A Pharmacokinetic Study of Two Oxybutynin Transdermal Formulations with Transient Heat Exposure

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INTRODUCTION

Heat sources such as heating pads and electric blankets can potentially alter the drug delivery profile from formulations applied to the skin. Local application of heat has been shown to enhance cutaneous blood flow, skin permeability, and drug solubility followed by increased drug absorption. Preliminary *in vitro* permeation tests (IVPT) were performed to help design an *in vivo* human pharmacokinetic (PK) study. The purpose of the PK study was to evaluate the influence of elevated heat on the transdermal delivery of oxybutynin from two formulations (Product A: Oxytrol® for Women transdermal delivery system (TDS) and Product B: Gelnique® 10% gel). For product A, the effect of heat was evaluated after steady state was achieved and later immediately after removal of the TDS. For product B, the effect of heat was evaluated immediately after application and also later in the wear duration.

METHODS

In Vitro Studies

Preliminary IVPT studies were performed using PermeGear In-Line flow-through diffusion cells. The purpose of the *in vitro* study design was to evaluate the extent of heat effect on the two transdermal products. Human skin from a single donor with three to four replicates was used for each study arm; one performed at normal skin surface temperature, and the other at elevated heat exposure. For product A, the heat arm had heat application for 72h. For product B, the heat arm had heat application for 1.5 h from 7 – 8.5 h. A 0.97 cm^2 circular disc of the TDS or a 10 mg/cm^2 dose of gel was applied to the skin within the permeation area of the diffusion cell. Skin temperature was maintained at either 32 ± 2°C or 42 ± 2°C to mimic normal and elevated skin temperature conditions, respectively. Skin temperature was monitored using an infrared thermometer. Receptor solution was collected at pre-determined time intervals and analyzed using a validated high performance liquid chromatography (HPLC) method.

In Vivo Pharmacokinetic Studies

An open-label, four-way crossover clinical PK study using two oxybutynin products was performed. Heat was applied using a Theratherm® heating pad for 1.5 h, with the target skin temperature of 42 ± 2°C during 2 of the 4 phases. Skin temperature was monitored using Novatemp® skin sensors series 400. For product A, heat was applied at 24 h and 30 h post TDS application. Product A was removed at 30 h. For product B, heat was applied at 0 h and 7 h post gel application. Product B was removed at 12 h. For product B, the skin surface area of gel application was covered with an occlusive backing film during the 1.5 h time period corresponding to heating pad application. Blood samples were drawn at pre-determined time points throughout the duration of the study. Serum samples were analyzed to determine oxybutynin concentrations using a validated LC-MS/MS method.

Figure 1. Clinical PK study design for product A baseline arm **(A)**, product A heat arm **(B)**, product B baseline arm **(C)** and product B heat arm **(D)**.

RESULTS

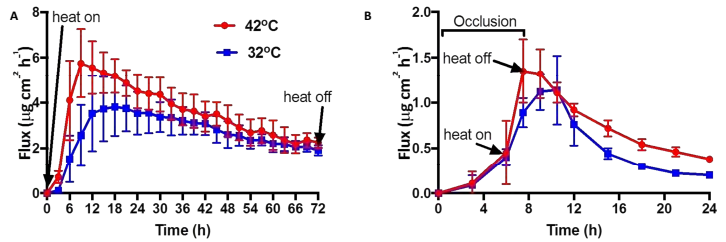

Figure 2. *In vitro* flux profile obtained from human skin donor for product A with and without continuous heat exposure **(A)** and product B with and without 1.5 h transient heat exposure **(B)**, mean ± SD, n=1 donor, 3-4 replicates/donor

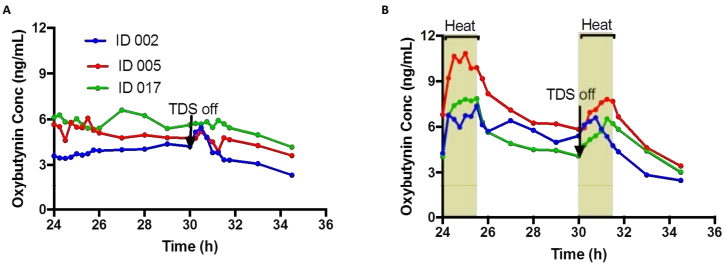

Figure 3. Serum oxybutynin concentrations obtained after applying product B with 1.5 h of either early or late occlusion (A) and 1.5 h of either early or late occlusion with heat exposure (B), n=3

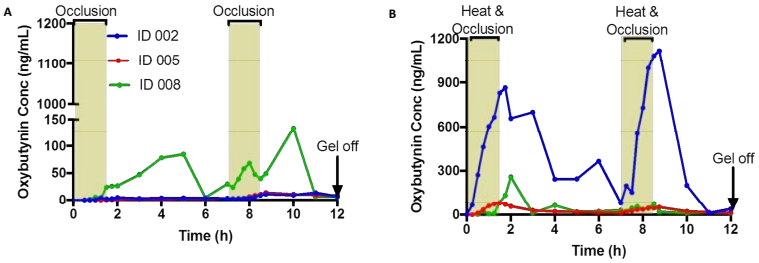

Figure 4. Serum oxybutynin concentrations obtained after applying product A with no heat exposure (A) and 1.5 h of either early or late heat exposure (B), n=3.

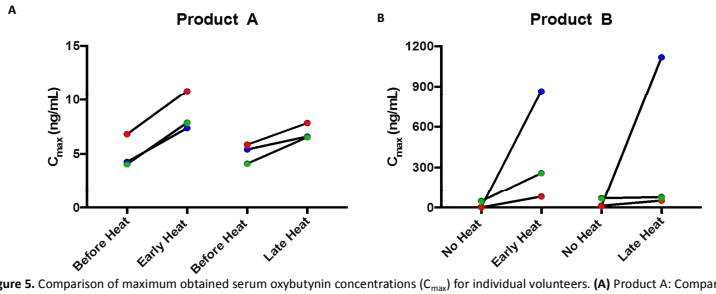

Figure 5. Comparison of maximum obtained serum oxybutynin concentrations (C_{max}) for individual volunteers. **(A)** Product A: Comparison of C_{max} obtained as a result of heat exposure with concentration reached immediately before heat application in heat study arm. **(B)** Product B: Comparison of C_{max} obtained as a result of heat exposure with C_{max} in the absence of heat application in baseline study arm.

Table 1. Heat induced enhancement ratio for C_{max} for product A with respect to concentration reached immediately before heat application in heat study arm.

	Early Heat	Late Heat
ID 002	1.7	1.2
ID 005	1.6	1.3
ID 017	1.9	1.6

Table 2. Heat induced enhancement ratio for C_{max} for product B with respect to C_{max} reached in the absence of heat in baseline study arm

	Early Heat	Late Heat
ID 002	176.7	103.2
ID 005	46.8	3.8
ID 008	5.5	1.1

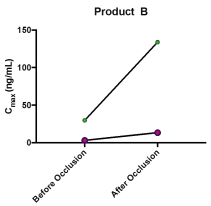

Figure 6. Comparison of C_{max} reached after occlusion at 7h with C_{max} reached at 7h in baseline study arm for product B.

CONCLUSIONS

- When exposed to an elevated temperature *in vitro*, both products exhibited an increase in the rate and extent of drug delivery relative to its baseline drug delivery at normal (ambient and skin) temperature conditions (fig 2).
- *In vivo* PK profiles for the two products obtained from three volunteers showed increased drug concentrations during heat application (fig 3 & 4). Additional data from 12 total subjects for Product A will be used to establish in vitro in vivo correlation between harmonized in vitro and in vivo datasets.
- Product B showed greater increase in systemic concentrations of oxybutynin under the influence of heat compared to product A (fig 5). Hence the study design for product B was modified to eliminate heat exposure.
- Product B also showed an increase in serum concentrations of oxybutynin upon occlusion of the area of formulation application (fig 6). The purpose of the new study design is to evaluate the effect of occlusion on product B. The skin surface area of gel application will be covered with an occlusive backing film during the 3 h time period from 7 – 10 h. The PK profile in the absence of occlusion will be characterized as the baseline study arm.
- For product B, heat application earlier in the wear period resulted in a greater enhancement in C_{max} values compared to heat application later in the wear period for each of the three volunteers (table 2).

ACKNOWLEDGMENT

Funding for this project was made possible, in part, by the Food and Drug Administration through grant U01FD004955. Views expressed in this poster do not reflect official policies of the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.