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Pharmacokinetics of Fentanyl after Using Reference and Generic Transdermal Fentanyl Patches With and Without Standardized Heat Application in Healthy Human Volunteers

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PURPOSE

There are numerous transdermal delivery systems (TDS) that are currently available in the United States, the first of which was approved by the Food and Drug Administration (FDA) in 1979. Drug absorption from these TDS varies significantly and is dependent on a number of factors, including system design, physicochemical properties of the drug, excipients, occlusion, sweat, skin condition, skin type and temperature The objective of this in vivo study was to conduct in vivo studies to compare the influence of heat on fentanyl drug absorption from three Fentanyl TDS (25 µg/h) products, Duragesic® (the reference listed drug product) and two generic products (Apotex and Mylan) each of which has different inactive ingredients.

METHOD

The study was an open-label, crossover study with six procedure days in healthy volunteers, with 14-day washouts between study periods. A heating pad was set to induce a skin temperature of 42.0 ± 2°C and applied for an hour, either 11 h (early-heat) or 18 h (late-heat) post-application of Fentanyl TDS (25 µg/h) (Duragesic®, Apotex and Mylan) (Figure 1).

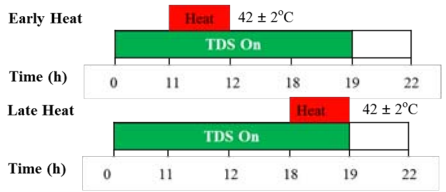

Figure 1. Schematic diagram representing the duration of the study, duration of TDS application and when early and late standardized heat was applied

Blood samples were collected from volunteers at: 0, 1:00, 10:00, 10:55, 11:05, 11:15, 11:25, 11:35, 11:45, 12:00, 13:00, 14:00, 16:00, 17:00, 17:55, 18:05, 18:15, 18:25, 18:35, 18:45, 19:00, 20:00, 21:00, and 22:00 h after TDS application. Serum samples were analyzed using an LC-MS/MS validated method.

Non-compartmental pharmacokinetic analysis was performed using Phoenix®WinNonlin®6.4 (Pharsight, a Certara company, CA). The heat effect was considered to last for a period of 3 h (i.e., 1 h during + 2 h post heat application).

Table 1. Inactive ingredients of fentanyl TDS used in the study

Duragesic®	Apotex TDS	Mylan TDS
Alcohol, ethylene vinyl acetate-copolymer membrane and hydroxyethyl cellulose, polyester film backing, silicone adhesive	Isopropyl myristate, octyldodecanol, polybutene and polyisobutene adhesive	Dimethicone NF, polyolefin film backing, silicon adhesive

RESULTS

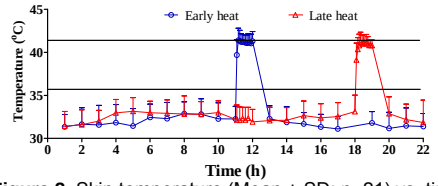

Figure 2. Skin temperature (Mean + SD; n=21) vs. time

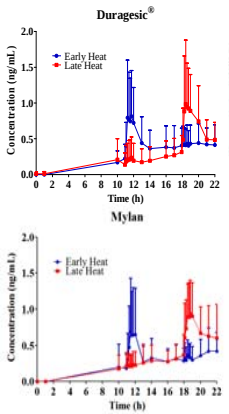

Figure 3. Mean serum fentanyl concentrations obtained from 7 healthy volunteers after applying the Duragesic®, Apotex, or Mylan TDS with 1 h of either early or late heat exposure. (n=7, Mean + SD)

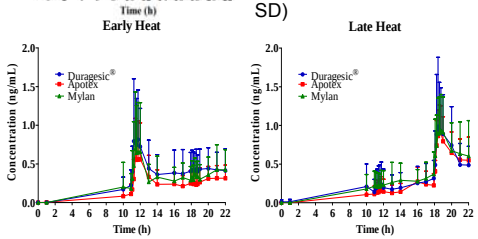

Figure 4. Mean serum fentanyl concentrations obtained from 7 healthy volunteers after applying the Duragesic®, Apotex, or Mylan TDS with 1 h of either early or late heat exposure. (n=7, Mean + SD)

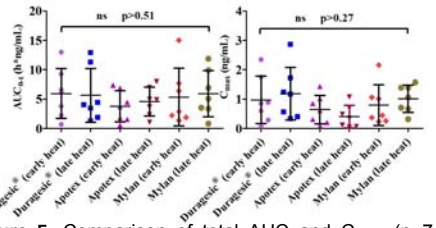

Figure 5. Comparison of total AUC and C_{max}. (n=7, Mean ± SD; Statistical analysis was conducted using ANOVA with Bonferroni posthoc test)

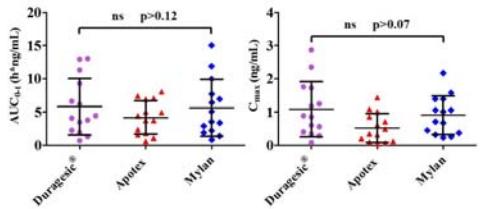

Figure 6. Data from early and late heat procedure days are combined for each TDS. (n=14, Mean ± SD; Statistical analysis was conducted using ANOVA with Bonferroni posthoc test)

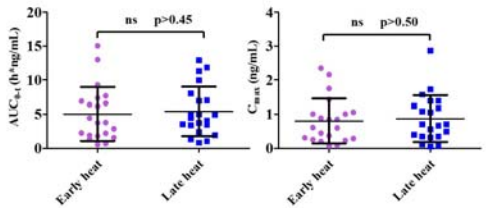

Figure 7. Data from all TDS are combined for early and late heat application. (n=21, Mean ± SD; Statistical analysis was conducted using paired t-test)

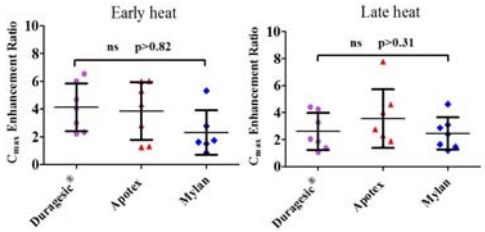

Figure 8. Heat effect determined by the C_{max} increase ratios during heat (11 to 14 h for Early Heat and 18 to 21 h for Late Heat). (n=7, Mean ± SD; Statistical analysis was conducted using ANOVA with Bonferroni posthoc test)

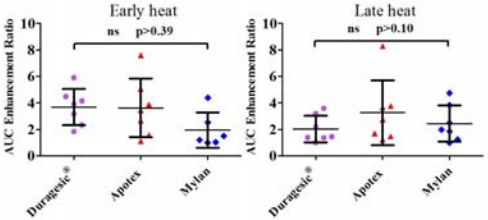

Figure 9. Heat effect determined by the partial AUC increase ratios during heat (11 to 14 h for Early Heat and 18 to 21 h for Late Heat). (n=7, Mean ± SD; Statistical analysis was conducted using ANOVA with Bonferroni posthoc test)

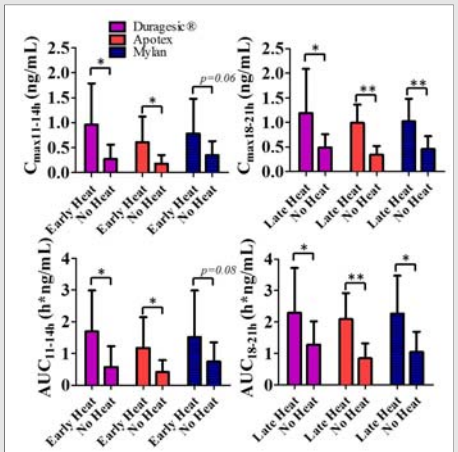

Figure 10. Comparison of the partial AUC and C_{max} for each TDS (11 to 14 h for Early Heat and 18 to 21 h for Late Heat). P values were obtained from paired t-test, *$p<0.05$, **$p<0.01$. (n=7, Mean + SD).

CONCLUSION

The current study evaluated the effect of transient heat exposure on Duragesic®, Apotex and Mylan TDS. Despite the inter-subject variability, the results show that all three fentanyl TDS exhibited a rapid increase in drug absorption in response to 1 h of elevated heat, and this relative elevation in serum fentanyl concentrations persisted for about 3 h. In the presence of heat (early or late), there were no significant differences in the three fentanyl TDS based on AUC and C_{max} enhancement ratio, despite the presence of different inactive ingredients.

In the preliminary data analysis from the three fentanyl TDS in seven healthy human volunteers, there was no significant difference between early vs. late heat application for AUC and C_{max}, suggesting that heat effects with these TDS, arising from 1 hour heat exposures may not be different depending upon when the heat is applied during wear.

ACKNOWLEDGEMENTS

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