Evaluation of Bioavailability of Lidocaine and Prilocaine from Topical Drug Products Using an *In Vitro* Permeation Test (IVPT)

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PURPOSE & OBJECTIVE

This exploratory study was designed to evaluate the bioavailability of lidocaine and prilocaine from two topical creams, each containing both lidocaine and prilocaine (2.5%; 2.5%). One of the creams was a reference listed drug (RLD) product and the other was an approved generic version of that RLD product. In addition to the two creams, the bioavailability of lidocaine and prilocaine was also evaluated from a topical gel containing both lidocaine and prilocaine (2.5%; 2.5%). The bioavailability from all three products was compared using an in vitro permeation test (IVPT). The generic cream was expected to serve as a positive control for establishing bioequivalence (BE) compared to its RLD cream. The topical gel was expected to have a different bioavailability, and was used as a negative control for BE compared to the RLD cream. The objective of this study was to assess whether an IVPT study has the potential to accurately and reproducibly demonstrate that the generic cream was bioequivalent to its RLD cream, and accurately and sensitively discriminate the gel product as not bioequivalent to the RLD cream.

METHOD(S)

Franz diffusion cells (2 cm^2) and cryopreserved, dermatomed, human cadaver skin were used for the IVPT studies. All the formulations were evaluated using six donors (with 6 replicates per donor). A 10 mg/cm^2 dose of the cream or gel product was used and studied for 24h. A phosphate buffer-based receptor medium was used, and samples were collected by replacing the entire receptor solution, every 1h between 0-4h, and every 4h between 4-24h. Lidocaine and prilocaine concentrations in the samples were quantified using a reverse phase high performance liquid chromatography (HPLC) method. A C18, 5 µm, reversed phase column (4.6 x 150 mm) was used to analyze the lidocaine and prilocaine concentrations in the samples using an ultraviolet detection wavelength of 220 nm. Cutaneous pharmacokinetic (PK) parameters such as area under the curve (AUC) of the incremental permeation profile, maximum concentration (J_{max}) and time to maximum concentration (T_{max}) were used to compare the three different formulations evaluated in the study. Data were averaged among replicates to calculate mean values for each donor, and the mean values for the six donors in the study were averaged and reported as the overall mean (± the standard error of the mean). The results were analyzed using Student's t test; a p value of 0.05 was considered to be statistically significant. The results were also analyzed using an alternate statistical method. (Please see Draft Guidance for Industry on Acyclovir Topical Cream 5%)

RESULT(S)

Figure 1: Flux of Lidocaine and Prilocaine from Cream and Gel Products (n=6 Donors; 6 Replicates/donor)

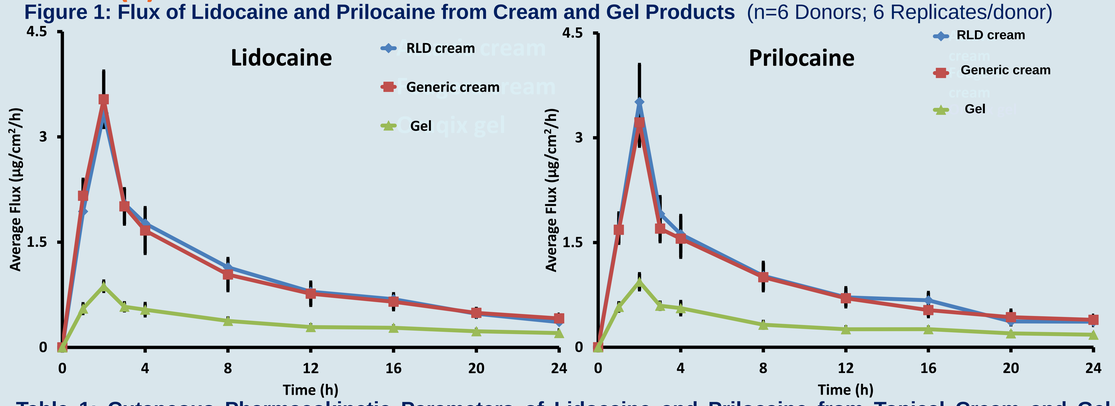

Table 1: Cutaneous Pharmacokinetic Parameters of Lidocaine and Prilocaine from Topical Cream and Gel Products (n=6 Donors; 6 Replicates)

	Product	Lidocaine-2.5% Prilocaine-2.5% RLD Cream	Lidocaine-2.5% Prilocaine-2.5% Generic Cream	Lidocaine-2.5% Prilocaine-2.5% Gel
AUC (µg/cm^2)	Lidocaine	24.87 ± 3.83	24.48 ± 2.59	8.47 ± 0.92
	Prilocaine	23.04 ± 4.47	22.00 ± 3.69	8.02 ± 0.71
J_{max} (µg/cm^2/h)	Lidocaine	3.34 ± 0.18	3.54 ± 0.22	0.87 ± 0.11
	Prilocaine	3.51 ± 0.43	3.22 ± 0.43	0.94 ± 0.08

Statistical analysis using Student's t test: The overall mean results from the six donors indicated that there were no significant differences between the generic and reference cream products with respect to AUC (0-24h) or J_{max}, for either lidocaine and prilocaine, however both AUC and J_{max} for both lidocaine and prilocaine were significantly lower for the topical gel compared to the RLD cream ($p<0.05$). The T_{max} for all the products was at 2h.

Statistical analysis using Reference Scaled Average BE Approach (RSABE) and ABE: Using this approach all products were found to be BE to itself (data not shown) and the Generic Cream was found to be BE to the RLD Cream, both Creams were found to be not BE compared to the Gel. RSABE was used for a specific assessment when the CV associated with a cutaneous PK parameter was observed to be > 30%, ABE is used in all other scenarios.

Lidocaine	Generic Cream vs. RLD Cream		Gel vs. Generic Cream		Gel vs. RLD Cream	
Cutaneous PK Endpoint	AUC	Jmax	AUC	Jmax	AUC	Jmax
Point Estimate	1.0593	1.0534	0.3541	0.2501	0.3751	0.2635
S Within Reference	0.3449	0.2837	0.3970	0.3064	0.3449	0.2837
SABE (0.80, 1.25) ABE (0.80, 1.25)	-0.0135	(0.8975, 1.2363)	1.1577	2.4514	1.4433	(0.1915, 0.3625
Prilocaine	**Generic Cream vs. RLD Cream**		**Gel vs. Generic Cream**		**Gel vs. RLD Cream**	
Cutaneous PK Endpoint	AUC	Jmax	AUC	Jmax	AUC	Jmax
Point Estimate	1.0710	1.0264	0.3807	0.3372	0.4078	0.3461
S Within Reference	0.3008	0.4677	0.3858	0.2535	0.3008	0.4677
SABE (0.80, 1.25) ABE (0.80, 1.25)	0.0032	-0.1160	1.3366	(0.2340, 0.4860)	1.5465	1.9047

CONCLUSION(S)

Three lidocaine and prilocaine topical products with the same concentration (2.5%) of lidocaine and prilocaine were compared using an IVPT study with excised human skin. The IVPT cutaneous pharmacokinetic results for the creams (which were comparable to each other) and the gel (which was distinct with respect to the creams) were consistent with the expectation that topical semisolid drug products with a similar composition and microstructure may provide a similar bioavailability of lidocaine and prilocaine. The results also suggested that IVPT studies may have the utility to help support an evaluation of BE for topical drug products containing multiple active ingredients, since the IVPT results appropriately showed the two creams (which were positive controls for BE relative to each other) to have a similar rate and extent of lidocaine and prilocaine permeation, and discriminated the cutaneous pharmacokinetics of the gel (which was a negative control for BE relative to the creams) as being different from that for the RLD cream.

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