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DRUG RECOVERY FOLLOWING BUCCAL ABSORPTION OF PROPRANOLOL

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1 Buccal absorption of propranolol in two volunteers was followed by repeated rinsing of the mouth with buffer solutions for twelve 2 min periods. Values for absorption, recovery and asymptotic recovery were calculated.

2 Large amounts of propranolol were recoverable from the buccal mucosa; recovery was biexponential and the amount recovered depended on the time allowed for absorption and on the pH of buffers used for recovery.

3 In the case of the drug studied, the buccal absorption test was not an adequate model of passive drug transfer through lipid membranes, and more clearly reflected partitioning into the buccal mucosa.

4 It does not follow from disappearance of drug from the buccal cavity that it has entered the circulation. Unabsorbed drug clearly cannot enter the circulation, but other conclusions about systemic absorption cannot be drawn with certainty from the buccal absorption model.

5 Partitioning back into the saliva after absorption also needs to be taken into account for a true model of systemic absorption of orally administered drugs, and a revised schematic representation of the kinetics of oral drug absorption is presented.

Introduction

The buccal absorption test was introduced by Beckett & Triggs in 1967 as an *'in vivo* model of passive drug transfer through lipid membranes', and the authors demonstrated that the mode of absorption is by partitioning into, or passage through, a lipid phase, in accordance with the pH-partition theory. Later work has clearly demonstrated by back-partitioning into freshly-introduced buffer solution that drugs may be recovered from the buccal mucosa (Beckett, Boyes & Triggs, 1968; Beckett & Pickup, 1975; Temple & Schesmer, 1978; Davis & Johnston, 1979), which is consistent with the hypothesis that passive buccal absorption of drugs is a reversible process.

We investigated this phenomenon further by performing sequential back-partitioning with buffer in an attempt to recover the drug absorbed after a typical buccal absorption experiment, using the lipophilic β-adrenoceptor antagonist drug propranolol.

Methods

Buffer solutions

Four buffer solutions were prepared in double distilled water according to Documenta Geigy (1959), namely, McIlvanie's citric acid/phosphate buffer (pH 5.2), Sörensen's phosphate buffer (pH 7.4), and Sörensen's glycine buffer (pH 9.0 and 9.5). The pH values of the solutions were adjusted at room temperature (20°C) with a digital pH meter (Orion Research Ltd). The pH 9.5 buffer was used for buccal absorption and the others for recovery experiments.

Drug solution

Propranolol 1mg/ml was prepared in double distilled water before each study and made up with pH 9.5 buffer to a solution of approximately 10 μg/ml.

Subjects

Two trained male subjects were used for this study. Several trials were performed before the study in order to ensure that the time course could be kept and that swallowing could be avoided. This was successful enough for the use of phenol red as a marker (as used in previous work on buccal absorption) to be deemed unnecessary.

Buccal absorption

Approximately 200 μg propranolol (20 ml of propranolol solution as prepared above in buffer at pH 9.5) was introduced into the buccal cavity after an

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initial 30 s period in which 20 ml of buffer without added drug was circulated around the mouth and discarded. The buffer containing the drug was circulated around the buccal cavity approximately once per second for 5 min, and then expelled into a measuring cylinder. Immediately after this, a further 20 ml of the same buffer not containing drug was rinsed around the mouth for 10 s (in order to remove any unabsorbed drug in the buccal cavity), and then expelled into the measuring cylinder. Aliquots of the original propranolol solution and of the expelled solution were assayed for propranolol content in order to obtain the amount of drug absorbed by the buccal mucosa.

In another series of experiments, absorption times of 1 and 15 min were used.

Recovery

As soon as the rinsing buffer had been expelled, 20 ml of fresh buffer at one of the three pH values was introduced into the mouth and circulated in the manner as for absorption, for 1 min 55 s. Five seconds were allowed for expulsion of the buffer and the introduction of a further 20 ml of fresh buffer solution of the same pH. This procedure was repeated twelve times, the duration of recovery time being 24 min. Back-partitioning was performed at each of the three pH values and also at pH 7.4 after absorption times of 1 and 15 min.

Handling of samples and assay

The volume of each sample was measured and the sample filtered with Whatman filter paper. Propranolol was measured spectrofluorometrically using the method of Shand, Nuckolls & Oates (1970), with an Aminco spectrofluorometer (model 5PF-125). Detection limit of the assay was 10 ng/ml.

Mathematical treatment of data

Curves were fitted for the data using an iterative curve-fitting programme to mono- and biexponential formulae, and asymptotic values were calculated.

Results

Mathematical analysis showed that the data were best fitted to a biexponential curve. The results for absorption and recovery at the different pH values are given in Table 1, and for recovery with three different absorption times in Table 2. Figure 1 illustrates cumulative recovery at different pH values in subject A; Figure 2 gives the same experimental data plotted logarithmically as sequential recovery. Figure 3 shows the mean sequential recovery at pH 7.4 following absorption for three different time intervals.

Discussion

The suggestion that the buccal absorption test is a valid *in vivo* model of passive drug transfer through lipid membranes appears not to have been challenged since its introduction by Beckett & Triggs in 1967. In fact, the concept of passage of a drug into the systemic circulation is implicit in kinetic models of drug absorption such as that of Schürmann & Turner (1978), where the systemic circulation acts as a sink of infinite volume of distribution in comparison with the amount of drug dissolved, hence absorption is unidirectional and back diffusion does not occur. On the other hand, studies by a number of workers have shown that drug absorbed into the buccal membrane may be recovered from the oral cavity (Beckett *et al.*, 1968; Beckett & Pickup, 1975; Temple & Schesmer, 1978; Davis & Johnston, 1979). The technique of repeated recovery does not appear to have been used previously and the results obtained from our experiment imply that, when propranolol is absorbed into the buccal membrane, a large proportion is accessible for removal by back partitioning, the amount recoverable in this way depending on the time allowed for absorption of the drug and also on the pH used for recovery. Passive absorption of propranolol into the circulation, therefore, must be, at least through the buccal membrane, a relatively slow process, and back-partitioning may account for the fate of a large part of the drug absorbed by the buccal membrane, since we have demonstrated that over 90% of absorbed drug was recoverable when using buffers covering the usual salivary pH range. This merits comparison with the observation of Kates (1977) that peak plasma levels of propranolol occurred at 1–2 h after sublingual administration; we suggest on the basis of our results that this may have been due to back diffusion and swallowing of propranolol followed by its intestinal absorption. The swallowing of 'absorbed' drug which has back-partitioned therefore needs to be excluded in order to verify systemic buccal mucosal absorption, particularly as the pH of saliva can be conducive to the back-partitioning of both lipophilic acids and bases. In view of this, we propose a revised schematic representation for the kinetics of buccally-presented drugs (Figure 4) based on that of Gibaldi & Kanig (1965).

This study underlines the fact that buccal mucosal absorption and systemic absorption are not synonymous. It does not follow from the disappearance of a drug from the buccal cavity that it has entered the systemic circulation. A clear

Table 1 The effect of pH on recovery of propranolol after absorption at pH 9.5

Subject	Absorption time (min)	Recovery pH	Total drug (μg)	Absorbed (μg)	% Absorption[1] (%)	Recovered (μg)	% Recovery (%)	Asymptotic value (μg)	% As. V.[2] (%)
A	5	5.2	180.2	146.5	81.3	82.3	56.2	139.6	95.3
B		5.2	200.4	150.0	72.4	82.4	54.9	137.4	91.6
A	5	7.4	200.6	161.6	80.9	82.9	51.3	138.9	86.0
B		7.4	200.6	155.8	77.7	74.3	47.7	144.6	92.8
A	5	9.0	168.0	136.0	80.9	25.3	18.6	37.2	27.4
B		9.0	168.0	140.6	83.7	27.6	19.2	42.4	30.2

(1) % Absorption = Total drug/Absorbed drug × 100
(2) % As. V = Absorbed/Asymptotic value × 100.

Table 2 The effect of absorption time on recovery of propranolol

Subject	Absorption time (min)	Recovery pH	Total drug (μg)	Absorbed (μg)	% Absorption (%)	Recovered (μg)	% Recovery (%)	Asymptotic value (μg)	% As. V. (%)
A	1	7.4	208.9	95.1	45.5	56.8	59.7	104.8	110.2
B		7.4	208.9	97.4	46.6	54.7	56.2	91.5	93.9
A	5	7.4	200.6	161.6	80.9	82.9	51.3	138.9	86.0
B		7.4	200.6	155.8	77.7	74.3	47.7	144.6	92.8
A	15	7.4	192.8	158.1	82.0	57.1	36.1	98.1	62.0
B		7.4	192.8	159.7	82.8	58.2	36.4	103.0	64.5

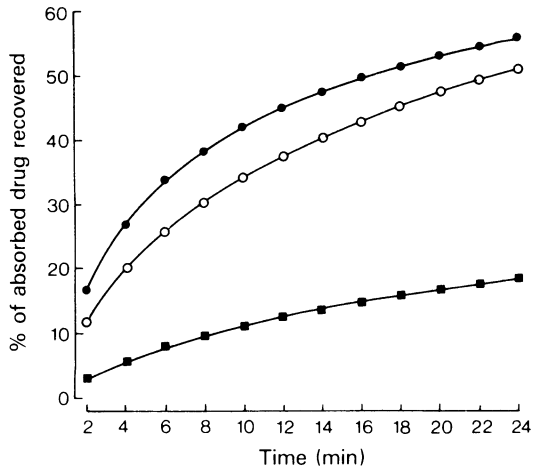

Figure 1 Cumulative recovery of propranolol at three different pH values (● pH 5.2, ○ pH 7.4 and ■ pH 9.0) after absorption for 5 min at pH 9.5.

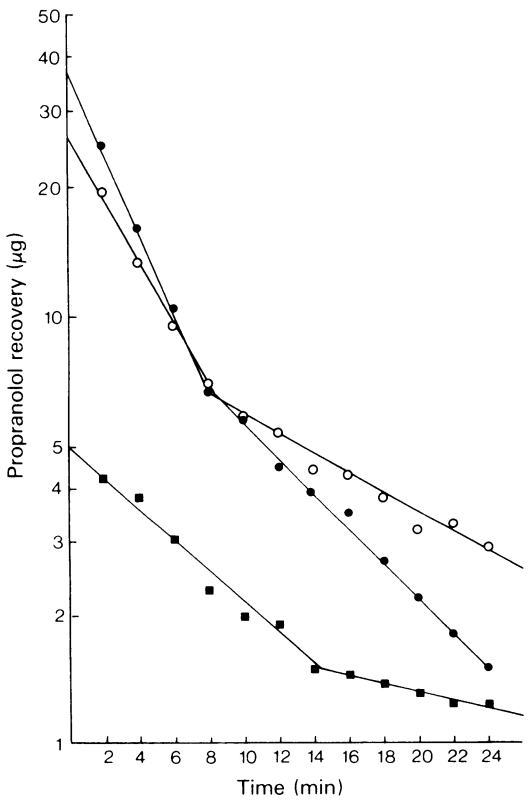

Figure 2 Propranolol recovery (logarithmic plot) at three different pH values (● pH 5.2, ○ pH 7.4 and ■ pH 9.0) after absorption for 5 min at pH 9.5.

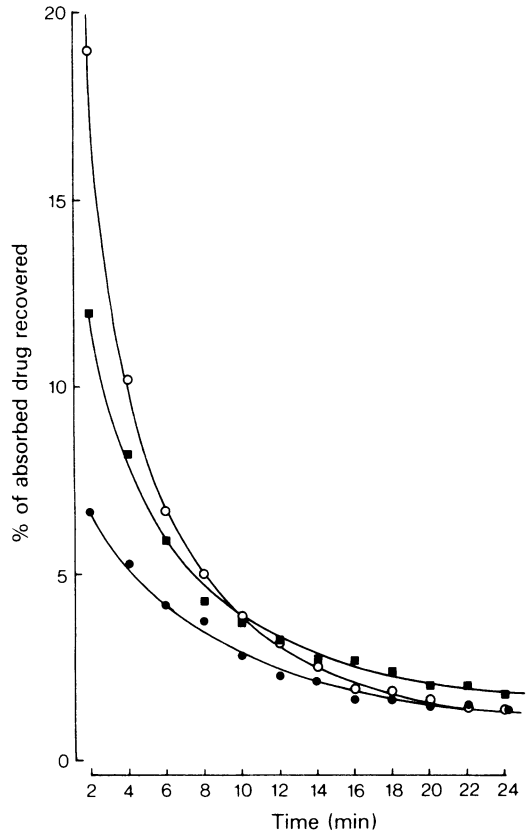

Figure 3 Mean % of absorbed drug recovered at pH 7.4 after absorption for 1 (○), 5 (■) and 15 (●) min at pH 9.5.

distinction must therefore be made and the term 'buccal absorption' used with care; 'buccal partitioning' might be a more accurate term. It is also apparent from this study that unidirectional passive transfer across membranes will only occur when sufficient drug is present on one side of the membrane. On removal of drug from the buccal cavity, the concentration gradient is altered, and back-partitioning into the mouth may occur; this process can be facilitated, as in our study, by the use of appropriate buffer solutions.

A clearer evaluation of the buccal absorption model is required in order to determine the rate constants, both for disappearance from the buccal cavity and for recovery of drug, as well as for its entry into the circulation, though we conclude that the buccal absorption test alone is not an adequate model of passive drug transfer through lipid membranes. It is possible that drug is stored mainly in the thicker parts of the buccal membrane and that absorption tends to occur through the thinner parts, such as the sub-lingual membrane which is only a few cells thick

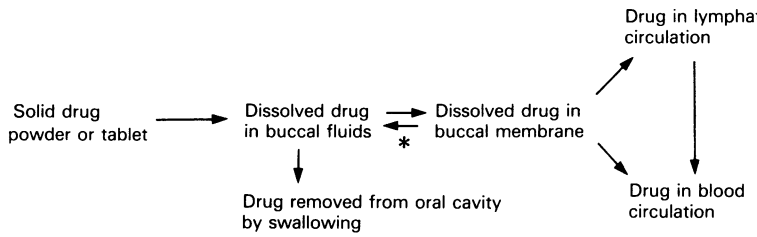

Figure 4 Schematic representation of the absorption kinetics of buccally presented drugs, modified from Gibaldi & Kanig (1965).

and has a rich blood supply. Sequential washing of the buccal mucosa with buffers in order to recover absorbed drug provides a further method for studying passive drug transfer through the buccal mucosal membrane and enables calculation of an asymptotic value for recoverable drug to be made. Extension of this type of study to drugs which undergo rapid and demonstrable passive absorption, such as glyceryl trinitrate, isosorbide dinitrate and isoprenaline, may throw further light on the nature of the passage of drugs through lipid membranes and on the buccal absorption model.

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