A clinical study to assess the bioequivalence of lidocaine and prilocaine topical drug products using dermal open flow microperfusion

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PURPOSE

In a previous clinical study, dermal open flow microperfusion (dOFM) has been used to evaluate the bioequivalence (BE) of cream products containing the hydrophilic drug acyclovir [1]. The purpose of the current study was to assess whether dOFM can also evaluate the dermal pharmacokinetics (PK) and BE of topical products containing the moderately lipophilic drugs lidocaine and prilocaine, that are expected to exhibit moderate or high protein-bounding, respectively.

OBJECTIVES

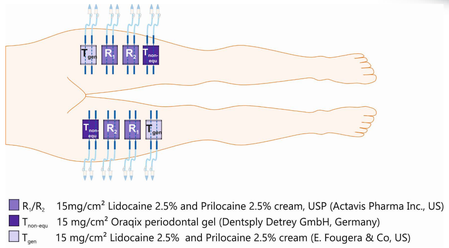
To demonstrate whether dOFM has the ability to evaluate the dermal BE of lidocaine and prilocaine products, the local bioavailability of both drugs was monitored based on the maximum drug concentration (C_{max}) and area under the curve (AUC). The following comparisons were performed:

1. **Positive control for BE 1:** reference product vs. reference product (R_2 vs. R_1)
2. **Positive control for BE 2:** marketed generic test product vs. reference product (T_{gen} vs. R_1)
3. **Negative control for BE:** different (non-equivalent) test product vs. reference product ($T_{non\text{-}equ}$ vs. R_2)

METHODS

- **Study design:** Single center, open label, pivotal study with 20 healthy subjects
- **Study duration:** dOFM was used to continuously sample interstitial fluid (ISF) for 13 hours (1 hr pre-dose, 12 hrs post-dose)
- **Test products:**
  - Reference product R_1/R_2: EMLA® (lidocaine and prilocaine) topical cream, 2.5%;2.5% from Actavis Pharma INC, USA
  - Generic test product T_{gen}: lidocaine and prilocaine topical cream, 2.5%;2.5%, from Fougera Pharmaceuticals INC.
  - Different (non-equivalent) test product $T_{non\text{-}equ}$: Oraqix ® (lidocaine and prilocaine) periodontal gel, 2.5%;2.5% from Dentsply Detrey GmbH, Germany
- **Dosing:** 15 mg/cm² of each product was applied and removed after 3 hours.
- **Sample analysis:** HPLC-MS/MS
- **Statistical analysis:**
  - Dermal PK endpoints: $AUC_{0\text{-}12}$ and C_{max}
  - BE evaluations using the scaled average BE (SABE) approach [2]: Condition for use: $s_{WR} > 0.294$

    Mixed criterion for BE:
    i. 95% upper confidence bound is ≤ 0 and
    ii. geometric mean ratios (GMR) for PK endpoints lie within the BE limits of 0.8 - 1.25.



RESULTS

For BE evaluations, the $AUC_{0\text{-}12}$ and C_{max} were calculated for each probe from the measured concentration-time profiles. The two sites which were located next to each other were selected for pairwise comparisons. The within-reference variability (S_{WR}) of both PK endpoints was greater than 0.294 confirming that SABE is an appropriate statistical approach.

1. **Positive control for BE 1** (Figure 1) and **positive control for BE 2** (Figure 2) were **confirmed**. Both comparisons passed the SABE criterion for both PK endpoints and for both lidocaine and prilocaine, as the 95% upper confidence bound CI was negative and the GMRs lay within the BE limits of 0.8 and 1.25 (Table 1).
2. **Negative control for BE** (Figure 3) was **confirmed** as the comparison didn't pass the SABE criterion and Oraqix ® gel wasn't found to be bioequivalent to EMLA® cream (Table 1).

CONCLUSIONS

The clinical study demonstrated that dOFM was **accurate and reproducible** to **demonstrate BE between equivalent topical products** (positive controls for BE 1 and 2) and was **sensitive** to **discriminate** a non-equivalent gel product (negative control for BE) from the reference cream with the same concentration of drug.

REFERENCES

[1] M. Bodenlenz *et al.*, "Open flow microperfusion as a dermal pharmacokinetic approach to evaluate topical bioequivalence," *Clin. Pharmacokinet.*, vol. 56, no. 1, pp. 91–98, Jan. 2017.
[2] U.S. FDA, "Draft Guidance on Acyclovir" for acyclovir cream, 5%. Dec. 2016.

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Successful PK-based BE evaluation of topically applied lidocaine and prilocaine products

REFERENCE VS. REFERENCE

Confirmed BE for both drugs (positive control for BE 1)

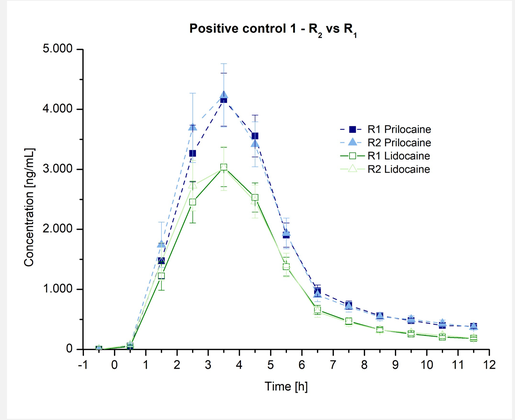

Figure 1: Mean concentration-time profile ± standard error (SE) for lidocaine (green) and prilocaine (blue) over all subjects (n = 40 limbs) for the reference cream products R_1 (■) and R_2 (▲).

NON-EQUIV. PRODUCT VS REFERENCE PRODUCT

Confirmed dOFM sensitivity to discriminate non-equivalent products (negative control for BE)

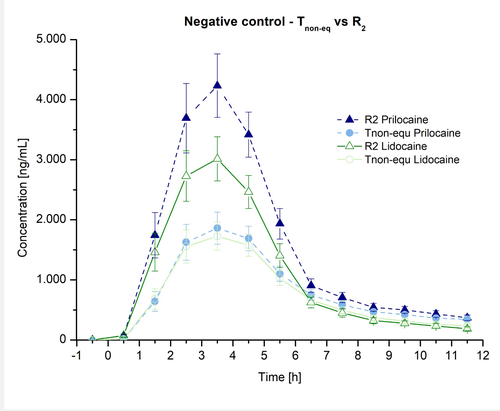

Figure 3: Mean concentration-time profiles (±SE) for lidocaine (green) and prilocaine (blue) overall subjects (n = 40 limbs) for the reference cream (R_2, ▲) and non-equivalent test gel ($T_{non\text{-}equ}$, ●).

GENERIC VS REFERENCE

Confirmed BE for both drugs (positive control for BE 2)

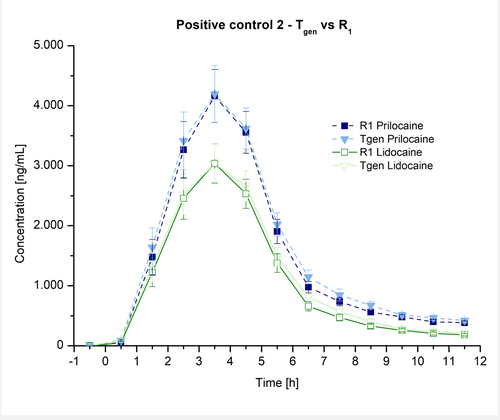

Figure 2: Mean concentration-time profiles (±SE) for lidocaine (green) and prilocaine (blue) over all subjects (n = 40 limbs) for the reference R_1 (■) and generic test T_{gen} (▼) products.

BE EVALUATION

Table 1: Summary of BE analysis. The GMR of positive controls for BE were within the BE limits of 0.8 and 1.25 and upper bounds of the 95% CI were ≤0. Hence, SABE criteria were satisfied for all positive controls for BE. The negative control for BE was not found to be bioequivalent according to SABE criteria.

	PK endpoint	API	GMR	95% upper confidence bound	SABE - criterion satisfied	Result
R_2 vs. R_1	$AUC_{0\text{-}12}$	lidocaine	1.13	-0.036	Yes	The reference cream product is **bioequivalent** to itself
	C_{MAX}		1.11	-0.057	Yes	
	$AUC_{0\text{-}12}$	prilocaine	1.12	-0.035	Yes	
	C_{MAX}		1.11	-0.056	Yes	
T_{gen} vs. R_1	$AUC_{0\text{-}12}$	lidocaine	0.95	-0.053	Yes	The generic cream is **bioequivalent** to the reference cream
	C_{MAX}		0.92	-0.055	Yes	
	$AUC_{0\text{-}12}$	prilocaine	0.94	-0.051	Yes	
	C_{MAX}		0.89	-0.043	Yes	
$T_{non\text{-}equ}$ vs. R_2	$AUC_{0\text{-}12}$	lidocaine	0.62	0.330	No	The gel product is **not bioequivalent** to the reference cream
	C_{MAX}		0.52	0.623	No	
	$AUC_{0\text{-}12}$	prilocaine	0.48	0.703	No	
	C_{MAX}		0.39	1.174	No	

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