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Kinetics of buccal absorption of amphetamines

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The buccal absorption of amphetamine, methylamphetamine and dimethylamphetamine in solutions at pH 8·16 and 9·18, was measured in man after 1, 2, 3, 4, 5 and 10 min. The recovery of the drugs from the buccal membrane after uptake was also measured by washing out the mouth for varying times with buffer solutions. An analogue computer model of the biological system was used and the kinetic parameters for the buccal absorption of the amphetamines were calculated.

RECENTLY, the importance of examining the kinetics of drug transfer between aqueous and organic phases has been emphasized (Doluisio & Swintosky 1964; Perrin 1967). These authors have devised various *in vitro* systems which allow rate of partition studies to be made, but as with partition coefficient experiments, rate of partition is profoundly influenced by the nature of the organic phase. Since these *in vitro* systems are intended to be models for the behaviour of drugs in various physiological functions i.e., gastrointestinal absorption, the success of the interpretation of the behaviour of a drug will depend on the extent to which the organic phase chosen simulates *in vivo* lipid membranes.

To overcome this major disadvantage in currently available *in vitro* partition systems, the buccal absorption of drugs has been proposed as an *in vivo* model system for the study of drug transfer across physiological membranes (Beckett & Triggs, 1967). A description of the kinetics of the buccal absorption of three chemically related drugs, amphetamine, methylamphetamine and dimethylamphetamine is now presented.

EXPERIMENTAL—BUCCAL ABSORPTION MEASUREMENTS

Apparatus. Perkin-Elmer F11 Gas Chromatograph. Dynacap pH Meter.

Buffer solutions. Potassium hydrogen phthalate (0·05 M) pH 4·00. Sodium tetraborate (0·05 M) pH 9·18. Sörensens phosphate buffer pH 8·16.

Drug solutions. Solutions of the drugs amphetamine, methylamphetamine and dimethylamphetamine were prepared in the buffers of pH 8·16 and 9·18 such that 25 ml contained the equivalent of 1 mg drug base.

Buccal absorption measurements. Male volunteers aged 20–40, who produced only small volumes of saliva, were used. A drug solution (25 ml) was introduced into the subject's mouth for 1, 2, 3, 4, 5 and 10 min. After each time the solution was expelled, diluted to a suitable volume and analysed for drug content. (For detailed procedure see Beckett & Triggs, 1967, and also Beckett & Moffat, to be published, in which analyses of acids under conditions of varying saliva flow are reported).

Immediately after the solution had been expelled from the mouth after contact times of 5 and 10 min, 25 ml of pH 4·0 buffer was placed in the

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mouth, circulated for 1 min and expelled. This was repeated every min for a further 4 min. The expelled solutions were diluted and analysed.

Analysis. Drug content in the expelled solutions was determined by the gas-liquid chromatographic procedure described by Beckett & Triggs (1967).

RESULTS—BUCCAL ABSORPTION

The data points in Fig. 1 represent the experimentally determined amounts of drug remaining in the mouth after each contact time in a buffer pH of 8·16. The cumulative return of drug to the mouth after the wash-out procedure is also shown. In each case the absorption appears to level off after a contact time of approximately 5 min. Also about 50%

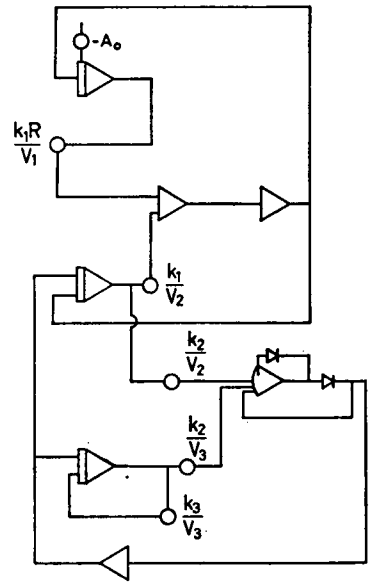

FIG. 1. Analogue computer program for the kinetics of buccal absorption of the amphetamines.

of the absorbed drug is returned to the mouth after washing out with the buffer of pH 4·0. The buccal absorption after contact times of 5 and 10 min using a buffer of pH 9·18 was: amphetamine 79·5 and 88·5%; methylamphetamine 68·5 and 80·5%; dimethylamphetamine 78·5 and 84·5%.

EXPERIMENTAL—MATHEMATICAL TREATMENT

Apparatus. Electronics Associates Ltd. TR-20R Analogue Computer.

Method. Inspection of the results of the buccal absorption experiments described above for the 'amphetamines', indicated that a simple three compartment model might mathematically simulate the physiological system. Although absorption appears to level off approximately 5 min

after placing the drugs in the mouth (see Fig. 1), less than 50% of the amount of the drug absorbed could be recovered by successive rinsing of the mouth after this period of time. This suggested that two absorption compartments were involved only one of which was in rapid equilibrium with buffer in the mouth. The model shown in Fig. 2 was therefore proposed to study the kinetics of the buccal absorption of the 'amphetamines.' The compartments were arranged such that transfer of drug between A and B was freely reversible, and movement from B to C depended on the apparent concentration difference in the compartments. Results indicated that reverse transfer from C to B was a very slow process compared to forward movement from B to C. In the total system this reverse process would be very difficult to estimate with any degree of confidence and therefore was considered to be zero for our purposes. A steady slow loss from compartment C was required to account for the slight absorption occurring between the 5 and 10 min contact times.

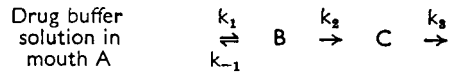

FIG. 2. Proposed kinetic model for the buccal absorption of the 'amphetamines'.

The following mathematical equations were used to describe the transfer of drug between the compartments:

$$\frac{dA}{dt} = -k_1\left(\frac{AR}{V_1} - \frac{B}{V_2}\right) \quad .. \quad .. \quad .. \quad .. \quad (1)$$

$$\frac{dB}{dt} = +k_1\left(\frac{AR}{V_1} - \frac{B}{V_2}\right) - k_2\left(\frac{B}{V'_2} - \frac{C}{V_3}\right) \quad .. \quad (2)$$

$$\frac{dC}{dt} = k_2\left(\frac{B}{V'_2} - \frac{C}{V_3}\right) - k_3\left(\frac{C}{V_3}\right) \quad .. \quad .. \quad .. \quad (3)$$

equations (2) and (3) apply when:

$$\frac{B}{V'_2} > \frac{C}{V_3}$$

when $\frac{B}{V'_2} \leqslant \frac{C}{V_3}$ the following differential equations were used to describe compartments A and B.

$$\frac{dB}{dt} = k_1\left(\frac{AR}{V_1} - \frac{B}{V_2}\right) \quad .. \quad .. \quad .. \quad (4)$$

$$\frac{dC}{dt} = -k_3\left(\frac{C}{V_3}\right) .. \quad .. \quad .. \quad - \quad (5)$$

where: A, B and C = the total amount of drug in the respective compartments; V_1 = volume of buffer solution placed in the mouth (25 ml); R = % unionized drug/100 at the particular buffer pH; V_2 = apparent

volume of compartment B with respect to compartment A; V'_2 = apparent volume of compartment B with respect to compartment C; V_3 = apparent volume of compartment C; and k_1, k_2 and k_3 are the rate constants governing the transfer of drug between the compartments.

The equations (1–5) were programmed on the analogue computer as shown in Fig. 3.

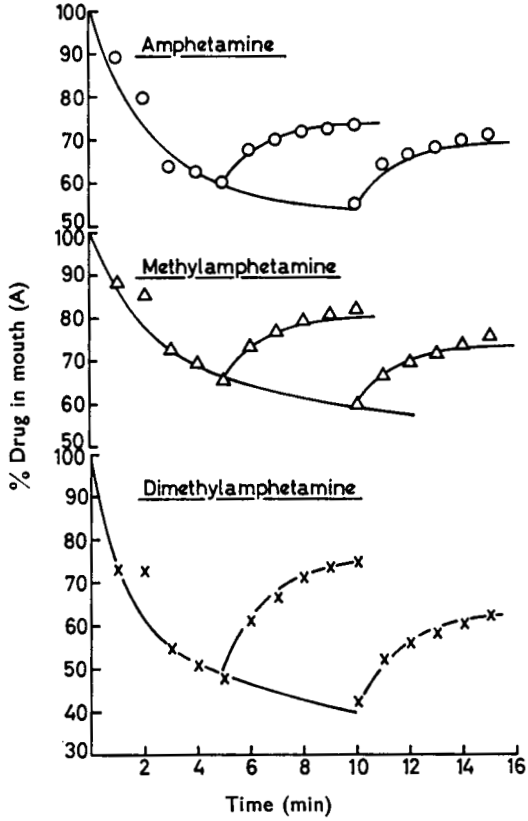

FIG. 3. Buccal absorption of some amphetamines. The points show the experimental data, the curves the computer calculations.

Conversion from equations 2 and 3 to equations 4 and 5 was made on the computer using a diode limiter; the term $k_2\left(\frac{B}{V'_2} - \frac{C}{V_3}\right)$ only exists on the computer when $\frac{B}{V'_2} > \frac{C}{V_3}$. The washout procedure was simulated on the computer by setting the value of the term k_1R/V_1 to zero.

Computer solutions for the equations (1–5) were obtained by systematically altering the potentiometers representing the constant parameters until good agreement was obtained between the computer calculations for

the amount of drug in compartment A and the experimental data for both absorption and wash-out procedures. For these calculations it was assumed that neither the rate constants nor the apparent volumes of the compartments changed appreciably during the course of each experiment. Since V_1 was known and R could be calculated for each drug at a particular buffer pH, the value of k_1 could be calculated from the potentiometer representing the term k_1R/V_1.

RESULTS—MATHEMATICAL TREATMENT

The continuous lines in Fig. 1 represent the computer-calculated amounts of drug in compartment A as a function of time at a buffer pH of 8·16; there is close agreement between the computer calculations and the experimental data points for both the absorption and wash-out procedures for all three drugs. The values of the constant parameters for each drug at a buffer pH of 8·16 are summarized in Table 1.

TABLE 1. KINETIC PARAMETERS FOR THE BUCCAL ABSORPTION OF THE AMPHETAMINES

Drug	Buffer pH	pK_a*	V_1(ml)	R	$\frac{k_1R}{V_1}$	k_1†	$\frac{k_1}{V_2}$	$\frac{k_2}{V'_2}$	$\frac{k_3}{V_2}$	$\frac{k_0}{V_2}$
Amphetamine	8·16	9·77	25	0·0240	0·2012	210·0	0·6515	4·292	2·485	0·0166
Methylamphetamine ..	8·16	9·87	25	0·0191	0·1740	227·5	0·6363	3·506	3·184	0·0920
Dimethylamphetamine	8·16	9·40	25	0·0544	0·3794	174·4	0·5794	3·000	7·343	0·2974

* Leffler, Spencer & Burger (1951).
† Units—ml min^{-1}.

Direct conversion of the parameter k_1R/V_1 from a buffer pH of 8·16 to one of 9·18 resulted in too rapid a predicted rate of absorption for all of the 'amphetamines', although the experimental and calculated amounts of the drugs absorbed after 10 min were in reasonably close agreement, i.e., for amphetamine the predicted amounts of the drug absorbed after 5 and 10 min were 80·0 and 89·0% respectively compared with the corresponding experimental values of 79·5 and 88·5%. Good agreement between calculated and experimental data at a buffer pH of 9·18 could be obtained for all the 'amphetamines' by making the value of the parameter k_1R/V_1 less than expected on the basis of the results at a pH of 8·16.

Discussion

Drugs may be classified in terms of their relative order of partitioning into a biological fluid by the 'Buccal Absorption Test' (see Beckett & Triggs, 1967). Our results indicate that the kinetics of the buccal absorption of drugs also may be useful in assigning numerical values to these relative partitioning properties.

Previous work (Beckett & Triggs, 1967) indicated that buccal absorption of the 'amphetamines' was related to the concentration of unionized drug in the mouth, i.e., as the buffer pH was made progressively more alkaline there were substantial increases in the amounts of the 'amphetamines'

absorbed in a fixed period of time. It was also found that optical isomers were absorbed to the same extent, and when more than one drug was placed in the mouth at the same time the same absorption occurred as when the drugs were placed in the mouth singly. This evidence indicated that buccal absorption involved passive diffusion of the unionized form of the drug from an aqueous phase to a lipid phase. Thus transfer from compartment A to B in the proposed model (see Fig. 2) involves a partitioning process and therefore the apparent volume (V_2) of compartment B will be a combination of the true volume and the partition coefficient of the drug between buffer and lipid. The nature of compartment C is unknown and therefore the apparent volume of B with respect to C was given as V'_2. Since it is possible to obtain good agreement between the computer calculations and the experimental data for the buccal absorption of the 'amphetamines' it is reasonable to assume that the proposed computer model is a valid mathematical description of the biological system.

The calculated parameters listed in Table 1 suggest that although more dimethylamphetamine than amphetamine and methylamphetamine is absorbed at any time, the rate constant for absorption (k_1) is less than for the latter two drugs. The more extensive absorption of dimethylamphetamine at a pH of 8·16 therefore results from the higher concentration of unionized drug in the buffer due to the pK_a differences between the drugs (see Table 1). This higher concentration of unionized moiety may result in association or reduced solubility of the dimethylamphetamine in the buffer and therefore the rate constant (k_1) for this drug may involve an availability (or activity) term. The failure to obtain good agreement between calculated and experimental absorption data on conversion of the parameter k_1R/V_1 from a pH of 8·16 to 9·18 indicates that, for all the 'amphetamines', availability or activity terms must be included in the calculations when the concentration of unionized drug is relatively high. Further experiments at various pH values are necessary to elucidate the relation between percentage of the 'amphetamines' which are unionized and the rate of buccal absorption.

References

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