Skin Forum 14th Annual Meeting 04 September 2014, Prague

Dermal open flow microperfusion illustrates the topical penetration of clobetasol-17-propionate into psoriatic lesional and non-lesional skin with time and space resolution

C Dragatin[1], *M Bodenlenz*[1], *K Benkali*[2], *T Augustin*[1], *C Höfferer*[1], *R Raml*[1], *P Martel*[2], *F Rony*[2], *TR Pieber*[1,3], *N Wagner*[2] *and F Sinner*[1,3]

CONTACT

[1] JOANNEUM RESEARCH
Forschungsgesellschaft mbH

HEALTH
Institute for
Biomedicine and
Health Sciences

Neue Stiftingtalstrasse 2
8010 Graz, Austria

Phone +43 316 876-40 00
Fax +43 316 8769-40 00

health@joanneum.at
www.joanneum.at/health

[2] Galderma R&D
Sophia Antipolis, France

[3] Medical University of Graz
Department of
Internal Medicine
Austria

Background & Aim

In psoriasis the hyperkeratosed stratum corneum has been reported to act as a trap compartment for topical drugs.
We aimed to investigate the role of the stratum corneum for topical penetration by continuous in vivo monitoring of the intradermal concentrations of clobetasol-17-propionate (CP-17) in psoriatic lesions and in non-lesional skin following single and repeated topical dosing of 0.05% CP-17 cream.

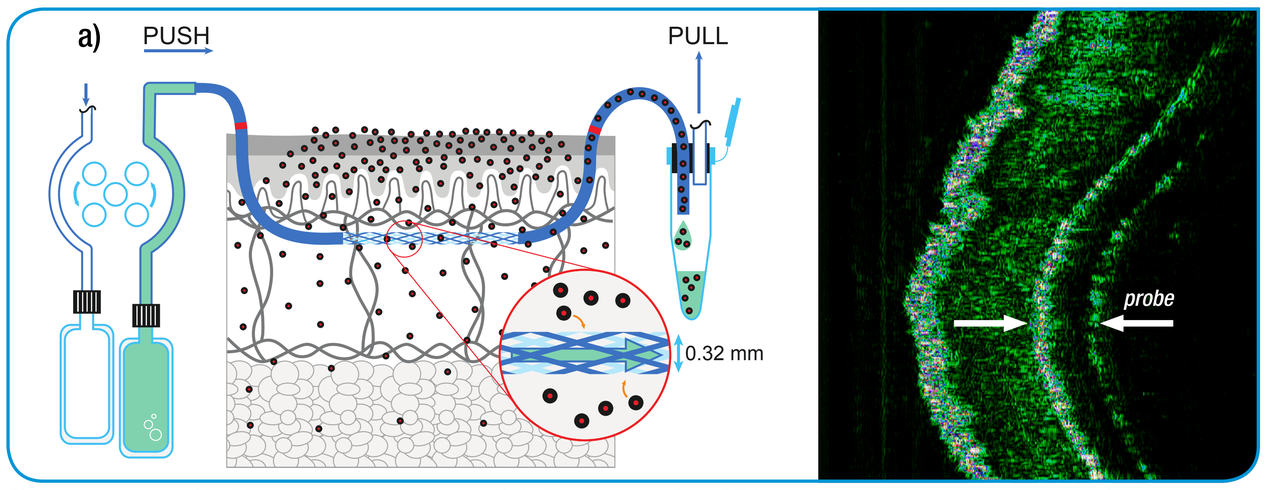

Figure 1. *a) principle of PK-PD sample collection by dermal dOFM. The membrane-free dOFM probe within the dermis is continuously perfused and delivers interstitial fluid for PK-PD analyses. b) ultra-sound skin imaging showing the dOFM probe in the dermis at a depth of ~ 0.6 mm.*

Methods

- 12 subjects with plaque type psoriasis
- 4 subjects in the pilot study (optimization only)
- 8 subjects in the main study (results shown):

Day 1:

- Lesional test site + 3 dOFM probes + topical Dermoval® cream (0.05% CP-17)
- Non-lesional test site + 3 dOFM probes + topical Dermoval® cream (0.05% CP-17)
- Continuous dOFM to sample dermal interstitial fluid at 1µL/min until 24 h post-dose
- 50 MHz ultrasound to measure the depth of each dOFM probe in the dermis
- LC-MS/MS to quantify CP-17 in dOFM samples

Days 2-13: once daily dosing of Dermoval® cream to test sites

Day 14 = Day 1

- Bioanalysis: LC-MS/MS (LOQ 0.35 ng/ml)
- Statistics: descriptive, AUC 0-24 h, and mixed-effects modelling to test which variables (e.g. skin site, time, depth) influence the AUCs in the dermis.

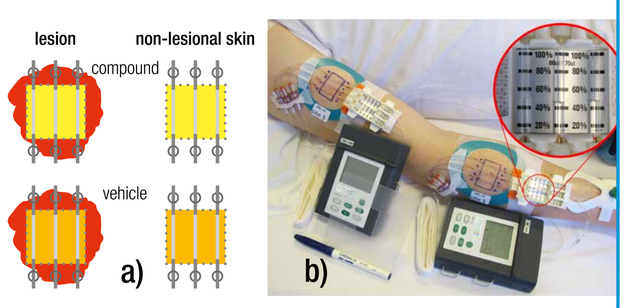

Figure 2. *a) Clobetasol and vehicle were applied once daily to 2 lesional and 2 non-lesional skin minizones for 14 days. After 1st and 14th application intradermal PK-PD parametes were profiled by 12 dOFM probes. b) Typical dOFM test setting with 2 of 4 minizones on an arm. Wearable dOFM pumps and sample collection units enable mobility of volunteers and > 24 h uninterrupted sampling.*

Results

dOFM sampling successfully provided intradermal CP-17 concentration profiles for 24 h (Fig. 3)

3 variables were identified to influence CP-17 levels (AUC 0-24 h mixed effects modelling):

a. skin site (lesional/non-lesional)
i.e. lower AUCs in lesional skin

b. the time (day 1/day 14)
i.e. higher AUCs at day 14

c. probe depth
i.e. the deeper in dermis the lower the AUCs

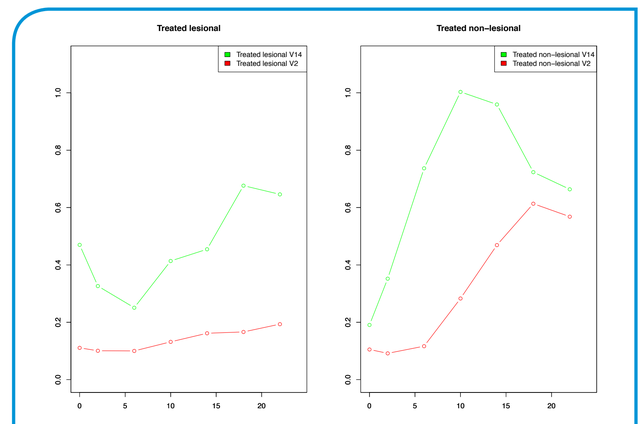

Figure 3. *CP-17 in dOFM samples (in ng/mL) from baseline to 24h post*

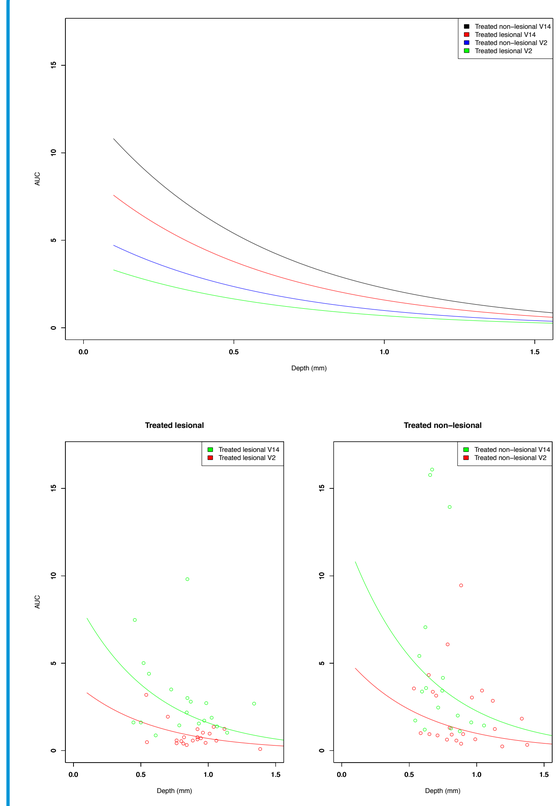

Figure 4: *AUC 0-24h for CP-17 in dOFM samples for lesional skin and non-lesional skin on day 1 and day 14 as a function of depth. Top: AUCs regression lines of both lesional and non-lesinoal skin. No individual AUC data points are shown. Bottom left: AUCs of lesional skin on day 1 and 14 including individual AUC data points. Bottom right: AUCs of non-lesional skin on day 1 and 14 including individual data AUC data points.*

Consequently, these **4 equations** including depth were best to describe the data (Fig. 4):

- Group 'LESIONAL', Visit 'V02':
  `AUC = exp (1.37 – 1.737* depth)`
- Group 'NON-LESIONAL', Visit 'V02':
  `AUC = exp (1.725 – 1.737* depth)`
- Group 'LESIONAL', Visit 'V14':
  `AUC = exp (2.199 – 1.737* depth)`
- Group 'NON-LESIONAL', Visit 'V14':
  `AUC = exp (2.554 – 1.737* depth)`

Summary and Conclusions

The hyperkeratosed, thickened stratum corneum in psoriasis

- acts as a trap compartment for lipophilic topical drugs, thus slowing penetration of lipophilic drugs into psoriatic skin plaques.

Dermal open flow microperfusion is known to provide PK profiles in the human dermis in vivo. This study demonstrates that dOFM provides PK data also

- for rather lipophilic topical entities
- for topical formulations with low strength (e.g. 0.05%)
- including drug concentration vs. depth

Dermal open flow microperfusion is a powerful tool in clinical research which provides intradermal PK with time as well as space resolution. Because dOFM is sensitive and tissue specific, the probe depth should be considered whenever dOFM is used in studies of topical bioequivalence.