Human Transbuccal Absorption of Diclofenac Sodium from a Prototype Hydrogel Delivery Device

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The buccal delivery of the nonsteroidal antiinflammatory drug, diclofenac sodium (Voltaren), from a prototype hydrogel was studied in man in a randomized crossover design of buccal delivery and i.v. infusion. After a 30-min delay, plasma levels of diclofenac increased to near steady-state levels of 100 ng/ml by 3 hr. With each subject serving as his own control, the i.v. infusion data facilitated the calculation of a mean steady-state flux of diclofenac sodium of 2.1 ± 0.6 mg/cm^2-hr across human buccal mucosa and a time lag of 1.0 ± 0.5 hr. The large flux of this ionized species indicates that the traditional lipoidal model of buccal permeation based on the partition coefficient is inadequate.

KEY WORDS: buccal delivery; diclofenac sodium; human clinical; hydrogel device.

INTRODUCTION

Buccal delivery of pharmaceuticals has potential advantages over conventional formulations. Drug administered through the buccal mucosa directly enters the systemic circulation, thereby minimizing first-pass liver and gastrointestinal (GI) metabolism. If complications arise, the input of medication can be conveniently terminated by removal of the device. Additionally, the buccal mucosa is more permeable than skin to a number of compounds.

Ebert *et al.* (1) have shown that the nonsteroidal antiinflammatory drug (NSAID) diclofenac sodium (Voltaren) can be delivered through the buccal mucosa of anesthetized dogs. Steady-state plasma levels were obtained within 1 hr of application of a saturated solution or a buccal hydrogel system loaded with Voltaren to a 1-cm^2 section of the buccal mucosa. While the *in vivo* flux was identical from both saturated solutions and the hydrogel system, the hydrogel yielded more reproducible plasma levels of diclofenac.

A limited clinical trial with Voltaren was undertaken to study buccal delivery in man. In the present study, a prototype hydrogel device was loaded with diclofenac sodium and the release profile determined by dissolution testing. The clinical protocol was a randomized crossover study of buccal delivery and i.v. infusion for 4 hr, with a 1-week washout period between administration routes. Using each subject as his own control, the steady-state flux and time lag of diclofenac absorbed across the buccal mucosa were calculated. The residual amount of drug within the buccal mucosa following removal of the device was also estimated.

MATERIALS AND METHODS

The 1-cm^2 hydrogel disks were formulated with an 80 wt% hydroxyethyl methacrylate (HEMA)–20 wt% hydrophobic difunctional macromolecular cross-linker (2). The water-washed, ethanol extracted hydrogel was dried under vacuum at 75°C for 48 hr. The concentrations of residual HEMA, monoethylhydroquinone, and t-butyl octoate were found to be less than 25 ppm as determined by gas chromatography following methylene chloride extraction. The dried disks were loaded from a 50 wt% solution of diclofenac sodium in 85.5% (v/v) methanol:water at 45°C for 48 hr. Solvent was removed in a vacuum oven at 37°C for 16 hr. Prior to use, the loaded disks were rehydrated in a 97% humidity chamber at 45°C for 48 hr. The dissolution was conducted at 32°C in 500 ml of distilled water using a standard USP apparatus with a stainless-steel basket and a rotation speed of 75 rpm. The concentration of diclofenac in the bath was monitored at 280 nm by a flow-through spectrophotometer.

The trial population was composed of healthy male volunteers (n = 6). Each received diclofenac sodium by an i.v. infusion and a buccal device utilizing a randomized crossover design with a 1-week drug washout between treatments. The i.v. infusion was for 4 hr at 3 mg/hr. For buccal administration, the rehydrated buccal device (Voltaren-loaded hydrogel) was placed on an oblong piece of nonpermeable Surlyn which was rimmed with dental adhesive (Super Polygrip, Dentco, Inc., Jersey City, NJ). This device was affixed to the center of the patient's cheek, hydrogel to buccal mucosa, and left in place for 4 hr. The device was held in place by the peripheral dental adhesive on the impermeable Surlyn backing, which ensured unidirectional drug flux of known contact area. Blood was withdrawn at varying intervals (see the results section) into heparinized tubes, and the plasma separated and stored frozen until assayed. The plasma samples, solutions both pre and post infusion, and residual extractable diclofenac from the used devices were quantified by HPLC (3).

The area under the plasma curve (AUC) was calculated by the trapezoidal rule through the last time point. Using the i.v. infusion data the clearance could be calculated for each subject from the AUC. The individual steady-state flux (J_s) of diclofenac through the buccal mucosa was calculated from the AUC and by Loo–Riegelman analysis (4) (Appendixes A and B).

RESULTS

The conditions described above allowed for reproducible high loading of Voltaren into the hydrogel. For a 1-cm^2 device, a total loading of 27 mg of Voltaren was achieved with a drug-to-dry hydrogel weight ratio of 0.7. As would be expected for a dispersed monolith, the dissolution of the rehydrated disk was linear with respect to the square root of time over 4 hr (Fig. 1). The one-sided release rate under

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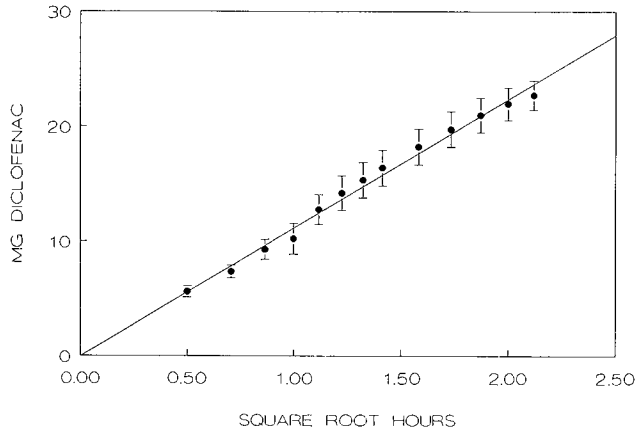

Fig. 1. The accumulation of diclofenac ± SD (n = 4) in the dissolution bath as a function of the square root of time. The dissolution was at 75 rpm into 32°C distilled water using a single 1-cm^2 hydrogel disk per stainless-steel basket. The two-sided dissolution yielded a diffusion coefficient of 3×10^{-7} cm^2/sec.

these conditions was 4 mg/cm^2-hr$^{1/2}$. Using Higuchi's equation (5) the calculated diffusion coefficient was 3×10^{-7} cm^2/sec. Note that the pH of a saturated solution of diclofenac is 7.86. Since the pK_a is 4 (6,7), the diclofenac was present almost exclusively in the ionized form.

The plasma diclofenac levels (mean and standard error) for both the i.v. infusion (n = 6) and the buccal delivery (n = 5) of diclofenac sodium are shown in Fig. 2. The plasma levels obtained from subject 5 with buccal delivery were flat and below the analytical standard curve. Statistically the values were greater than 2 standard deviations from the mean data. The loss of good contact of the loaded hydrogel with the buccal mucosa would explain the results for subject 5. Therefore, the results for this subject were excluded from the mean calculations.

For the i.v. infusion at 3 mg/hr, the plasma levels of diclofenac increased rapidly and reached a mean steady-state plasma level of 125 ng/ml in 1.5 to 3 hr. This was to be expected given the short initial half-life of diclofenac (6,7). In contrast, measurable plasma levels of drug following buccal

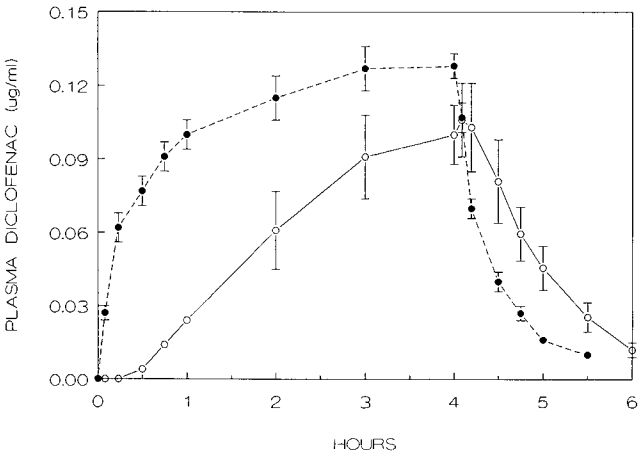

Fig. 2. The mean and SE plasma diclofenac concentrations created by a 4-hr infusion of 3 mg diclofenac sodium per hr (-----; n = 6) or a diclofenac sodium-loaded buccal hydrogel device (——; n = 5).

administration were not obtained until 0.5 hr after application. The increase in plasma diclofenac from the buccal device approached a mean steady-state level of 100 ng/ml at 4 hr. The calculated mean area under the plasma curve for the i.v. infusion is 500 ± 28 ng/ml-hr, while buccal delivery yielded a mean value of 340 ± 47 ng/ml-hr. The i.v. clearance was 400 ± 20 ml/min; while in good agreement with the literature value of 350 ml/min (6), it differs with another literature value of 263 ± 56 ml/min (7). While the plasma levels of diclofenac rapidly decreased after termination of administration by both routes, the two curves were not identical. The delay in buccal clearance probably reflected a depot within the buccal mucosa. The amount of diclofenac within the buccal tissue has been calculated to be 1.5 ± 0.7 mg/cm^2 and ranged from 0.83 to 2.49 mg/cm^2 (Table I).

Two mathematical methods were used to calculate the steady-state flux across buccal mucosa from the plasma levels. In all cases, each subjects' i.v. data were compared to the buccal permeation data. The AUC method (Appendix A) (11,12) does not require the actual achievement of steady-state transport to calculate a steady-state flux. By this method, the range of steady-state fluxes was 1.4 to 2.8 mg/cm^2-hr, with a mean and standard deviation of 2.1 ± 0.6 mg/cm^2-hr. At this rate, a 1.5-cm^2 buccal device would be sufficient to deliver the equivalent of a 150 mg/day oral tablet since the human oral bioavailability is approximately 50% (6,7). A Loo–Riegelman analysis of the buccal plasma data (Appendix B) was employed utilizing the individual i.v. pharmacokinetic parameters to calculate the amount of diclofenac absorbed as a function of time. The steady-state flux was calculated from the slope of the linear portion of the accumulation curve. This method yielded a range of values for the steady-state flux of 1.7 to 3.0 mg/cm^2-hr, with a mean and standard deviation of 2.3 ± 0.5 mg/cm^2-hr. The agreement between the steady-state fluxes calculated by the two methods was quite good and was quite close to the 3 mg/cm^2-hr flux for the buccal permeation of diclofenac sodium in dogs (1).

In addition to the steady-state plasma levels, the time lag to reach steady-state plasma levels provides additional information. The t_L is a measure of the time required to reach the steady-state flux (i.e., $2t_L$ = 90% steady-state flux). A diffusional time lag (t_L) of 1.0 ± 0.5 hr was determined. While some time lag was to be expected for permeation across a membrane, this time lag was long compared to that observed in dogs (1). Moreover, rapid delivery is a feature of sublingual delivery. Although the degree of adhesion of this device to the buccal mucosa has been questioned, a far less reproducible set of results would have been expected if this was a major problem. The reason for the observed time lag has yet to be determined. Furthermore, for ideal membranes, the time constant for depletion of a tissue depot is related to the diffusional time lag by an approximate proportionality constant of 0.6 (8). The accumulation and clearance of a buccal depot agreed well with the observation of this time lag.

The sizable steady-state flux of diclofenac across buccal mucosa was some 1000-fold higher than that observed across human skin *in vitro* (9). For an ionized species, which diclofenac was at pH 7.86, this substantial flux is hard to reconcile with the accepted partition coefficient model (10).

Table I. The Calculated Individual and Mean Absorption Values of Diclofenac from the Buccal Delivery Device

Subject no.	Amount released from the device (mg)[a]	Amount absorbed (mg)[b]	Amount in membrane (mg/cm²)[c]	J_s (mg/cm²/hr)[d]	J_s (mg/cm²/hr)[e]	t_L (hr)[e]
1	9.8	9.59	2.49	2.4	2.5	1.3
2	8.6	5.53	0.83	1.4	1.7	1.2
3	9.9	6.49	1.61	1.6	1.8	1.3
4	12.3	8.49	1.78	2.2	2.5	1.4
5	4.4	1.78	0.40	0.5	0.39	0.04
6	13.9	10.85	0.85	2.8	3.0	0.67
Mean ± SD without No. 5	10.9 ± 2.1	8.18 ± 2.2	1.5 ± 0.7	2.1 ± 0.6	2.3 ± 0.5	1.2 ± 0.3

[a] Initial load (26.8 mg) − amount extracted after removal of the device.
[b] Calculated from 12 mg × ($AUC_{buccal}/AUC_{i.v.}$).
[c] From Loo–Riegelman analysis, amount absorbed at 6–7 hr versus 4 hr.
[d] Calculated by the method of Keister (Appendix A).
[e] From Loo–Riegelman analysis, least squares fit of amount absorbed.

More likely, most studies of buccal permeation were performed at constant concentration and emphasized the solubility in water, rather than the solubility in the buccal tissue. An aqueous permeation pathway is consistent with the present data, and this could have important implications for small potent peptide drugs. The variability of buccal absorption was reflected by a coefficient of variation of the AUC of 30.9%, versus 13.6% for i.v. infusion. This presumably reflected variation in membrane permeation and would be smaller for a membrane-controlled buccal system.

Among the minor adverse reactions, one of the subjects complained of soreness and another showed signs of inflammation of the mucosa at the site of application following the removal of the buccal device. This type of reaction may have been related to the local delivery of a high concentration of NSAID. There was, however, no need for treatment and the symptoms dissipated by the second day.

CONCLUSION

The data from this human clinical trial demonstrate that diclofenac was readily transported across the human buccal mucosa, with a steady-state flux calculated to be 2.1 ± 0.6 mg/cm²-hr. This steady-state flux of diclofenac across the buccal mucosa in man from the hydrogel device agreed remarkably well with the 3 mg/cm²-hr value obtained for buccal delivery in the dog (1). The time to measurable blood diclofenac levels and the time lag in humans were, however, longer than experienced in dogs. This time lag is negligible for sublingual dosage forms and may reflect depletion of drug. However, the time lag for buccal delivery requires further investigation. Finally, transport of diclofenac, an ionized species, was rapid through buccal mucosa and was consistent with an aqueous pathway for transport.

APPENDIX A: METHOD OF AREA UNDER THE CURVE (AUC)

Keister (11) and, more generally, Siegel and Schoenwald (12) have shown that for ocular delivery, J_s, the steady-state flux may be obtained by

$$J_s = \frac{(\text{AUC})\ (\text{Clearance})}{At_a} \tag{1}$$

where A is the area to which the drug is applied and t_a is the application time. This equation results from solution of the diffusion equation with the boundary conditions

$$\begin{aligned} C &= 0, && \text{at } x = s \\ C(t) &= C_o(t), && \text{at } x = 0 \text{ and } t \leq t_a \\ C &= 0 && \text{at } x = 0 \text{ and } t > t_a \end{aligned} \tag{2}$$

where o and s are the mucosal and serosal side of the tissue, respectively. To apply Eq. (1) to the case of buccal delivery, one assumed that the donor concentration was constant, C_o, throughout the application period, the mucosal side was well-washed with saliva following removal of the disk, and there was negligible drug absorbed by swallowing.

APPENDIX B: LOO–RIEGELMAN METHOD

The i.v. infusion data for each subject were fit to a two-compartment pharamcokinetic model. Loo–Riegelman (4) analysis with the parameters determined for each subject was used to calculate for that subject, Q, the amount of diclofenac absorbed versus time for the i.v. infusion and the buccal device application. As a check on the method, the calculated amount absorbed (i.v.) for each subject was within 10% of the theoretical amount absorbed at 1 hr and 3% at 4 hr. The residual amount of diclofenac in the buccal tissue, Q_m, after removal of the device was calculated as

$$Q_m = Q_{24} - Q_4 \tag{3}$$

where the time in hours is indicated by the subscript. The calculated buccal cumulative absorption data for $t < t_a$ were then treated analogously to a membrane diffusion problem from a well-stirred infinite reservoir and a receiver with sink conditions. The only two adjustable parameters were the steady-state flux, J_s, and the diffusional time lag t_L.

The two-compartment model solution for the i.v. infusion data for $t \leq t_a$ was

$$C = k_1\left[\frac{A}{\alpha} + \frac{B}{\beta} - \frac{A}{\alpha}e^{-\alpha t} + \frac{B}{\beta}e^{-\beta t}\right] \quad (4)$$

and that for $t > t_a$ was

$$C_m = k_1\left[\frac{A}{\alpha}(e^{-\alpha(t-t_a)}) + \frac{B}{\beta}(e^{-\beta(t-t_a)} - e^{-\beta t})\right] \quad (5)$$

where k_1 is the input rate, assumed to be 3 mg/hr, and A, B, α, and β are the adjustable parameters that may be derived from the solution for an i.v. bolus (4).

The amount absorbed, Q, as calculated by Loo–Riegelman analysis was linear with time beginning at 2 hr, i.e., approximately twice the time lag. A linear least-squares fit was executed for the amount absorbed per area versus time (2 to 4 hr) for each subject. In this regime, the slope is the steady-state flux, J_s, and the time axis intercept is the diffusional time lag, t_L, that is,

$$\frac{Q}{A} = J_s(t - t_L) \quad (6)$$

These values were compared to a non-steady-state diffusion model for an ideal membrane and found to agree within 10%.

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