Clinical study to assess the cutaneous bioequivalence of topically applied lidocaine/prilocaine products using dermal open flow microperfusion

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Introduction

In a previous clinical study, dermal open flow microperfusion (dOFM) was used to evaluate the bioequivalence (BE) of topically applied drug products containing the hydrophilic active pharmaceutical ingredient (API), acyclovir [1]. The current study aimed to assess whether dOFM can be used to evaluate the cutaneous (dermal) pharmacokinetics (PK) and BE of topical drugs that are moderately lipophilic and at least moderately protein-bound, which would be representative of many topical drugs. Products containing a fixed combination of lidocaine and prilocaine were selected for this comparative study and BE evaluation:

- Reference product vs. reference product (R_2 vs. R_1) – BE positive control 1
- Generic product vs. reference product (T_{gen} vs. R_1) – BE positive control 2
- Non-equivalent test product (different formulation) vs. reference product ($T_{non\text{-}equ}$ vs. R_2) – BE negative control

Methods

- Single center, open label, pivotal study with **20 healthy volunteers**
- dOFM was used to continuously sample dermal interstitial fluid for 13 hours (1 hour pre-dose, 12 hours post-dose)
- Lidocaine and prilocaine products, 2.5%;2.5% were applied at a product dose of 15 mg/cm² (Fig. 1) and removed after 3 hours:
  - **Reference product R_1/R_2**: EMLA® (lidocaine and prilocaine) topical cream, 2.5%;2.5% (Actavis Pharma Inc., USA)
  - **Generic test product T_{gen}**: Lidocaine and prilocaine topical cream, 2.5%;2.5% (Fougera Pharmaceuticals Inc., USA)
  - **Non-equivalent test product $T_{non\text{-}equ}$**: Oraqix® (lidocaine and prilocaine) periodontal gel, 2.5%;2.5% (Dentsply Detrey GmbH, Germany)

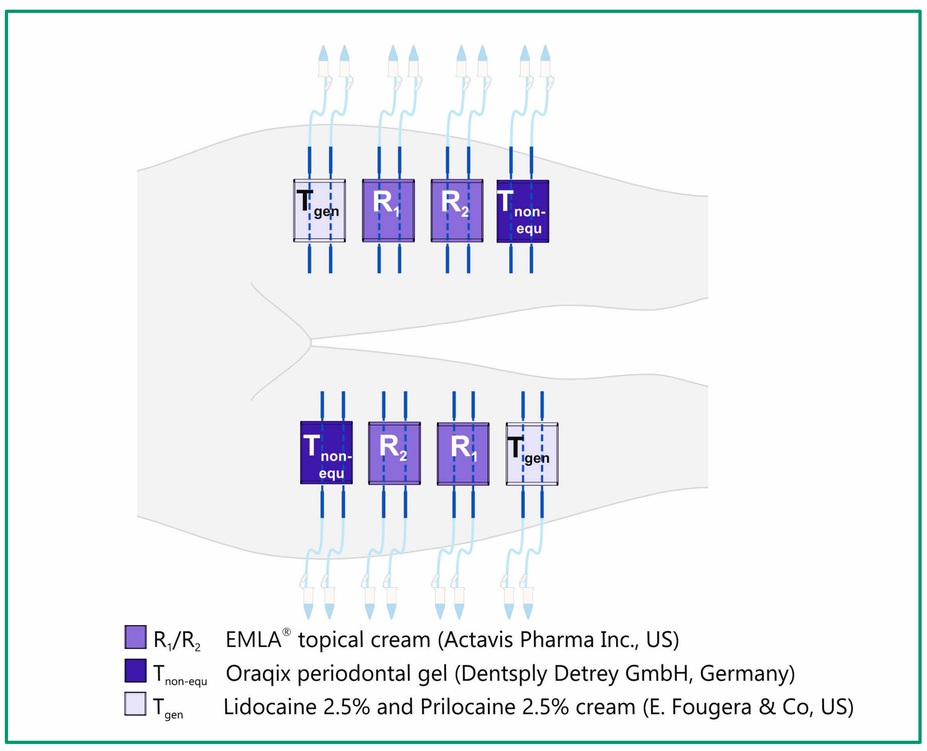

Figure 1: Each thigh had four application sites with two dOFM probes per site. On each thigh the reference product was applied on two application sites (R_1,R_2), and the generic product (T_{gen}) and the non-equivalent test product ($T_{non\text{-}equ}$) were applied on one application site each.

- **Statistical analysis:** The PK endpoints of area under the concentration-time curve ($AUC_{0\text{-}12h}$) and maximum concentration (C_{max}) were used to assess BE using the **scaled average BE (SABE) approach** [2]:
  - Condition for use: within-reference variability s_{WR} > 0.294
  - Mixed criterion for BE:
    - 95% upper confidence bound is ≤ 0 and
    - geometric mean ratios (GMR) for PK endpoints lie within the BE limits of 0.8 - 1.25.

Results

Mean concentration-time profiles showed comparable dermal concentrations for R_1, R_2 and T_{gen} for each API, lidocaine and prilocaine (Fig. 2). Lidocaine and prilocaine PK profiles of $T_{non\text{-}equ}$ were clearly visible as being discriminated from R_1, R_2 and T_{gen} PK profiles.

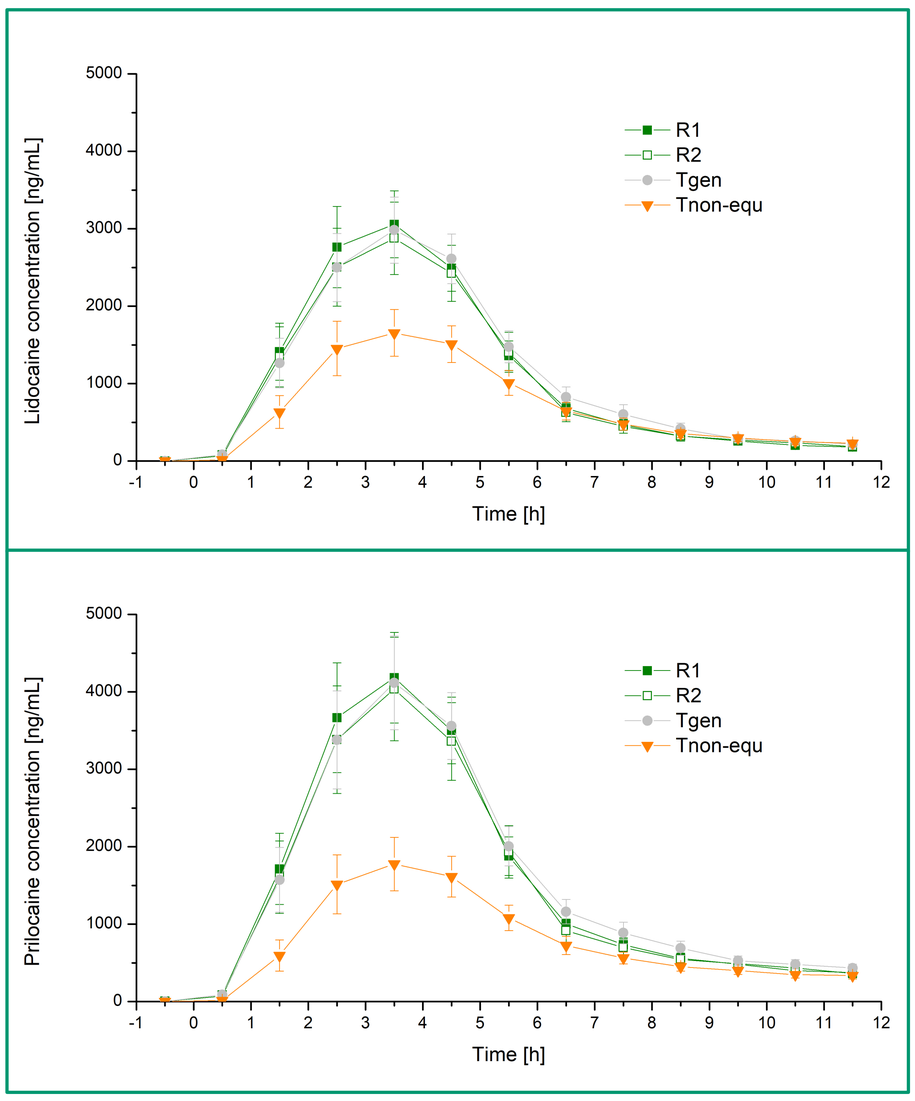

Figure 2: Mean dermal lidocaine (upper panel) and prilocaine (lower panel) concentration-time profile ± standard error (SE) for R_1, R_2, T_{gen} and $T_{non\text{-}equ}$ across all thighs (R_1: 38 thighs, R_2: 40 thighs, T_{gen}: 39 thighs, $T_{non\text{-}equ}$: 38 thighs)

For BE evaluation the two application sites next to each other were selected for pairwise comparisons. The s_{WR} of all comparisons for both PK endpoints ($AUC_{0\text{-}12h}$, C_{max}) were greater than 0.294, satisfying the criteria for the use of SABE.
SABE evaluations **confirmed BE for the positive control 1** (R_2 vs. R_1) and positive control 2 (T_{gen} vs. R_1) as the 95% upper confidence limit (UCL) was negative and GMRs lay within the BE limits of 0.8 and 1.25 (Tab. 1). The negative control ($T_{non\text{-}equ}$ vs. R_2) failed the SABE criterion **and the gel was found not to be BE to the reference product.**

Table 1: Summary of SABE evaluation

	API	PK endpoint	s_{WR}	GMR	UCL	Result
R_2 vs. R_1	Lidocaine	$AUC_{0\text{-}12h}$	0.404	1.14	-0.035	The reference cream was **bioequivalent** to itself. ✓
		C_{max}	0.424	1.11	-0.057	
	Prilocaine	$AUC_{0\text{-}12h}$	0.380	1.12	-0.034	
		C_{max}	0.415	1.11	-0.056	
$T_{generic}$ vs. R_1	Lidocaine	$AUC_{0\text{-}12h}$	0.364	0.97	-0.060	The generic cream was **bioequivalent** to the reference cream. ✓
		C_{max}	0.400	0.96	-0.069	
	Prilocaine	$AUC_{0\text{-}12h}$	0.365	0.95	-0.055	
		C_{max}	0.408	0.91	-0.055	
$T_{non\text{-}equ}$ vs. R_2	Lidocaine	$AUC_{0\text{-}12h}$	0.351	0.63	0.330	The gel was **not bioequivalent** to the reference cream. ✓
		C_{max}	0.330	0.52	0.624	
	Prilocaine	$AUC_{0\text{-}12h}$	0.335	0.48	0.703	
		C_{max}	0.321	0.39	1.174	

Conclusions

These results show that dOFM **reproducibly demonstrated BE** of a product to itself (positive control 1) and **accurately demonstrated BE** of an **approved generic product** to its reference product (positive control 2). Further, dOFM was able to discriminate a prospectively non-equivalent gel product relative to EMLA® cream (products representing a negative control for BE). These data corroborate the results from a previous dOFM study with topical acyclovir products [1] and suggest that dOFM has the potential to assess BE for a range of different topical drug products containing hydrophilic and hydrophobic APIs with differences in protein binding.

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References

[1] M. Bodenlenz *et al.*, "Open flow microperfusion as a dermal pharmacokinetic approach to evaluate topical bioequivalence," *Clin. Pharmacokinet.*, 2017.
[2] U.S. FDA, "Draft Guidance on Acyclovir" for acyclovir cream, 5%. (Recommended Dec 2014; Revised Dec 2016)

Unterhalb dieser Linie werden keine Inhalte mehr gesetzt!