A Pharmacokinetic Study of the Effect of a Standardized Exposure to Heat on Nicotine Transdermal Delivery in Adult Smokers

Sherin Thomas[1], Soo Hyeon Shin[1], Inas Abdallah[1] , Priyanka Ghosh[3], Bryan Newman[3], Sam G. Raney[3], Dana C. Hammell[1], Samer S. El-Kamary[2], Wilbur H. Chen[2], Hazem E. Hassan[1], Audra L. Stinchcomb[1]

[1]Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, Baltimore, MD

[2]University of Maryland School of Medicine, Baltimore, MD

[3]Office of Generic Drugs, U.S. Food and Drug Administration

INTRODUCTION

Transdermal absorption is governed by various factors such as skin permeability and local tissue perfusion. Local application of heat has been shown to enhance cutaneous blood flow, skin permeability, and drug solubility followed by increased drug absorption. In daily life, an increase in skin temperature can be caused by the use of heating pads, sauna, hot climate, exercise, etc. The purpose of this pharmacokinetic (PK) study was to compare serum nicotine and cotinine concentrations in adult smokers in order to evaluate the influence of elevated heat on the transdermal delivery of nicotine from two transdermal delivery systems (TDS) (Product A and Product B nicotine transdermal systems). Although they contain the same active ingredient they are not expected to have comparable bioavailability. A central consideration in the study design was to evaluate the influence of exposure to elevated heat early in the wear duration when the drug load in the TDS is relatively high (before nicotine levels reach steady-state) compared with exposure to elevated heat later in the wear duration (after nicotine levels reach steady-state) when a greater portion of the drug load in the TDS has been depleted.

METHODS

Subjects and study design

Ten adult smokers were recruited for an open-label, four-way cross-over study with four procedure days. The TDS used were Product A and Product B nicotine transdermal delivery systems each delivering 14 mg/d nicotine. Early heat was applied for one hour, 4 h after application of Product A (procedure day 1) or Product B nicotine transdermal systems (procedure day 3). Late heat was applied for one hour, 8 h after application of Product A (procedure day 2) or Product B nicotine transdermal system (procedure day 4). A washout period of at least one week was used between procedure days. Targeted elevated skin temperature of 42.0 ± 2°C was achieved by using a theratherm® heating pad. The baseline skin temperature was 32.0 ± 2°C. An Oakton® FEB insulated temperature probe connected to a Temp 10 Type J thermocouple thermometer was secured to the skin for the entire 12-h (study duration), with skin temperatures recorded prior to blood withdrawals. A Kevlar sleeve was used to wrap the arm with a window cut open for the TDS application and heat. The heating pad was applied on top of the sleeve. Blood samples were collected at predetermined time-points post-TDS application. Serum samples were extracted for nicotine and cotinine; analyzed using a validated LC-MS/MS method.

Pharmacokinetic and statistical analysis

The primary PK parameters (AUC and Cmax) were calculated using a non-compartmental analysis approach. Analysis of variance (ANOVA) followed by post-hoc Bonferroni test was used for comparing the differences in the variance of the means of the PK parameters and significant differences were indicated as follows: ***$p \le 0.05$; **$p \le 0.01$; ***$p \le 0.001$; ****$p \le 0.0001$**

Table 1. Comparison of Product A and Product B TDS (14 mg/d)

	Product A	Product B
Inactive ingredients	Ethylene vinyl acetate-copolymer polyisobutylene and high density polyethylene between pigmented and clear polyester backings	Acrylic adhesive, silicone adhesive, polyester
TDS type	Matrix	Matrix

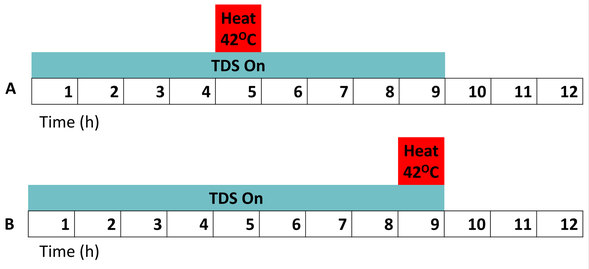

Figure 1. Schematic diagram representing the duration of study, TDS and heat application **A.** Procedure day 1 and 3 (early heat application). **B.** Procedure day 2 and 4 (late heat application).

RESULTS

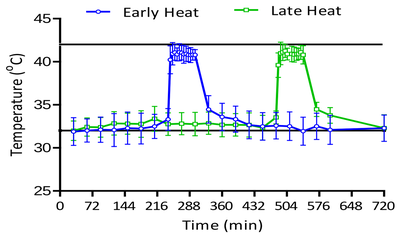

Figure 2. Skin temperature (mean ± SD; n=20) vs. time

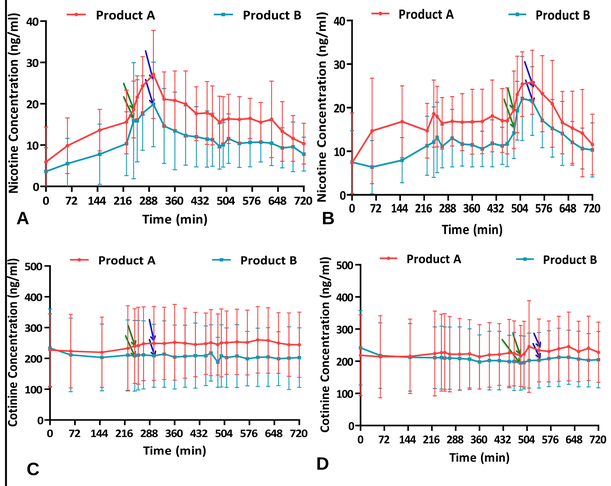

Figure 3. Mean serum nicotine and cotinine concentration profile **A, C.** Early heat application (mean ± SD) (n=10/TDS) **B, D.** Late heat application (mean ± SD) (n=10/TDS) (green arrow: heat on, blue arrow: heat off)

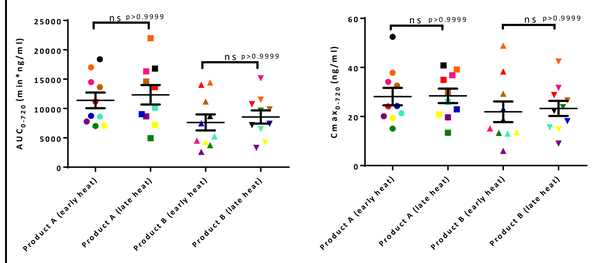

Figure 4. Comparison of total AUC and C_{max}. Data represents mean ± SD; n=10 (Statistical analysis was conducted using ANOVA with Bonferroni posthoc test)

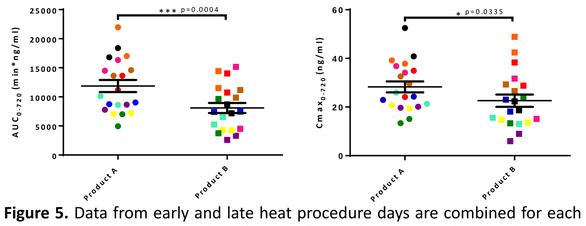

Figure 5. Data from early and late heat procedure days are combined for each TDS (i.e., Combining Procedure day 1 with 2 and Procedure day 3 with 4) Data represents mean ± SD; n=20. (Statistical analysis was conducted using paired t-test) Products A and B are not expected to have comparable bioavailability

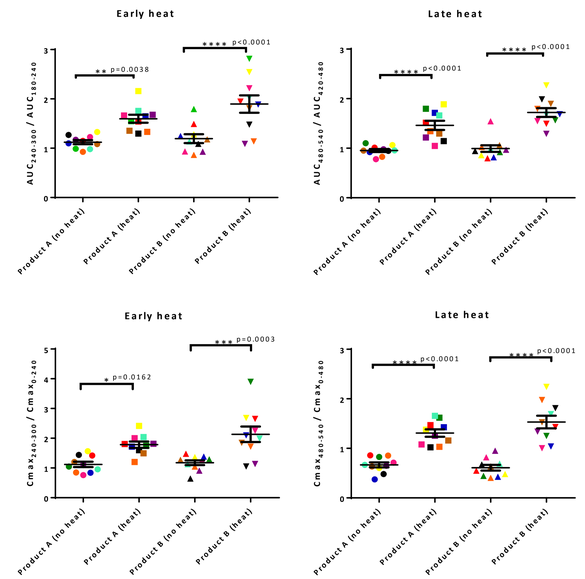

Figure 6. Inter-procedure day comparisons of heat enhancement normalized for the baseline to neutralize the variability in serum nicotine levels before heat application. Data represents mean ± SD; n=10 (Statistical analysis was conducted using ANOVA with Bonferroni post-hoc test)

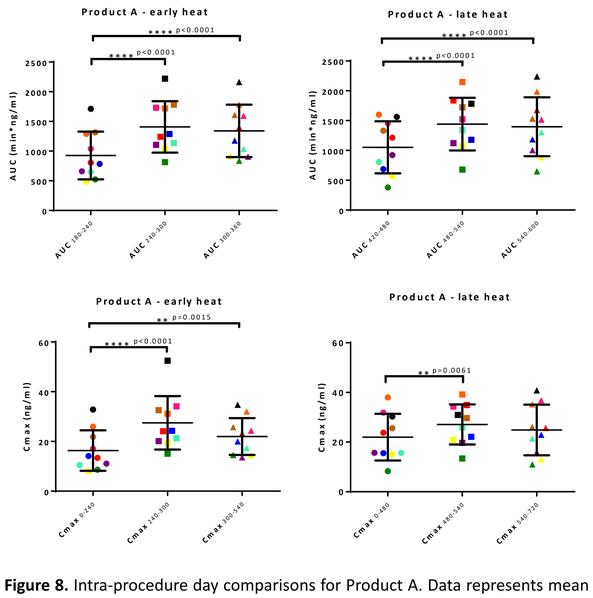

Figure 8. Intra-procedure day comparisons for Product A. Data represents mean ± SD; n=10 (Statistical analysis was conducted using ANOVA with Bonferroni posthoc test)

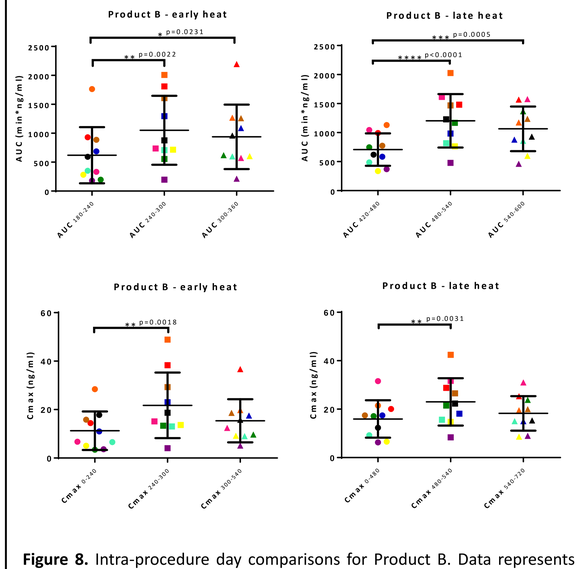

Figure 8. Intra-procedure day comparisons for Product B. Data represents mean ± SD; n=10 (Statistical analysis was conducted using ANOVA with Bonferroni posthoc test)

Table 2. Comparison of % CV (Coefficient of variation) of Heat Enhancement

	Variable	Heat %CV	No Heat %CV
Product A			
	AUC (4-5 h)/(3-4 h)	15.7	10.8
	AUC (8-9 h)/(7-8 h)	19.8	9.4
Product B			
	AUC (4-5 h)/(3-4 h)	33.6	22.5
	AUC (8-9 h)/(7-8 h)	15.6	21.2

CONCLUSIONS

- In the presence of heat (early or late), there were no significant differences between Product A and Product B for AUC and Cmax despite the presence of different inactive ingredients (Figure 6)
- Heat application causes significant increase in AUC and Cmax relative to baseline (Figure 6)
- For both Product A and Product B, there was no significant difference between early vs. late heat application for AUC or Cmax indicating that TDS heat effects may not necessarily be sensitive to when the heat is applied during the wear period (Figure 4 and Figure 6)
- Heat effect (elevated serum nicotine concentration) persisted even after removal of heating pad (AUC values in Figures 7 and 8)
- Heat application does not appear to affect the cotinine levels (Figure 3)
- Product A showed more variable nicotine levels (higher %CV) during heat application (either early or late) as compared to when no heat was applied. Product B TDS showed higher variability in nicotine levels only during early heat application compared to when no heat was applied. (Figure 6 and Table 2)

ACKNOWLEDGEMENT

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Refer to poster R6025 for information on IVIVC of this study