Open Flow Microperfusion as 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. Dermal OFM provides continuous in vivo measurement of interstitial drug concentrations up to 48 hours and with no restriction in terms of sophistication and size of the drug being investigated (Fig. 1). The utility of OFM has been demonstrated by pharmaco-kinetic-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 BE 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 contribute to variability in the data and might be better controlled, and (ii) to compare the in vivo OFM bioavailability data which might correspond to the dermis. It is unclear whether such results would even better discriminate the dermal pharmacokinetics of acyclovir from the two sites dosed with the same product.

Methods

- 20 healthy volunteers investigated, providing written informed consent.
- 7 females, 13 males, caucasian, age 28.1 ± 5.1, BMI 23.7 ± 2.4.
- Right leg: 3 test sites, each with an area of 5.5 cm² for dosing T-R1-R2 (Test-Reference-Reference).
- Double testing of test vs. reference product, as well as a double testing of the method/setting itself based upon the expectation that the reference product falls within the traditional BE limits of log(0.8) = -0.223 and log(2) = 0.301.
- No serious adverse events occurred. No dropouts occurred.

Results & Discussion

Be data evaluation: 20 subjects delivered 240 acyclovir profiles for statistical evaluation (each 36h, in total 6480h of intradermal data, Fig. 3). No serious adverse events occurred. No dropouts occurred.

Conclusions

Dermal OFM results showed relatively low variability and high robustness; factors contributing to variability in dermal PK were well-controlled. Dermal OFM is capable of directly measuring dermis bioavailability from a topical product based on pharmacokinetic principles. Further clinical studies with different topical drugs to investigate dermal OFM as a pharmacokinetic method of value.

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