In Vivo Evaluation of Lidocaine Bioavailability from Two Topical Patch Products by Pharmacokinetic and Skin (Tape) Stripping Analyses

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Introduction

The site of action for many topical drug products is in the skin and/or in surrounding local tissues. Therefore, the local bioavailability for these products may influence their therapeutic efficacy and may be relevant for evaluating bioequivalence. The bioavailability of lidocaine from two 5% lidocaine topical patch products (A and B) were assessed both in serum and stratum corneum (SC) samples obtained from healthy volunteers. Tape stripping was used to quantify the amount of drug present in the SC.

Objective

Two pharmacokinetic methodologies (PK and Tape Stripping) were utilized to investigate the bioavailability of two different lidocaine dermal products. Lidocaine serum concentrations and SC lidocaine amounts were compared between the two products.

Methods

Study Design

Pharmacokinetics

Two different lidocaine topical patch, 5% products (A and B, 140 cm^2 each) are currently under evaluation. To obtain serum concentrations, healthy volunteer were dosed with two patches of one product applied to the upper arms and removed after a 10 h application time. Blood samples are withdrawn at specific time points; prior to patch application through 15 h post patch application. Serum samples were analyzed using a validated LC-MS/MS method and pharmacokinetic (PK) analysis was conducted using Phoenix WinNonlin® to calculate the AUC and C_{max} from each product (A and B).

Tape Stripping

In a following session, six patch pieces (8.25 cm^2, each of product A and B) are applied to the volar forearms of the same subjects in order to quantify the amount of lidocaine in the SC. The locations of patch pieces applied are randomized to one of six sites corresponding to three different time points: uptake (10 h post application), 5 h clearance (15 h post application) and 14 h clearance (24 h post application) for each lidocaine product (A and B, Figure 1). All patch pieces are removed after a 10 h application period; followed by tape stripping of a 5 cm^2 section of the application sites at the designated time points for uptake and clearance. The uptake site is tape stripped immediately following patch removal and consists of a minimum of 12 tape strips and a maximum of either 30 tape strips or when a site reaches 6 times the baseline transepidermal water loss (TEWL) value. TEWL readings were obtained using a Delfin VapoMeter. The clearance time points are tape stripped at 5 h or 14 h following patch removal. Successive tape strips are grouped together based on combined SC weight of at least 750 µg or 6 tapes, whichever occurs first. Lidocaine is extracted from skin tape strips using methanol and analyzed using a validated HPLC method.

Analytical Method

The amount of lidocaine in the tape strip extracts (10 µL injections) were determined using 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) operated under isocratic conditions (20:80 v/v acetonitrile:50 mM phosphate buffer, pH 5.9) at a flow rate of 1.0 mL/min. Lidocaine concentrations in serum (20 µL injections) were quantified using an Atlantis HILIC Silica (3 µm, 3.0 x 50 mm) column with a Phenomenex SecurityGuard™ HILIC cartridge (4 x 2.0 mm) under isocratic conditions (91:9 v/v acetonitrile: ammonium formate, pH 3.2)) at a flow rate of 0.5 mL/min.

Results

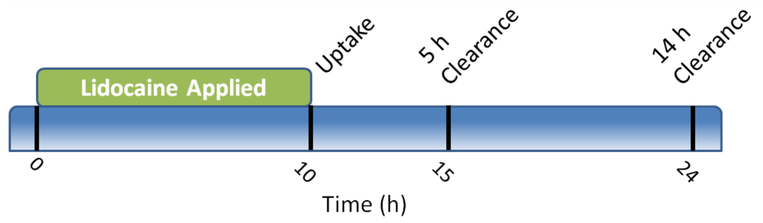

Figure 1. Tape Stripping clinical study design. Tape Stripping occurs at 10, 15 and 24 h post patch application.

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

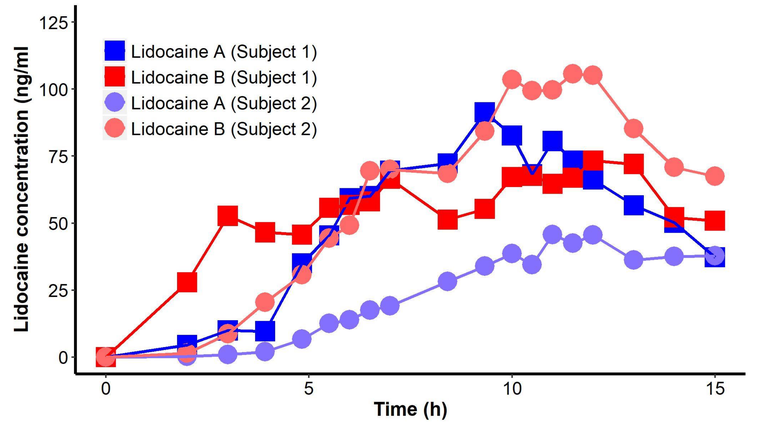

Figure 2. Lidocaine serum concentration versus time from two subjects following the 10 h administration of two patches (Lidocaine A or B).

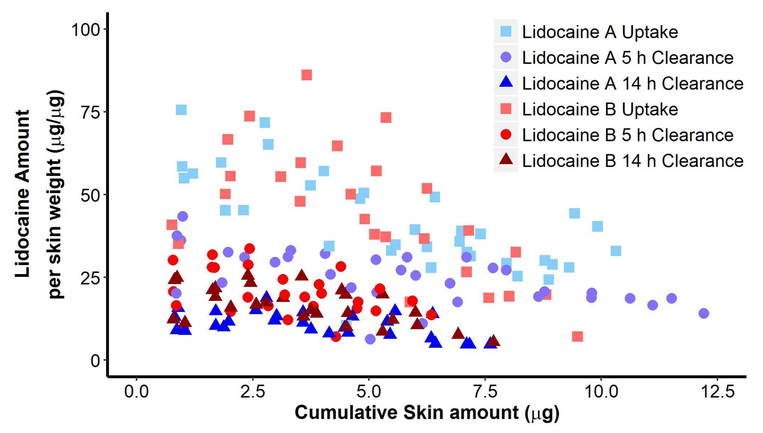

Figure 3. Lidocaine amount per skin mass in each tape group versus cumulative skin mass from two subjects and two different lidocaine dermal patches.

Table 2. Non-compartmental analysis and tape stripping results for the first two volunteers

Subject	1		2	
Product	**A**	**B**	**A**	**B**
Non-compartmental analysis				
AUC (ng*h/mL)	696.8	771.9	320.1	833.7
C_{max} (ng/mL)	91.3	73.3	45.7	105.6
Stratum Corneum Lidocaine Amount (2 replicates)				
10 h uptake (µg)	442.8, 386.4	319.1, 369.6	333.5, 322.0	386.2, 314.8
5 h Clearance (µg)	210.3, 159.7	97.7, 104.8	287.1, 199.4	110.8, 109.1
14 h Clearance (µg)	86.9, 62.5	129.2, 93.0	70.3, 57.8	86.0, 82.6
Percent Cleared from SC following patch removal				
5 h Clearance (%)	55	71	25.8	68.6
14 h Clearance (%)	82	68	80.5	75.9

Results

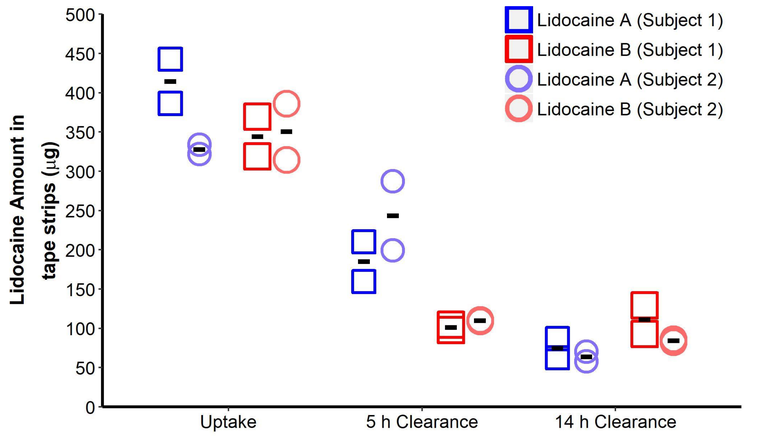

Figure 4. Amount of lidocaine (average represented by line) in tape strips per topical patch product (Lidocaine A; blue, Lidocaine B; red) and per subject (Subject 1; square, Subject 2; circle). Amount of lidocaine was quantified at three different time-points, immediately following 10 h patch application, 5 h and 14 h following patch removal.

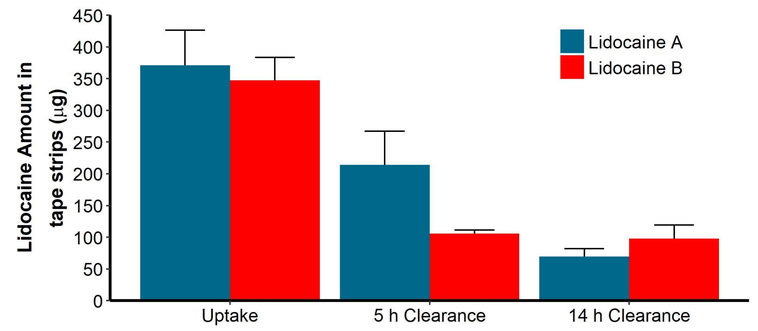

Figure 5. Comparison of the amount of lidocaine (mean ± SD) in tape strips of two different subjects (n=4 replicates per lidocaine product). Amount of lidocaine was quantified at three different time-points, immediately following 10 h patch application, 5 h and 14 h following patch removal.

Conclusions

Based on the limited data available from the study of two healthy volunteers, it appears that the PK, drug delivery and SC clearance (at least at 14 h) of products A and B are not different, relative to each other (Table 2, Figure 2, 4 and 5). These observations could change as measurements from a larger number of subjects (n=12) are added to the study. The combination of PK and in vivo skin tape stripping may provide insight into the relationship between systemic and local bioavailability of topical products. Therefore, the addition of skin tape stripping to traditional PK studies might provide additional information on the bioavailability close to the site of action, which cannot be obtained with systemic PK studies alone, particularly for drugs locally acting in the skin or surrounding tissue.

Acknowledgment

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