2015 AAPS Annual Meeting and Exposition, Oct 25 – 29, Orlando, USA

Open Flow Microperfusion as Dermal Pharmacokinetic Approach to Evaluate Topical Bioequivalence

M. Bodenlenz[1], K. Tiffner[1], R. Raml[1], B. Tschapeller[1], T. Augustin[1], C. Dragatin[1], T. Birngruber[1], S. Kainz[1], G. Schwagerle[2], S. Korsatko[2], S.G. Raney[3], I. Kanfer[4], ***F. Sinner[1,2]***

CONTACT

1
JOANNEUM RESEARCH
Forschungsgesellschaft mbH

HEALTH
Institute for Biomedicine and Health Sciences
Graz, Austria

2
Medical University of Graz
Department of Internal Medicine
Division of Endocrinology and Metabolism
Graz, Austria

3
Division of Therapeutic Performance
Office of Research and Standards
Office of Generic Drugs
U.S. FDA
Silver Spring, MD, USA

4
Faculty of Pharmacy
Rhodes University
Grahamstown, South Africa

Acknowledgement

Funding for this project was made possible, in part, by the Food and Drug Administration through grant FD004946. The views expressed in this abstract do not reflect the official policies of the Food and Drug Administration, or the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

Study was approved by FDA-RIHSC (FDA Research Involving Human Subject Committee) & local IRB of the Medical University Graz, Austria

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 intradermal drug concentrations up to 48 hours and with no restriction in terms of lipophilicity and size of the drug being investigated (Fig.1). 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 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 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 BE) between two application sites dosed with the same topical acyclovir cream 5% (R vs. self) and against a different commercially available topical acyclovir cream 5% with a different formulation (R vs. T).

Methods

- 20 healthy volunteers investigated, providing written informed consent
  - 7 females, 13 males, caucasian, age 28.1 ± 5.1, BMI 23.7 ± 2.4
- 40 test settings - 2 per volunteer - each test setting involving 3 test sites, see Fig. 2
  - Right leg: 3 test sites, each with an area of 5.5cm^2 for dosing T-R_1-R_2 (Test-Reference-Reference)
  - Left leg: 3 test sites, each with an area of 5.5cm^2 for dosing R_2-R_1-T (Reference-Reference-Test)
- 2 dOFM probes per test site inserted into the dermis and perfused for sampling at 1µL/min
  - OFM Probe 'DEA15003' (linear type, 0.5mm OD, 15mm open mesh, Fig.1)
  - OFM Pump 'MPP102' (wearable, operates 3 to 6 probes)
- **t=0:** Topical dosing of 2 commercial 5% acyclovir creams at 15mg/cm^2
  - R_1 = R_2 = Reference = Acyclovir Cream 5% (Product A)
  - T = Test = Acyclovir Cream 5% (Product B)
- **t=-1h…36h:** Continuous dOFM sampling from all 12 probes in 4h intervals
  - Study duration and interval determined for acyclovir in a pilot study
- Controlled environmental conditions: 22±1°C, 40-60% RH
- *Analysis*:
  - UHPLC-MS method for acyclovir quantification in dOFM samples
  - Secondary analyses: Glucose in dOFM samples by Super GL bedside measurement to monitor probe stability based on % loss from perfusate
- *Data Management & Statistics:*
  - eCRF within OpenClinica Enterprise Edition hosted by JOANNEUM RESEARCH
  - Thoroughly validated and 21 CFR Part 11 compliant
  - All data management activities are covered by relating SOPs
  - AUC0-36h, CMAX, for each site (i.e. for R_1, R_2, T); ratios T/R_1 and R_2/R_1
  - All tests are based on log-transformed data
  - Results are analyzed to evaluate whether the 90% confidence interval of the mean difference between products falls within the traditional BE limits of log(0.8)=-0.223 and log(1.25)=0.223.
  - 40 test settings in 20 volunteers were treated as independent; independence of sites and settings was demonstrated in a pilot study (no lateral, no systemic carry-over)

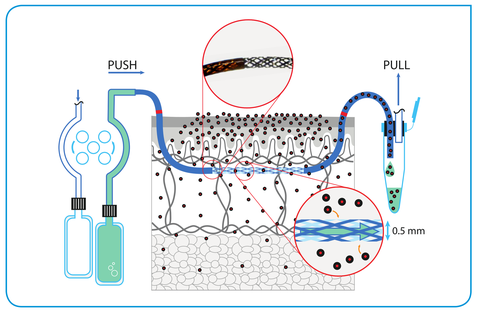

Figure 1: Open Flow Microperfusion (OFM). *dOFM, a universal linear certified probe designed for dermal and subcutaneous use in humans, continuously delivers dermal interstitial fluid for the study of PK and PD in the target tissue. Continuous sample collection is controlled by a wearable pump. All devices are CE-certified for human use and were designed and patented by JOANNEUM RESEARCH, Graz, Austria*

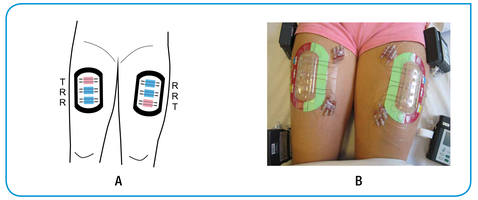

Figure 2: A) Schematic of test setting in volunteers. *Three adjacent topical test sites form one test setting. The setting is implemented twice on each volunteer. Test and reference (lateral) is always compared against the reference in the center, enabling double testing of test vs. reference product, as well as a double testing of the method/setting itself based upon the expectation that the dermal pharmacokinetics of acyclovir from the two sites dosed with the same (reference) product should be the same.*

B) Test setting in volunteers. *The wearable pumps are driving the continuous dermal sample collection for 36h. Skin is protected from stretching using adhesive stabilization rings. Non-occlusive covers prevent the treated site from any impact during day and night and bathroom visits.*

Results & Discussion

- **Data evaluation:** 20 subjects delivered 240 acyclovir profiles for statistical evaluation (each 36h, in total 8640h of intradermal data, Fig. 3).
  No serious adverse events occurred. No dropouts occurred.

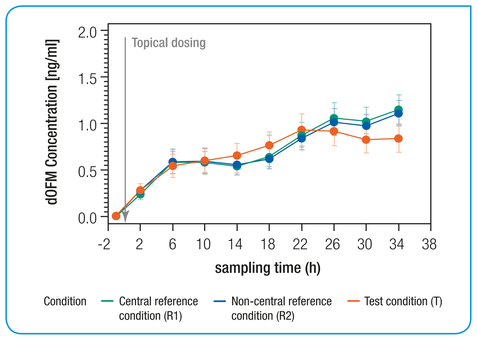

Figure 3: dOFM acyclovir concentrations as a function of time.
Mean +/- SE. Acyclovir profiles 0-36h for the test and the two reference sites. The AUC0-36h of the adjacent test sites were compared to each other statistically based upon the 90% confidence interval of the mean difference between products (T vs. R_1, R_2 vs. R_1, N=40).

- **CONFIRMED (Similar Rate and Extent of Bioavailability):** The 90% confidence interval of the mean difference between the two sites dosed with the same (reference) product were demonstrated to fall within the limits of 80% to 125% for both dermal pharmacokinetic parameters (AUC and CMAX). *(See Table 1)*
- **CONFIRMED (Different Rate and Extent of Bioavailability):** The 90% confidence interval of the mean difference between the sites dosed with different products (test vs. reference product) were demonstrated to fall outside the limits of 80% to 125% for both dermal pharmacokinetic parameters (AUC and CMAX). *(See Table 1)*

Even though the study successfully evaluated the in vivo dermal pharmacokinetics of acyclovir for 36h post-dosing, throughout which the dose remained on the skin, the CMAX for the reference product was the terminal time point. A reduction in the dose duration may have facilitated measurement of a more traditional pharmacokinetic profile with a defined peak for CMAX followed by a tail of declining concentration corresponding to the elimination of drug from the dermis. It is unclear whether such results would even better discriminate the dermal pharmacokinetics between a test and reference product.

Table 1: *Test results*

Test condition	Variable	90% confidence interval	Traditional BE-Limits	Mean Difference within 80% – 125%
R_2 versus R_1	Log(AUC0-36h)	[-0.148; 0.161]	[-0.223; 0.223] or [80–125%]	✓ Passed
R_2 versus R_1	Log(CMAX)	[-0.154; 0.189]		✓ Passed
T versus R_1	Log(AUC0-36h)	[-0.369; 0.050]		✗ Failed
T versus R_1	Log(CMAX)	[-0.498; 0.022]		✗ Failed

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 the dermal PK in vivo.**
- **Dermal OFM is capable of evaluating comparative dermal bioavailability from a topical product based on pharmacokinetic principles.**
- **Further clinical studies with different topical drugs to investigate dermal OFM as a pharmacokinetic method may be of value.**