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The buccal absorption of some barbiturates

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The buccal absorptions of five barbiturates have been determined over the pH range 3 to 9. The absorptions increased as the pH decreased until pH 5·5 when they remained constant. No correlation between the absorptions and chloroform–0·1N HCl partition coefficients was apparent, indicating that the adsorptive power of the buffer-buccal membrane interface may represent more exactly the real affinity of the membrane for barbiturates than do partition coefficients with chloroform.

The 5 min cumulative buccal absorption test of Beckett & Triggs (1967) has been used to examine the buccal absorptions of alkyl substituted carboxylic acids (Beckett & Moffat, 1968, 1969a), *N*-alkyl amines (Beckett & Moffat, 1969b) and imipramine and its metabolites (Bickel & Weder, 1969). These results have also been related to aqueous-organic phase partition coefficients (Beckett & Moffat, 1969b; Bickel & Weder, 1969). This test is now used to examine the absorptions of some barbiturates.

MATERIALS AND METHODS

Aqueous solutions of the sodium salts of the barbiturates were used with the method of Beckett & Moffat (1968).

For analysis, the method of Beckett & Moffat (1968) was used, omitting the treatment with diazomethane. The gas-liquid chromatographic conditions used were: $\frac{1}{4}$ inch o.d. glass tube packed with Chromosorb G (acid washed, DMCS treated, 80–100 mesh) coated with 0·75% Neopentylglycol sebacate; nitrogen pressure 13 lb/inch^2, hydrogen pressure 18 lb/inch^2 and air pressure 30 lb/inch^2; injection block temperature approximately 50° above the oven temperature. The oven temperature and internal standard used for each barbiturate are summarized in Table 1.

RESULTS AND DISCUSSION

Analysis

The use of gas-liquid chromatography allowed multicomponent mixtures of barbiturates to be separated and analysed individually. Although the column had an efficiency equivalent to only 210 plates, nearly symmetrical peaks were obtained (e.g., Fig. 1). All calibration graphs were linear over the range 0·1 to 1·0 mg barbiturate in buffer solution or buffer solution containing saliva; the calibrations were identical for both solutions. Standard deviations, obtained from twelve replicate assays, were 0·88, 1·08 and 1·68% for barbitone, probarbitone and methylphenobarbitone respectively.

Buccal absorption

Absorptions increased as the pH decreased and the concentration of unionized barbiturate increased (e.g., Fig. 2) indicating that the unionized, and not the ionized,

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Table 1. *Gas-liquid chromatographic conditions for the analysis of some barbiturates on a 0·75% Neopentylglycol sebacate column*

Barbiturate	Retention time (min)	Oven temperature (°C)	Internal standard	Retention time (min)
Barbitone	6·0	190	Diallylbarbituric acid	10·0
Probarbitone	7·6	190	,,	10·0
Methylphenobarbitone	18·1	190	,,	10·0
Thiopentone	5·8	205	Hexobarbitone	3·7
Phenobarbitone ..	18·6	205	,,	3·7

species is absorbed. This is in agreement with Katz (1954), who found the free barbiturates to be more effectively absorbed by the oral mucosa than their ionized sodium salts. The pK_a values of the barbiturates are between 7·4 and 8·0 (Table 2), so at pH 5·5 all were at least 99% unionized which explains the relatively constant absorptions obtained at pH values below 5·5.

Since the absorptions above pH 5·5 were small, and therefore difficult to measure accurately, the mean absorptions below pH 5·5 were calculated (Table 2). Thiopentone was absorbed to the greatest extent, followed by methylphenobarbitone. These results are similar to the findings of Kakemi, Arita & others (1967a,b) who showed that the gastric and intestinal absorptions of barbituric acid derivatives were in the order oxy-<*N*-methyl-<thio-. These differences are also reflected in the chloroform–0·1N HCl partition coefficients (Table 2), although no correlation between buccal absorption and partition coefficients is apparent.

The n-heptane–0·1N HCl partition coefficients of thiopentone, barbitone and benzoic acid are 3·3, 0·002 and 0·19 respectively (assuming no dimerization in either phase; Hogben, Tocco & others, 1959). Thus, since the buccal absorption of benzoic acid at pH 3·0 is 70% (Beckett & Moffat, 1968), a much larger absorption for thio-

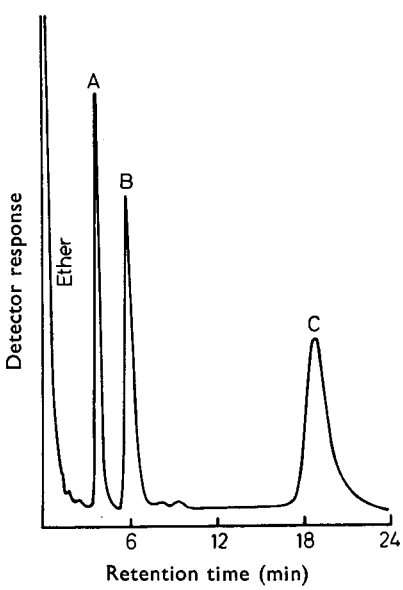

FIG. 1. Chromatogram of some barbiturates, extracted from saliva-buffer solution, on a 0·75% Neopentylglycol sebacate column at 205°: A, hexobarbitone; B, thiopentone; C, phenobarbitone.

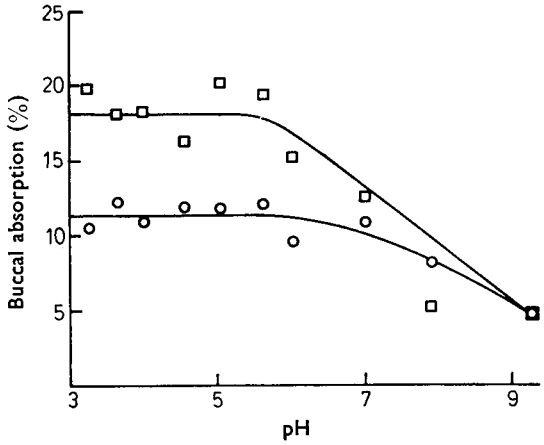

FIG. 2. Buccal absorption of some barbiturates (Subject I): □, thiopentone; ○, phenobarbitone.

Table 2. *Buccal absorption data (Subject I), chloroform–0·1N hydrochloric acid partition coefficients and* pK_a *values for some barbiturates*

Barbiturate	Mean maximum absorption (%)	Partition coefficient (37°)*	pK_a (25°)
Phenobarbitone	11·4	4·44	7·41†
Probarbitone	11·6	1·60	8·01†
Barbitone	16·3	0·72	7·91†
Methylphenobarbitone ..	16·4	95·5	7·7‡
Thiopentone	18·5	321	7·6§

* Kakemi & others (1967c) (assuming no association of molecules in either phase).
† Krahl (1940).
‡ Butler (1955).
§ Schanker & others (1957).

pentone than that actually obtained would be expected. Conversely, a very small absorption, compared to that of thiopentone, would be expected for barbitone. These comparatively small absorptions for the barbiturates are similar to those obtained using other tissues, e.g., Schanker, Shore & others (1957) showed that thiopentone, barbitone and benzoic acid were passively absorbed at pH 1 into the rat gastric mucosa in the same time, to the extent of 46, 4 and 55% respectively.

Thus, unlike the buccal absorption of the amines and carboxylic acids studied previously (Beckett & Moffat, 1968, 1969a,b, 1970), the relation between lipid solubility and absorption into the buccal mucosa is not clear for barbiturates. From the above results, the buccal mucosa is clearly selectively permeable to the unionized form. However, it is likely that this step is preceded by interaction or complex formation between the drug molecule and the protein of the mucosa, and, unlike the situation which obtains with the carboxylic acids and amines already studied, the release of the barbiturates into the lipid is the rate controlling step in the buccal absorption of barbiturates.

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