Quantitative Discrimination of Cutaneous Pharmacokinetic Profiles for Topical Drug Products

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BACKGROUND

Dermal open flow microperfusion (dOFM) has been used to measure the cutaneous pharmacokinetics (PK) of topical dermatological drug products and has the potential to support a demonstration of bioequivalence (BE) for prospective generic topical dermatological drug products.[1] A dOFM method should be designed to be sensitive at discriminating the differences in cutaneous bioavailability of the drug substance (e.g., from different formulations or different dose amounts). Currently the discriminatory capability of a dOFM method is evaluated via a qualitative assessment of the cutaneous PK profiles (Figure 2). The purpose of this study was to investigate different quantitative analyses to establish the discrimination sensitivity of cutaneous PK studies.

METHODS

The dOFM pilot study using EMLA® (lidocaine; prilocaine) topical cream, 2.5%;2.5% at different dose amounts (5, 10, or 15 mg/cm^2) and Oraqix® (lidocaine; prilocaine) periodontal gel at 10 mg/cm^2 in six healthy subjects conducted by Joanneum Research was used for this analysis.[1] The schematic of the study designs is shown in Figure 1. Analyses of average bioequivalence [ABE], reference scaled ABE [SABE], and an assessment of difference (f_1) and similarity (f_2)[2] were evaluated for their ability to discriminate the cutaneous PK profiles from R (cream at 10 mg/cm^2) and T treatments (cream at 5 and 15 mg/cm^2 and gel at 10 mg/cm^2). The f_1 and f_2 factors were analyzed for two different parameters, using the percent concentration ($\%C_t = \frac{C_t}{C_{max\,T\,or\,R}}$), and percent area under the curve (AUC) profiles ($\%AUC_t = \frac{AUC_{0-t}}{AUC_{0-tlast\,T\,orR}}$). A bootstrap analysis was also performed. For the purpose of this study, cutaneous PK profiles were considered to be discriminated if **f_1 > 15 or f_2 < 50** and with bootstrap analysis when the 90% confidence interval (CI) for f_1 > 15 or for f_2 < 50.

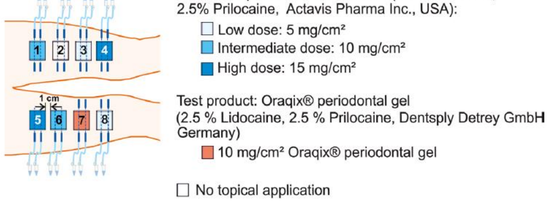

Figure 1. Diagram illustrating the study design[1]

Quantitative analyses (average bioequivalence [ABE], reference scaled ABE [SABE], and assessment of difference (f1) and similarity (f2)) **are** generally **consistent** with the results of the **visual assessment for discriminating the PK profiles.**

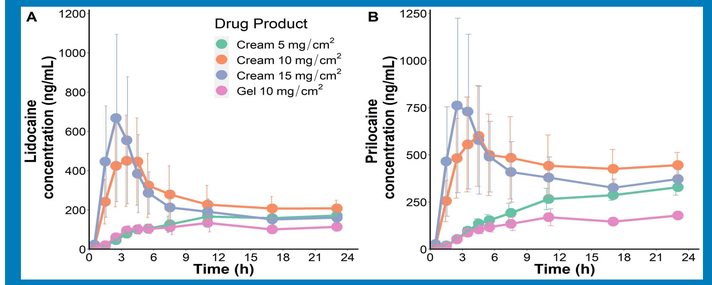

Figure 2. Concentration versus time profiles (mean ± SE, n=6 volunteers) from the dOFM pilot study . (A: Lidocaine dermal concentrations, B: Prilocaine dermal concentrations).

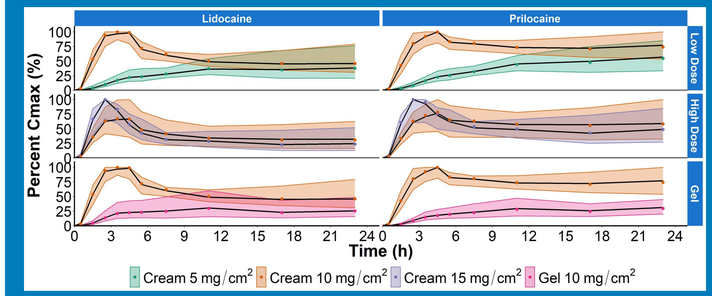

Figure 3. Mean percent concentration versus time profiles (n=6 volunteers) from the dOFM pilot study (points). Shaded region represents the 5th and 95th percentiles from the bootstrap and the solid line represents the 50th percentile (n=1000).

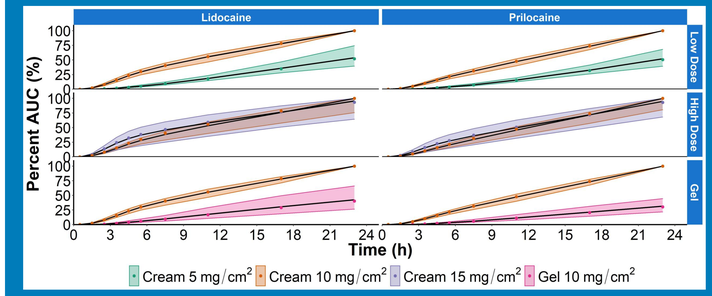

Figure 4. Mean percent AUC versus time profiles (n=6 volunteers) from the lidocaine; prilocaine dOFM study (points). Shaded region represents the 5th and 95th percentiles from the bootstrap and the solid line represents the 50th percentile (n=1000).

Table 1. f_1 and f_2 analysis comparing lidocaine; prilocaine formulations to EMLA® cream 10 mg/cm^2 using data from the pilot study and from a bootstrap analysis (n=1000).

Dose vs Cream 10 mg/cm²	Point Estimate				Bootstrap (n=1000)			
	Percent conc profile		Percent AUC profile		Percent conc profile		Percent AUC profile	
	Lidocaine	Prilocaine	Lidocaine	Prilocaine	Lidocaine	Prilocaine	Lidocaine	Prilocaine
f_1								
Cream 5 mg/cm² (n=12)	65.5	63.4	64.6	63.1	63.1 (48.7 – 74.2)	61.3 (47.3 – 72.4)	62.1 (47.1 – 73.0)	61.0 (47.3 – 71.8)
Cream 15 mg/cm² (n=12)	30.5	24.1	14.6	13.3	39.4 (21.6 – 73.4)	33.2 (17.4 – 62.2)	30.3 (11.4 – 68.0)	25.7 (10.1 – 56.4)
Gel 10 mg/cm² (n=6)	70.2	76.0	69.4	75.7	67.2 (49.0 – 80.6)	74.2 (61.9 – 83.0)	65.7 (43.4 – 80.6)	73.5 (60.0 – 84.2)
f_2								
Cream 5 mg/cm² (n=12)	15.6	15.7	27.6	29.8	16.8 (14.8 – 19.9)	16.6 (13.9 – 22.7)	29.0 (23.6 – 37.5)	31.0 (25.8 – 38.4)
Cream 15 mg/cm² (n=12)	39.6	38.8	60.7	65.7	35.2 (27.9 – 42.3)	35.2 (27.2 – 43.9)	48.7 (33.1 – 65.1)	53.7 (38.2 – 70.2)
Gel 10 mg/cm² (n=6)	15.5	13.0	25.3	24.6	17.0 (14.0 – 22.3)	13.6 (11.0 – 18.6)	27.3 (20.9 – 38.2)	25.5 (21.6 – 31.1)

RESULTS

In all BE comparisons using both ABE and SABE, the cream product at 10 mg/cm^2 dose was found not to be bioequivalent to the higher and lower doses, nor to the gel product based on the confidence interval (CI), with the exception of comparison between EMLA® cream at 10 mg/cm^2 to 15 mg/cm^2 dose using an SABE analysis.

Table 1. BE assessment comparing EMLA® cream at 10 mg/cm^2 with test treatments using ABE and SABE (SCI_{UB} [upper bound of the 95% CI]). Negative values indicate BE and lack of discrimination.

Dose vs Cream 10 mg/cm²	ABE Point Estimate (CI)		SCI_{UB} (m=1.25)	
	Lidocaine	Prilocaine	Lidocaine	Prilocaine
Cmax				
Cream 5 mg/cm² (n=12)	0.59 (0.45 – 0.79)	0.65 (0.52 – 0.82)	0.23	0.17
Cream 15 mg/cm² (n=12)	1.33 (0.96 – 1.83)	1.16 (0.85 – 1.57)	**-0.03**	**-0.05**
Gel 10 mg/cm² (n=6)	0.42 (0.34 – 0.51)	0.36 (0.30 – 0.44)	0.74	1.15
AUC				
Cream 5 mg/cm² (n=12)	0.64 (0.51 – 0.80)	0.59 (0.48 – 0.74)	0.16	0.30
Cream 15 mg/cm² (n=12)	0.99 (0.76 – 1.30)	0.96 (0.75 – 1.23)	**-0.18**	**-0.14**
Gel 10 mg/cm² (n=6)	0.49 (0.40 – 0.62)	0.35 (0.29 – 0.43)	0.56	1.29

CONCLUSIONS

The presented analyses quantitatively discriminated profiles that were visually separated and tended not to discriminate between the PK of EMLA® cream at 10 mg/cm^2 compared to 15 mg/cm^2 dose, for which the profiles were largely overlapping (visually). Although the different quantitative approaches have the potential to provide an objective, dichotomous determination about whether two profiles are discriminated or not, the appropriateness of such analysis for the purpose of this study needs further evaluation. While an (S)ABE analysis of pilot study data would typically be under-powered, f_1/f_2-evaluation coupled with a bootstrap analysis may be a practical way to establish the sensitivity of a cutaneous PK methodology.

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Abstract and detailed study design