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

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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 product to itself and the sensitivity to discriminate a non-BE product. 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
  - 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 BE for a reference product 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. Instead analysis attributed > 82% of overall variability to subjects, and the intra-subject variability of <18% to local variability of drug penetration [2].
- Separate analysis of females and males (Profiles in Fig. 2, BE tests in Fig.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. Significant differences between male and female skin penetration had already been reported from IVPT-studies in 1993 by Bialik et al. [3].

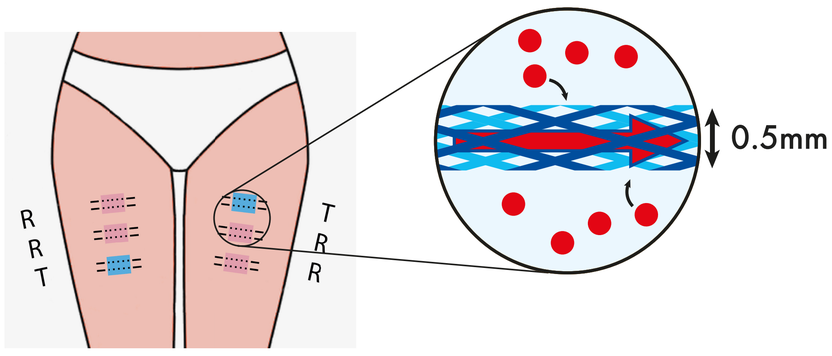

Fig. 1: *Schematic of the application sites with dOFM inserted in the dermis during the clinical study in 20 volunteers (7 females, 13 males). The study delivered 240 profiles of intradermal acyclovir for BE evaluation of a reference product vs itself (R vs R) and a test product vs reference (T vs R)*

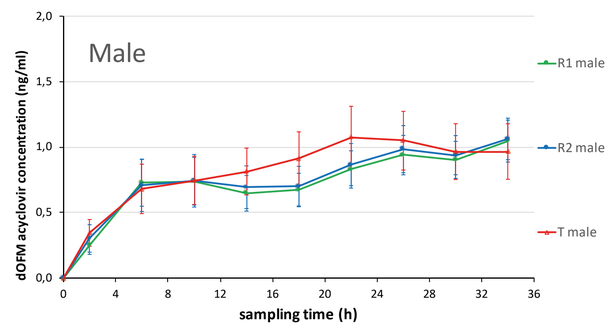

Fig. 2: *Acyclovir concentration profiles for R and T. In males concentrations rise fast and do not discriminate T from R. In females dermal concentrations rise slowly and after 20 hours clearly discriminate T from R. Concentrations are plotted as mean ±SE.*

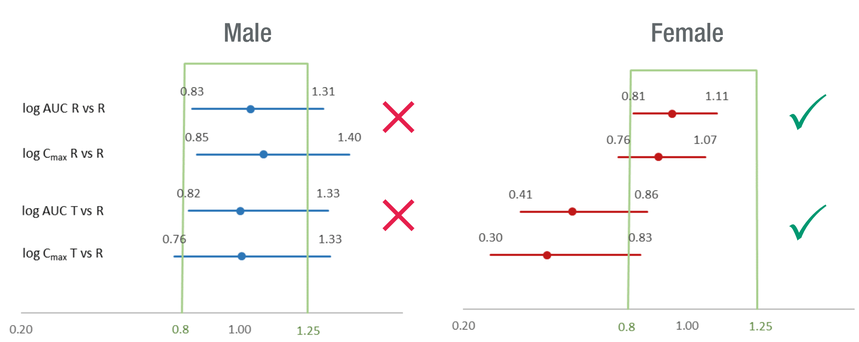

Fig. 3: *Results of BE evaluation for male (N=13) and female subjects (N=7) for two acyclovir products. In female subpopulation the negative control produced more discriminating results, compared to the male subpopulation.*

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.**

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.

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