Increased Bioavailability of Miconazole In Human Skin with a Novel Polymer Vehicle

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OBJECTIVE

The purpose of this study was to evaluate a novel polymer-based topical vehicle to deliver miconazole to human skin. The current study compared the dermato-pharmacokinetic uptake/excretion profiles of miconazole nitrate in a cream vehicle and miconazole base in the novel polymer delivery vehicle. To account for the differences in weight between the base and nitrate forms of miconazole, the drug concentrations were 1.738% miconazole base in the polymer vehicle and 2% miconazole nitrate in the cream.

Miconazole uptake into, and elimination from, the skin was quantified by harvesting the rate-limiting barrier, stratum corneum, with adhesive discs (after skin stripping), then extracting the adhesive discs and quantifying drug content by High Performance Liquid Chromatography (HPLC).

RESULTS

Six subjects, aged 38 ± 4 yrs, completed the trial. All of the available data were used in the pharmacokinetic analyses. As shown in Table 1, the novel polymer vehicle produced 3.6-fold greater mean Cmax and AUC0-t of miconazole base than the cream (6.53 vs. 1.82 µg/hr/sq cm, respectively, p<0.10), a 2.3-fold longer T1/2 (22.5 vs. 9.5 hr, respectively, p<0.10) with a similar Tmax (1.4 vs. 0.75 hr, respectively).

RESULTS

Miconazole nitrate and base were quantified in stratum corneum samples harvested from treated skin sites using a validated HPLC assay (sensitivity limit 1 ng) following a single ~5 mg dose of each product (4.8 µl cream & 5.6 µl novel polymer vehicle) applied to each subject in the same study period. Ten sites (1.33 sq cm diameter) on each arm were randomly treated with both products for 0, 0.17, 0.75, 2.0, 4.0, 12 or 24 hours. Two skin sites above the forearm were used as untreated controls. Residual product was removed with 2 adhesive discs. Stratum corneum was harvested from skin sites with a forceps and 12 additional adhesive discs (CuDerm Corp) at the end of application and 4, 8, 12, 24 hours after application (elimination). Discs 1 and 2 of the 12 were discarded as possible drug contaminated and the remaining 10 discs combined for extraction and quantification by HPLC analysis.

ANALYSIS

Peak concentration (Cmax) was the observed maximum value during the absorption period 0.0 to 24.0 hr. The time to peak concentration (Tmax) was the collection time at which Cmax was observed during the absorption period, 0.0 to 24.0 hrs. Area-under-the-drug content-time curve to the last measured concentration (AUC0-t) was calculated by the linear trapezoidal method. Cmax, Tmax, and T1/2 were statistically evaluated for each product using pairwise-t test on means using Statview (Abacus Concepts, Calabassas, CA, version 4.1).

CONCLUSIONS

Statram corneum drug content is presented as µg miconazole / sq cm adhesive disc normalized for control and dose. As shown in Table 2, the novel polymer vehicle (B) delivered more drug into human volar forearm stratum corneum in vivo than the cream (A) at 6 of the 10 time points investigated. Two to three-fold greater miconazole concentrations were produced with the polymer vehicle over the initial 0-12 hour uptake time interval than the semi-solid cream vehicle. Three to ten fold greater drug concentrations were achieved with the polymer vehicle (B) than the cream product (A) over the 24-48 hour time interval.