Bioavailability of Flurbiprofen Following Buccal Administration

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The buccal absorption of flurbiprofen was evaluated in nine normal volunteers. Twenty milliliters of 2.5 mg/ml flurbiprofen solution (pH 8.03) was administered as a 1-min mouthwash or a 5-min mouthwash or swallowed. Serum was harvested from blood samples taken at specified times over a 12-hr period. Serum flurbiprofen concentration data indicate that the extent, but not the rate, of drug absorption was dependent upon the time of exposure of the flurbiprofen solution to the buccal membrane. Following the 1- and 5-min mouthwash treatments, 5.2 and 9.4% of the administered doses were absorbed, respectively.

KEY WORDS: bioavailability; flurbiprofen; buccal administration; periodontal disease.

INTRODUCTION

Flurbiprofen is a phenylpropionic acid derivative with antiinflammatory, analgesic, and antipyretic properties (1–4). Recent studies in animals and humans have shown flurbiprofen to be potentially efficacious in the treatment of periodontal disease (5–8). A variety of topical drug delivery systems (solution, gel, devices, etc.) is under consideration for use in this disease state.

Flurbiprofen has a pK_a of 4.22 and its absorption from the oral cavity would be expected to be pH dependent. In a study in which the disappearance of flurbiprofen was measured from a device applied to the buccal membrane, flurbiprofen absorption was found to be greater at pH 5.5 than at pH 7.0 (9). It was suggested from that study that buccal absorption of flurbiprofen from solutions of pH 7.0 or greater would be insignificant.

The current study was undertaken to evaluate the absorption characteristics of flurbiprofen from the oral cavity when administered as an aqueous solution (pH 8.03) of 2.5 mg/ml. A modification of the method described by Beckett *et al.* (10), in which the drug solution was circulated throughout the oral cavity, expelled, and followed by distilled water rinses, was employed for this study.

METHODS

Nine normal healthy adult volunteers were selected for participation in this study after obtaining informed consent. All subjects completed a physical examination and had normal laboratory parameters for blood and urine analysis. The average age of the subjects (eight females and one male) was 30 years (range, 19 to 46 years) and their average weight was 64.1 kg (range, 54.1 to 73.6 kg).

The subjects received each of three flurbiprofen solution treatments according to a three-way crossover experimental design. Each flurbiprofen dose (50 mg) was administered as 20 ml of 2.5 mg/ml aqueous solution at pH 8.03. The treatments were administered as follows: (A) the solution was circulated throughout the mouth as a mouthwash using the tongue and cheeks for *1 min* and then expelled into a specimen container; (B) the solution was circulated throughout the mouth as a mouthwash with the tongue and cheeks for *5 min* and then expelled into a specimen container; and (C) the solution was swallowed and was followed by 6 oz of water. Following the 1- and 5-min mouthwash treatments, the subjects rinsed their mouths with two 10-ml portions of distilled water and expelled the rinses into the above-mentioned specimen containers.

The subjects fasted at least 9 hr prior to receiving each treatment and for 4 hr following dose administration. For Treatments A and B, blood was drawn just prior to drug administration and at 1, 3, 5, 10, 15, 30, and 45 min and 1, 2, 4, 6, 8, and 12 hr following drug administration. With Treatment C, blood was drawn just prior to drug administration and at 15, 30, and 45 min, and 1, 2, 4, 6, 8, and 12 hr after drug administration. Serum was harvested from the blood samples as soon after collection as possible, immediately frozen, and kept frozen until assayed for flurbiprofen. Flurbiprofen concentrations in serum and expelled solutions were determined using a high-performance liquid chromatographic procedure. The sensitivity of the method is reported as 0.1 μg/ml (11).

Bioavailability Parameters

The bioavailability parameters of C_{max}, T_{max}, AUC(0–∞), k_{el}, k_a, and F were derived from the resultant serum flurbiprofen concentrations. The maximum serum flurbiprofen concentrations (C_{max}) and time of maximum concentration (T_{max}) were observed values. The apparent elimination rate constant (k_{el}) was determined by linear least-squares regression analysis of the terminal log-linear portion of the serum flurbiprofen concentration profile. Areas under the serum flurbiprofen concentration–time curve (AUC) from time 0 to 12 hr were determined by trapezoidal rule and the AUC from 12 hr to infinity was estimated by dividing the concentration at 12 hr by k_{el}. The bioavailability of the mouthwash treatments relative to the oral administration (F) was calculated by dividing the AUC(0–∞) for the mouthwash treatments by the AUC(0–∞) for the oral treatment. The amount of flurbiprofen absorbed from the mouthwash treatments was also determined by calculating the difference in the amount of flurbiprofen recovered from the expelled solutions and the amount of flurbiprofen administered. Absorption rate constants were determined by the best fit of each subject's data to either a one-compartment or a two-compartment model with first-order absorption and elimination using NONLIN84 (12).

Statistical Analysis

Evaluation of differences among treatments for mean bioavailability parameters was undertaken using the General Linear Model procedure of the Statistical Analysis System (Cary, NC, USA). Pairwise comparisons between treat-

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ments were made using the Waller–Duncan K-ratio t test. The level of significance for all statistical tests was $P < 0.05$.

RESULTS

The mean serum flurbiprofen concentrations-versus-time profiles for all three treatments are shown in Fig. 1 and the profiles for the two mouthwash treatments are shown together in Fig. 2. The bioavailability parameters derived from the serum flurbiprofen concentration data are provided in Table I. Results of the study indicate that the extent of flurbiprofen absorption from the oral cavity was dependent upon the time of exposure of the drug solution to the absorbing membrane. The area under the serum flurbiprofen concentration-versus-time curve values from 0 hr to infinity, AUC(0–∞), for Treatments A, B, and C were 2.12, 4.02 and 43.9 μg × hr/ml, respectively. Due to the variability in the data from the mouthwash treatments (i.e., Treatments A and B) AUC(0–∞) values were not significantly different. The bioavailabilities of Treatments A and B relative to the oral administration were significantly different. With 1 min of exposure (Treatment A) 5.2% of the dose was absorbed, whereas 9.4% of the dose was absorbed with 5 min of exposure (Treatment B). The peak concentration attained from the 5-min treatment (0.963 μg/ml) was 1.84 times greater than that from the 1-min treatment (0.522 μg/ml). The difference, however, was not statistically significant.

The fraction of drug absorbed was also calculated from the expelled flurbiprofen solution and subsequent rinses. The values obtained by this method are compared to those calculated from the blood-level data in Table II. On average, the fraction absorbed as calculated from the amount remaining in mouth rinse data was estimated at a higher level and was more variable than when calculated from the serum flurbiprofen concentration data. Using this method, 9.87% of the dose was absorbed from the 1-min treatment and 13.6% was absorbed with the 5-min mouthwash. The difference in the fraction absorbed as calculated by this method was not statistically significant.

There were no statistically significant differences among the treatments in the time of maximum serum flurbiprofen concentration (T_{max}) and no differences were found among treatments in the apparent absorption rate constant (k_a).

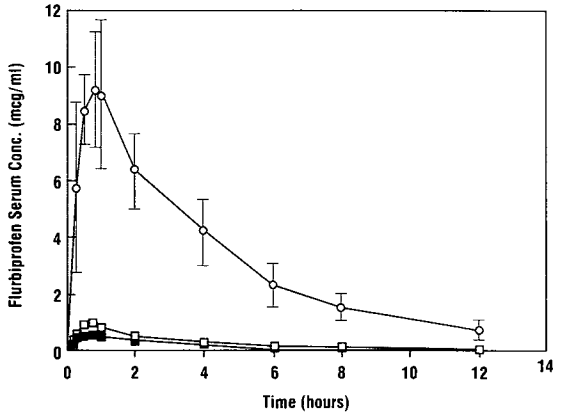

Fig. 1. Serum flurbiprofen concentration–time profiles following the administration of 20 ml of a 2.5 mg/ml flurbiprofen solution as a 1-min mouthwash (■——■), as a 5-min mouthwash (□——□) or orally (○——○). Mean ± SD; $N = 9$.

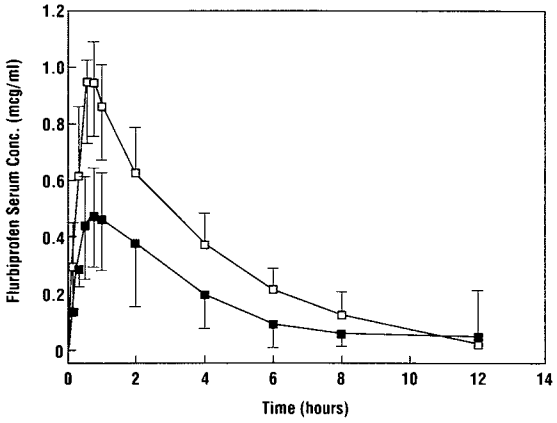

Fig. 2. Serum flurbiprofen concentration–time profiles following the administration of 20 ml of a 2.5 mg/ml flurbiprofen solution as a 1-min mouthwash (■——■) or a 5-min mouthwash (□——□). Mean ± SD; $N = 9$.

These findings indicate there was no difference in the rate of flurbiprofen absorption with the 1-min mouthwash or the 5-min mouthwash or the oral administration of the flurbiprofen solution.

No significant differences were detected among treatments in the values obtained for the apparent elimination rate (k_{el}). These results support that there were no differences in the disposition characteristics for flurbiprofen among the treatments.

DISCUSSION

In this study, administration of 20 ml of a 2.5 mg/ml flurbiprofen solution (pH 8.03) as a mouthwash for 1 or 5 min resulted in bioavailabilities of 5.2 and 9.4% relative to orally administered drug. These values should be considered more reliable than those determined by calculating the amount of drug remaining in the expelled solution and rinses, because of variability in procedure and assay. Therefore, when estimating the amount of drug absorbed following buccal administration, blood drug concentration data should be utilized when possible rather than the expelled drug solution and rinses.

The serum flurbiprofen data, however, were quite variable for the mouthwash treatments and the 5-min treatment was found to be less variable than the 1-min treatment. The coefficients of variation (CV) for AUC(0–∞) values for the 1- and 5-min mouthwash treatments were 50.9 and 30.8%, respectively, and the CVs for the calculated relative bioavailabilities for the 1- and 5-min mouthwash treatments were 67.3 and 24%, respectively. Significant differences between the 1- and the 5-min mouthwash treatments were detected for the calculated relative bioavailabilities but not for the AUC(0–∞) values. With the degree of variability described above, four subjects per group or a total of 12 subjects would have been necessary to detect the observed difference in AUC(0–∞) values. The CVs for F as calculated from the amount remaining in 1 and 5 min expelled solutions and rinses were 77.5 and 71.8%, respectively.

There is a possibility that the apparent increase in bioavailability of the 5-min mouthwash treatment over the 1-min mouthwash treatment may be due to a small amount of the dosing solution having been swallowed. The methods of

Table I. Bioavailability of Parameters (Mean ± SD) Following 20 ml of a 2.5 mg/ml Flurbiprofen Solution

	Mouthwash		Oral administration	Statistical significance*
	1 min	5 min		
C_{max} (μg/ml)	0.522 (0.195)	0.963 (0.221)	9.55 (2.26)	C B A
T_{max} (hr)	0.806 (0.542)	0.583 (0.125)	0.778 (0.232)	NS[a]
AUC(0–∞) (μg × hr/ml)	2.12 (1.08)	4.02 (1.24)	43.9 (11.6)	C B A
F	0.052 (0.035)	0.094 (0.023)	—	B A
k_{el} (hr^{-1})	0.283 (0.053)	0.257 (0.060)	0.208 (0.023)	A B C
k_a (hr^{-1})	5.18 (1.77)	7.67 (4.35)	4.82 (1.27)	NS

[a] Not statistically significant by analysis of variance ($P > 0.05$).
* Treatments under a common bar are not significantly different at $\alpha = 0.05$ by Waller–Duncan K-ratio t test.

this experiment do not allow the direct evaluation of this possibility. The subjects were instructed not to swallow any of the dosing solution and to inform the study monitor if any solution was swallowed. None of the subjects reported swallowing any of the solution. If, however, small amounts of the drug solution were swallowed by some of the subjects, it would be expected that greater variability in bioavailability would be observed for a longer buccal retention time than for a shorter retention time. The CV for F from the 1-min mouthwash was 67.3%, but the CV for F from the 5-min mouthwash was only 24%. The measurements of CV for F for the two mouthwash treatments suggest that the influence, if any, of swallowed drug solution on the estimates of bioavailability in this study was consistent for both treatments or less with the longer retention time.

Results of Barsuhn *et al.* (9) suggest that relatively insignificant drug absorption would occur at pH's 7.0 and above. The results of this study, however, suggest that even at pH 8.03, reasonable drug absorption occurred.

In summary, flurbiprofen was absorbed from the oral cavity when administered as a mouthwash under the described conditions. The findings of this study suggest that the amount of drug absorbed was dependent upon the time of exposure of the solution to the absorbing membrane. No differences in the rate of flurbiprofen absorption were detected among the methods of administration.

This study assessed flurbiprofen absorption from 20 ml of a 2.5 mg/ml aqueous solution. In the development of a dosage form for local administration for the treatment of periodontitis, several other conditions would have to be evaluated. The volume and concentration of an aqueous or nonaqueous solution, the rate of release from a solid dosage form, and vehicle effects such as viscosity and pH would all have to be considered before selection of a final dosage form.

Table II. Comparison of Fraction Absorbed (F) Determined by Blood-Level Data (AUC) and Expelled Solution Data (Rinse)

	1-min mouthwash		5-min mouthwash	
Subject	F (rinse)	F (AUC)	F (rinse)	F (AUC)
1	0.113	0.130	—[a]	0.103
2	0.0655	0.016	0.0410	0.049
3	0.0086	0.071	0.165	0.091
4	—[a]	0.036	0.263	0.099
5	0.205	0.031	0.256	0.107
6	0.017	0.039	—[a]	0.090
7	0.105	0.030	0.0254	0.101
8	0.0655	0.045	0.131	0.074
9	0.210	0.072	0.0693	0.132
Mean	0.0987	0.052	0.136	0.094
SD	0.0765	0.035	0.0976	0.023

[a] Amount of drug in rinse was calculated to be greater than what was administered.

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