ADHESION CHARACTERISTICS OF A TOPICAL LIDOCAINE PATCH 1.8% (36MG)

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INTRODUCTION:

In general, adhesion of medicated patches is an important attribute as it contributes to optimal safety, efficacy and patient compliance.[1] Clinicians should understand the adhesion characteristics of patches under different conditions such as with heat and exercise.

Topical lidocaine 5% patches are approved and indicated for the relief of pain associated with postherpetic neuralgia (PHN). Lidocaine is an amide local anesthetic agent that blocks fast voltage-gated sodium channels in the cell membrane of postsynaptic neurons. The amount of lidocaine systemically absorbed from a patch is thought to be related to the pharmaceutical properties of the patch, the duration of application and how well the patch adheres to the skin.

SCILEX Pharmaceuticals has submitted an NDA for a bioequivalent lidocaine patch, 1.8%, formulated as a thin, flexible, single-layer, anhydrous drug-in-adhesive delivery system, also for the relief of pain associated with PHN. Based upon previous clinical and PK data, this formulation offers more efficient delivery of lidocaine by requiring less drug to achieve similar plasma concentrations and therapeutic effect. Less residual drug in the patch after use may have potential benefits from an accidental or prolonged exposure.

OBJECTIVE:

To describe the adhesion properties of the lidocaine patch 1.8% during a twelve-hour dosing period under normal conditions and with heat and exercise.

METHODS AND MATERIALS:

Two separate studies were conducted to evaluate the adhesion characteristics of the patch under normal conditions and with exposure to heat and exercise.

Study SCI-LIDO-ADH-001, was an open label, single-treatment, single period, single application adhesion performance study in fifty-four (54) healthy adult, human subjects. A single lidocaine patch 1.8% was applied over a predetermined fixed area on the subjects lower/mid back according to a randomization schedule and worn for the 12-hour study period.

The primary endpoint of adhesion performance was evaluated immediately after application (0 hour) and at 3, 6, 9 and 12 (before patch removal) hours after application with a window period ±15 minutes.

The patch was checked for degree of adhesion by a trained scorer using the recommended rating scale (see Table 1).

Table 1. Adhesion Rating Scale.

0	=	≥ 90% Adhered (essentially no lift off the skin)
1	=	≥ 75% to < 90% Adhered (some edges only lifting off the skin)
2	=	≥ 50% to < 75% Adhered (less than half of the patch lifting off the skin)
3	=	> 0% to < 50% Adhered but not detached (more than half of the patch lifting off the skin without falling off)
4	=	0% Adhered - patch detached (patch completely off the skin)

Safety of all subjects was assessed thorough out the study period. Skin irritation was evaluated at the site of application: 30 minutes (with window period +10 minutes) after post patch removal, and at 2 hours post patch removal with window period +/- 15 minutes. Skin irritation was evaluated using two standard dermal scales.

METHODS AND MATERIALS: (CONT)

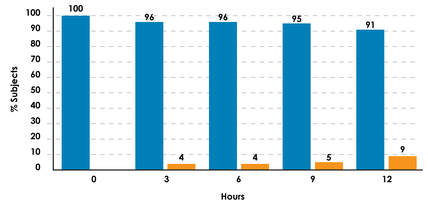
Study SCI-LIDO-HEX-001, was an open label, randomized, three-treatment, three-sequence, three-period, cross-over, pharmacokinetic and adhesion performance study of lidocaine patch 1.8% (3 patches) in fasting, healthy, adult, human subjects, during physical exercise, exposed to heat, and under normal conditions. Three treatment periods were as follows: Treatment A: physical exercise condition, subjects were instructed to perform 30 minutes on an exercise bike achieving heart rate of 108 beats/minute (with continuous heart monitoring during exercise). Exercise was done immediately after patch application and at 2.50, 5.50 and 8.50, hour post-patch application with a window period of ±10 minutes. Treatment B: with heating condition, a heating pad adjusted to medium setting was applied for 20 minutes immediately after patch application and at 8.50 hours post-patch application. A blanket/towel was placed between the patches and heating pad to reduce the chance of skin burning. Treatment C: normal conditions. Blood sample was taken from each subject in each of the treatment periods to evaluate pharmacokinetics profile of the lidocaine patch 1.8% under different conditions. A total of 16 venous blood samples pre-dose and post-dose were collected over a 48-hour time period. Each subject was evaluated for adhesion scores (Table 1) and standard dermal irritation scales during each of the study periods.

For both studies adhesion was calculated as the Cumulative Adhesion Score (CAS) during the 12-hour application period. Descriptive statistics (e.g. mean, standard deviation, median, minimum and maximum) on CAS was generated. In addition to mean scores, proportion of subjects with a meaningful degree of detachment (i.e. score ≥3) was provided.

RESULTS:

In Study SCI-LIDO-ADH-001, no subjects dropped out and none had any degree of meaningful detachment of the patch (i.e. score ≥3). Most subjects had an adhesion rating score of 0 or 1 over the 12- hour dosing period (see Figure 1). Ninety-one percent (49/54) of subjects had a score of 0 (essentially no lift off the skin); and 9% (5/54) of subjects had a score of 1 (some edges only lifting off the skin) at the end of the 12-hour period. No subjects had a meaningful degree of detachment (i.e. score ≥3).

Figure 1: SCI-LIDO-ADH-001. Adhesion score over 12- hour dosing period. Score of 0 (blue bar), Score of 1(orange bar).

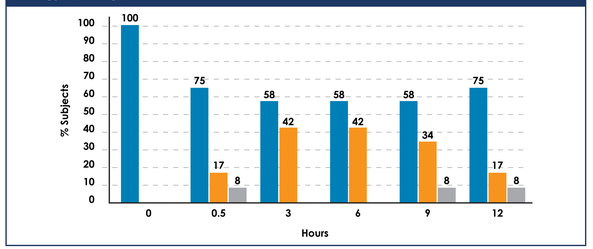


Considering the adhesion scores of the subjects at all assessment time points and the proportion of subjects with a meaningful degree of detachment (i.e. score ≥3), it was concluded that greater than 90% of subjects had >90% adhesion (Score 0). In this study, no meaningful irritation was reported in any of the subjects.

In Study SCI-LIDO-HEX-001, which evaluated the effects of heat and exercise on PK profile and patch adhesion, no patches completely detached during the study, none were removed early for unacceptable irritation, and no subjects dropped out of the study before the end of the 12-hour application during any of the treatment periods.

RESULTS: (CONT)

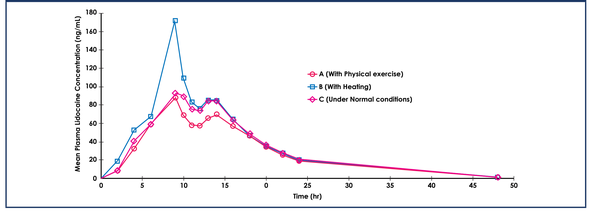
Figure 2: SCI-LIDO-HEX-001. Adhesions scores during exercise over the 12-hour dosing period. Score of 0 (blue bar), Score of 1(orange bar), and Score of 2 (grey bar).



Exercise appeared to have an effect on adhesion. While the percentage of patients with adhesion scores of 0 decreased initially, these scores rose by the end of the 12-hour dosing period, reflecting our observation that the patch appeared to re-adhere in some subjects.

Adhesion scores during heating were minimally effected during first 6 hours; all subjects had an adhesion score of 0 (essentially no lift of the skin). At 9 hours (83%) and at 12 hours (75%), respectively had adhesion score of 0. All subjects had an adhesion scores of 0 during normal conditions at all time points throughout the 12- hour dosing interval.

Figure 3. SCI-LIDO-HEX-001. Linear Plot of Mean Plasma Lidocaine patch 1.8% Concentrations Vs Time with physical exercise, heat and normal conditions.



As seen in Figure 3, the mean values of the primary PK parameters, C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, were lower during Treatment A (with physical exercise) than during Treatment C (under normal conditions). The effects of physical exercise on the rate and extent of lidocaine patch 1.8% absorption was not significant. The median T_{max} was 9.0 hours for Treatment A (with physical exercise) and 11.5 hours for Treatment C (under normal conditions). The half-life observed was similar for Treatment A (5.6 h) and Treatment C (5.2 h).

The effects of heating on lidocaine patch 1.8% absorption appeared to be immediate and reversible. These effects were noticeable when the heat was applied at 8.5 hours, and returned baseline following removal after 20 minutes. Under heated conditions, maximum lidocaine levels reached approximately to 180 ng/mL, which is up to ten times less than therapeutic antiarrhythmic levels.

RESULTS: (CONT)

Table 2. SCI-LIDO-HEX-001. Pharmacokinetic parameters for Lidocaine patch 1.8% with physical exercise, heat and normal conditions.

Parameters	Geometric Mean			Intra Subject CV (%)
	Physical Exercise	Heat	Normal Conditions	
C_{max}	87.26	134.43	91.72	24.4
AUC_{0-t}	1264.15	1513.10	1400.70	17.9
$AUC_{0-\infty}$	1281.92	1526.88	1416.03	17.4

Given the timing, heating appears to have increased the C_{max} with little overall effect on the AUC as seen in Table 2. There was little difference observed between the three treatments at all other time points.

CONCLUSIONS:

In general, adhesion of a topical patch is critical to the safety, efficacy and quality of the delivery system/ product. FDA has received numerous reports of "adhesion lacking" for numerous transdermal or topical products.[1] Poor adhesion performance of a patch may lead to reduced skin contact, which may consequently lead to improper drug absorption, or replacement of the patch earlier than the prescribed dosing period and/or safety concerns. Most topical/ transdermal patches on the market lack a characterization of the adhesive performance of the patch in their prescribing information.

In the studies presented here, we described the adhesion profile of an investigational, thin and flexible, single-layer, anhydrous drug-in-adhesive lidocaine patch 1.8% under normal conditions as well as with heat and exercise. Under normal conditions study demonstrated that greater than 90% of subjects had >90% adhesion (Score- 0). There were no effects on patch adhesion associated with exposure to heat. There was some patch lifting observed during exercise that may be associated with sweat excretion between the patch and skin; however, there was some level of patch re-adherence observed that may be associated with the skin drying. No meaningful irritation was reported within both studies across all time points in any of the subjects.

We also examined the impact of heat and exercise on the pharmacokinetic profile of the patch. As expected, heat had an effect on C_{max}, but the drug returned to normal levels after removal of heat and there was no effect on AUC. Heat did not appear to have a deleterious effect on patch performance which may have presented as either a complete (lidocaine) dose dump (immediate and rapid rise C_{max}) or reduced drug delivery due to changes in the adhesion system, resulting in a much lower AUC. There was no significant effect on PK observed with exercise when compared to subjects under normal conditions.

To our knowledge, we are the first to report the effects of heat and exercise on a topical lidocaine patch formulation. If approved, the SCILEX lidocaine patch 1.8% may offer an alternative to existing lidocaine patches, with adhesion throughout the dosing period and adhesion characteristics that withstand heat and exercise.

REFERENCES.

1. Wokovich AM, Prodduturi S, Doub WH, Hussain AS, Buhse LF. Transdermal drug delivery system (TDDS) adhesion as a critical safety, efficacy and quality attribute. Eur J Pharm Biopharm 2006;64:1-8