DETERMINATION OF SERUM FENTANYL LEVELS AFTER USING REFERENCE AND GENERIC TRANSDERMAL FENTANYL PATCHES WITH AND WITHOUT STANDARDIZED HEAT APPLICATION IN HEALTHY HUMAN VOLUNTEERS

Short title: The Effect of Heat on Fentanyl Release from Fentanyl Patches in Healthy Adults

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CLINICAL STUDY STATISTICS

IVIVC

For IVIVC, three correlation levels were examined. Level A was selected to use for analysis of the data. Three different (I, II & III) approaches were examined for Level A.

Level A: a point-to point correlation between in vitro and in vivo profiles.

Level B: comparison between in vitro dissolution time and in vivo residence time.

Level C: a single point correlation between in vitro and in vivo parameters (e.g. J_{max} vs. C_{max}).

Approach I: IVPT data, PK-based mathematical equations and in vitro heat effect coefficient (H_i) were used to predict in vivo concentrations.

• Eq. 1 Prediction while TDS was worn:

[redacted]

• Eq. 2 Prediction after TDS removal:

[redacted]

C_s: Predicted in vivo serum concentration

F: Absolute bioavailability for TDS $F = \frac{AUC_{0-\infty,TDS} \times Dose_{IV}}{AUC_{0-\infty,IV} \times Dose_{TDS}}$

R_{in}: Rate of input (mean flux during steady-state in IVPT experiments)

H_i : In vitro heat effect coefficient (composite heat effect during and after heat exposure); ratio of flux values with heat and without heat

CL: Total body clearance obtained from literature/product package information

k: Elimination rate constant obtained from literature/product package information (k_1: after IV dose; k_2: after TDS dose)

t: Time after administration of TDS for Eq.1 and time after removal of TDS for Eq. 2

C_0: Initial concentration after TDS removal

Approach II and III:

1. Reconstruct baseline (32°C) profile by combining the non-heat (32°C) portion of each profile from the early and late heat study designs.
2. Deconvolute the in vivo baseline concentration vs time profile using Phoenix®.
3. Construct an IVIVC model by plotting the fraction permeated in vitro vs the fraction absorbed in vivo.
4. Predict the in vivo fraction absorbed using the IVIVC model and IVPT data.

5. Convolute the predicted in vivo fraction absorbed data using Phoenix® to obtain concentration vs time profile
6. Apply in vitro heat effect coefficient H_i (Approach II) or the in vivo heat effect coefficient H_{ii} (Approach III) to the predicted in vivo profile.

Pharmacokinetic parameters of fentanyl used for Approach I, II and III were obtained from:

- Bower et al. Br J Anaesth 1982
- McClain et al. Clin Pharmacol Ther 1980
- Scott et al. J Pharmacol Exp Ther 1986
- Fung et al. J Clin Pharmacol 1980
- Study [NIPTE-U01-MD-2015-001: Transdermal Drug Delivery Systems-Fentanyl] at University of Maryland, Baltimore; *still in progress*

- *F* [absolute bioavailability for TDS] for Duragesic® (0.36) and Mylan (0.42) were each determined from study [NIPTE-U01-MD-2015-001: Transdermal Drug Delivery Systems-Fentanyl] at the University of Maryland, Baltimore
- *F* [absolute bioavailability for TDS] for Apotex was estimated (0.39) by the mean of 0.36 and 0.42, due to lack of available data