In Vivo Dermal Open Flow Microperfusion: Understanding and Controlling Sources of Variability to Evaluate Topical Bioequivalence

M. Bodenlenz1, T. Birngruber1, K. Tither1, R. Ram1, B. Tschapeller1, T. Augustin1, G. Schwagerl1, S. Krosatko1, L. Kanler2, S.G. Raney3, F. Sinner1,4

Purpose

Open-flow microperfusion (OFM) is a technique that facilitates the direct (in situ) assessment of tissue drug concentrations in human volunteers, enabling the continuous in vivo measurement of drug concentrations in the interstitial fluid. In this study, we evaluated whether dermal OFM (dOFM) could be a suitable in vivo method with which to characterize and compare the intradermal pharmacokinetics (PK) and bioequivalence (BE) of acyclovir from topical acyclovir cream, 5% products based upon an assessment of dermal PK endpoints like maximum concentration (Cmax) and area under the concentration-time curve (AUC). Moreover, to evaluate how accurate, sensitive, and reproducible dOFM could be as a potential approach to evaluate topical BE, we characterized sources of variability in the clinical in vivo BE study, with a focus on understanding controlled and uncontrollable sources of variability that could impact the precision and power of such BE assessments.

Methods

- 20 healthy volunteers, written informed consent
- Each OFM probe inserted into the dermis was perfused with saline
- Each OFM probe measured skin temperature (ultrasound)

Results & Discussion

Twelve probes in each of 20 subjects provided 240 acyclovir dermal PK profiles (each 36 h, in total 8640 h of intradermal data, Fig. 3). No serious adverse events and no dropouts occurred.

The positive controls (R vs. T) were accurately and reproducibly confirmed to be bioequivalent, while the negative control products (T vs. R) were sensitively discriminated not to be bioequivalent (Table 1).

Table 1: BE results

Results & Discussion

- Inter-subject variability of logAUC for R and T was low at 16% and 9%, respectively, of the total variability (Fig. 4). This type of variability is most likely due to the differences in the subjects’ stratum corneum (SC) (i.e., in vivo skin impedance method was sensitive enough to reflect SC properties and correlated with logAUC (r = 0.69 – 0.75, p < 0.0001), while the established TIV method showed a lower correlation (r = 0.29 – 0.37, not significant). Similar results were observed for LogTmax.

- Intra-subject variability of logAUC for R and T was low at 16% and 9%, respectively. The site-to-site variability for R and T (9% and 4%, respectively) could have been caused by local differences in SC properties and/or local differences in skin temperature (p = 0.25, p < 0.05). The remaining variability for R and T (7% and 5%, respectively) is attributed to probe-to-probe variability which could have been caused by the user (e.g., variability in probe insertion depth) and/or variability in the sampling process (e.g., relative recovery). Similar results were observed for LogCmax. A comprehensive statistical analysis of influencing factors is currently ongoing.

Conclusions

- Dermal OFM results showed relatively low variability and high robustness.
- Inter-subject variability accounted for more than 84% of total variability in this clinical study setting and is most likely caused by different properties of the stratum corneum in different subjects. Skin impedance was found to correlate with topical bioavailability.
- Inter-subject variability accounted for less than 16% of total variability. This indicates reasonably good control and reproducibility of the OFM test setting.
- Further clinical studies with different topical drugs to investigate dermal OFM as a pharmacokinetic method may be of value.

Acknowledgement

Funding for this project was made possible, in part, by the Food and Drug Administration through grants 1U1HD050496 and 1U1HD055661. The views expressed in this poster do not reflect the official policies of the Food and Drug Administration, or any department or agency of the United States Government.

Study was approved by FDA/FRHE.

CONTACT

1. JOANNEUM RESEARCH Forschungsgesellschaft mbH

Address: E2BRR-Network Meeting, 27 September 2017, Salzburg, Austria