Dermal OFM indicates differences in acyclovir skin permeation between males and females

Manfred Bodenlenz [1], Thomas Augustin [1], Felipe Teles-Barbosa [1], Thomas Birngruber [1], Katrin Tiffner [1], Reingard Raml [1], Tannaz Ramezanli [3], Sam G. Raney [3], Frank Sinner [1,2]

CONTACT

1
JOANNEUM RESEARCH
Forschungsgesellschaft mbH

HEALTH
Institute for Biomedical
Research and Technologies

Neue Stiftingtalstrasse 2
A-8010 Graz

+43 316 876-4000
health@joanneum.at
www.joanneum.at/health

2
Medical University of Graz
Austria

3
Office of
Generic Drugs Center for Drug
Evaluation and Research
U.S. FDA

Silver Spring, MD, USA

Purpose

Clinical dermal open flow microperfusion (dOFM) can provide time-resolved dermal concentration profiles that have the potential to support pharmacokinetics- based topical bioequivalence (BE) assessments. A study evaluating acyclovir products in 20 volunteers demonstrated the reproducibility of dOFM data to evaluate the BE of a reference cream product to itself and to discriminate a non-BE product and the reference cream [1]. Initial data analysis characterized the overall sources of inter- and intra-subject variability but did not focus on the factors that may affect the discrimination of products.

This analysis investigated which methodological and biological factors may affect the sensitivity of clinical dOFM studies to discriminate topical acyclovir products.

Methods

Summary of the clinical study with dOFM [1]:

- 20 healthy volunteers (7 females, 13 males)
- Two topical products investigated by dOFM for 36 hours (Fig. 1)
  - Controlled clinical conditions: 22 ± 1°C, 40 – 60% relative humidity
  - R = Reference = acyclovir cream 5% (Zovirax®, USA)
  - T = Test = acyclovir cream 5% (Aciclovir 1A Pharma-Crème, Austria)
    T and R have previously been shown to exhibit substantial differences in drug release and skin permeation in vitro (e.g., using an in vitro permeation test (IVPT)).
- Analysis of BE, variability, and subpopulations
  - Average bioequivalence (ABE) evaluation of R vs. R and T vs. R based on log AUC_{0-36h} and logC_{max} of dermal acyclovir concentrations
  - BE criteria based on the 90% confidence intervals of geometric mean ratios of logAUC and logC_{max} falling between 0.80 - 1.25
  - Analysis of the sources of variability for T and R by Analysis of Variance (ANOVA); analysis of distribution, regression, correlation and probe-to-probe differences of various methodological and biological parameters
  - Analysis of factors affecting the ratios T vs. R and R vs. R, including separate statistical analysis of N=7 females and N=13 males.

Results

- Joint data analysis of N=20 subjects
  - The data enabled the verification of topical ABE for a reference cream vs. itself and the identification of a test product as being non-bioequivalent [1].
  - Data analysis demonstrated that methodological factors (test site location, probe depths, flow-rate, relative recovery) did not significantly contribute to data variability. ANOVA attributed >82% of the variability to subjects. The remaining variability of <18% was attributed to local variability of drug permeation [2].
- Separate analysis of females and males is shown in Figure 3.
  In female subpopulation the negative control produced more discriminating results, compared to the male subpopulation.
  - 7 Females: Profiles rose slowly showing clear differences T vs. R.
    - Negative control (T vs. R) and positive control (R vs. R) were confirmed.
  - 13 Males: Profiles rose faster showing no consistent differences.
    - Negative control (T vs. R) and positive control (R vs. R) not confirmed.
  - Results of ex vivo dOFM in male and female skin confirmed the difference (data not shown). Significant differences between male and female skin penetration had already been reported from IVPT-studies in 1993 by Bialik et al. [3].

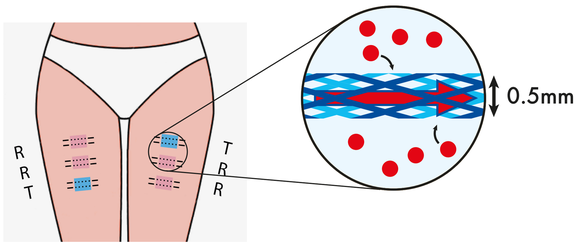

Fig. 1: *Schematic of the application sites with dOFM inserted in the dermis during the clinical study in 20 volunteers (7 females, 13 males). The study delivered 240 profiles of intradermal acyclovir for BE evaluation of a reference product vs itself (R vs R) and a test product vs reference (T vs R)*

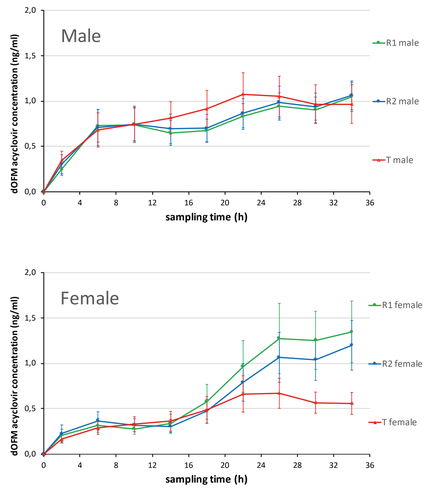

Fig. 2: *Acyclovir concentration profiles for R and T. In males concentrations rise fast and do not discriminate T from R. In females dermal concentrations rise slowly and after 20 hours clearly discriminate T from R. Concentrations are plotted as mean ±SE.*

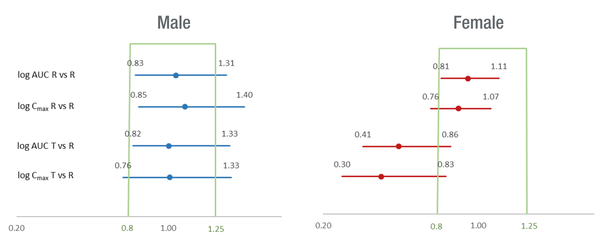

Fig. 3: *Results of BE evaluation for male (N=13) and female subjects (N=7) for two acyclovir products. In female subpopulation the negative control produced more discriminating results, compared to the male subpopulation.*

Conclusions

- **Clinical dOFM may reveal sex- and product-related differences in acyclovir skin penetration in a low number of volunteers.**
- **We hypothesize that the observed differences can be due to differences in the skin microstructure or daily skin care of men and women.**
- **Further studies may be of value to better understand the underlying biological and pharmacological mechanisms and their impact on clinical BA-BE evaluation.**

New data: Do dermal profiles also differ between males and females for topical lidocaine and diclofenac?

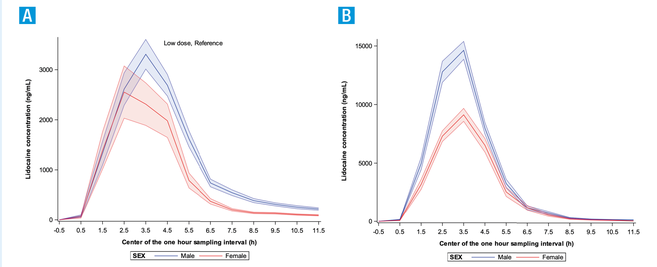

Fig. 4: *Lidocaine dOFM concentrations for 15 mg/cm² of the reference cream (Plot A, 14 males + 6 females) and 150 mg/cm² (Plot B, 11 males + 9 females) dosed at t=0 hours, occluded, and removed at t=3 hours (mean±sem).*

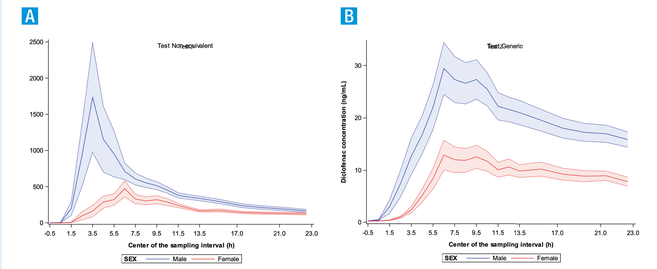

Fig. 5: *Diclofenac dOFM concentrations for 20 mg/cm2 of test product 1, diclofenac sodium topical solution, 2% (Plot A) and test product 2, diclofenac sodium topical gel, 1% (Plot B) dosed simultaneously at t=0 hours, both not occluded, and both removed at t=6 hours (mean±sem; 8 males + 8 females).*

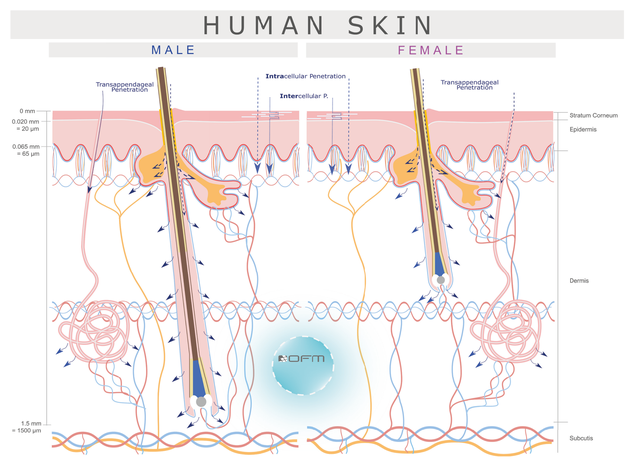

Fig. 6: *Morphology of male and female skin with known permeation pathways and a dOFM probe in mid to low dermis.*

Acyclovir, lidocaine, and diclofenac bioavailability appeared to differ in male vs. female dOFM study sub-populations. What makes this difference?

- Skin morphology & appendageal penetration [Fig.6]?
- Hydration, transepidermal water loss, sebum, microcirculation, pH [4]?
- What else is different?

References

[1] Bodenlenz et al. "Open Flow Microperfusion as Dermal Pharmacokinetic Approach to Evaluate Topical Bioequivalence", Clin. Pharmacokinet. 2016.

[2] Bodenlenz et al."Variability of skin pharmacokinetic data: Insights from a topical BE-study using dermal open flow microperfusion" Pharm. Res. 2020.

[3] Bialik W, Walters KA, Brain KR, Hadgraft J. „Some factors affecting the in vitro penetration of ibuprofen through human skin", Int J Pharm. 1993.

[4] Rahrovan et al. "Male versus female skin: What dermatologists and cosmeticians should know", Int J Womens Dermatol. 2018.

Acknowledgement

This project is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of grants (U01FD004946 and U01FD005861) totaling $ 3.55 M with 70 percent funded by FDA/HHS. The views are those of the author(s) and do not necessarily represent the official views of, nor an endorsement by, FDA/HHS or the U.S. Government

We thank Maike Sophie Rindler and Elmar Veitlmeier for poster design and graphics.