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In Vitro and In Vivo Evaluation of Three Fentanyl Transdermal Delivery Systems In Conjunction With Transient Heat Exposure

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PURPOSE

At increased temperatures, drug molecules can be released from transdermal delivery systems (TDSs) and permeate through skin at a faster rate. The increased temperature can also interact with factors such as the design of the TDS and its formulation components and contribute to an altered drug delivery/permeation rate. The present study investigated such heat effects on three fentanyl TDSs, each having different types of adhesive and other inactive ingredients. In vitro permeation tests (IVPT) and in vivo pharmacokinetic (PK) studies were performed under harmonized study designs and conditions of heat exposure to evaluate the correlation between in vitro and in vivo performance of fentanyl TDSs under the influence of a transient (1h) heat exposure.

METHODS

In Vitro Studies

IVPT experiments using three fentanyl TDSs (Table 1) were performed for two different designs (Fig. 1). A flow-through In-Line diffusion system was used with dermatomed ex vivo human skin (thickness of 240 ± 60 µm). Receiver solution was normal saline with 0.005% gentamicin, with a flow rate of ~7.5 mL/h. A circulating water bath was used to control the temperature at either 32 ± 1°C or 42 ± 2°C to mimic normal physiological skin temperature or a typical heat exposure temperature. Skin temperature was monitored using an infrared thermometer. Samples were analyzed using a validated HPLC method.

Table 1. Characteristics of fentanyl TDSs (25 µg/h)

	Duragesic®	Apotex	Mylan
Drug Load (mg)	4.20	2.76	2.55
Size (cm^2)	10.50	10.70	6.25
Adhesive	Polyacrylate	Polyisobutene	Silicone
Other Inactive Ingredients	Polyester/ ethyl vinyl acetate backing film, copovidone	Isopropoyl myristate, octyldodecanol, polybutene, polyethylene/ aluminum/ polyester film backing	Dimethicone NF, polyolefin film backing

In Vivo Clinical Pharmacokinetic Studies

A six-way crossover clinical study using three fentanyl TDSs (Table 1) was performed with 7 healthy adults. Heat was applied using a theratherm® heating pad for 1h according to Fig 1, with the target skin temperature of 42 ± 2°C. The skin temperature was monitored using a probe connected to a thermometer. Blood samples were drawn at pre-determined time points and serum samples were analyzed to determine fentanyl concentration using a validated LC-MS/MS method.

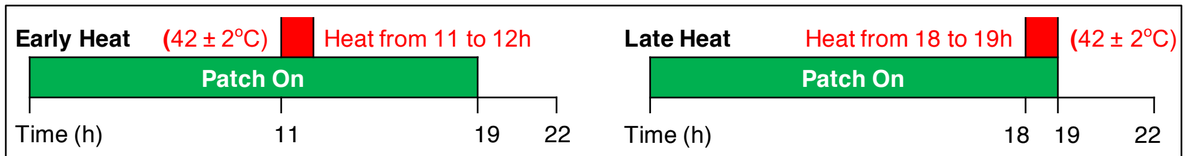

Fig 1. Schematic diagram of two study designs representing the duration of the study, duration of TDS wear, and early and late heat application times for in vitro and in vivo studies

RESULTS

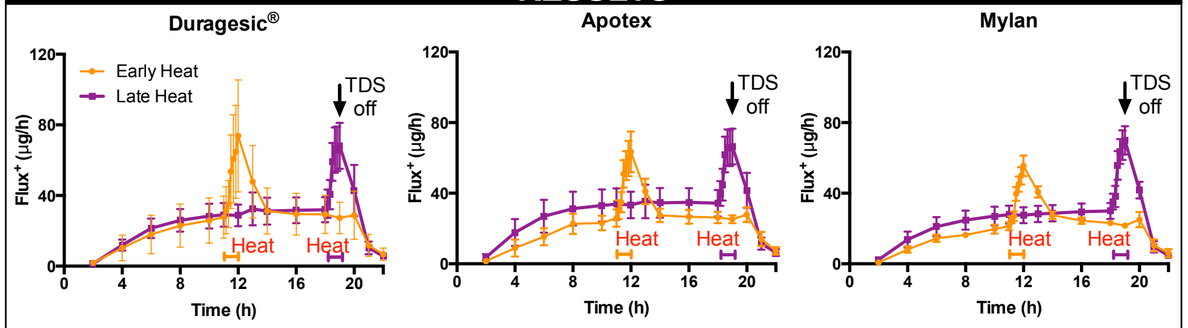

Fig 2. Flux profiles of the three fentanyl TDSs with either early or late heat exposure. Flux values corrected for TDS size. Mean ± SEM from 3 donors with n=4 replicates per donor.

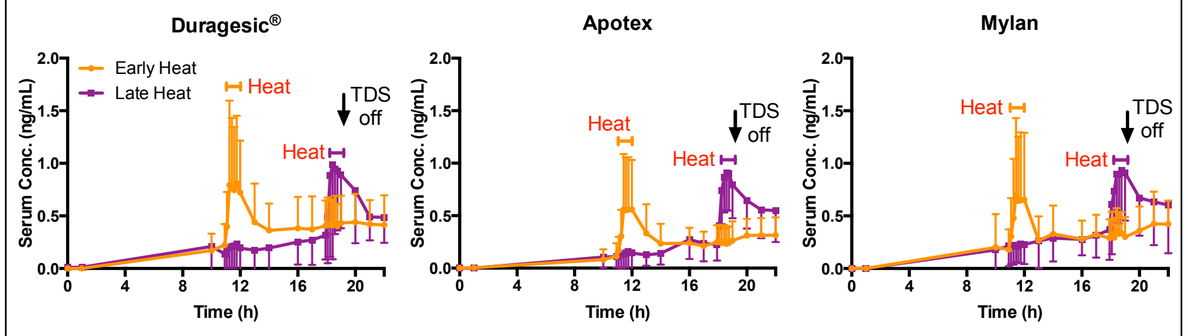

Fig 3. Serum fentanyl concentrations obtained from seven healthy adults after applying fentanyl TDS with 1h of either early or late heat exposure. Mean ± SD, n=7.

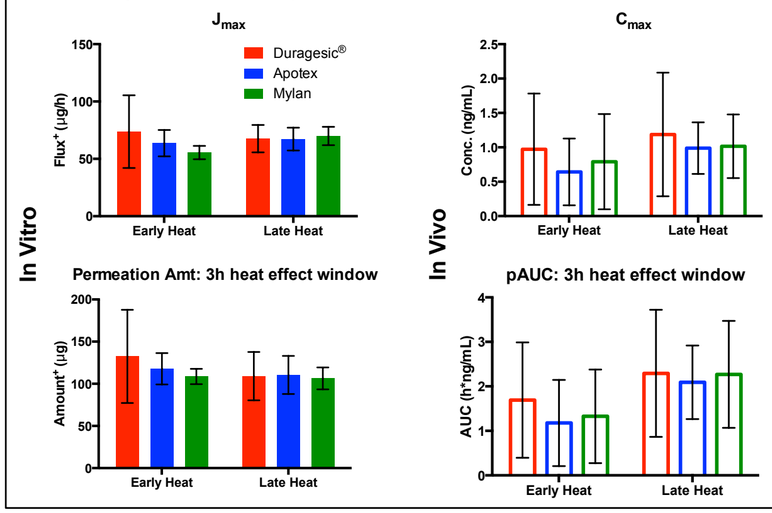

Fig 4. Comparisons of J_{max} and permeation amount over 3 h heat effect window among three fentanyl TDSs in vitro (left panel) and C_{max} and partial AUC of 3 h heat effect window among three fentanyl TDSs in vivo (right panel).

No significant difference ($p > 0.05$) was found among three TDSs for all comparisons.
(two-way ANOVA, followed by Bonferroni's post-hoc analysis).

In Vitro: Mean ± SEM from 3 donors with n=4 replicates per donor
In Vivo: Mean ± SD from 7 subjects

RESULTS

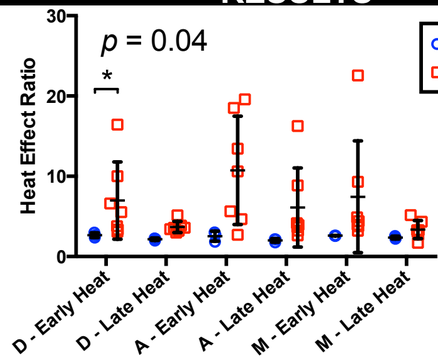

Fig 5. Heat effect, determined by the ratio of J_{max} (for in vitro) or C_{max} (for in vivo) during the 3h heat effect window and the value immediately before the heat exposure. %CV for in vivo data was significantly higher (p = 0.01; unpaired t-test) compared to %CV for in vitro data.

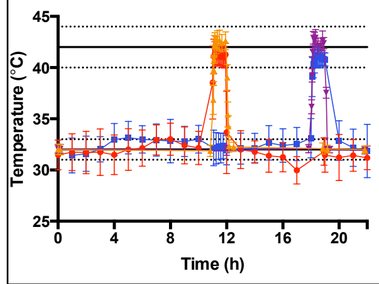

Fig 6. Mean ± SD skin surface temperature measured from in vitro and in vivo studies

CONCLUSION

The heat effect among three fentanyl TDSs with different formulation characteristics showed similar behavior upon heat exposure, and in vitro results correlated with in vivo results (Fig. 4). Based on a ratio analysis of pharmacokinetic parameters at 42°C vs. 32°C (Fig 5), the mean heat effect ratio based upon C_{max} in vivo showed a significantly higher inter-subject variability and was higher compared to in vitro effect ratio based upon J_{max}.

Many studies have shown that IVPT may have the potential to predict in vivo performance of TDS in the absence of external factors such as heat. When evaluating heat effects by IVPT, the physiological effects in the skin, microcirculation, and subcutaneous tissues in human subjects upon heat exposure may need to considered. These results also suggest that appropriate analyses to define and compare heat effects need to be developed. The current study is still in progress, and further methods of data analysis will be examined.

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