Practical applications to evaluate topical drug products in patients

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N. Wagner
Introduction

• Initially, PK in dermatology focused mainly on systemic exposure and Skin PK were investigated using non-clinical models (i.e. *in vitro*: human skin model, *in vivo*: minipig model)

• Recently, skin PK became a key element of drug development at Galderma R&D

• The objective of this presentation is to share new results on Skin PK and open the discussion:
  – On the future use of these approaches
  – Improvement on methodological aspects
Presentation Plan

1. Pathology effect
   - Psoriatic skin versus healthy skin
2. Formulation effect
3. Dose effect
4. Time effect
Skin drug distribution and pathology effect in drug penetration – Example #1

• Two clinical studies on healthy volunteers and subjects with psoriasis
  
  – **Study #1**: Evaluation of the cumulative irritation potential of CD cream at 3 concentrations (1%, 3% and 5%)
    • 27 Healthy male volunteers
    • Topical treatment (QD) during 3 weeks
    • Non occlusive conditions : 2 mg/cm²
  
  – **Study #2**: Evaluation of local tolerance and systemic safety of CD cream at different concentrations (1% and 5%)
    • 8 subjects with *psoriasis vulgaris*
    • Topical treatment (QD) during 3 weeks
    • Non occlusive conditions : 16 mg/cm²

• Cutaneous PK
  
  – Tape-stripping 24 hours after the last application
    • 20 strips /zone for healthy volunteers
    • 10 strips /zone for psoriatic subjects
  
  – Skin Punch Biopsy after tape stripping
    • One 3-mm punch biopsy
Healthy volunteers vs subjects with psoriasis

- Higher quantity of drug in SC of psoriatic skin in comparison to healthy skin
- Similar to lower quantity of the drug in Epidermis/dermis despite higher applied quantity of drug (2 mg/cm² vs 16 mg/cm²)
Skin drug distribution and pathology effect in drug penetration

**Normal skin**, scan magnification x20
See the basket woven pattern of the SC

**Psoriatic skin**, scan magnification x20
Hyperkeratosis (increased thickness) with very compact pattern Parakeratosis (retention of nuclei in SC)

Normal skin versus psoriatic skin:
**Critical role of the stratum corneum**
Barrier or Reservoir effect of SC?
Skin drug distribution and pathology effect in drug penetration – Example # 2

- Open-Flow Microperfusion (OFM):
Open flow microperfusion (OFM) Study design

- Study population
  - 12 patients (4 in Part I and 8 in Part II)
    - Males or females,
    - 18 to 50 years old,
    - With a diagnosis of stable plaque type of psoriasis having at least two psoriatic plaques on the upper extremities or proximal lower extremities
Open flow microperfusion (OFM) Study design

• Phase I, exploratory study, open label, multiple dose

• Monocenter in Austria (Graz Medical University)

• Dermoval Cream® (Clobetasol 17-propionate) and its vehicle ➔ 14 days on lesional and non-lesional skin sites

➢ 12 x OFM sampling per patient

➢ 2 lesions (6 OFM sampling) and 2 unaffected skin areas (6 OFM sampling) treated per patient
Study objectives: PK/PD assessment

- To investigate the dermal PK profile of **Clobetasol propionate-17** (CP-17)

- To investigate the PD of CP-17 to modulate levels of **skin-produced cytokines:**
  - INF-γ, IL-1β, IL-6, IL-8, IL-12, IL-15, IL-17, IP-10, TNF-α, VEGF

- on both lesional and non-lesional skin of psoriatic patients

- At two periods: Day 1 and Day 14
**CP-17 individual profiles in skin (n=8)**

- **Non-Lesional skin**
  - First application: Quantifiable subjects: 63%; % quantifiable data: 29%

- **Lesional skin**
  - First application: Quantifiable subjects: 63%; % quantifiable data: 20%

- **14th application**
  - Quantifiable subjects: 100%; % quantifiable data: 70%
CP-17 mean Profiles

**T_{lag}: 5.2h**

**T_{lag}: 9.5 h**

Treated Non-Lesional V2
Treated Non-Lesional V14
Treated Lesional V2
Treated Lesional V14

Non-Lesional skin
Lesional skin
Skin drug distribution and pathology effect in drug penetration

**Normal skin**, scan magnification x20
See the basket woven pattern of the SC

Psoriatic skin, scan magnification x20
Hyperkeratosis (increased thickness) with very compact pattern Parakeratosis (retention of nuclei in SC)

**Normal skin versus psoriatic skin:**
significant differences were identified on lag time

**Decrease of drug penetration rate?**
Interleukin 8 (IL-8) Levels

Significant Difference on IL-8 levels after CP17 treatment
Same treatment effect in Lesional AND non Lesional skin
Significant Difference on IP-10 levels after CP17 treatment
Same treatment effect in Lesional AND non Lesional skin
IP-10 levels are significantly different in Psoriatic skin compared to non lesional skin.

**IP-10: potential pathology marker?**
Presentation Plan

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Formulations comparison

• Clinical PK study in healthy volunteers to evaluate systemic exposure at steady state
  – 10 subjects/group, once daily application for 29 days, Plasma samples collected at days 1, 5, 15, 29
  – In addition, skin sampling for formulation comparison were performed on dedicated mini-zones after 5 days of treatment: tape stripping + skin punch biopsies

• Tested formulations:
  – Gel formulation: early formulation tested in the proof of efficacy study ➔ clinical efficacy demonstrated in patients with acne vulgaris
  – Creams A and B formulations: New formulations with more appropriate cosmetic properties
50 µg/g formulations
Skin penetration

Significant different skin penetration of NCE when formulated in Cream A in comparison to:

- Gel/Cream A ratio: 3.0
  IC 90% [2.0; 4.5]
- Cream B/A ratio: 2.4
  C90% [1.6; 3.7]

No statistical differences on skin penetration of NCE when formulated in Cream B:

- Gel/Cream B ratio: 1.2
  IC 90% [0.8; 1.2]

Formulation effect on NCE skin penetration: significantly lower penetration with cream A
50 µg/g formulations
Efficacy on acne

- Gel and Cream B formulations demonstrated clinical efficacy on acne
  - Comparison versus vehicle (Intra individual comparison)

Cream A has not demonstrated a clinical efficacy in acne ➞ may be due to the lower skin penetration?
Conclusions

• Skin PK assessment (tape stripping and skin punch biopsies) allowed formulations comparison

• Skin PK results were in accordance with clinical efficacy results
  – Skin PK assessment after 5 days of treatment
  – Clinical efficacy after 1 month of treatment
Presentation Plan

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Dose effect

• Dose selection ➔ Critical step during drug development
  – Need for data for optimal dose selection ➔ efficacy vs safety
  – Local tolerance
  – Avoid over-exposure to drug ➔ better safety margin
  – May have an impact on formulation cost

• Phase 2 data are currently used for dose selection

• Skin PK/PD data on dose effect should be available for dose selection
Cutaneous Pharmacokinetics in healthy volunteers

Dose proportionality demonstrated in Epidermis /Dermis (statistically not rejected)

Saturation of *stratum corneum*?
Patient with psoriasis (N=3/4)

- Over proportionality in *stratum corneum* (High/ Low dose ratio: 12)
- Dose proportionality (trend) in Epidermis + Dermis
Cutaneous Pharmacokinetics in healthy volunteers

Dose proportionality (High/Low dose ratio)
- Epidermis + dermis ratio: 2
  IC 90% [1.3; 2.5]
- Stratum corneum ratio: 7
  IC 90% [4.0; 12.8]
- Total skin ratio: 4
  IC90% [3.2; 7.5]

Dose proportionality statistically demonstrated when using total penetrated drug quantity in the skin
Dose proportionality

- Same formulation ranking observed whatever the skin compartments considered (SC or viable epidermis / dermis)

- **But** Dose proportionality not consistent across different studies:

<table>
<thead>
<tr>
<th>Skin type</th>
<th>Stratum corneum</th>
<th>Epidermis + Dermis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>(saturation??)</td>
<td></td>
</tr>
<tr>
<td>Psoriatic</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>(Over proportionality)</td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>(Over proportionality)</td>
<td>(under proportionality)</td>
</tr>
</tbody>
</table>

Pending question: is the “dose proportionality” dependent to compound, formulation and/or to skin compartments?
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Formulation comparison in healthy volunteers: Gel versus Lotion

DPK method

• Study objective:
  – Comparison of the drug penetration in stratum corneum when using two different formulations at the same strength (Gel and Lotion)

• Design/study chronology
  – 2 pilot studies were conducted on limited number of subjects (single and repeated dose)
  • Study #1: Single Dose
  • Study #2: Repeated Dose
DPK Methodology
Study #1 : Single dose

- Application (single dose)
  - 2 mg/cm²
  - Massage

- Mini-zones covered with non-occlusive dressing
  - 4 application times tested for each formulation (2, 4, 8, 12 hours)

- Stripping
  - Template to avoid edge effect (in order to reduce variability)
  - Tape stripping : each tape strip analyzed individually with an appropriate LOQ
4 subjects (4 application areas per subject):

- Low inter and intra individual variability CV < 50 % for Lotion and Gel
- Formulation effect noticeable from the individual profile
Study #1: Single dose DPK

Cumulated Quantity of NCE delivered by the Lotion in the *stratum corneum* was significantly lower compared to the Gel.

No effect of application time: plateau reached after only 2 hours.

**Bioequivalence acceptance criteria CI 90%: [0.80; 1.25]**
Study #1: Single dose – key results

- NCE penetration in *stratum corneum* approximately 2-fold higher with the Gel compared to the Lotion
  - BUT difference mainly observed in the first 10 tape strips
- plateau reached after only 2 hours post-dose
  - NCE seems to move rapidly into the outermost layers of *Stratum corneum* after the application

Hypothesis

- Formulations create a NCE “depot” in the upper SC
- Reaplications should solubilise this NCE “depot” present in the upper SC

Due to the difference in formulation composition, NCE concentrations may not reach steady-state after one single application ➔ Repeated dosing will be more representative of the clinical intended use

Second Pilot study (study #2) with multiple dose application
Study #2:
Mean quantity of NCE versus the strip number
**Study #2: Multiple dose DPK**

Gel: Steady state achievement at day 5,

Lotion: No accumulation in the *stratum corneum*

*At steady state, the cumulated Quantity of NCE delivered by the Lotion in the *stratum corneum* was significantly different compared to the Gel (5-fold lower)*

<table>
<thead>
<tr>
<th>Sampling time</th>
<th>N</th>
<th>Ratio (Lotion/Gel)</th>
<th>Geometric mean</th>
<th>90% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>4</td>
<td>0.51</td>
<td>0.37</td>
<td>0.71</td>
</tr>
<tr>
<td>D3</td>
<td>4</td>
<td>0.30</td>
<td>0.22</td>
<td>0.42</td>
</tr>
<tr>
<td>D5</td>
<td>4</td>
<td>0.21</td>
<td>0.17</td>
<td>0.25</td>
</tr>
<tr>
<td>D7</td>
<td>4</td>
<td>0.20</td>
<td>0.12</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Bioequivalence acceptance criteria CI 90%: [0.80; 1.25]
### DPK studies – Single vs. Multiple

<table>
<thead>
<tr>
<th></th>
<th>Single dose DPK study Study #1</th>
<th>Repeated dose DPK study Study #2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study year</strong></td>
<td>2011</td>
<td>2012</td>
</tr>
<tr>
<td><strong>Number of applications</strong></td>
<td>1</td>
<td>1, 3, 5 and 7</td>
</tr>
<tr>
<td><strong>DPK assessment</strong></td>
<td>2, 4, 8 and 12 hrs after application</td>
<td>(2 hrs after application)</td>
</tr>
</tbody>
</table>

**Low and similar Inter- study variability !!**
CONCLUSION
**Skin PK techniques**

- Depending on the skin compartment different phenomenon may be observed. Then, different technique(s) should be used to characterize formulations:
  - **Tape stripping**: Main of the applied drug being located in the SC, useful tool for
    - Formulation comparison, Dose effect (in some cases)
    - However, SC is not always representative of the total skin penetration
  - **Skin punch biopsy**
    - Proof of skin exposure in viable skin
    - Should be combined with PD assessment for better understanding of drug effect
    - Must be combined with tape stripping to assess the global skin distribution (SC effect) and avoid sampling contamination
  - **Micro-dialysis /OFM**
    - Gold standard to investigate skin PK-PD
    - However, technical complexity, cost may limit the use of these approach
Perspectives

• Efforts have to be made for better understanding of:
  – Pathology impact on penetration
  – Interaction between Formulation / Pathology
  – Techniques reliability

• Skin PK-PD investigation should be assessed in early clinical stages:
  – For an optimal formulation and dose selection (efficacy/safety)
  – To consolidate “proof of concept” results

• Take-home message: Combined skin PK sampling methods are necessary to understand the skin distribution of a given NCE