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Investigation of the Relationship Between Product-Dose and Dermal Exposure of Lidocaine and Prilocaine from a Topical Cream Product Using Dermal Microdialysis

Sharareh Senemar[1], Tannaz Ramezanli[2], Priyanka Ghosh[2], Sam Raney[2], Benjamin A. Kuzma[3] and Grazia Stagni[1]

1 Division of Pharmaceutical Sciences, Arnold and Marie Schwartz College of Pharmacy, Long Island University, Brooklyn, New York, USA

2 Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, USA

3 Wellman Center for Photomedicine, Massachusetts General Hospital, Harvard Medical School, Charlestown, Massachusetts, USA

Contact Information: HS 623 75 DeKalb Ave, Brooklyn NY 11201, Long Island University
email: sharareh.senemar@liu.edu

PURPOSE

The purpose of this study is to investigate the relationship between the product-dose applied and the dermal exposure of lidocaine (LDC) and prilocaine (PLC) following topical application of the LDC and PLC topical cream, (2.5%;2.5%) at four product doses (3, 10, 20, and 30 mg/cm^2) using dermal microdialysis (dMD) in a New Zealand rabbit model.

METHOD(S)

Nine microdialysis probes were inserted into the dorsum of each tranquilized rabbit (N=4) using a predetermined scheme (Figure 1). Two dMD probes were inserted under each of the (4) test sites, whereas the ninth probe was inserted more than 3 cm away from application sites to evaluate the potential redistribution of LDC and PLC into to the dermis due to systemic absorption and recirculation. The LDC and PLC topical cream, 2.5/2.5% (manufactured by Actavis Pharma Inc.) was applied at doses of 3, 10, 20, and 30 mg/cm^2 at each test site.
All probes were perfused with 1.0 µL/mL of normal saline solution containing 5 ng/mL deuterated LDC as probe marker. Dialysate samples were collected at predetermined time points for up to 14 hours. Samples were analyzed for LDC, PLC, and their metabolites monoethylglycinexylidide (MEGX) and ortho-toluidine (OTE). Area under the curve (AUC_{0-14}) for dermal concentration vs. time profile, maximum dermal concentrations (C_{max}), and terminal half-life ($t_{1/2}$) were estimated. The relationship between the product dose applied and the dermal exposure parameters were evaluated.

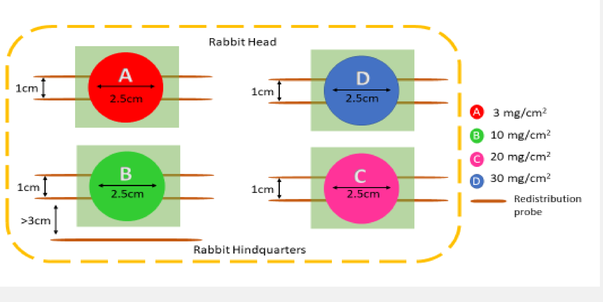

Figure 1. Mapping of the probes and corresponding product- dose applied on the rabbit's dorsum. The dose-product pattern was randomized for each rabbit.

RESULT(S)

- The average dermal concentration (mean ± SEM, N=4) profiles for LDC, PLC, and their respective metabolites MEGX and OTE are shown in Figure 2.
- Investigation of the relationship between the product-dose and the exposure parameter AUC_{0-14}, indicates that LDC and PLC exposure increased with the increase in product dose in the range of 3-20 mg/cm^2, yet no further enhancement was observed between the 20 and 30 mg/cm^2 dose (Figure 3).
- Investigation into the metabolite data and its relationship with product dose and LDC/PLC exposure showed that the dermal metabolites exposure slightly increased with increase in the product dose.
- The amounts of LDC/PLC or dermal metabolites observed in the redistribution probes were negligible, indicating that the amounts of LDC, PLC, MEGX, OTE observed in dialysate samples resulted from absorption of drug from the cream product into the skin and dermal metabolism of LDC/PLC in epidermis and dermis.

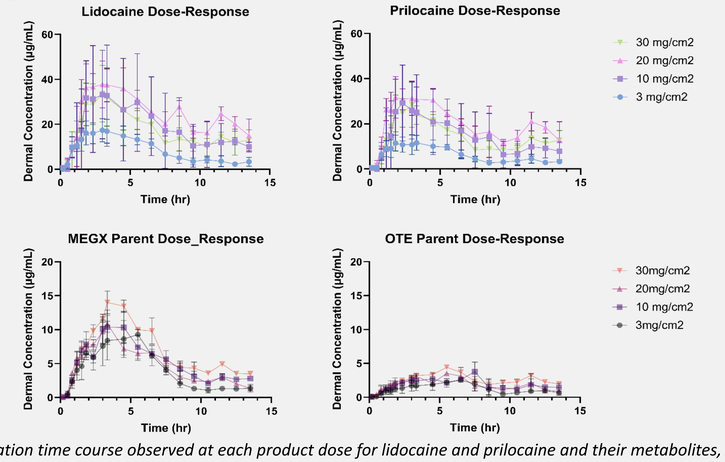

Figure 2. Dermal concentration time course observed at each product dose for lidocaine and prilocaine and their metabolites, MEGX and OTE, respectively. Data are presented as mean ± SEM for 4 rabbits.

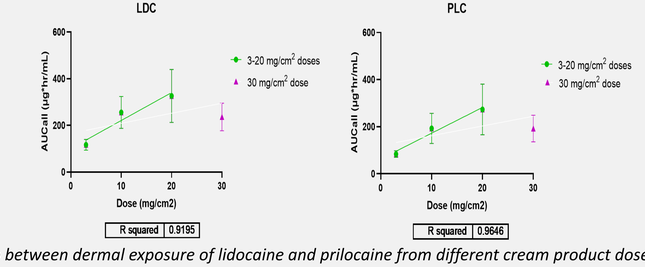

Figure 3. The relationship between dermal exposure of lidocaine and prilocaine from different cream product doses. The exposure of lidocaine and prilocaine is linear in the range of 3-20 mg/cm^2 doses

CONCLUSION(S)

- The observed relationship between product-dose and cutaneous pharmacokinetics for the LDC/PLC topical cream in this study suggests that dermal exposure plateaus at doses higher than 20 mg/cm^2.
- A previous study [1] on the dermal disposition of LDC and PLC when delivered directly to the dermis (using dermal infusion) at similar or higher drug concentrations, demonstrated that the dermal clearance, dermal volume of distribution, and dermal elimination half-life of LDC and PLC are independent of the dose delivered. Thus, it can be concluded that the non-proportional relationship between product dose and dermal exposure of LDC and PLC and their metabolites observed in this study are due to potential saturation of the drug permeation from the dosage form into the skin, and not attributed to lack of proportionality in the distribution/elimination process or technical performance issues of the dMD probes.
- Therefore, a dose of less than 20 mg/cm^2 may be appropriate for a prospective bioequivalence study with LDC and PLC topical cream product.
- Study designs similar to the one described in this poster can be potentially utilized during the method development to identify appropriate dose (in the sensitive portion of the dose-permeation curve) for a bioequivalence study.

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REFERENCE

[1] Senemar, S., et al., Dermal Clearance, Elimination Half-life, and Apparent Volume of Distribution of Lidocaine And Prilocaine Are Independent of the Dose Delivered Directly in Dermis Using a Dermal Infusion Technique, in ASCPT 2022: Online Annual Meeting.