Open Flow Microperfusion as a Dermal Pharmacokinetic Approach to Evaluate Topical Bioequivalence

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Purpose

There is practical utility for exploring methods that may be able to reliably evaluate the bioequivalence (BE) or non-bioequivalence of topical dermatological products based upon a comparative dermal pharmacokinetic measure of bioavailability. Open-flow microperfusion (OFM) is a technique that provides direct access to target tissues in human volunteers for the continuous in vivo measurement of drug concentrations in the interstitial fluid. The utility of OFM has been demonstrated by pharmacokinetic-pharmacodynamic studies with a wide range of substances, ranging from small lipophilic drugs to large proteins and antibodies, and these could be monitored in the dermis of both, healthy volunteers and patients. The overall aim of this study was to explore the utility of dermal OFM to assess comparative dermal bioavailability in a clinical setting, evaluating commercially available topical acyclovir products in a head-to-head comparison based upon a bioequivalence study concept. Specific aims of the study were (i) to identify factors that influence the dermal pharmacokinetic profiles observed in vivo, particularly when these factors contributed to variability in the data and might be better controlled, and (ii) to compare the in vivo OFM bioavailability data (which might correspond with determinations of bioequivalence) among the same products that are also tested by a validated in vitro release test (IVRT), and thereby to evaluate whether in-vitro/in-vivo correlations existed.

Methods

A single-center, multi-phase clinical study was comprised of an initial phase for OFM method optimization (6 volunteers), a subsequent phase for the identification of suitable reference (R) and test (T) products (6 volunteers), and a BE-type study (4 volunteers) intended to support sample size estimation for the final BE-type study (20 volunteers). Six topical test sites (each 5.5cm2) were marked on the skin; 3 adjacent test sites on the leg and 3 adjacent test sites on the volar aspect of the arm or on the contralateral leg. Two dOFM probes (linear type, 0.5mm OD, CE-certified, Joanneum Research GmbH, Austria) were inserted into the skin at each test site and the probes were continuously perfused with sterile perfusate at 1µL/min for interstitial fluid sampling.. Five acyclovir cream 5% products (Zovirax® [U.S.], Zovirax® [U.K.], Zovirax® [Austria], and 2 Austrian generics, Aciclostad® and Aciclovir 1A®) were applied to the test sites and dermal OFM samples collected in 1h or 2h intervals for 12h to 36h post-dosing. Acyclovir in dOFM samples was quantified by an UHPLC-UV method. AUC0-36h, Cmax and Tmax were calculated from the dOFM profiles and subjected to statistical analysis.

Results

During the initial study phase methodologies were successfully established to support prolonged dermal sampling from multiple probes and the 12h post-dose sampling duration was extended to 36h to address a very slow dermal penetration of acyclovir. Potential carry-over effects by lateral diffusion between adjacent test sites and systemic carry-over were found to be insignificant, confirming that each triplet of probe insertion sites could be considered statistically independent and that the inclusion of 20 subjects into the main study could potentially correspond to an N of 40 independent results. The product identification study phase with 6 volunteers showed that the acyclovir bioavailability from the two Austrian generic acyclovir cream 5% products was greatly inferior to the acyclovir cream 5% (Zovirax® [U.S.]), whereas there were no clearly distinguishable differences in the bioavailability among the three Zovirax® creams in the small population of subjects. As expected, considerable variation was found between intradermal acyclovir profiles between subjects, and also between the profiles from different probes (which might have been caused by anatomical and methodological variation). Transient fluctuations were also observed affecting all twelve profiles which may reflect day-night differences.

Conclusions

This study illustrates a novel methodology for directly measuring the dermal pharmacokinetics of topically applied drugs, and elucidates procedural variables that must be controlled in order to avoid potential pitfalls and sources of variation, in order to facilitate a discriminating comparison of dermal bioavailability. This work provides insights into how challenges associated with measuring the local bioavailability of topical drug products may be overcome to support the development of in vivo dermal pharmacokinetic-based topical BE studies.

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