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

S. Shukla1, P. Ghosh1, S. Raney2, H. Hassan1, A. Bunge3, A. Stinchcomb1
1University of Maryland, 2U.S. Food and Drug Administration, 3Colorado School of Mines

Purpose
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 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 to monitor the bioavailability of lidocaine into and through the skin, that may potentially become available to proximal tissues.

Methods
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 cm²) were applied to human skin mounted in 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). Receiver solution samples were collected at 3, 6, 9, and 10 h. 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. The IVPT samples, tape strips and the remaining skin were analyzed using Ultra Performance Liquid Chromatography.

Results
The cumulative amount of lidocaine that permeated through the skin into the receiver solution, and the amount of lidocaine in the SC, were determined following a 10 hour patch application time. Tape stripping results showed that product A had a significantly greater amount of lidocaine in the SC (58.0 ± 16.1 μg) compared to product B (15.2 ± 12.1 μg)(paired t-test p-value of <0.05). Conversely, the cumulative amount of lidocaine that permeated through the skin during the study was lower for Product A (42.7 ± 48.3 μg) compared to Product B (75.0 ± 2.0 μg). However, the total lidocaine absorption (mass in tapes + remaining skin + mass permeated) from the two products was similar (Product A: 103.8 ± 52.8 μg, Product B: 92.7 ± 13.3 μg).

Conclusion
Based upon this limited in vitro data set, the amount of lidocaine in the SC at 10 h following patch application compared to what permeated through the skin appeared to be different for products A and B, although the total absorption of lidocaine was similar for the two products. The reported lidocaine in vivo absorption from these patches in humans is 3 ± 2% and 11 ± 4% of the lidocaine in the patch from Products A and B, respectively, which is consistent with the total absorption measured in vitro in this study: 2.2 ± 1.1% and 9.8 ± 1.4% from Products A and B, respectively. Total permeation from product A exhibited more variability than Product B. Product A has several permeation enhancers in a hydrogel matrix, while Product B has no enhancers in a polyisobutylene matrix. Skin permeation from products with permeation enhancers has been shown to be more variable. Interestingly, the significant difference between products A and B in the amount of lidocaine in the SC was predominantly due to differences in the amount of lidocaine measured in the outer third of the SC. Further evaluation of this difference in SC profile will be performed by microscopic examination of the surface for any potential hydrogel contamination, since the skin surface was not cleaned following patch removal. Further study may also be warranted to elucidate other factors that could influence the interpretation of tape stripping results following removal of an adhesive patch. Although the clinical relevance of these results is unclear, these results suggest that the local bioavailability of some topical formulations may be of value to evaluate in the skin, proximal to the site of action.

Acknowledgment. Funding for this project was made possible, in part, by the Food and Drug Administration through grant 1U01FD004947. The views expressed in this abstract 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.