Pharmacokinetic Characterization of a Novel Non-Occlusive Transdermal System for Fentanyl.

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INTRODUCTION

Opioids represent the mainstay therapy for the alleviation of chronic severe pain.

Fentanyl is a lipophilic opioid analgesic that is well absorbed through intact skin, allowing for transdermal administration. It is available as transdermal patches which deliver doses from 12.5–100 µg per hour over a 3-day application period. However, limitations of the patches include application site irritation and varying delivery of fentanyl over the 3-day period (with a decline on day 3).

A Unit-Dose Transdermal System (UDTS™) is being developed for the delivery of therapeutic levels of fentanyl to patients with chronic, severe pain. The UDTS is a small, hand-held applicator that delivers pre-determined liquid dose formulation of fentanyl to the skin. The applied formulation dries quickly on the skin leaving an invisible depot from which drug is released into the blood stream on a sustained basis over 24-hours after daily application.

Two pharmacokinetic studies in humans have been conducted to characterize the pharmacokinetics of fentanyl after single and multiple doses of fentanyl UDTS™ formulations.

OBJECTIVES

Study 1

The primary objective of study 1 was to compare the pharmacokinetics and relative bioavailability of fentanyl after a single dose of Fentanyl formulation to the upper arm or upper thigh compared to Duragesic® 25 patch in order to determine the optimal application site of Fentanyl formulation.

Study 2

The primary objectives of study 2 was to determine and compare the steady state pharmacokinetics of fentanyl following applications to the inner forearm at various time intervals: every 12, 24 or 48 hours.

METHODS

INTRODUCTION

Six subjects completed each of the three dosing periods in Study 1, with 12 subjects completing Study 2.

Study 1

Study design

Each study was conducted as a single centre study in Australia, in healthy male volunteers, aged from 18–49 years, who were each blocked to the opioid effects of fentanyl with naltrexone.

Study 1 was an open-label, three-way cross-over pharmacokinetic study in 6 volunteers using a prototype applicator.

Study 2 was a single centre, randomized, multiple dose PK study in 12 volunteers. The Fentanyl UDTS formulation was administered via a unit dose applicator (Figure 1). Each volunteer received a dose of 220 µL applied to the inner forearm every 48 hours for 8 days, followed by 220 µL either 24 or 12 hourly for the next 6 days. Intensive blood sampling was performed on Days 7–9 and Days 14–15.

Each study included a 4 week screening phase, a treatment period of 4 to 6 weeks, and post study evaluations.

Treatments

Study 1 participants were randomly assigned to each received a single dose of treatment as follows:

- Treatment 1: 220 µL Fentanyl formulation applied to the upper arm
- Treatment 2: 220 µL Fentanyl formulation applied to the thigh
- Treatment 3: Duragesic® 25 Patch applied to the upper arm

Study 2 participants received two of the three study treatments, applied to the same forearm as follows:

- Treatment A: 220 µL Fentanyl UDTS formulation applied every 48 hours
- Treatment B: 220 µL Fentanyl UDTS formulation applied every 24 hours
- Treatment C: 220 µL Fentanyl UDTS formulation applied every 12 hours

Plasma fentanyl concentrations were measured using a validated LC/MS/MS assay. Some results below the LOQ were also included in the analysis.

PARAMETERS

AUC\textsubscript{0-\textit{last}}, \textit{C}\textsubscript{max} and \textit{T}\textsubscript{max} were determined from fentanyl plasma concentration-time curves.

Study 1

\textit{C}\textsubscript{max} and \textit{T}\textsubscript{max} were determined from plasma concentration-time curves after 7.8 days (48 hourly dosing) or 6 days (12 and 24 hourly dosing) of multiple dosing.

Study 2

\textit{AUC}\textsubscript{0-\textit{last}}, \textit{C}\textsubscript{max}, and \textit{T}\textsubscript{max} were determined from fentanyl plasma concentration-time curves.

OBJECTIVES

Study 1

- Study design
- Treatments
- Evaluations and Pharmacokinetic Analysis

RESULTS

Study 1

- Six subjects completed each of the three dosing periods in Study 1, with 12 subjects completing Study 2.

- Study 1: Fentanyl PK parameters (arithmetic mean ± s.d.; n = 6) after single dose application of Fentanyl UDTS to the arm or thigh and Duragesic® 25 patch to the arm.

- Table 1: Study 1: Fentanyl PK parameters (mean ± s.d.) after single dose application of Fentanyl UDTS™ and Duragesic® 25 patches.

- Study 2: Fentanyl PK parameters (mean ± s.d.) after multiple application of Fentanyl UDTS™ formulation to the inner forearm every 48, 24 or 12 hours.

- Table 2: Study 2: Fentanyl PK parameters (mean ± s.d.) after multiple application of Fentanyl UDTS™ formulation.

CONCLUSIONS

Study 1 demonstrated that the absorption of fentanyl from the UDTS formulation was significantly higher from the upper arm in comparison with the outer thigh. The Duragesic 25 patch demonstrated fentanyl absorption consistent with levels previously reported in the literature.

In Study 2, multiple-dosing to the forearm showed predictable accumulation, linearly related to the frequency of dosing. The mean steady-state \textit{C}\textsubscript{max} values were similar to those previously reported for Duragesic® patches delivering 25–100 µg per hour.

OBJECTIVES

Study 2

- Study design
- Treatments
- Evaluations and Pharmacokinetic Analysis

RESULTS

Study 2

- Six subjects completed each of the three dosing periods in Study 1, with 12 subjects completing Study 2.

- Study 1: Fentanyl PK parameters (arithmetic mean ± s.d.; n = 6) after single dose application of Fentanyl UDTS to the arm or thigh and Duragesic® 25 patch to the arm.

- Table 1: Study 1: Fentanyl PK parameters (mean ± s.d.) after single dose application of Fentanyl UDTS™ and Duragesic® 25 patches.

- Study 2: Fentanyl PK parameters (mean ± s.d.) after multiple application of Fentanyl UDTS™ formulation to the inner forearm every 48, 24 or 12 hours.

- Table 2: Study 2: Fentanyl PK parameters (mean ± s.d.) after multiple application of Fentanyl UDTS™ formulation.

CONCLUSIONS

Study 1 demonstrated that the absorption of fentanyl from the UDTS formulation was significantly higher from the upper arm in comparison with the outer thigh. The Duragesic 25 patch demonstrated fentanyl absorption consistent with levels previously reported in the literature.

In Study 2, multiple-dosing to the forearm showed predictable accumulation, linearly related to the frequency of dosing. The mean steady-state \textit{C}\textsubscript{max} values were similar to those previously reported for Duragesic® patches delivering 25–100 µg per hour.