Bioavailability of Flurbiprofen Following Buccal Administration

Dennis J. Stalker1,2 and Steven R. Pollock1

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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 pKa 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 solu-
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 x 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 ($T_{\text{max}}$) 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; $N = 9$.](image1)

![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; $N = 9$.](image2)

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 ($k_e$). 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 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