

Variables Affecting Delivery of Glycopyrronium Tosylate Through Human Skin In Vitro

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Introduction

- Hyperhidrosis is a medical condition characterized by excessive sweating beyond what is required for normal thermal regulation, and can involve multiple body areas including the axillae, palms, soles, or craniofacial regions¹
- Glycopyrronium tosylate (GT) is a topical anticholinergic recently approved by the US Food and Drug Administration for the treatment of primary axillary hyperhidrosis in patients ≥9 years (glycopyrronium cloth, 2.4%, for topical use)²
- In vitro permeation models can be a powerful tool to gain insight into drug absorption (flux) profiles under varying conditions and to optimize clinical trial design³

Objective

- To determine using in vitro skin penetration studies how GT delivery through human skin is impacted by varying conditions including occlusion, wash-off, and skin thickness

Methods

- Across all experiments:
 - Human skin was dermatomed to a thickness of approximately 0.5 mm and mounted into flow-through diffusion cells (MedFlux-HT[®])
 - GT solution was applied at 10mg/cm² and allowed to dry

Occlusion

- Human abdominal skin was obtained from 3 donors after abdominoplasty
- Two methods of occlusion were used: 1) parafilm was pressed on the surface for the donor compartment, which leaves a small closed-off column of air above the skin; 2) saran wrap was pressed down on top of the surface of the skin
- Non-occluded skin was used as control
- The receiving fluid was collected over 12 hours, and the GT flux was assessed using liquid chromatography with tandem mass spectrometry (LC/MS/MS)

Wash-off

- Human abdominal skin was obtained from 3 donors after abdominoplasty
- After drying, GT was removed from the skin by wiping the skin surface once with the following: 1) a dry cotton swab; 2) a cotton swab dipped in one of the six washing solutions; 3) a cotton swab dipped in warm water
- Six washing solutions were used: 1) "hand soap" = 0.5% Dial Gold in warm water; 2) "bar soap" = 5% Dove White Bar Soap in warm water; 3) "dish soap" = 5% Dawn Original in warm water; 4) "Germ-X" = 70% ethanol hand sanitizer; 5) 70% IPA = rubbing alcohol; 6) warm water.
- To assess the amount of GT left on the surface of the skin after this washing procedure, the surface of the skin was wiped with 1) dry cotton swab, 2) cotton swab immersed in ethanol:water (9:1), 3) dry cotton swab, followed by 4) one tape strip. These three cotton swabs and one tape strip were combined and assayed for GT by LC/MS/MS
- The amount of GT in the stratum corneum was assessed by tape stripping 5 times (D-squame tape), and tapes were combined and assayed for GT

Exposure Time

- Human abdominal skin was obtained from 4 donors after abdominoplasty
- After application, GT was left on the skin for 5, 15, or 60 minutes before using the "hand soap" method to remove GT from the skin surface
- During this exposure period the skin was either occluded using the saran wrap method or not occluded
- Not-occluded and not-washed off skin served as control

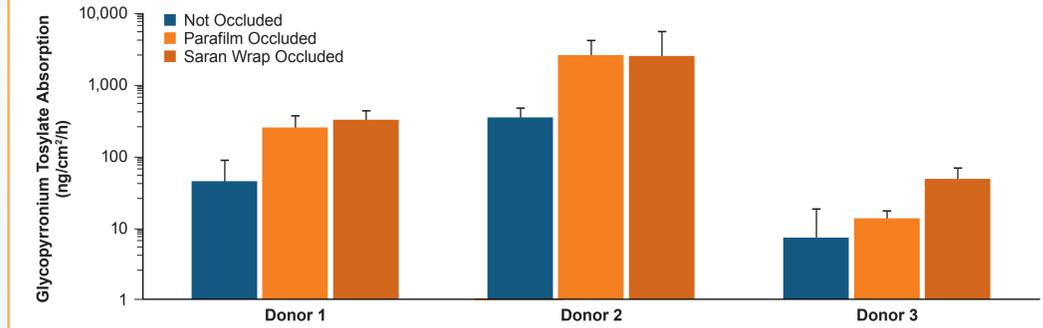
Skin Thickness

- Human skin from 4 anatomical sites (abdominal [control], axillary, palmar, and plantar skin) was obtained from 3 donor/cadavers
- The receiving fluid was collected over 12 hours, and the GT flux was assessed using LC/MS/MS

Results - Occlusion

- Occlusion increased skin flux 7-10 fold, independent of donor to donor differences and independent of the occlusion method used (Figure 1)

Figure 1. The effect of occlusion on steady state flux of Glycopyrronium Tosylate through human skin

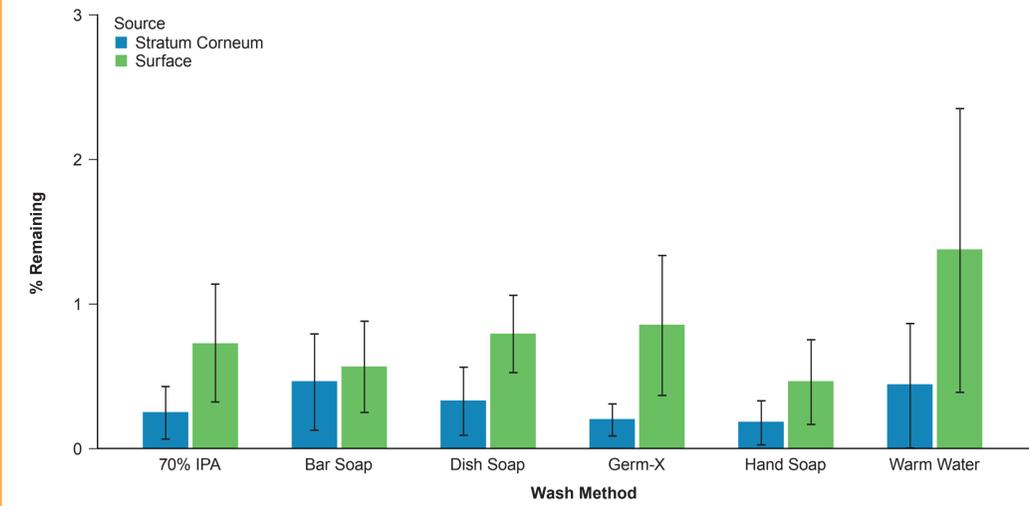


Each bar represents the mean and standard error of 4 replicates per donor

Results - Wash-off and Exposure Time

- All wash-off techniques were effective; however, washing with hand soap was the most effective method (99.5% removal of GT from skin surface) while use of water alone was the least effective method (96.2% removal; Figure 2)
- It is expected that in a real-life situation washing GT off the skin will be even more effective when using running water and rubbing hands for several seconds

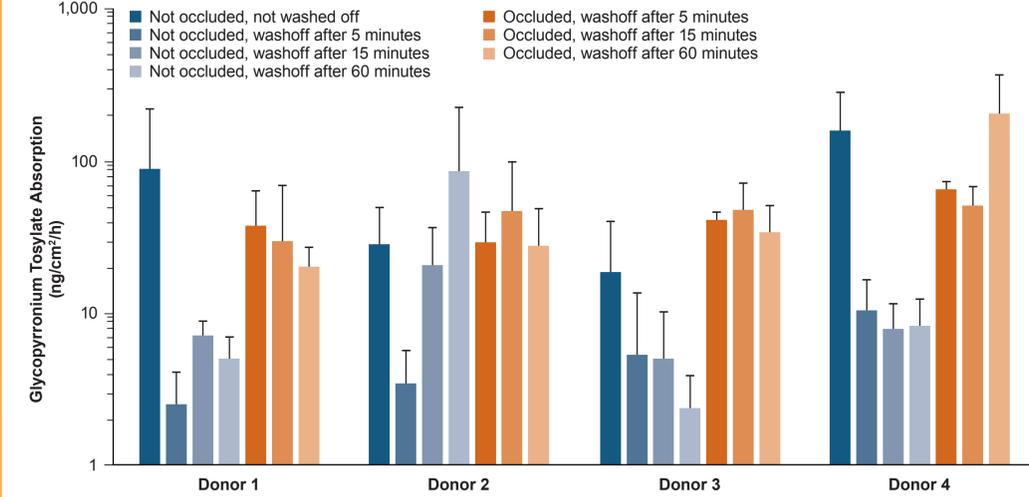
Figure 2. The effectiveness of various wash-off methods on Glycopyrronium Tosylate from human skin



Each bar represents the mean and standard error of 4 replicates per donor

- The amount of GT delivered through human skin was reduced by 90% after washing. This reduction appeared independent of the length of time the product was left on the skin before washing. However, in one of the 4 donors (Donor 2) there appeared to be a benefit of leaving the product on the skin before washing (Figure 3)
- Occlusion for as short as 5 minutes restored the GT flux to approximately control levels (i.e., not washed off, not occluded). Longer occlusion does not appear to increase the flux beyond control levels (i.e., not washed off, not occluded) (Figure 3)

Figure 3. The effect of exposure time and occlusion on Glycopyrronium Tosylate delivery through human skin

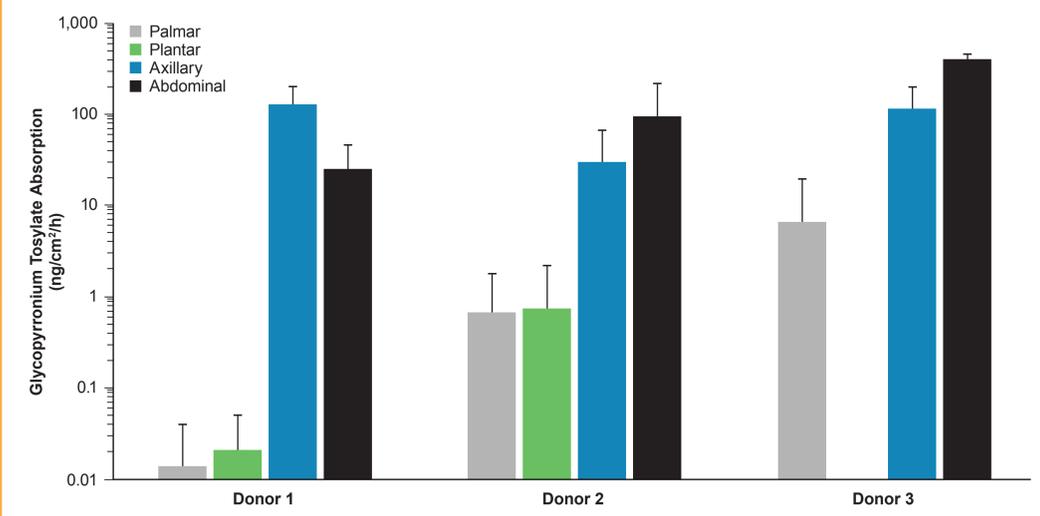


Each bar represents the mean and standard error of 4 replicates per donor

Results - Skin Thickness / Anatomical Sites

- On average 30 to 40-fold less GT delivery was observed through palmar skin vs axillary skin (Figure 4)
- Variability was observed within and between donor results, though in general, similar delivery of GT was observed through axillary vs abdominal skin and for palmar vs plantar skin (for 2 to 3 donors)

Figure 4. The effect of skin thickness on steady state flux of Glycopyrronium Tosylate through human skin obtained from various anatomical sites, including palmar, plantar, axillary and abdominal skin



Each bar represents the mean and standard error of 4 replicates per donor; absorption not detected for plantar sample from Donor 3

CONCLUSIONS

- In these in vitro studies, wash-off, occlusion and skin thickness substantially influenced GT delivery
 - Occlusion increased GT steady state flux by 7-10 fold
 - All wash-off methods worked well and were able to remove up to 99.5% surface GT (0.5% hand soap in water)
 - A 90% decrease in flux was observed after washing, independent of how long GT was left on the skin (5, 15, or 60 min)
 - Occlusion for as short as 5 minutes was able to restore the flux to levels found in control group (not washed off, not occluded)
 - Longer occlusion (up to 60 min) did not increase the flux above control group
 - GT delivery through palmar and plantar skin is 30-40 fold lower compared to delivery through axillary or abdominal skin
 - GT delivery through axillary and abdominal skin is similar
- It should be noted that the in vitro skin penetration studies summarized here involved a single dose of GT; skin penetration of GT upon chronic application was not assessed in these studies
- These data underscore the importance of characterizing skin flux under clinical conditions and will inform future hyperhidrosis clinical trial designs with topical agents

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AUTHOR DISCLOSURES

FC & JH: Employees of MedPharm HH: Employee of Dermira, Inc.