Buccal absorption of ergotamine


From the Department of Medicine, Royal Brisbane Hospital, University of Queensland, Brisbane, Australia

SYNOPSIS  The rate of disappearance of ergotamine from the mouth after buccal administration has been studied in seven subjects. Allowance has been made for non-absorptive losses of the drug due to experimental technique. The absorption of ergotamine across the buccal mucosa appears to be a passive process, pH-dependent but independent of ergotamine concentration or the simultaneous presence of caffeine. Because of the low solubility of ergotamine at the pH of saliva, it is unlikely that therapeutically useful amounts of the drug would have absorbed across the buccal mucosa even after the drug had been in the mouth for five minutes.

Ergotamine, widely used in treating attacks of migraine, may be administered by injection (intravenous, intramuscular, or subcutaneous), taken rectally, buccally or sublingually, swallowed, inhaled as an aerosol, or applied to the nasal mucosa. The oral route of administration is the most convenient and simple. However, vomiting often tends to occur in migraine and ergotamine may increase this tendency. Vomiting may cause partial or total loss of the dose of ergotamine swallowed. Therefore, alternative routes of ergotamine intake may be preferred when the drug is to be self-administered. Rectal administration has been shown to be effective (Kadish, 1950; Graham, 1954), though it may lead to problems such as immediate defaecation with loss of a portion of the dose, constipation, or poor patient acceptance.

Absorption across the mucous membranes of the mouth might circumvent these problems and would appear to be of great potential value. Ergotamine might enter the circulation faster if absorbed from the mouth rather than from lower portions of the alimentary tract, and a greater proportion of the dose might be available to reach the cranial blood vessels. However, buccal and sublingual absorption of ergotamine has not been extensively studied. Clinically, there is some evidence that sublingual or buccal absorption of ergotamine is more effective than oral administration but less effective than intravenous, intramuscular, subcutaneous, rectal, or aerosol therapy (Kelly, 1937; von Storch, 1938; Graham et al., 1960; Sutherland and Eadie, 1961; Crooks et al., 1964; Cristol and Unger, 1971).

Ergotamine is often combined with caffeine in preparations used for the treatment of migraine. Clinical studies have indicated that the combined preparations were more effective than ergotamine alone when given orally or rectally (Horton et al., 1948; Cohen and Crip, 1949; Bercel, 1950; Friedman and von Storch, 1951). Zoglio et al. (1969) suggested that at least part of the effectiveness of the combined oral preparations may be due to complex formation between caffeine and ergotamine leading to enhanced alimentary absorption of ergotamine. The relative effectiveness of the combined preparation as compared with ergotamine alone when administered by the buccal route does not appear to have been studied.

The lack of a sensitive and specific assay for ergotamine has considerably hampered studies of the clinical pharmacology of the drug, so that hitherto its absorption in man has had to be assessed in terms of subjective criteria. However, with the development of a sensitive fluorimetric assay of ergotamine by Hooper et al. (1974), a greater understanding of the use of ergotamine may be attained.
Buccal absorption of ergotamine

In the present study, an attempt was made to measure the buccal absorption of ergotamine, alone and in the presence of caffeine, to try to assess the potential effectiveness of the drug in migraine when given by this route.

METHODS

SUBJECTS Three healthy female volunteers (17, 26, and 31 years of age) and four healthy male volunteers (23, 25, 28, and 34 years of age) participated in the study.

SOLUTIONS USED Two buffer systems were used to maintain the pH of the ergotamine solution during buccal contact—namely, 0.2 M acetate buffer (pH 4.3 ± 0.1) and 0.2 M phosphate buffer (pH 6.3 ± 0.1 and pH 8.2 ± 0.1). These solutions will be referred to as the pH 4.3, the pH 6.3, and the pH 8.2 solutions despite ± 0.1 pH unit range. Subsequent measurement showed that these buffers satisfactorily maintained pH after exposure to the buccal mucosa. The buffer solutions containing the drug(s) stood overnight at 20–22°C and were then filtered twice through Whatman No. 42 filter paper to avoid the presence of undissolved drug. The concentrations of ergotamine tartrate studied ranged from 0.7 μg/ml to 90.1 μg/ml (pH 4.3), 0.6 μg/ml to 9.3 μg/ml (pH 6.3) and 0.28 μg/ml to 4.4 μg/ml (pH 8.2).

BUCCAL ABSORPTION TEST The technique used was a modification of the buccal absorption test of Beckett and Moffat (1968). Twenty millilitres of a buffered solution of the drug(s) was circulated around the subject’s mouth by movement of the tongue and cheeks for a predetermined time, and then expelled into a
beaker. The subject then quickly rinsed his mouth for 5 s with a 5 ml aliquot of the same buffer without ergotamine, but containing caffeine citrate (5 mg/ml) when appropriate. Both expelled solutions were combined and the pH measured. This solution was then diluted as necessary for assay. The interval between successive tests in each subject was at least 15 minutes. Buccal absorption was measured after $\frac{1}{2}$, one, two, and five minutes of drug contact with the buccal mucosa. Each subject was given ergotamine solutions of various concentrations at each of three different pHs, both with and without added caffeine citrate (5 mg/ml) on one or more occasions. Furthermore, each subject was given ergotamine solutions of at least one of the pHs on a minimum of two occasions. Where more than one solution was studied in one day in a subject the order of exposure was randomized.

ANALYTICAL METHOD Ergotamine concentration in saliva and the other solutions used was measured by the technique of Hooper et al. (1974). To provide a ‘blank’ solution for these assays, each subject kept in his mouth for five minutes, on at least two occasions, a non-ergotamine containing buffer, with or without caffeine citrate (5 mg/ml). After expulsion, this solution was assayed by the routine technique to provide blank values for ergotamine determination in saliva with, and without, caffeine citrate.

RESULTS

EFFECT OF TIME Figure 1 shows the mean percentage of ergotamine lost at $\frac{1}{2}$, one, two, and five minutes for the seven subjects when exposed to ergotamine at each of the three pHs. The correlation coefficient for linear regression of percentage of drug lost against time was significant at the 0.001 level for pH 4.3 and 6.3 and at the 0.01 level for pH 8.2; hence ergotamine losses increase with time. However, at the most, less than 40% of the ergotamine dose was lost after five minutes’ exposure.

EFFECT OF pH Analysis of covariance showed that the elevation of the regression line for pH 4.3 in Fig. 1 differed at a statistically significant level of confidence (P < 0.01) from the elevations of the regressions for pH 6.3 and 8.2. Thus proportionately less ergotamine was lost at pH 4.3 than at the higher pH values studied.

EFFECT OF CONCENTRATION Over the range of concentrations studied, which was limited by the low solubility of ergotamine, there was no statistically significant effect of concentration on per cent of ergotamine lost at any of the pH's.

EFFECT OF CAFFEINE Figure 1 shows the time course of the loss of ergotamine from the mouth in the presence and absence of caffeine at pH 4.3, 6.3, and 8.2. For each of the three pHs studied a two-way hierarchical analysis of variance (Croxton and Cowden, 1965) was performed on the data. These analyses showed that the presence of caffeine had no statistically significant effect on the percentage of the ergotamine dose lost at any of the three pHs studied.

DISCUSSION

While Gibaldi and Kanig (1965) drew a distinction between the buccal and the sublingual routes of drug administration, in practice ergotamine for buccal administration is often chewed and the disintegrating material is then often allowed to move about the mouth. Therefore, the drug is likely to absorb through both the buccal and the sublingual mucosae. In the present experimental study the solution of ergotamine was presented to both buccal and sublingual mucosae.
As measured in the present study, the percentage of ergotamine lost is not necessarily equal to the true percentage of the drug dose absorbed across the buccal mucosa. Non-absorptive losses due to spillage, swallowing, binding to mucosal surfaces, and perhaps teeth, and possible metabolism might have occurred while ergotamine was in the mouth, and would have been included in the percentage of drug lost. A more satisfactory method would have been to measure the appearance of ergotamine in plasma after absorption, but the method of assay used, though very sensitive (limit of detection 0.002 μg/ml), was not capable of measuring the drug concentration in plasma. Alternatively, a non-absorbable marker compound could have been kept in the mouth together with the ergotamine, and measured after expulsion from the mouth, but this might not have accounted for all the factors that could be involved in non-absorptive ergotamine loss. Two possible methods of more nearly estimating the true absorption of ergotamine are considered below.

Figure 1 shows that ergotamine is lost faster in the first half minute of buccal contact than in the subsequent 4½ minutes, during which time the rate of loss is approximately linear. This high initial rate of loss, irrespective of ergotamine concentration, may reflect the combined effects of both drug absorption and of most of the non-absorptive loss due to the various factors mentioned above. Consequently, a better estimate of buccal ergotamine absorption might be obtained by extrapolating the linear regression between per cent of ergotamine lost and time (over the interval half to five minutes) back to zero time, and taking the differences between this zero-time loss and the observed losses at subsequent times as more realistic estimates of ergotamine absorption. When these values are plotted against time (Fig. 2), absorption is greater at pH 6·3 and 8·2 than at pH 4·3. For instance, after five minutes of buccal contact with ergotamine, 7% of the dose would have been absorbed at pH 4·3, 16% at pH 6·3, and 10% at pH 8·2.

The data of the present study are consistent with ergotamine being absorbed passively across the buccal mucosa. Ergotamine is a base with a pKₐ of 6·25 (Maulding and Zoglio, 1970). Consequently only about 1% of the drug would be non-ionized, and likely to absorb passively, at pH 4·3, whereas much more would be non-ionized at higher pH. The present study has shown better ergotamine absorption at the higher pH values, in accordance with the pH partition hypothesis of passive absorption (Levine, 1971). Also ergotamine absorption is not concentration-dependent, which again is consistent with passive absorption, though we cannot be certain that the range of concentration studied was wide enough to exclude an active process obeying Michaelis-Menten kinetics. Since so little ergotamine is ionized at pH 4·3, if the drug's absorption is passive, the data obtained for ergotamine loss at pH 4·3 in the present study may represent almost entirely non-absorptive losses of the drug due to the experimental technique. Therefore subtraction of percentage of ergotamine lost at pH 4·3 from the losses at higher pH values (Fig. 3) may provide a reasonable estimation of true ergotamine absorption at pH 6·3 and pH 8·2. The mean percentage absorbed, calculated in this way, appears to increase slightly with time and, after five minutes' buccal contact, 18% of the dose would be absorbed at pH 6·3 and 13% at pH 8·2. Personal unpublished studies indicate that saliva pH varied in the range pH 6 to 8, and that after chewing a buccal ergotamine tablet containing

![Graph showing data obtained for mean percentage of ergotamine lost plotted against time after the values at pH 4·3 are subtracted from those at pH 6·3 (---- A ---) and pH 8·2 (---- A ----).]
caffeine for five minutes the saliva pH varied between 7.1 and 7.4.

From the above data, it appears that only about one-sixth of an ergotamine dose in solution might absorb from saliva across the buccal mucosa in five minutes. This is probably as long as a patient would keep a chewed ergotamine tablet in his mouth. Does this represent the absorption of a therapeutically useful dose? An ergotamine preparation administered in tablet form would have to disintegrate and the drug dissolve before absorption could begin, so that in five minutes there might be less drug absorbed from a tablet than from a previously prepared solution of the drug. Crooks et al. (1964) found that the average ‘dissolution time’, which appears to be actually the average ‘disintegration time’ of the sublingual ergotamine tablets used in their clinical trial, was five minutes. Further, Zoglio et al. (1969) found that, at pH 6.65 only about 9 μg ergotamine would dissolve per ml of water at 30°C. It is unlikely that 20 ml of saliva would be produced in the mouth in five minutes, but even assuming this amount of saliva were present when a patient chewed an ergotamine tablet, it is improbable that more than a total of 0.2 mg of the drug would be in solution at any one time. Of this, about one-sixth—that is, 0.03 mg—might be expected to absorb across the buccal mucosa in five minutes. Comparison of this 0.03 mg intake of ergotamine with the intravenous drug dose of 0.25 to 0.50 mg, which itself does not always relieve migraine, suggests that it is scarcely an adequate intake.

The present study also suggests that concurrently administered caffeine would be unlikely to enhance the buccal absorption of ergotamine. However, it should be noted that caffeine may still be of benefit with other routes of administration where different physicochemical environments would be encountered.

These results suggest that therapeutically useful quantities of ergotamine are unlikely to be absorbed from commercial ergotamine preparations across the buccal mucosa in a tolerable period of time. It might be suspected that ergotamine, intended for buccal absorption, is often helpful in migraine only if the drug is accidentally swallowed.

Ergotamine tartrate was supplied by Sandoz Australia, North Ryde, New South Wales.

REFERENCES


Bercel, N. A. (1950). Treatment of migraine; results with dihydroergocornine methan sulfate (DHO-180) and other ergot derivatives. California Medicine, 72, 234–238.


