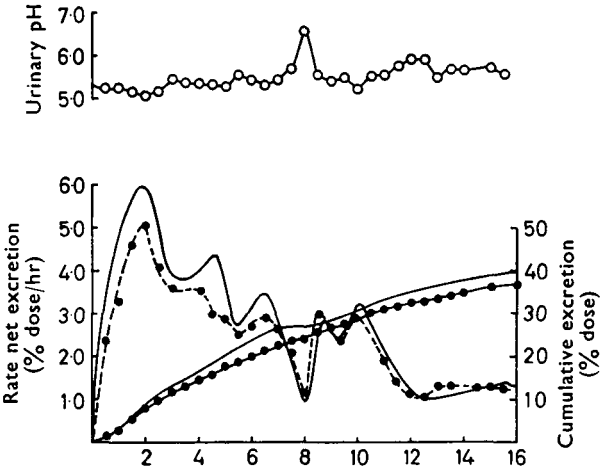

FIG. 3. A comparison of computer predicted and actual rates of excretion n cumulative excretion of amphetamine after oral administration of 15 mg (+)-amphetamine sulphate in solution (subject 2). Continuous lines: computer predictions. - - ● - - Experimental data. —○— Urinary pH.

gas chromatography (Beckett & Rowland, 1965). When the analyses were completed, a plot of actual rate of excretion of amphetamine against time was constructed and compared with the computer calculated prediction. Predicted and actual cumulative excretion curves were also compared for each subject.

Results and discussion

Comparisons of predicted and actual excretion rate and cumulative excretion curves for amphetamine in the two subjects are very close (Figs 2 and 3). Even when the urinary pH fluctuated markedly (see Fig. 2) the prediction is in excellent agreement with the actual data. The greatest differences are apparent in the first few hours after drug administration, when absorption is still occurring and distribution is being established. The cumulative excretion curves indicate that over a period of 16 hr the difference between actual and predicted amount of drug excreted is only 2·5 and 3% of the dose respectively in the two subjects.

The close correlation of the predicted and actual excretion curves is acceptable evidence that the relation between excretion or kidney tubular reabsorption and urinary pH is valid (eqn 1).

The calculations necessary to predict the rate of excretion of the drug at any time involve a prediction of the body level of the drug at the same time. If the predicted rates of excretion are reasonably close to the actual rates, it may be assumed that the predicted body levels will also be close to the actual body levels. Since it is possible to plot the predicted body levels as a function of time using the analogue computer, detailed studies of the effect of urinary pH on the body levels of drugs can be made.

Fig. 4 (curve 2) shows the predicted body levels of amphetamine corresponding to the rate of excretion curve shown in Fig. 2 (a similar curve was obtained with subject 2); the body levels of the drug after 16 hr corresponds to 40% of the total administered dose. This represents about 6 mg of amphetamine, calculated as the sulphate, in the body, and it is significant that the volunteer experienced considerable difficulty in going to sleep after the 16 hr period. Curve 3 of Fig. 4 indicates that if the dose had been given to the subject in the form of three 5 mg solution doses at 4-hrly intervals, 50% (7·5 mg) of the total dose would be present in the body 16 hr after the administration of the first dose.

By programming typical urinary pH against time figures, it is possible to study the effect of administration of a formulated product on the body levels of a drug. The body level against time curves illustrated in Fig. 5 were obtained after programming two different pH against time patterns, and "administering" the dose to the computer, in solution and in a typical prolonged-release form [20% (f_i) initial "free" dose; 80% (f_m) "maintenance" dose (D_m): first-order release rate constant $kr = 0{\cdot}300\ hr^{-1}$, see insert on Fig. 1 for modification of computer program for prolonged-release dosage forms]. Curves 1 and 3 in Fig. 5 were obtained using pH/time pattern A and curves 2 and 4 using pattern B. Comparison of curve 1 with curve 2, and curve 3 with curve 4 indicates that there is a greater difference between body levels, with the two urinary pH/time patterns, when the drug is given in solution compared with drug given in the prolonged-release form; the latter makes the dose available to the body over a longer period of time, and this tends to compensate for changes in body levels of drug resulting from large changes in urinary pH.

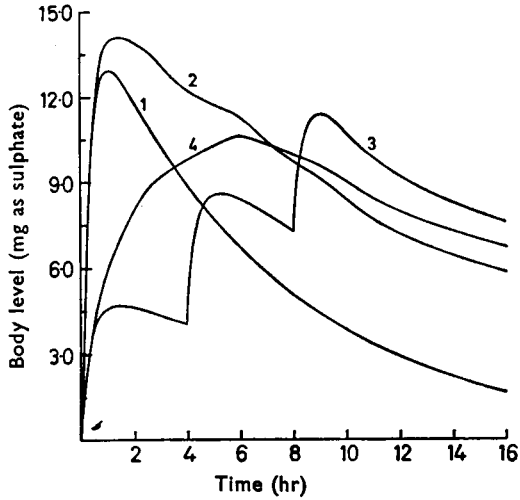

FIG. 4. Computer predicted body level (subject 1) of amphetamine (as sulphate) after oral administration of 15 mg doses in various dosage forms.

1. Single solution dose; acidic urinary pH control. 2. Single solution dose; fluctuating urinary pH as in Fig. 2. C. Three divided solution doses at 4 hrly intervals; fluctuating urinary pH as in Fig. 2. 4. Prolonged release form (20% free dose; 80% maintenance dose; kr = 0·300 hr^{-1}); fluctuating urinary pH as in Fig. 2.

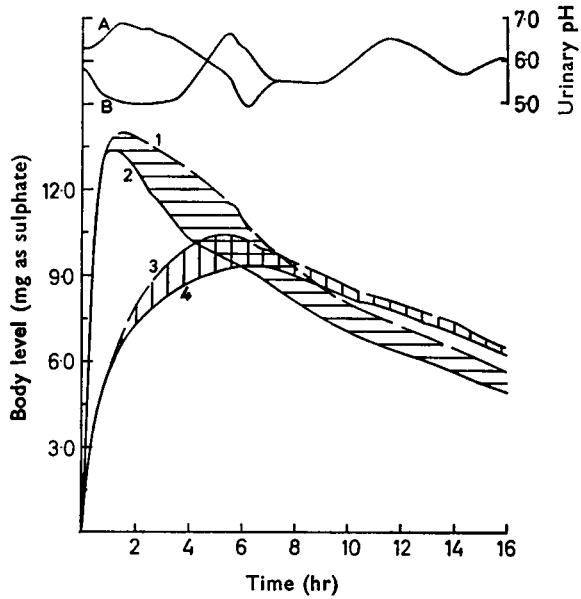

FIG. 5. The effect of urinary pH on computer predicted body levels of amphetamine after oral administration of the drug in solution and a prolonged-release form.

1 and 2. After the solution form with urinary pH/time patterns A and B respectively. 3 and 4. After the prolonged-release form with urinary pH/time patterns A and B respectively.

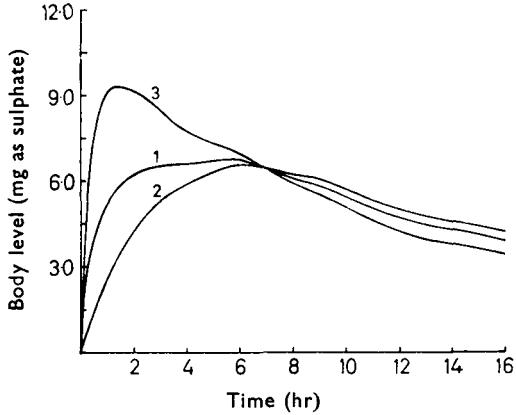

FIG. 6. A comparison of computer predicted body levels of amphetamine after oral administration of 10 mg (+)-amphetamine sulphate to subject 1 (urinary pH/time pattern as in Fig. 2). 1. 'Ideal' sustained-release form (40% free dose; 60% maintenance dose; kr = 0·300 hr^{-1}). 2. As in curve 1, but total dose in maintenance form. 3. Total dose in free (solution) form.

More effective and economical formulations could thus be designed by taking into account the urinary pH dependent excretion of drugs. Curve 4 in Fig. 4 shows the predicted body levels pattern of amphetamine if the subject had been given 15 mg (+)-amphetamine sulphate in the prolonged-release preparation previously described while curve 3, Fig. 4, shows the body level using a 3 × 5 mg regimen. Assuming a body level of about 6 mg unchanged amphetamine produces an optimum therapeutic effect, reduction of the total dose to 10 mg and alteration of the proportions of "free" and "maintenance" dose to 40 and 60% respectively, will give a much better sustained release formulation (see curve 1, Fig. 6); a similar curve was obtained with the pH figures for subject 2.

Thus correctly designed sustained-release preparations can eliminate not only the peaks and troughs resulting from the use of divided doses, but also reduce differences in the body levels of the drug obtained when the dose is administered during a period in which the urine is relatively acidic and when it is relatively alkaline. Furthermore, such formulations would allow the maintenance of constant therapeutic drug levels with smaller total dosage requirements, compared with the use of divided dose regimens. Convenience to the patient is thus not the only justification for the use of sustained-release formulations.

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