Absolute Bioavailability, Pharmacokinetic and Residual Drug Analysis of Two Fentanyl Transdermal Delivery Systems and Its Correlation to In Vitro Permeation Tests
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Purpose
The purpose of the study was to determine serum fentanyl levels after administration of two fentanyl transdermal systems, 25 μg/h (TDS) and calculate absolute bioavailability after intravenous (IV) dosing of fentanyl citrate in healthy adult subjects. Additionally, correlations of the in vivo pharmacokinetic (PK) data to residual drug content in the TDS and in vitro permeation tests (IVPT) have been explored.

Methods
The in vivo study was an open-label, randomized, crossover study with three treatments. Each subject received a single dose of 100 μg of IV fentanyl citrate (50 μg/mL) infusion, and a single dose of two fentanyl TDS 25 μg/h (Duragesic® and Mylan), worn for 72 h. A washout period of at least one week was effected between each study session. The blood samples were collected up to 36 h post-IV fentanyl citrate administration and up to 192 h post-TDS application. The primary PK parameters for TDS were calculated using a non-compartmental analysis. At 72 h post-TDS application, TDS was removed from each subject and the residual amount of fentanyl was extracted to evaluate its relationship to the PK data. IVPT were performed using ex vivo human skin to investigate the in vitro/in vivo correlations (IVIVC) of the two fentanyl TDS.

Results
The maximum concentrations (Cmax) observed after IV fentanyl citrate, Duragesic® and Mylan TDS were 3.4 ± 2.4, 1.0 ± 0.2, and 1.0 ± 0.2 ng/mL, respectively. The absolute bioavailabilities (F) calculated for the two TDS were similar without a significant difference (p > 0.05): 0.29 ± 0.02 for RLD and 0.28 ± 0.09 for the generic TDS. When the amount of residual TDS analysis was used to calculate F, the resulting values were in agreement with the calculated values from PK analysis (p > 0.05; paired t-test) for both TDS. The IVIVC between the in vitro fraction of drug permeation at 23 time points of the total permeation and the in vivo fraction of drug absorption, calculated by deconvolution of the time versus serum fentanyl concentration data in human subjects, up to 72 h for both TDS showed a high correlation with (R² > 0.9). The prediction errors (%PE) calculated for Cmax and AUC were less than 15%.

Conclusion
The current study evaluated the absolute bioavailability and PK profiles of two fentanyl TDS in healthy subjects. In addition, the utility of residual TDS analysis was investigated by examining the correlation between the residual drug content in TDS and the in vivo PK data. Preliminary results suggest that analysis of residual drug content in TDS might predict the extent of drug delivery/absorption. Finally, IVIVC results shown in this study indicate the usefulness of IVPT in comparing the drug delivery from TDS in vivo.

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