Impact of operator variability on the reproducibility of tape stripping results

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Introduction

Site of action for topical dermatological drug products is in the skin and/or in the surrounding local tissues. Therefore, local bioavailability of such products may be relevant for evaluating bioequivalence. Tape stripping is a relatively non-invasive methodology that can be used to determine the stratum corneum (SC) bioavailability of a drug, but to our knowledge the variability and reproducibility of tape stripping from different operators have not been investigated.

Objective

In order to evaluate operator differences, two lidocaine and two diclofenac products were used as model compounds. In addition, two different operators (operators 1 and 2) were used for collecting data from each volunteer.

Methods

Study Design

Two different commercially available lidocaine topical delivery systems (TDS), 5% products (Lidocaine A and B, 140 cm^2 each) and diclofenac topical products (diclofenac TDS, 1.3% [A] and diclofenac topical solution, 2% [B]) were evaluated. Two separate clinical studies (lidocaine and diclofenac) that closely followed the protocol from N'Dri-Stempfer et al.[1] were conducted with twelve planned volunteers per study. For the two studies, the tape stripping session consisted of applying Products A and B to three sites on each volar forearm of each volunteer (Figure 1). For each site, a TDS piece cut to approximately 8.25 cm^2 or 10 mg/cm^2 of solution spread over 8.25 cm^2 was applied (Figures 1 and 2). Locations of the applied products were randomized to one of six sites and duplicated on the other arm. Each operator was responsible for one arm (6 sites). Products were removed and skin surface cleaned from each site following the uptake time point (lidocaine: 10 h post application; diclofenac A: 10 h post application; diclofenac B: 6 h post application, Figures 3 and 4). A 5-cm^2 section of each site was tape stripped to determine the amount of drug in the SC at each designated time point (uptake, clearance 1 [lidocaine: 5 h post removal; diclofenac: 17 h post removal] and clearance 2 [lidocaine: 14 h post removal; diclofenac: 41 h post removal], Figures 3 and 4). To insure that most of the SC is collected (and thereby most of the drug) without too much discomfort to volunteers, each site was tape stripped with a minimum of 12 tape strips up to a maximum of either 30 tape strips or when the site reached 6x the baseline transepidermal water loss (TEWL) value, determined using a Delfin VapoMeter. Successive tape strips were grouped together based on a combined SC weight of at least 750 µg or 6 tapes, whichever came first. Lidocaine or diclofenac, respectively, were extracted from the tape strip groups with methanol and analyzed using validated high pressure liquid chromatography (HPLC) methods.

Analytical Method

The amount of lidocaine in tape-strip extracts (10 µL injections) was 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.

The amount of diclofenac in tape-strip extracts (10 µL injections) was 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 (65:35 v/v methanol:20 mM phosphate buffer, pH 2.3) at a flow rate of 1.0 mL/min.

Analysis

The parameters investigated include skin mass collected, skin drug amount and drug skin clearance. Drug skin clearance is calculated as the percent of drug cleared from the skin from uptake to the clearance time point. These were chosen because they are useful in portraying the variability associated with tape stripping, amount of skin collected and amount of drug in the skin and the rate of elimination of drug from the skin.

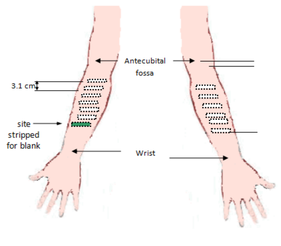


Figure 1. Diclofenac and lidocaine tape stripping site locations on volar forearm.

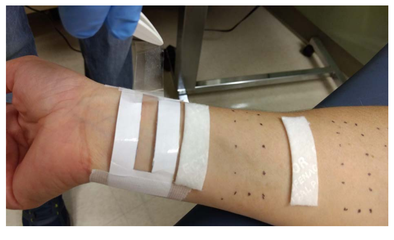


Figure 2. Example tape strip from clinical study

Methods

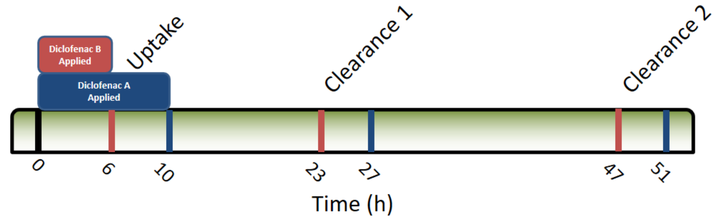


Figure 3. Diclofenac tape stripping clinical study design. Tape stripping occurs at 6 or 10, 23 or 27 and 47 or 51 h post application for diclofenac B and A respectively.

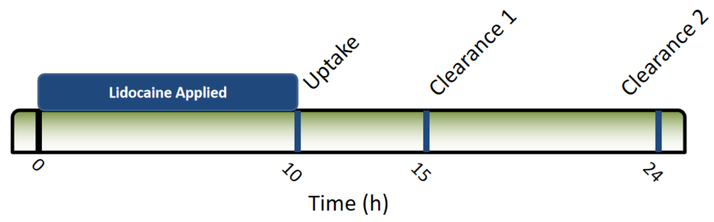


Figure 4. Lidocaine tape stripping clinical study design. Tape stripping occurs at 10, 15 and 24 h post application.

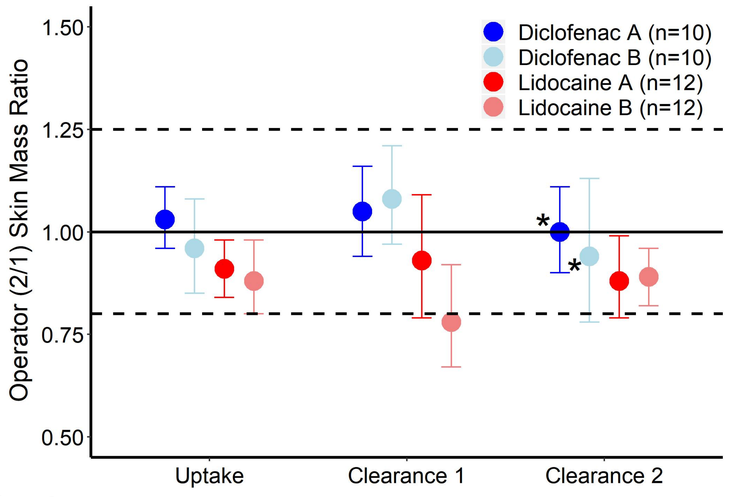
Results

Twenty-two volunteers (lidocaine: n=12; diclofenac: n=10) have completed the studies to date. The comparison of results between operators showed a similar drug skin clearance, tape strip skin amount removed and tape strip drug amount extracted following tape stripping for both drugs (Table 1, Figures 5, 6 and 7).

Table 1. Geometric mean operator ratio for skin mass, skin drug amount and drug skin clearance ratio (90% confidence interval) for both lidocaine and diclofenac clinical studies

Study	Lidocaine (n=12)		Diclofenac (n=10)	
Product	**A**	**B**	**A**	**B**
Operator (2/1) Skin Mass Ratio, geometric mean (90% CI)				
Uptake	0.91 (0.84 - 0.98)	0.88 (0.80 - 0.98)	1.03 (0.96 - 1.11)	0.96 (0.85 - 1.08)
Clearance 1	0.93 (0.79 - 1.09)	0.78 (0.67 - 0.92)	1.05 (0.94 - 1.16)	1.08 (0.97 - 1.21)
Clearance 2	0.88 (0.79 - 0.99)	0.89 (0.82 - 0.96)	1.00 (0.90 - 1.11)*	0.94 (0.78 - 1.13)*
Operator (2/1) Skin Drug Amount Ratio, geometric mean (90% CI)				
Uptake	0.88 (0.78 - 0.99)	0.87 (0.77 - 0.98)	0.97 (0.86 - 1.10)	0.95 (0.72 - 1.27)
Clearance 1	0.83 (0.69 - 0.99)	0.77 (0.63 - 0.94)	0.97 (0.89 - 1.07)	1.03 (0.78 - 1.34)
Clearance 2	0.75 (0.65 - 0.87)	0.93 (0.77 - 1.11)	0.84 (0.72 - 1.00)*	1.22 (0.97 - 1.53)*
Operator (2/1) Drug Skin Clearance Ratio, geometric mean (90% CI)				
Clearance 1	0.98 (0.67 - 1.44)**	1.05 (0.80 - 1.36)	0.97 (0.88 - 1.08)	0.96 (0.87 - 1.06)
Clearance 2	1.03 (1.00 - 1.06)	1.01 (0.96 - 1.06)	1.02 (0.99 - 1.07)*	0.96 (0.91 - 1.01)*

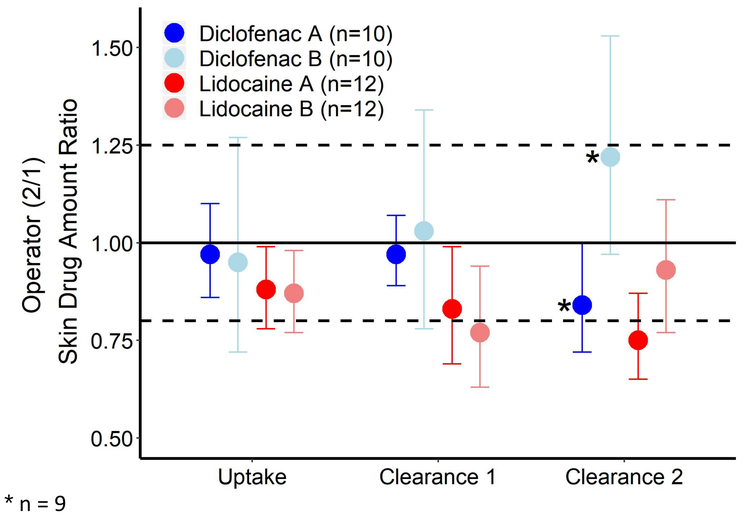
* n = 9
**n = 10



* n = 9

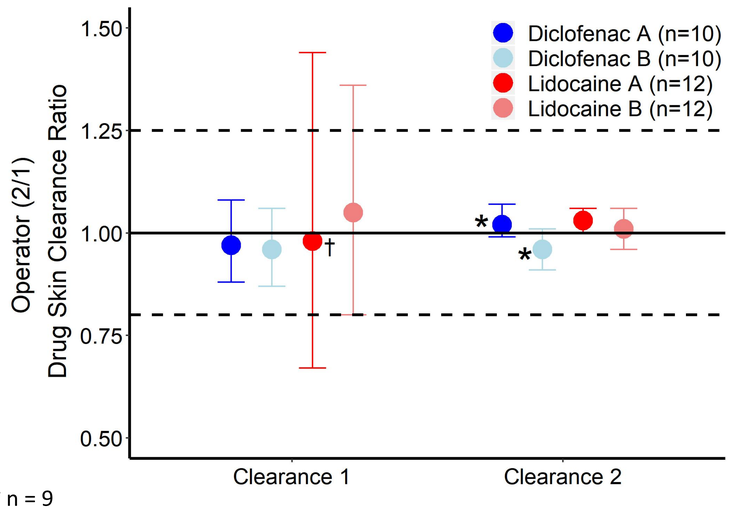
Figure 5. Operator ratio for skin mass from tape strips (geometric mean and 90% confidence interval) for lidocaine and diclofenac clinical study

Results



* n = 9

Figure 6. Operator ratio for skin drug amount from tape strips (geometric mean and 90% confidence interval) for lidocaine and diclofenac clinical study



* n = 9
† n = 10

Figure 7. Operator ratio for drug skin clearance from tape strips (geometric mean and 90% confidence interval) for lidocaine and diclofenac clinical study.

Conclusions

The mass of SC collected on each tape strip and the number required to collect most of the SC from a site is highly variable even for the same operator on the same subject (data not shown). To reduce variability, the number of tape strips collected from each site is based on a TEWL criterion (6x baseline) combined with a minimum of 12 and maximum of 30 tape strips that insures most of the SC, and therefore most of the drug, is collected. From the results, it appears that some of the 90% confidence intervals for skin mass, skin drug amount and drug skin clearance ratios are close to 1.0 indicating good reproducibility on the amount of skin removed following tape stripping (Table 1, Figures 5, 6 and 7). These results are only from 10 or 12 volunteers and it is likely that with additional volunteers it may be possible to move the mean closer to 1.0 to get a tighter 90% confidence interval. These are promising results and show it is possible to perform tape stripping with multiple operators without increasing variability.

Acknowledgment and Reference

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[1]. B N'Dri-Stempfer, RH Guy, WC Navidi and AL Bunge, Improved bioequivalence assessment of topical dermatological products using dermatopharmacokinetics, *Pharm Res*, 26:316-328 (2009) doi:10.1007/s11095-008-9742-9, PMID:18941872