Impact of operator variability on the reproducibility of tape stripping results

T0930-13-84

Sagar Shukla[1], Sherin Thomas[1], Dana Hammell[1],
Annette Bunge[2], Hazem E. Hassan[1], Audra L. Stinchcomb[1]

[1]School of Pharmacy, University of Maryland, Baltimore, MD,
[2]Chemical and Biological Engineering, Colorado School of Mines, Golden, CO

sshuk001@umaryland.edu

aaps PharmSci 360

Advancing Pharmaceutical Sciences, Careers, and Community

PURPOSE

The 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 epolamine 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 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 3). 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 3 and 4). 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 the 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 1 and 2). 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 1 and 2). 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.

Analysis

The HPLC method for both studies was validated with an LLOQ of 0.1 µg/ml. 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 parameters were chosen because they are useful in determining variability associated with tape stripping, amount of skin collected, amount of drug in the skin and rate of elimination of drug from the skin.

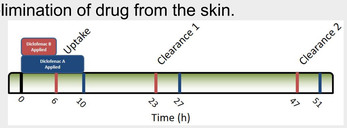

Figure 1. Diclofenac tape stripping clinical study design. Tape stripping occurs at 6 or 10, 23 or 27 and 47 or 51 h post application for Diclofenac B and A, respectively.

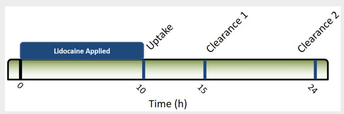

Figure 2. Lidocaine tape stripping clinical study design. Tape stripping occurs at 10, 15 and 24 h post application.

RESULTS

Twenty-four volunteers (lidocaine: n=12; diclofenac: n=12) have completed the studies. 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 5-7).

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=12)	
Product	**A**	**B**	**A**	**B**
Operator (2/1) Ratio of the Skin Mass, geometric mean (90% CI)				
Uptake	0.91 (0.84 - 0.98)	0.88 (0.80 - 0.98)	1.04 (0.97 - 1.10)	0.91 (0.80 - 1.03)
Clearance 1	0.93 (0.79 - 1.09)	0.78 (0.67 - 0.92)	1.00 (0.90 - 1.12)	1.09 (1.00 - 1.20)
Clearance 2	0.88 (0.79 - 0.99)	0.89 (0.82 - 0.96)	1.00 (0.92 - 1.09)*	0.93 (0.80 - 1.08)*
Operator (2/1) Ratio of the Skin Drug Amount, geometric mean (90% CI)				
Uptake	0.88 (0.78 - 0.99)	0.87 (0.77 - 0.98)	0.95 (0.85 - 1.07)	0.96 (0.76 - 1.21)
Clearance 1	0.83 (0.69 - 0.99)	0.77 (0.63 - 0.94)	1.00 (0.9 - 1.10)	1.11 (0.87 - 1.42)
Clearance 2	0.75 (0.65 - 0.87)	0.93 (0.77 - 1.11)	0.82 (0.71 - 0.94)*	1.22 (1.01 - 1.46)*
Operator (2/1) Ratio of the Drug Skin Clearance, geometric mean (90% CI)				
Clearance 1	0.98 (0.67 - 1.44)**	1.05 (0.80 - 1.36)	0.97 (0.89 - 1.05)	0.94 (0.86 - 1.03)
Clearance 2	1.03 (1.00 - 1.06)	1.01 (0.96 - 1.06)	1.03 (0.99 - 1.06)*	0.97 (0.93 - 1.00)*

* n = 11, because there is no clearance 2 data for one volunteer
** n = 10, because the percent cleared was greater than 1 for two volunteers

Table 2. Mean number of tape strips used per timepoint and product and operator. Blue highlighted region indicates larger number of tape strips used.

Study	Lidocaine (n=12)		Diclofenac (n=12)	
Operator	**1**	**2**	**1**	**2**
Number of Tapes used, Mean (SD)				
Product A (%)				
Uptake	22.5 (6.6)	19.1 (6.3)	19.3 (5.7)	17.6 (6.4)
Clearance 1	24.2 (5.1)	23.3 (6.2)	24.2 (6.0)	20.4 (5.0)
Clearance 2	24.2 (5.1)	23.1 (7.2)	25.5 (5.2)*	22.3 (7.5)*
Product B (%)				
Uptake	17.3 (5.2)	15.6 (5.4)	22.1 (6.6)	22.9 (6.9)
Clearance 1	26.7 (4.9)	23.3 (6.9)	20.4 (4.0)	17.7 (4.8)
Clearance 2	26.7 (5.4)	22.9 (6.9)	24.1 (4.9)*	22.7 (6.5)*

* n = 11

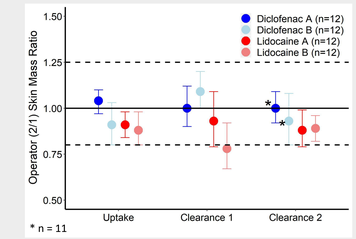

Figure 5. Operator ratio for skin mass from tape strips (geometric mean and 90% confidence interval) for lidocaine and diclofenac clinical study

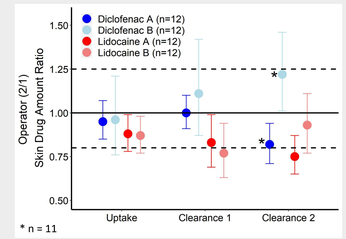

Figure 6. Operator ratio for skin drug amount from tape strips (geometric mean and 90% confidence interval) for lidocaine and diclofenac clinical study

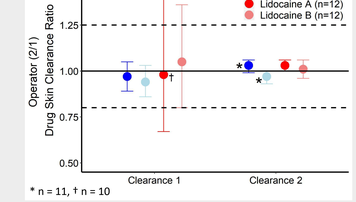

Figure 7. Operator ratio for drug skin clearance from tape strips (geometric mean and 90% confidence interval) for lidocaine and diclofenac clinical study.

METHODS

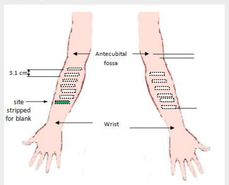

Figure 3. Diclofenac and lidocaine tape stripping site locations on volar forearm.

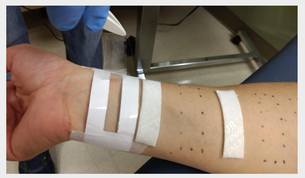

Figure 4. Example tape strip from clinical study

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 to insure most of the SC, and therefore most of the drug, is collected. In this study, the operator-to-operator ratios are all close to 1.0 for the drug skin clearance and the 90% confidence intervals are mostly close to 1.0 for the skin mass and skin drug amount (Table 1, Figures 5-7). This indicates good reproducibility even though on average operator 1 required more tapes to reach the required TEWL value (Table 2). These results are only from 12 volunteers and it is likely that additional volunteers (and greater statistical power) would reduce the width of the 90% confidence interval or move the mean closer to 1.0. These are promising results and demonstrate it is possible to perform tape stripping with multiple operators without increasing variability.

FUNDING/REFERENCE

Funding for this project was made possible, in part, by the Food and Drug Administration through grant 1U01FD004947. The views expressed in this poster do not reflect the official policies of the U.S. Food and Drug Administration or the U.S. Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

[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

UNIVERSITY of MARYLAND SCHOOL OF PHARMACY