Pharmacokinetic study between a bilayer matrix fentalyl patch and a monolayer matrix fentanyl patch: single dose administration in healthy volunteers*

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Transdermal fentanyl is a standard treatment for cancer pain.
- The current research in the pharmaceutical field has the objective of improving the efficiency and reliability of delivery systems.

WHAT THIS STUDY ADDS

- The results of the present study demonstrate the bioequivalence between a new bilayer matrix type patch (Fentalgon®) and the reference monolayer matrix type fentanyl patch (Durogesic SMAT).
- The bilayer system of Fentalgon® maintains a stable concentration gradient between the patch and the skin and it provides a constant drug delivery over time.

AIMS

Transdermal fentanyl is a well established treatment for cancer pain. The aim of the present study is to assess the relative bioavailability of fentanyl from two different transdermal systems by evaluating plasma drug concentrations after single administration of Fentalgon® (test), a novel bilayer matrix type patch, and Durogesic SMAT (reference), a monolayer matrix type patch. In the Fentalgon patch the upper 6% fentanyl reservoir layer maintains a stable concentration gradient between the lower 4% donor layer and the skin. The system provides a constant drug delivery over 72 h.

METHODS

This was an open label, single centre, randomized, single dose, two period crossover clinical trial, that included 36 healthy male volunteers. The patches were applied to non-irritated and non-irradiated skin on the intraclavicular pectoral area. Blood samples were collected at different time points (from baseline to 120 h post-removal of the devices) and fentanyl concentrations were determined using a validated LC/MS/MS method. Bioequivalence was to be claimed if the 90% confidence interval of $AUC(0,t)$ and C_{max} ratios (test: reference) were within the acceptance range of 80–125% and 75–133%, respectively.

RESULTS

The 90% confidence intervals of the $AUC(0,t)$ ratio (116.3% [109.6, 123.4%]) and C_{max} ratio (114.4% [105.8, 123.8%]) were well included in the acceptance range and the C_{max} ratio also met the narrower bounds of 80–125%. There was no relevant difference in overall safety profiles of the two preparations investigated, which were adequately tolerated, as expected for opioid-naïve subjects.

CONCLUSIONS

The new bilayer matrix type patch, Fentalgon®, is bioequivalent to the monolayer matrix type Durogesic SMAT fentanyl patch with respect to the rate and extent of exposure of fentanyl (Eudra/CT no. 2005-000046-36).

Introduction

Since its introduction in clinical practice in the last decades, transdermal fentanyl has rapidly become a standard treatment for cancer pain.

The pharmacokinetic (high liposolubility, low molecular weight) and pharmacodynamic (full μ-opioid receptors agonist, high potency with low plasma concentration) features of fentanyl make it an ideal transdermal analgesic, recommended as a non-invasive alternative to oral opioids in the treatment of cancer pain, in particular for patients unable to swallow [1].

The clinical pharmacokinetics of fentanyl including its transdermal administration have been extensively analyzed and reviewed by several authors in the past years. Transdermal drug delivery enables the continuous systemic application of strong opioids through the intact skin, producing constant serum concentrations comparable with those achieved by continuous infusion [2–5].

The first reservoir type transdermal therapeutic system of fentanyl was introduced in the early 1990s for the treatment of chronic cancer pain [6]. Since that time, the research in the pharmaceutical field has focused on improving the efficiency and reliability of delivery systems. The first products containing fentanyl (Durogesic®, now no longer available) for transdermal use were composed of a reservoir with fentanyl and a rate controlling-layer. Reservoirs were easily breakable and fluid could be swallowed for recreational use or more analgesic effect [7]. Later, acrylic matrix patches were developed, with fentanyl dissolved in a semi-solid matrix and a release layer (Durogesic®) or a release layer with rate controlling layer (Matrifen®) [8]. These two matrix systems have already been shown to be bioequivalent [9, 10]. Today, a number of non-branded fentanyl matrix patches are available, with similar pharmacokinetic and physical (adhesiveness, skin tolerability) features [11].

Fentalgon® is a novel matrix type patch, with an advanced bilayer matrix (European Patent EP 1 503 743 B1), designed to deliver fentanyl through intact skin in a controlled manner over a period of 72 h and is available in four strengths, 25, 50, 75 and 100 μg h^{-1}.

The aim of this study was to assess the relative bioavailability of fentanyl between two different fentanyl transdermal therapeutic systems, a new bilayer matrix type fentanyl transdermal patch (Fentalgon®, HELM AG, Germany) and a monolayer matrix-type patch (Durogesic® SMAT, Janssen-Cilag GmbH, Germany),with a releasing rate of 25 μg h^{-1}, after a single dose administration in healthy male subjects.

Methods

The study was approved by an ethics committee (Ethik-Kommission - Ärztekammer Hamburg, Bearb. No 2436),

performed in accordance with GCP, Declaration of Helsinki and WHO/ CIOMS guidelines, and registered with Eudra/CT no. 2005-000046-36. All subjects gave their informed consent to participate in the study.

The present study was a single centre, randomized, single dose, open label, two period crossover trial to compare a new transdermal fentanyl delivery system (Fentalgon®) with an established comparable product (Durogesic®).

Fentalgon® contains fentanyl in two layers, an upper reservoir layer (containing 6% fentanyl) and a lower donor layer in contact with the skin (containing 4% fentanyl). The total amount of fentanyl in a 25 μg h^{-1} patch is 4.8 mg. The two layers are comprised of different polymeric adhesive matrixes. The donor layer is lined by a siliconized polyester film (release liner), which is peeled away prior to application, so that the exposed adhesive surface can be fixed to the skin. The donor layer releases active drug to the skin surface. The upper layer, which acts as a reservoir, is lined by a backing film (polyester/ethyl vinyl acetate laminated film). The upper layer replenishes the donor layer so that the donor layer can maintain its fentanyl concentration and therefore deliver a constant flux of fentanyl over the 72 h treatment period.

The trial enrolled healthy Caucasians male subjects, aged between 18 to 45 years, with a body mass index between 19 and 28 kg m^{-2} (body weight >50kg), who had not consumed any alcohol within 48 h prior to each administration. The complete list of exclusion criteria is reported as supplementary text, in appendix S1. In agreement with sample size calculation, at least 30 subjects had to complete the study in order to confirm bioequivalence with an error risk <5% and a power >80%.

The subjects remained as inpatients in a clinical setting (Scope International Life Sciences, Hamburg, Germany) during 5 days from 11 h prior to until 110 h following patch application. The treatment periods were spaced by a 7 day washout period. An anaesthesiologist experienced in analgesic therapy supervised all fentanyl treatments. Clinical examination (including vital signs, skin tolerability, electrocardiogram, respiratory rate, pulse oximetry, blood pressure, heart rate and vigilance), laboratory monitoring as well as patch adhesion monitoring was performed throughout the study. Adverse events were actively evaluated at 0, 2, 4, 6, 8, 12, 16, 24, 30, 36, 48, 60, 72, 84, 96, 108 and 120 h after the beginning of the administration, rated according to severity (mild, moderate, severe) and an assessment of the causal relationship of the adverse event with fentanyl therapy was performed.

The patches were applied to non-irritated and non-irradiated skin on the infraclavicular pectoral area. Blood samples were collected at 0, 4, 8, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, and 72 h, following the application of each of the patches. After 72 h the systems were removed and

additional blood sampling was conducted at 84, 96, 108 and 120 h post-application of the devices.

Primary variables were the area under the concentration time curve from administration to the last measured concentration above lower limit of quantification (LLOQ) (AUC(0,t)) and peak plasma concentration (C_{max}). The pharmacokinetic profile was calculated and used as a surrogate parameter for efficacy. All calculations of pharmacokinetic parameters were carried out with validated software modules (BABE 8.3) based on SAS language and procedures (SAS 8.2, SAS-Institute). All calculations were based upon the reported concentrations and sampling times. Pharmacokinetic variables were calculated without fitting to a compartment model. Estimates for missing concentrations were obtained by linear interpolation when required.

Bioequivalence was claimed if the 90% confidence interval of AUC(0,t) and C_{max} ratios (test: reference) were within the acceptance range of 80–125% and 75–133%, respectively.

Blood sampling

Blood samples of 5 ml were drawn by means of an indwelling catheter or venipuncture in order to extract at least 1.5 ml plasma. Blood was drawn directly from a vein into EDTA-coated tubes (Monovette, Sarstedt, Germany). They were centrifuged for 10 min at 2750 g at 4 °C, and the plasma transferred into fresh tubes (Serumröhrchen, Sarstedt). The samples were stored at −20 °C. Blood samples obtained immediately before each patch application were defined as 0 h (baseline). The concentration of fentanyl was determined in the EDTA plasma samples using a validated LC/MS/MS method [12]. The standard substance of certified purity for calibration and quality control purposes was used. The LLOQ was 10 pg ml^{-1} and the upper LOQ was 2000 pg ml^{-1}. The coefficient of variation (CV%) ranged from 7.4% at 10 pg ml^{-1} to 3.6% at 1400 pg ml^{-1} and the accuracy from 103.9% at 10 pg ml^{-1} to 96.9% at 200 pg ml^{-1}.

Statistical methods

All statistical calculations were performed using SAS software. All subjects receiving the study medication at least once were included in the safety evaluation. Subjects who completed the study according to the protocol (per protocol population) were included in the statistical evaluation. The data of subjects who dropped out were reported as far as available but not included into descriptive and confirmatory statistics. The arithmetic mean, and for concentration related parameters, also the geometric mean, the standard deviation, coefficient of variation, absolute minimum and

maximum, and median were reported for each parameter. The individual subject values for concentrations and pharmacokinetic parameters were tabulated with descriptive statistics. After logarithmic transformation of data, analyses of variance (ANOVA) were performed on all parameters except t_{max}, primarily in order to estimate the residual error which was used to construct the confidence intervals. Moreover, ANOVA were used to evaluate the presence of period or sequence effects. The effects considered in the ANOVA model were treatment, sequence, study period and subject within sequence. The error variance of the model was taken as test variance for all the effects except the sequence effect. The latter was tested using the variance 'subject within sequence' as an error term. The probability for erroneously rejecting the hypothesis H$_0$ of no significant effect was presented with values <0.05 regarded as significant. For AUC(0,t), AUC, AUC(0,72 h), C_{max}, $t_{1/2}$, the parametric point estimators for the ratio and the shortest 90% confidence intervals were calculated using the LSmeans and the root of residual mean squares from the ANOVA of log-transformed data with subsequent exponential transformation [13]. Non-parametric point estimators for the ratios of expected medians of treatment A (test) and B (reference) and the corresponding non-parametric 90% confidence intervals were calculated based on Wilcoxon statistics using log-transformed data [14, 15]. For t_{max} the non-parametric point estimator and the non-parametric 90% confidence intervals for the difference of expected medians were calculated according to the Wilcoxon statistics using the untransformed data. The non-parametric approach was preferred if the Shapiro/Wilk statistics [16] indicated a highly significant ($P < 0.01$) deviation from normal distribution which was a conservative procedure in favour of the normality assumption.

Results

A total of 36 healthy males were enrolled into the study. Their mean age and body mass index were 32.5 ± 6.3 years and 24.0 ± 2.47 kg m^{-2}, respectively. From the initially enrolled 36 patients, 34 completed both treatment periods. One patient dropped out prior to patch administration and another during the first treatment period. Thus, data from 35 patients and 69 pharmacokinetic data sets (two treatment periods from 34 patients and one treatment period from one patient) were included in the safety and efficacy evaluation, respectively. The kinetic variables are summarized in Table 1 and the PK profiles are given in Figure 1. The 90% confidence intervals of the AUC(0,t) ratio (116.3% [109.6, 123.4%]) and the C_{max} ratio (114.4% [105.8, 123.8%]) were well included in the acceptance range stipulated in the protocol and the C_{max} ratio also met the narrower bounds of

80–125%. Also t_{max} is comparable within relatively narrow confidence intervals (Table 1). It was thus concluded that the bilayer matrix type fentanyl transdermal patch (test) was bioequivalent to the monolayer matrix type Durogesic SMAT fentanyl transdermal therapeutic system (reference) with respect to these kinetic parameters.

There was no relevant difference in overall safety profiles of the two preparations investigated. The study preparations were adequately tolerated, as expected for opioid-naïve subjects. There was an equal distribution of adverse events between the two treatments. Fifty-five adverse events were reported by 26 subjects during treatment with the test patch and 51 adverse events by 24 subjects during treatment with the reference patch. The most frequently reported adverse events were headache (12 events), nausea (11 events), tiredness (10 events), dizziness (eight events), drowsiness (eight events), itching under patch (seven events), itching of whole body (seven events), muscle ache in different regions (six events) and localized itching in different regions (five events). The intensity was rated mild in the majority of cases (84 events). No severe adverse events were recorded. Altogether, 22 adverse events were classified with a probable/likely causal relationship to the study drugs (10 with test, 12 with reference). No significant laboratory alterations or safety-related issues occurred during the study.

No major protocol deviations were recorded during this study. Overall skin tolerability of both test and reference patch was considered quite good. There was no difference between test and reference patch with respect to patch adhesion.

Discussion

Fentanyl is an appropriate drug for transdermal application because of its physicochemical properties and high analgesic potency. Its transdermal administration provides particular benefit in patients with dysphagia or nausea or in patients with poor compliance (provided the pain is stable), and is less constipating than oral morphine [17].
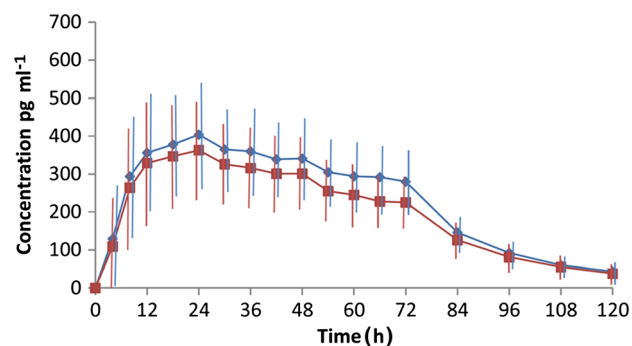

Figure 1

Mean fentanyl plasma concentrations with SDs of the bilayer (test) and of the monolayer (reference) formulation after single dosing. ◆, bilayer; ■, monolayer

Following the development of the new bilayer matrix matrix type patch Fentalgon®, the aim of this study was to assess its bioequivalence after single administration in comparison with a reference monolayer matrix type patch. Bioequivalence between Durogesic DTrans matrix patch and other matrix patches has been shown in several studies [8, 11], but no actual studies investigated this novel bilayer matrix transdermal fentanyl patch.

Pharmacokinetic profiles suggest that the two study matrix types patches are bioequivalent in terms of plasma fentanyl concentration, mean onset and peak time, peak concentration, AUC and AUC(0,72 h). These parameters satisfy accepted criteria for bioequivalence [18] which, however, do not include rate of absorption. It is also known that transdermally delivered fentanyl bioavailability is less than 100%, probably due to the reduced concentration gradient between the system and the skin in the latest period of the dosing interval [19]. It would therefore be important to investigate if the double matrix system affects absorption rate and bioavailability during the last hours of dosing and, beyond kinetic considerations, to compare clinical effects between the bilayer and monolayer delivery systems.

It is also worthwhile underlining the interindividual variability of plasma concentrations, as shown by the standard deviations in Figure 1 and as already described [20].

Table 1

Pharmacokinetic data. Values are reported as mean value ± SD ($n = 34$)

Parameter	Test	Reference	Ratio test: reference (%)	90% CI
AUC(0,t) (pg ml^{-1} h)	28270 ± 8312	24609 ± 8371	116.3	109.6, 123.4
C_{max} (pg ml^{-1})	439 ± 136	390 ± 145	114.4	105.8, 123.8
AUC(0,72 h) (pg ml^{-1} h)	22748 ± 7076	19884 ± 6950	113.5	107.0, 121.9
AUC (pg ml^{-1} h)	29616 ± 9125	25885 ± 9351	113.4	108.4, 121.4
t_{max} (h) [range]	28.8 ± 8.0 [8.0–71.9]	28.6 ± 12.0 [12.0–66.0]	101.0	97.0, 106.0
$t_{½}$ (h)	19.3 ± 7.4	20.1 ± 7.3	94.9	89.2, 101.7

After absorption both patches maintained a plateau state from 18 h following application until the patch was removed. There were no major differences in the decay of fentanyl during the washout period. In addition there was an equal distribution of adverse events between the two treatments.

As expected, the pharmacokinetics and tolerability of Fentalgon® did not differ significantly from the reference patch, thus confirming both efficacy and safety of this novel bilayer matrix type fentanyl patch.

The fentanyl-containing matrix prevents leak from the patch and the bilayer system (upper 6% fentanyl reservoir layer and a lower 4% fentanyl donor layer) maintains a stable concentration gradient between the patch and the skin. It is noteworthy that there is an absence of alcohol, whose evaporation can compromise a constant drug delivery to the skin.

In conclusion, the presented data provide sufficient information to consider this new transdermal fentanyl patch after single administration, as appropriate as the Durogesic monolayer patch in the treatment of chronic cancer pain [1]. Bioequivalence of the bilayer matrix type fentanyl transdermal therapeutic system with the approved reference transdermal therapeutic system has been demonstrated.

As based on known data on biopharmaceutics, clinical pharmacology, efficacy and safety of transdermal fentanyl, and in agreement with the results of the present study, Fentalgon® appears to be an appropriate and innovative option for the treatment of chronic cancer pain.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). AF and TP are employed by Italfarmaco S.p.A. DS was employed by the conducting CRO Scope International Life Sciences, during the conduct of the study and later by Helm AG, the sponsor of the study. EZ and FC received a grant from Italfarmaco S.p.A. AF, TP, EZ, FC and EB declare no support from any other organizations for the submitted work, no financial relationships with any other organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work. AM declares no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years. AC declares grants received by his institution from Molteni, Gruenenthal, Prostrakan, Mundipharma, Teva Pharmaceutici, board membership participaton for Gruenenthal and Pfizer, and honoraria from Molteni.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appenix S1
List of exclusion criteria