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A clinical study design to evaluate whether the systemic bioavailability of topical drugs may influence the assessment of local dermal pharmacokinetics by dermal open flow microperfusion (dOFM)

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PURPOSE

Dermal microdialysis (dMD) and dermal open flow microperfusion (dOFM) can directly sample interstitial fluid (ISF) from the dermis and **characterize the cutaneous (dermal) pharmacokinetics (PK) of topically applied drug products**. Hence, dMD and dOFM may be useful to compare the rate and extent to which topically applied drugs become available in the skin from test and reference products, which can be dosed in parallel at different skin sites on the same subject.

However, topical drugs could potentially 1) diffuse laterally between skin sites, and/or 2) be absorbed and accumulate sufficiently in the systemic circulation to get redistributed back into the dermis. These **two "crosstalk" phenomena could increase (background) drug levels at a skin site**, and might compromise how well dOFM or dMD studies can discriminate independent dermal PK profiles between test and reference dosing sites. Such crosstalk phenomena may be particularly confounding for highly permeable drugs and/or those applied on large body surface areas.

OBJECTIVES

The objective of this work was to develop a (pilot) study design that could evaluate/deconvolute the relative contribution of lateral diffusion and systemic-to-local crosstalk to dermal PK profiles, using lidocaine and prilocaine (co-administered in a topical cream) as model drugs.

Specific aims of the study were to evaluate the relative extent to which the **applied topical dose** is

- ✓ **Quantifiable locally** vs. **systemically** (i.e., the magnitude difference in the amount of drug)
- ✓ **Redistributing from the systemic circulation back to the dermis** (at a non-dosed test site)
- ✓ **Diffusing laterally between adjacent dosing sites** on the thigh (vs. a non-dosed test site)
- ✓ **Discriminating the bioavailability from different doses** (15 vs 150 mg/cm² of EMLA® cream)
  - One sub-objective was to compare the dermal PK profiles characterized by dOFM vs. dMD
  - Another sub-objective was to evaluate different dose removal times for the pivotal study

METHODS

- **Study design:** Single center, open label pilot study with **6 healthy subjects**
- **Study duration:** 13 hours (1 hour pre-dose, 12 hours post-dose)
- **Test Product:** EMLA® cream (2.5% lidocaine, 2.5% prilocaine; Actavis Laboratories UT INC, US)
- **Dosing** (Figure 1):
  - dOFM high-dose: 150 mg/cm² for 3 hours on test-sites [2], [3], [6] and [7]
  - dMD high-dose: 150 mg/cm² for 3 hours on test-sites [1] and [5]
  - dOFM low-dose: 15 mg/cm² for 2 h (un-even ID, n=3) or 4 h (even ID, n=3) on test-site [8]
  - dOFM non-dosed test sites on the thigh [4] and on the arm [9]
  - Test-site on the abdomen: 150 mg/cm² for 3 hours (total dose: 60 g per subject)
  - **4 dMD** and **14 dOFM probes** per subject (see Figure 1)

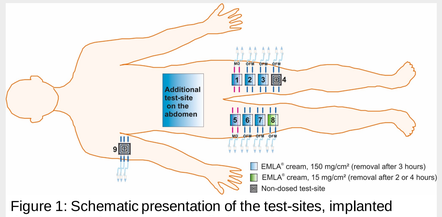

Figure 1: Schematic presentation of the test-sites, implanted dOFM and MD probes and applied products.

- **Sampling**: 13 dermal ISF samples and 13 serum samples
- **Sample analysis**: High performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS)
- **Statistical evaluations**: PK endpoints:
  - Area under the concentration-time curve (AUC) from 0 to 12 hours
  - Peak concentration: C_{max}

RESULTS

- Lidocaine and prilocaine were quantifiable in the systemic circulation as well as in the dermis of the non-dosed test-site on the arm (Figure 2, Table 1).

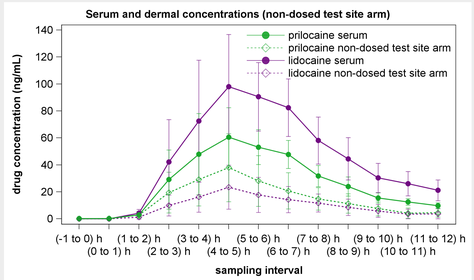

Figure 2: Concentration-time profiles (mean ± SD, n = 6 subjects) for lidocaine (violet) and prilocaine (green) sampled from serum (solid line) and from ISF of the non-dosed test on the arm (dotted line) using dOFM.

- dMD and dOFM sampling techniques resulted in similar PK profiles for both lidocaine and prilocaine (Figure 3,Table 1).

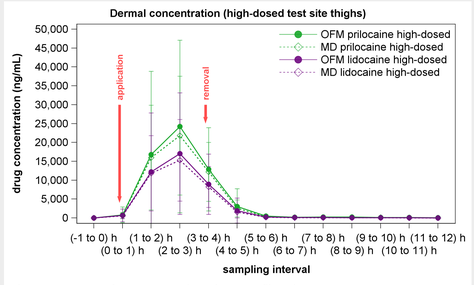

Figure 3: Dermal concentration-time profiles (mean ± SD, n = 6 subjects) for prilocaine (green) and lidocaine (violet) for the high-dosed test sites (150 mg/cm², removed after 3 hours) sampled with dOFM (solid line) and dMD (dotted line).

- Measured lidocaine and prilocaine dermal concentrations derived from the low-dosed (15 mg/cm²) test-sites (Figure 4) were more than 10 times lower than those from the high-dosed (150 mg/cm²) test-sites (Figure 3, Table 1).

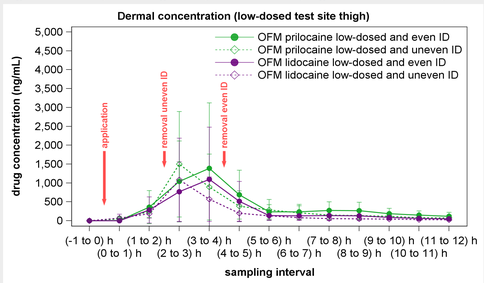

Figure 4: Dermal concentration-time profiles (mean ± SD, n = 6 subjects) for prilocaine (green) and lidocaine (violet) for the low-dosed test-sites (15 mg/cm²) sampled with dOFM. Products were removed after 4 hours (even subject, solid line) or after 2 hours (uneven subject, dotted line).

- PK profiles of the non-dosed test-site on the arm and on the thigh (Figure 5) were comparable (Table 1).

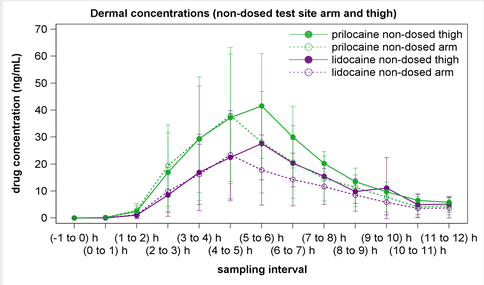

Figure 5: Dermal concentration-time profiles (mean ± SD, n = 6 subjects) for prilocaine (green) and lidocaine (violet) for the non-dosed test-sites on the thigh (solid line) and on the arm (dotted line) sampled with dOFM.

Table 1: Calculated PK parameters AUC and C_{max} for lidocaine an prilocaine sampled from ISF (high-dose, low-dose, non-dosed) and blood (serum).

PK parameter	dOFM[1] high-dose (150 mg/cm², 3h, n=6)	dMD[1] high-dose (150 mg/cm², 3h, n=6)	dOFM[1] low-dose (15 mg/cm², 2h, n=3)	dOFM[1] low-dose (15 mg/cm², 4h, n=3)	dOFM[1] non-dosed thigh (n=6)	dOFM[1] non-dosed arm (n=6)	Serum[2] (n=6)
$AUC_{Lidocaine}$ [(ng•h)/mL]	41,640.20	37,976.68	2,522.49	3,391.75	140.75	114.43	559.24
$C_{max,Lidocaine}$ [ng/mL]	17,038.30	15,282.83	1,086.28	1,100.60	27.63	23.43	98.06
$AUC_{Prilocaine}$ [(ng•h)/mL]	59,308.40	54,258.89	4,093.08	4,900.45	210.71	78.81	330.61
$C_{max,Prilocaine}$ [ng/mL]	24,211.23	21,820.91	1,497.50	1,387.46	41.57	38.00	60.49

1) PK parameters were calculated from the mean concentration-time curve across all probes and subjects.
2) PK parameters were calculated from the mean concentration-time curve across all subjects.

CONCLUSIONS

- ✓ Lidocaine and prilocaine were quantifiable in the local as well as the systemic circulation, however the systemic C_{max} (Figure 2; Table 1) for each drug was more than 10-fold lower than the low-dose dermal C_{max} (Figure 3; Table 1), and more than 100-fold lower than the high-dose dermal C_{max} (Figure 4; Table 1)
- ✓ Lidocaine and prilocaine did redistribute from the systemic circulation to the dermis at non-dosed test sites on the arm and thigh (Figures 2 and 5; Table 1)
- ✓ The PK profiles of the non-dosed test sites on the arm and thigh were similar, suggesting negligible lateral diffusion from the adjacent dosed test sites on the thigh (Figure 5; Table 1)
- ✓ Despite the redistribution of some systemically available drug back into the dermis, the dOFM methodology had the sensitivity to discriminate differences in the bioavailability of lidocaine and prilocaine from the high vs. low dose treatments (See Y axis in Figure 4 vs. Figure 5; Table 1)
- ✓ dOFM and dMD PK profiles were similar (Figure 3)
- ✓ Further research is warranted to evaluate the potential impact of crosstalk phenomena on the ability of dOFM and dMD discriminate differences in the bioavailability of drugs from test and reference products

FUNDING

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