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Evaluation of Dermal Open Flow Microperfusion (dOFM) as a General Methodology to Assess the Bioequivalence of Hydrophobic, Protein-Bound Topical Drug Products

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PURPOSE

Dermal open flow microperfusion (dOFM) is a methodology that characterizes the cutaneous pharmacokinetics (PK) of drugs from topical dermatological drug products.

Previously, dOFM was successfully used to evaluate bioequivalence (BE) of topical cream products containing acyclovir, , a hydrophilic drug which exhibits little protein binding [1]. To extend the applicability of dOFM results to other topical drug products, a pilot dOFM study was performed in human subjects to **evaluate the cutaneous PK of lidocaine** (moderately lipophilic, moderately protein-bound) **and prilocaine** (moderately lipophilic, highly protein bound) from two different topical products, each of which contained both drugs.

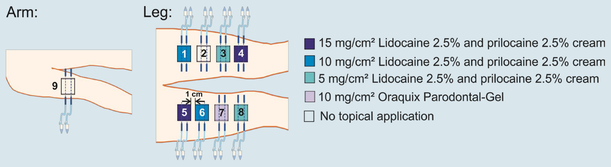
OBJECTIVES

The overall objective of this work was to evaluate whether dOFM can be a general BE test method for all topical drug products. A specific objective of the pilot study was to verify and/or optimize following parameters for a pivotal in-vivo study with lidocaine and prilocaine:

- Characterize the **dose-response relationship** for the reference cream product.
- Characterize the influence of potentially confounding factors:
  - **Local "cross-talk"** between probes in adjacent treatment sites.
  - Redistribution of the drug via clearance into the systemic circulation and **recirculation into the skin.**
- Evaluate the suitability of a test **gel product** to serve as a **negative control** for BE relative to the reference cream product.

METHODS

- Single center, open label pilot study in 6 healthy subjects
- Study duration: 25 hours (1 hour pre-dose and 24 hours post-dose)
- Products:
  - Reference cream: Lidocaine 2.5% and Prilocaine 2.5% cream, USP (Actavis Pharma INC, USA)
  - Designated negative control: Oraqix Parodontal-Gel (periodontal gel, 2.5% lidocaine and 2.5% prilocaine, Dentsply DETREY GmbH, Germany)
- Product Dosing (at 9 test sites):



- Sampling: 17 dermal interstitial fluid (ISF) samples and 8 blood samples
- Sample analysis: High performance liquid chromatography (HPLC) tandem mass spectrometry (MS/MS) analysis (LLOQ: 1 ng/mL)
- BE statistics (reference cream versus negative control):
  - PK parameter: Dermal concentration-time curve (AUC_{0-24}) and maximum concentration (C_{max})
  - For BE 90% confidence interval of the mean difference between the products must fall within the BE limits of 0.8 - 1.25 for both PK parameter.

RESULTS

Dermal ISF was sampled from 18 individual dOFM probes in the dermis to determine the PK profiles of lidocaine and prilocaine (figure 1) in 6 healthy subjects.

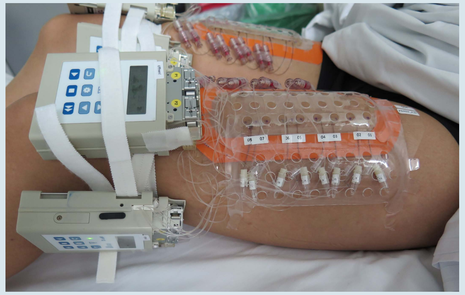


Figure 1: *dOFM setup*

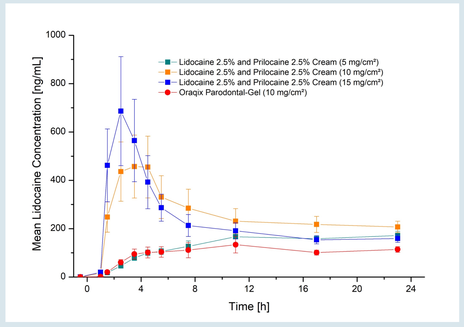


Figure 2: *Mean lidocaine concentration-time profiles (±SE) for three different doses of Lidocaine 2.5% and Prilocaine 2.5% cream, USP and for Oraqix Parodontal-Gel*

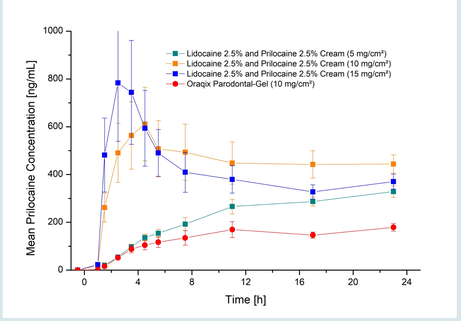


Figure 3: *Mean prilocaine concentration-time profiles (±SE) for three different doses of Lidocaine 2.5% and Prilocaine 2.5% cream, USP and for Oraqix Parodontal-Gel*

- The **cutaneous PK profiles** for lidocaine (figure 2) and prilocaine (figure 3) were comparable between the six subjects and showed low inter- and intra-subject variability.
- The reference cream showed a **dose-response relationship** with a peak around 3-5 hours following dose application.
- Dermal ISF samples from non-dosed sites on the thigh showed very low levels of lidocaine and prilocaine indicating that **"cross-talk" between adjacent test sites is negligible.**
- Dermal ISF sampled from the arm and blood samples showed no detectable levels of lidocaine or prilocaine indicating **no systemic redistribution**.
- **Negative Control**:
  At the same product dose of 10 mg/cm², the PK profiles for the gel were well differentiated from the reference cream profiles. A preliminary statistical analysis showed that the 90% confidence interval of the mean ratios did not fall within the BE limits of 0.80–1.25 (table 1) suggesting that the gel may represent a reasonable negative control for BE with respect to the reference cream.

	PK Parameter	Calculated BE Limits
Lidocaine	AUC_{0-24}	1.51 – 2.64
	C_{max}	1.75 – 3.21
Prilocaine	AUC_{0-24}	2.14 – 3.63
	C_{max}	2.15 – 3.51

Table 1: *Calculated BE limits for the comparison Lidocaine 2.5% and Prilocaine 2.5% cream, USP versus Oraqix Parodontal-Gel , both dosed with 10 mg/cm². BE limits were calculated for both PK parameters and for lidocaine and prilocaine.*

CONCLUSIONS

- When the cream dose was increased or decreased relative to the 10 mg/cm² dose level, the dose-dependent response of the PK profiles for both drugs indicated that the system was **sensitive and discriminating to an increase or decrease in the topical bioavailability** of lidocaine and prilocaine.
- At the same dose (10 mg/cm²) the gel delivered substantially less lidocaine and prilocaine than the reference cream suggesting that **the gel may serve as a suitable negative control** for BE.
- The ability of **dOFM** to **successfully monitor and characterize the cutaneous PK profiles for lidocaine and prilocaine** supports the general utility of dOFM as an approach that can investigate the cutaneous PK of lipophilic and protein bound topical drugs.
- The **absence of systemic redistribution** and the **lack of any substantial "cross-talk"** between adjacent test sites indicates that each individual dOFM probe can monitor the rate and extent of lidocaine and prilocaine locally without interference from different treatments at other sites.

FUNDING/REFERENCE

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[1] M. Bodenlenz et al., "Open Flow Microperfusion as a Dermal Pharmacokinetic Approach to Evaluate Topical Bioequivalence," *Clin. Pharmacokinet.*, vol. 56, no. 1, pp. 1–8, 2016.

[2] FDA, "Guidance for Industry: Statistical Approaches to Establishing Bioequivalence," *Guid. Ind.*, 2001.

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