Evaluation of Two Lidocaine Topical Patch 5% Products by Cutaneous Pharmacokinetic Methods: *In Vitro* Tape Stripping and *In Vitro* Permeation Testing

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Introduction

For many topical drug products the site of action may be in the skin or in surrounding tissues, and for these products the local bioavailability may be particularly relevant for efficacy and bioequivalence. The relative bioavailability of two lidocaine topical patch 5% products (A and B) was tested using two cutaneous pharmacokinetic methods, *in vitro* tape stripping (IVTS) and *in vitro* permeation testing (IVPT). Tape stripping was used to determine the amount of drug present in the stratum corneum (SC) and IVPT was used as a surrogate to monitor the bioavailability of lidocaine into and through the skin, that may potentially become available to proximal tissues.

Objective

Two dermal pharmacokinetic methodologies (IVPT and IVTS) were utilized to investigate the *in vitro* kinetics of two different lidocaine topical products. Flux through the skin and stratum corneum lidocaine amounts were compared between the two products.

Methods

Study Design

Two different lidocaine topical patch 5% products (A and B) were applied to excised human skin and evaluated by IVPT and IVTS using skin from three donors with four replicate skin sections per treatment group. Patches (0.97 cm^2) were applied to human skin mounted on In-Line flow-through diffusion cells containing isotonic phosphate buffer (pH 7.4) as the receiver solution (at 0.5 mL/h), and a permeable mesh was mounted atop the patches to ensure consistent adhesion to the skin throughout the study. The study design involved a patch application time of 10 h followed by immediate tape stripping (to evaluate the amount of lidocaine in the SC at that time point). Successive tape strips were grouped in sets based on a combined SC weight of at least 400 µg or 6 tape strips, whichever came first, and also evaluated by weight of SC removed. Lidocaine was extracted with methanol from each set of tape strips and from the skin section remaining after tape stripping.

In Vitro Permeation Test

Receiver solution samples were collected at 3, 6, 9, and 10 h. The IVPT samples were analyzed using ultra performance liquid chromatography (UPLC).

Tape Stripping

The mass of skin on each tape was determined by weighing before and after tape stripping. Successive tape strips were combined into groups with a combined SC weight of at least 400 µg. Lidocaine was extracted from each group of tapes and from remaining skin section after tape stripping using 3 mL methanol and shaking in 15 mL centrifuge tubes for 20 h. The extracts from the tape strips and remaining skin were analyzed using UPLC.

Analytical Method

An Agilent ZORBAX 300SB-C8 (3.5 µm, 4.6 x 150 mm) column with a Phenomenex SecurityGuard™ C18 cartridge (5 µm, 4 x 3.0 mm) was used for the analytical method for IVPT samples and IVTS samples for lidocaine. The mobile phase composition used for lidocaine was A:acetonitrile, B:50 mM phosphate buffer (pH 5.9); isocratic conditions (A:20, B:80, v/v) at a flow rate of 1.0 mL/min. An injection volume of 10 µL was used for all samples.

Results

Table 1. Inactive ingredients in each lidocaine patch

Lidocaine A patch	Lidocaine B patch
dihydroxyaluminum aminoacetate, disodium edetate, gelatin, glycerin, kaolin, methylparaben, polyacrylic acid, polyvinyl alcohol, propylene glycol, propylparaben, sodium carboxymethylcellulose, sodium polyacrylate, D-sorbitol, tartaric acid, and urea	polyisobutylene adhesive matrix

Results

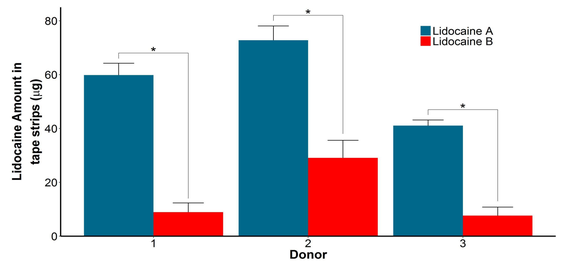

Figure 1. Comparison of the amount of lidocaine (mean ± SD) from tape strips of three different donors (n=4 per lidocaine product) following the administration of two different lidocaine dermal patches [* represents significantly different ($p < 0.05$)].

Table 2. Total permeation and drug amount from tape strips following 10 h patch application from each donor: A) lidocaine patch A and B) lidocaine patch B [values reported as mean ± SD].

	Lidocaine A patch		Lidocaine B patch	
	Total permeation (µg)	Skin lidocaine amount (µg)	Total permeation (µg)	Skin lidocaine amount (µg)
Donor 1	98.2 ± 11.8	59.8 ± 4.4	77.0 ± 15.4	8.9 ± 3.4
Donor 2	10.0 ± 3.6	73.2 ± 5.3	74.9 ± 6.9	29.1 ± 6.5
Donor 3	20.0 ± 7.6	41.1 ± 2.1	73.0 ± 12.1	7.6 ± 3.1

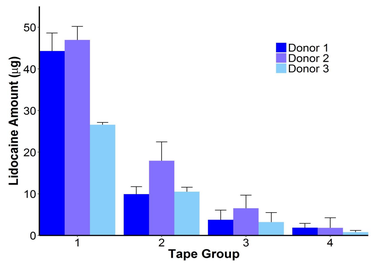

Figure 2. Amount of lidocaine (mean ± SD) per tape group (n=4 per donor and tape group) from three different donors administered lidocaine product A patch.

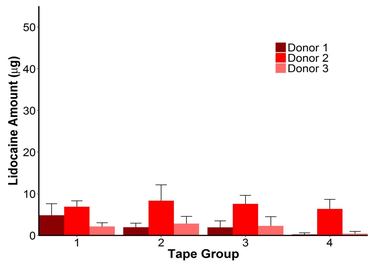

Figure 3. Amount of lidocaine (mean ± SD) per tape group (n=4 per donor and tape group) from three different donors administered lidocaine product B patch.

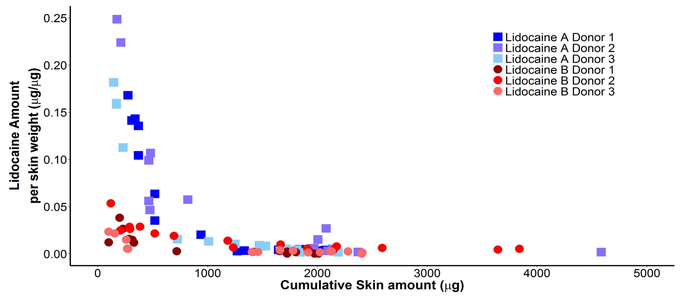

Figure 4. Lidocaine amount per skin mass in each tape group versus cumulative skin mass from three donors and two different Lidocaine dermal patches.

Results

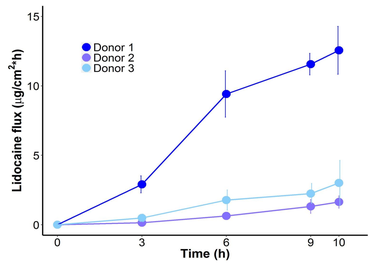

Figure 5. IVPT results of lidocaine permeation after administration of lidocaine topical patch A for 10 h in three donors (n=4).

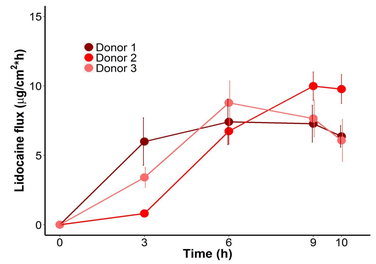

Figure 6. IVPT results of lidocaine permeation after administration of lidocaine topical patch B for 10 h in three donors (n=4).

Table 3. Total permeation and drug amount from tape strips following a 10 h patch application: A) lidocaine patch A, and B) lidocaine patch B [values reported as mean ± SD].

	Lidocaine A patch	Lidocaine B patch	*p*-value (A vs. B)
Lidocaine Permeation (µg)	42.7 ± 41.9	74.9 ± 11.0	0.267
Lidocaine from Tape Strips (µg)	57.9 ± 14.1	15.2 ± 11.1	0.015
Total Lidocaine Absorption (µg)	103.8 ± 52.8 ??	92.7 ± 13.3 ??	0.742
Lidocaine Delivery (%)*	2.2 ± 1.1	9.8 ± 1.4	-

Conclusions

Based upon this limited *in vitro* data set, the amount of lidocaine in the SC at 10 h following patch application appeared to be different for lidocaine products A and B (Figure 1), although the total absorption of lidocaine was similar for the two products (Table 3). Assuming a zero order release the bioavailability of the reported data (2.2 ± 1.1% and 9.8 ± 1.4%) could be extrapolated over a patch application time of 12 h, amounting to 2.6 and 11.8% of the amount of lidocaine in products A and B respectively (Table 3). This is consistent with the reported lidocaine *in vivo* absorption from these patches in humans of 3 ± 2% and 11 ± 4% of the lidocaine in the patch from Products A and B, respectively. Total permeation from Product A exhibited more variability than Product B (CV% was 98 and 15% for Products A and B, respectively, Table 3). Interestingly, a significant difference was observed between Products A and B in the amount of lidocaine in the top layer (tape group 1) of the stratum corneum (Figures 2, 3 and 4). Residual hydrogel left by Product A on the skin surface, which was not cleaned after patch removal, could have influenced this measurement. Another possibility is that Product A has several permeation enhancers in a hydrogel matrix, while Product B has no enhancers in a polyisobutylene matrix (Table 1). The apparently larger concentration gradient in the stratum corneum for Product A (Figure 4) could occur if permeation enhancers were depleted from the patch and left a large (and partially stranded) lidocaine depot near the skin surface. The smaller concentration gradient observed for Product B might arise if lidocaine diffusion was initially faster but then became matrix limited by 10 h when skin sampling occurred. Microscopic examination of the skin surface might be able to address the question of hydrogel contamination from the adhesive patch. Although the clinical relevance of these results is unclear, they suggest that the local bioavailability of some topical formulations may be of value to further evaluate in the skin, proximal to the site of action.

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