Assessment of Bioavailability of Diclofenac from Two Topical Drug Products using Pharmacokinetic and Skin (Tape) Stripping Analyses

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PURPOSE

Local bioavailability of the active pharmaceutical ingredient (API) may be important for therapeutic efficacy of topical drug products that act locally in the skin and/or in surrounding local tissues. For such products, systemic bioavailability measured using serum levels may not be the best indicator of availability of API at or near the site of action. Therefore, techniques that can be used for measurement of local bioavailability, may be better (more accurate) for evaluating bioequivalence of locally acting topical products.

OBJECTIVES

The goal of the current study was to obtain a mechanistic understanding of the local and systemic bioavailability of the API following application of a locally acting product and evaluate the correlation between the two bioavailability values for multiple drug products with different formulation characteristics. The bioavailability of diclofenac from two locally acting topical dermatological products (A: diclofenac epolamine topical patch, 1.3% and B: diclofenac sodium topical solution, 2%) were assessed, both in serum and stratum corneum (SC) samples obtained from healthy volunteers.

METHODS

PK Study Design

Serum concentrations were determined after application of four patches (140 cm^2/patch, 2 patches per arm) or 4 g per 400 cm^2 of topical solution (2 g per arm) to the upper arms. The solution was cleaned and the patches were removed from the skin at 6 h and 10 h post application, respectively. Blood samples were drawn at pre-specified time points starting prior to product application and proceeding through 41 h after the product was removed. Serum samples were analyzed using a validated liquid chromatography mass spectroscopy (LC-MS/MS) method and pharmacokinetic (PK) analysis was conducted using Phoenix WinNonlin® to calculate the area under the concentration (AUC) vs. time curve and maximum concentration (C_{max}) from each product.

Tape Stripping Study Design

In a following session with each volunteer, six patch pieces (8.25 cm^2) and six aliquots of topical solution (10 mg/cm^2 over 8.25 cm^2) were randomized to 12 sites on the volar forearms. Locations of the applied products were randomized to one of six sites corresponding to three different time points. A blank site was also tape stripped as a control. As in the PK study, the solution was cleaned and the patch pieces removed at 6 h and 10 h post application, respectively. A 5 cm^2 section of each site was tape stripped to determine the amount of drug in the SC either immediately following product removal (designated "uptake") or after 17 h and 41 h of "clearance" following drug removal. Tape stripping of each site continued for a minimum of 12 tape strips up to a maximum of either 30 tape strips or when the site reached 6 times the baseline transepidermal water loss (TEWL) value, determined using a Delfin VapoMeter. Successive tape strips were grouped together based on combined SC weight of at least 750 µg or 6 tapes, whichever came first. Diclofenac was extracted from skin tape strips using methanol, which was analyzed using a validated HPLC method.

METHODS

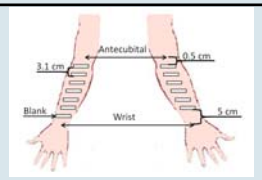

Figure 1. Diagram of diclofenac product locations for tape stripping sites on the volar forearm.

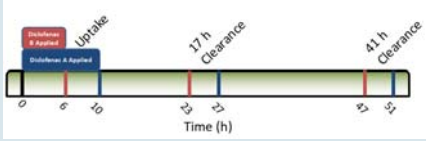

Figure 2. Tape stripping clinical study design. Tape stripping occurs at 10, 27 and 51 h post Diclofenac A (patch) application and at 6, 23 and 47 h post Diclofenac B (solution) application.

RESULTS

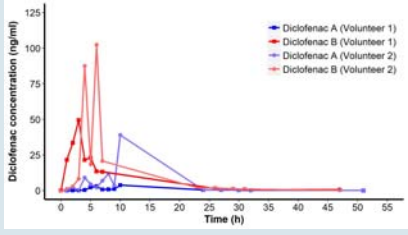

Figure 3. Diclofenac serum concentration versus time from two volunteers following administration of two diclofenac products (Diclofenac A or B).

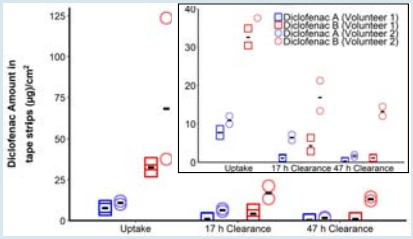

Figure 4. Amount of diclofenac (mean represented by line) in tape strips per diclofenac product (Diclofenac A; blue, Diclofenac B; red) and per volunteer (Volunteer 1: square, Volunteer 2: circle) three times following product removal: immediately, 17 h and 47 h.

Table 1. Non-compartmental analysis and tape stripping results for the first two volunteers

Subject	1		2	
Product	A	B	A	B
Non-compartmental analysis				
AUC (ng*h/mL)	46.0	326.7	342.2	436.2
C_{max} (ng/mL)	3.8	49.4	39.1	102.4
Stratum Corneum Diclofenac Amount (2 replicates)				
Uptake (µg/cm²)	87.6 9	305. 34.9	120. 9.9	123.6, 37.6
17 h Clearance (µg/cm²)	12, 1.0	64, 2.9	72, 5.7	213, 13.4
41 h Clearance (µg/cm²)	0.4, 0.3	12, 1.1	20, 1.4	145, 12.1
Percent Cleared from SC following product removal				
17 h Clearance (%)	85.9	85.8	41.2	78.5
41 h Clearance (%)	95.6	96.5	84.7	83.5

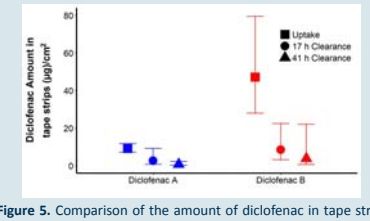

Figure 5. Comparison of the amount of diclofenac in tape strips (mean ± SD of the log-transformed geometric mean in each volunteer; n = 4) of two different volunteers at three times following product removal: immediately, 17 h and 41 h.

CONCLUSIONS

Based on the limited data available from the study of two healthy volunteers, it appears that there is more drug present in the SC with the application of the topical solution compared to the patch (Figure 4 and 5). The clearance rate of diclofenac, calculated as percent diclofenac present at each clearance time point compared to uptake, from the skin is similar between the two products. There was one uptake time point where the amount of diclofenac present in the tape strips was much larger then the other data points (Figure 4). This may have been caused by inefficient cleaning at the time of product removal. The observations illustrated here could change as additional data from future volunteers are incorporated into the findings. Both, the rate of clearance of drug from the skin, and the amount of drug in the skin may be important when characterizing the rate and extent bioavailability of a drug for which the site of action is in the skin.

FUNDING

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