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Impact of allergic rhinitis and its treatment on the pharmacokinetics of nasally administered fentanyl

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Key words
breakthrough pain in cancer – fentanyl – intranasal – pharmacokinetics – allergic rhinitis

Abstract. Objectives: Fentanyl pectin nasal spray (FPNS, Lazanda® in the US and PecFent® in Europe and Australia) is a novel analgesic approved for the management of breakthrough pain in cancer patients. Given that the fentanyl is nasally administered, it is important to understand whether concomitant allergic rhinitis, or its treatment with a vasoconstrictor, would affect its absorption and, potentially, its efficacy or safety. Methods and subjects: Subjects with a history of allergic rhinitis were screened to identify subjects who developed at least moderate rhinitis symptoms on exposure to pollen allergen (either ragweed or tree) in an environmental exposure chamber (EEC). These were entered into a randomized, three-way crossover study in which each subject received 100 µg of FPNS under three exposure conditions; Control (no rhinitis), Rhinitis (symptomatic without decongestant), Treated (symptomatic with concomitant oxymetazoline). Blood samples for fentanyl were collected over a 24-hour period. Results: A total of 132 subjects was screened to identify 54 for inclusion in the study; 31 were evaluable for pharmacokinetics. Measures of fentanyl absorption (mean or median) were similar between Control and Rhinitis conditions: C_{max} 453.0 vs. 467.8 pg/ml; AUC_t 1,292.3 vs. 1,325.4 pg×h/ml, $AUC_{0-\infty}$ 1,430.6 vs. 1,387 pg×h/ml and t_{max} 20 vs. 17 minutes. When oxymetazoline was co-administered, overall fentanyl absorption was slightly reduced ($AUC_{0-\infty}$ 1,362.4 pg×h/ml); but, more clinically relevant were the delayed rate of absorption (t_{max} 53 minutes) and reduced C_{max} (235.3 pg/ml). Conclusions: Patients treated with FPNS will be unaffected by the development of allergic rhinitis; but, if oxymetazoline is prescribed, the patient would benefit from added supervision when oxymetazoline is started and stopped.

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Introduction

Fentanyl, a lipophilic opioid analgesic, has a high potency and a short effective half-life [1, 2] which makes it very suitable for the management of acute pain of limited duration, e.g., breakthrough pain in patients with cancer (BTPc) [3, 4, 5]. But, orally administered fentanyl is subject to significant first-pass metabolism and delayed absorption which reduces its effectiveness for acute onset pain. Intranasal delivery avoids first-pass metabolism and allows for "almost i.v. kinetics" [6] from a route of administration with high clinician, caregiver, and patient acceptability [7, 8]. Fentanyl pectin nasal spray (FPNS) is a fentanyl citrate solution containing the PecSys® drug delivery system (Archimedes Development Ltd, Nottingham, UK) which allows the product to form a gel when sprayed into the nose, thus retaining it on the nasal mucosa [9]. This formulation was developed to reduce nasal drip [10] as well as to facilitate opioid administration and optimize absorption kinetics.

FPNS is approved for the management of BTPc as PecFent® (Europe and Australia) or Lazanda® (US). Fentanyl diffuses from the gel layer and is absorbed across the nasal mucosa. This gel-modulated absorption results in an early t_{max}, a modulated C_{max}, and a more prolonged action of fentanyl, with no significant nasal reactogenicity [11]. In a previous pharmacokinetic study, a single dose of FPNS achieved an earlier t_{max} than the same dose (200 µg) of oral transmucosal fentanyl citrate, (OTFC; Actiq®; Cephalon Inc., Salt Lake City, UT, USA; t_{max}, 15 vs. 90 minutes) and greater C_{max} (781 vs. 317 pg/ml) [12].

A substantial program of trials confirmed the efficacy and safety of FPNS in the clinical setting of BTPc [4, 13, 14, 15, 16, 17]. FPNS was shown to provide a rapid onset of analgesia (as early as 5 minutes) with clinically meaningful pain relief within 10 minutes and persistent benefits over the duration of follow-up (60 minutes). Furthermore, FPNS provides significantly greater pain relief than immediate-release morphine sulphate [4, 15]. FPNS was shown to be generally well tolerated, with low rates of patient withdrawal from treatment and without negative nasal tolerability findings [13, 14, 15, 16].

The principal objective of this trial was to define whether the pharmacokinetics of FPNS is affected by co-existing seasonal allergic rhinitis or the co-administration of the vasoconstricting decongestant oxymetazoline.

Methods and subjects

This pharmacokinetic study was conducted at Allied Research International, Inc. (Mississauga, ON, Canada). The study protocol and amendments were independently reviewed and approved by IRB Services Ltd (Aurora, ON, Canada). The study was conducted in accordance with the Declaration of Helsinki, Health Canada's regulations and guidelines, and International Conference on Harmonization good clinical practice guidelines. Written approval was obtained from Health Canada (Clinical Trial Application (CTA) control number 114998; CTA file number 9427-A1916-21C) before commencement of clinical activities.

Study design

This was an open-label, single-center, randomized, three-way crossover trial in which healthy subjects were administered single 100 µg doses of FPNS with naltrexone cover; co-administration of naltrexone does not affect the pharmacokinetics of fentanyl [18, 19]. All subjects underwent an initial screening visit. If inclusion/exclusion criteria were met, their ability to develop at least "moderate rhinitis" was assessed when exposed to the relevant allergen pollen (ragweed or birch tree) for at least 30 minutes in an EEC. Subjects remained in the chamber for 1 hour after FPNS administration. Subjects meeting all screening criteria were randomized into the cross-over phase of the study where each subject received 100 µg of FPNS on three separate occasions, under three different exposure conditions:

1. Control (no rhinitis),
2. Rhinitis (symptomatic without decongestant),
3. Treated (symptomatic with concomitant vasoconstrictor (0.05% oxymetazoline solution, Dristan® Long Lasting; Wyeth Consumer Healthcare, Inc., Madison, NJ, USA) administered as 2 sprays into each nostril 2 hours before FPNS).

This was a three-period six-sequence crossover trial and the subjects were randomized to 1 of the 6 randomization sequences; each exposure was separated by a 14-day wash-out period. A follow-up visit occurred 1 – 2 weeks after the last exposure assessment.

Subjects

The eligible population included male and female subjects aged 18 – 65 years; all had a diagnosis of allergic rhinitis defined by a positive case history plus positive findings on skin prick, intradermal test, for either ragweed pollen (*Ambrosia spp.*) or birch tree pollen (*Betula spp.*) within 12 months of screening. Each subject's "moderate" response to allergen was confirmed through exposure in an EEC (i.e., a screening exposure). Subjects were otherwise healthy. Subjects had no clinically significant abnormal laboratory findings at the screening assessment and no positive drug abuse tests; body mass index ranged between 18 and 29 kg/m^2.

All subjects that were treated with one or more doses of FPNS were defined as the safety population. The evaluable population was defined as all subjects that had valid pharmacokinetic data for at least two exposure conditions. A sample size of at least 30 evaluable subjects was considered sufficient to assess any potential differences in pharmacokinetic parameters between exposure conditions. Given the wide intra-subject coefficient of variation (CV) of fentanyl and the lack of information regarding potential

effects of exposure conditions, this study was neither designed, nor study sample size powered, to determine statistical bioequivalence of FPNS under different exposure conditions.

Confirmation of at least moderate symptomatic rhinitis

In order to assure that all subjects had at least moderate symptoms of allergic rhinitis before dosing with FPNS nasal symptoms of allergic rhinitis were recorded on diary cards at screening and on each FPNS dosing day. Four symptoms were measured: runny nose (anterior rhinorrhea/postnasal drainage), itchy nose, nasal congestion (stuffy nose) and sneezing. The severity of each symptom was rated on a 4-point scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe). To be classified as symptomatic, subjects had to have a total nasal symptom score (TNSS) ≥ 6 with a nasal congestion score of ≥ 2 (minimum for "moderate rhinitis"), on 2 consecutive diary cards. Subjects were classified as asymptomatic if the TNSS was ≤ 3 with a nasal congestion score of ≤ 1. Symptoms were recorded at 30 minute intervals while in the EEC; FPNS was not administered for Rhinitis and Treated conditions unless the subject was classified as symptomatic.

PK assessments

All subjects received naloxone hydrochloride (100 mg) 1 hour before and 12 hours after dosing with FPNS to block opioid effects.

Blood samples were collected at specific time points up to 24 hours after dosing with FPNS: before dose administration (predose, within 10 minutes of dosing) and at 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 360, 480, 720, and 1,440 minutes after dosing.

Blood samples were kept on ice until they were centrifuged at ~ 2,000 g for 15 minutes at 4 °C. The resultant plasma was removed and frozen at –20 °C within 1 hour of collection for transfer to the bioanalytical laboratory (Ba Research International-Cetero Research, Houston, TX, USA). Plasma fentanyl concentrations were determined using a validated method of high-pressure liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS); the lower limit of quantification of the assay was 10.0 pg/ml. The analyst was blinded to the exposure conditions.

Pharmacokinetic parameters included maximum plasma concentration of fentanyl (C_{max}), time when maximum plasma concentration of fentanyl (t_{max}) was achieved, area under the plasma concentration time curve to the last measurable time point of fentanyl detection (AUC_t), area under the plasma concentration time curve extrapolated to infinity ($AUC_{0-\infty}$), an $AUC_{0-\infty}$ value was considered unreliable if the area under the plasma concentration time curve for the extrapolated portion (AUC_{extr}) was > 20%. Relative bioavailability (F_{rel}) was assessed relative to Control or Rhinitis exposure. All parameters were computed using WinNonLin version 5.3 (Pharsight Corporation, Mountain View, CA, USA) software.

Safety and tolerability

Safety and tolerability parameters were recorded during and after each exposure condition as well as during and after FPNS administration. These included adverse event (AE) incidence and relationship to treatment, standard symptom questionnaire before dosing, plus a nasal reactogenicity questionnaire before and after each FPNS dose; local reactions listed that continued beyond 24 hours were regarded as AEs. Any signs or symptoms of allergic rhinitis were not necessarily considered AEs when the subjects had been exposed to pollen. Subjects were asked if there were any changes to their health that they did not usually experience with pollen exposure; these changes were recorded as AEs. Subjects received a local safety assessment by an Ear, Nose, and Throat specialist (or a suitably trained clinician) at screening and at the follow-up visit. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 10.1), and all AEs captured in the database were listed by subject. Hematology and biochemistry blood sampling was performed at the screening and final follow-up visits in the fasting state.

Table 1. Subject disposition n (%).

Screened for ragweed or tree pollen allergy	132
Randomized (safety population)	54
Ragweed allergen exposure	37 (68.5)
Tree pollen allergen exposure	17 (31.5)
Evaluable PK population*	31 (57.4)
Completed the study	28 (51.9)
Discontinued from study	26
Reason for discontinuation	
Adverse event	2 (7.7)
Medical reasons other than adverse events	1 (3.8)
Pregnancy	1 (3.8)
Subjects' decision to withdraw	6 (23.1)
Poor vein structure for cannulation	1 (3.8)
Failed to meet TNSS requirements during the study	15 (57.7)

*Subjects completed at least 2 exposure conditions.

Table 2. Demographic and baseline characteristics for the randomized population.

Randomized	54
Age, y: mean (SD) (range)	39.1 (10.9) (22 – 60)
Sex, n (%)	
Male	28 (51.9)
Female	26 (48.1)
Height, m, mean (SD)	1.69 (0.09)
Weight, kg, mean (SD)	75.6 (9.33)
Body mass index, kg/m^2 (SD)	26.52 (2.04)
Ethnicity, n (%)	
Caucasian	34 (63.0)
African	12 (22.2)
Asian	2 (3.7)
Indian	1 (1.9)
Arabic/North African	1 (1.9)

Statistical analysis

Plasma concentrations over time were summarized using standard dispersion parameters. Data from ragweed and tree pollen allergen populations were pooled and treatment by allergen interaction tested within an analysis of variance (ANOVA) using ln-transformed parameters for AUC_t, $AUC_{0-\infty}$ and C_{max}. The model included fixed effects for the interaction between treatment and allergen. A significance level of $p = 0.1$ (10%) was used to test for this effect and if the interaction was above this point the observed pharmacokinetic data from both tree pollen and ragweed allergen exposed subjects were considered valid for pooling. Although the study was not designed, nor powered, to demonstrate statistical bioequivalence, comparative statistical assessments of bioequivalence were undertaken to provide guidance. Consistent with the two one-sided t-test approach for bioequivalence 90% confidence intervals (CIs) for the differences between exposure conditions least-squared mean (LSM) values were calculated for the parameters AUC_t, $AUC_{0-\infty}$, and C_{max} using log-transformed data and using untransformed data for t_{max}. Ratios (%) of mean values were calculated using the geometric LSM values for AUC_t, $AUC_{0-\infty}$, and C_{max} and the arithmetic mean value for t_{max}. SAS® version 9.1 (SAS Institute, Inc., Cary, NC, USA) was used for the statistical analysis.

Results

Subject disposition and demographics

A total of 132 subjects with a history of pollen allergy were screened; of these, 54 subjects attained nasal scores that confirmed symptomatic pollen allergy and were randomized into the study. Their disposition is detailed in Table 1. A total of 31 completed at least two exposures and formed the evaluable population (28 subjects completed all three exposures). Of the 26 discontinuations, most (58%) were related to a failure to achieve at least moderate symptomatology in the EEC, even though this had occurred at screening. Only two discontinuations were due to AEs. Demographics for the randomized subjects are presented in Table 2. Most of the subjects were Caucasian and equally balanced for gender.

Pharmacokinetics

Pharmacokinetic data from the ragweed and tree pollen allergen populations were pooled; no significant interaction of allergen type by treatment was detected at the 10% level for AUC_t, $AUC_{0-\infty}$, or C_{max} ($p = 0.1304$, 0.1442, 0.2032 respectively) and therefore pooling was considered valid.

Mean plasma concentrations of fentanyl over time for the three exposure conditions (Control, Rhinitis, and Treated) are shown in Figure 1; The fentanyl absorption phase was not affected by Rhinitis (vs. Control), but appeared blunted in the Treated condition (vs. Rhinitis or Control); the elimination phases

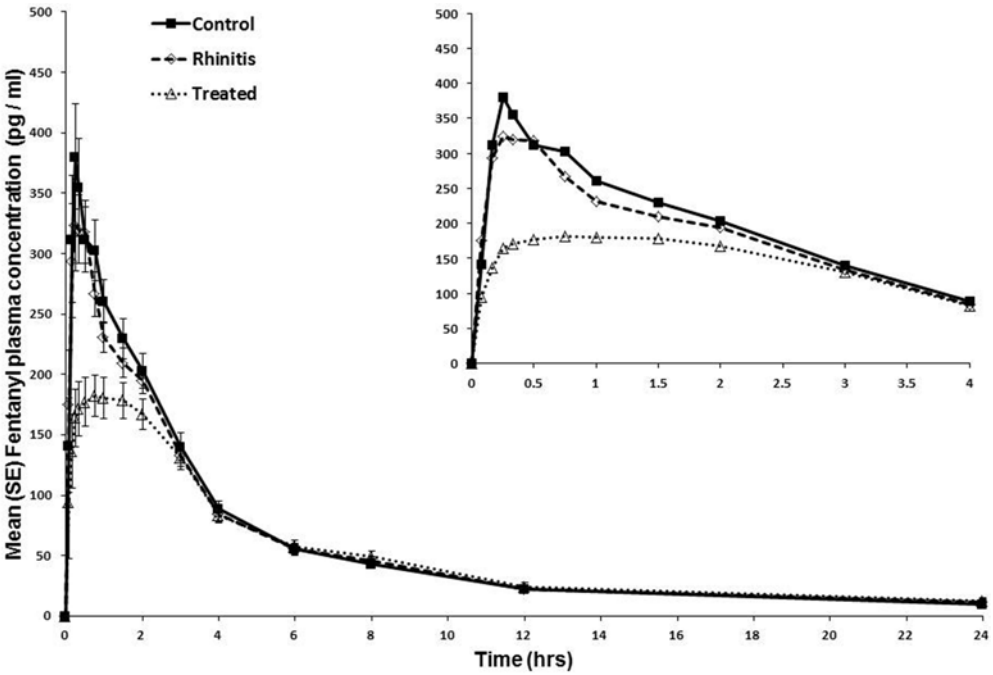


Figure 1. Mean (SE) fentanyl plasma concentration under Control, Rhinitis, and Treated conditions: main 0 – 24 h; insert 0 – 4 h.

Table 3. Mean (CV%) of pharmacokinetic parameters after FPNS administration during the three exposure conditions.

Parameter (units)	Control	n	Rhinitis	n	Treated	n
C_{max} (pg/ml)	467.8 (52.9)	28	453.0 (49.4)	30	235.3 (86.6)	30
t_{max} (min)	17 (10 – 120)[a]	28	20 (5 – 180)[a]	30	53 (5 – 180)[a]	30
AUC_t (pg×h/ml)	1,325.4 (45.2)	28	1,292.3 (41.4)	30	1,172.2 (46.6)	30
$AUC_{0-\infty}$ (pg×h/ml)	1,387.0 (50.2)	23	1,430.6 (51.9)	23	1,362.4 (63.0)	22
$t_{1/2}$ (h)	5.56 (66.4)	23	6.38 (63.7)	23	6.16 (65.5)	22
F_{rel}						
vs. Control						
AUC_t	–	–	0.994 (27.8)	27	0.860 (23.5)	27
$AUC_{0-\infty}$			0.997 (28.4)	18	0.876 (32.2)	19
vs. Rhinitis						
AUC_t					0.914 (27.2)	29
$AUC_{0-\infty}$					0.916 (26.4)	17

[a]Median (range).

for fentanyl FPNS appeared similar in all three conditions.

The pharmacokinetic parameters for the three exposure conditions are shown in Table 3, and the statistical comparisons of the relative exposure comparisons are shown in Table 4. The absorption of fentanyl was unaffected by the presence of allergic rhinitis; the individual pharmacokinetic parameters overlap (C_{max}, AUC_t and $AUC_{0-\infty}$) (Table 3) and F_{rel} for AUC_t and $AUC_{0-\infty}$ were very close to 1. The 90% CIs for differences between the exposure conditions were between 76 and 109% (C_{max}, AUC_t and $AUC_{0-\infty}$) (Table 4). By contrast, fentanyl absorption was slowed by the co-administration of oxymetazoline (t_{max} delayed, with lower C_{max}); bioavailability was reduced by 8 – 9% as demonstrated by reduced F_{rel} for AUC_t and $AUC_{0-\infty}$ (91.44 and 91.63%, respectively) (Table 3). The 90% CIs for differences between these exposure conditions were between 48 and 102% (Table 4).

Table 4. Summary of pharmacokinetic comparisons after FPNS administration under three exposure conditions.

FPNS exposure comparisons	Pharmacokinetic parameter[a] (units)	Ratio of means[b]	90% confidence interval (%)
Rhinitis vs. Control	AUC_t (pg×h/ml)	0.919	83.5 – 101.3
	$AUC_{0-\infty}$ (pg×h/ml)	0.910	79.7 – 104.0
	C_{max} (pg/ml)	0.910	76.0 – 109.0
	t_{max} (h)	1.059[b]	66.8 – 145.2
Treated vs. Control	AUC_t (pg×h/ml)	0.814	74.1 – 89.6
	$AUC_{0-\infty}$ (pg×h/ml)	0.820	72.4 – 92.9
	C_{max} (pg/ml)	0.516	43.2 – 61.7
	t_{max} (h)	2.062[b]	187.7 – 244.8
Treated vs. Rhinitis	AUC_t (pg×h/ml)	0.886	80.8 – 97.2
	$AUC_{0-\infty}$ (pg×h/ml)	0.900	79.4 – 102.1
	C_{max} (pg/ml)	56.7	47.7 – 67.5
	t_{max} (h)	194.6	158.3 – 231.0

[a]All parameters are log_n-transformed, apart from t_{max}, which is untransformed; [b]ratios are of geometric least squares means (LSM), except t_{max}, which is arithmetic mean.

Safety and tolerability

No deaths or treatment-related serious AEs were reported during this study. Most of the 58 reported AEs in 27 subjects were mild; none was rated as severe. In the Control, Rhinitis, and Treated conditions there were 12, 8, and 12 subjects, respectively, who reported AEs. While most AEs were assessed as having a degree of relationship (remotely, possibly, probably, or definitely related) to study drug, only two AEs (vomiting, one moderate and one mild severity) were considered definitely related to study drug with 6 probably related to study drug (nausea and dizziness of moderate severity, plus nausea, abnormal coordination, and somnolence, all of mild severity). No abnormal hematology or biochemistry was noted.

Discussion

Patients with breakthrough pain experience multiple episodes of acute pain in spite of adequate around the clock analgesia [20]; typically, patients experience pain lasting 30 – 60 minutes 4 times a day [20, 21]. As is usual practice in this setting, dose-selection for FPNS (Lazanda® in the US and PecFent® in Europe and Australia), and for all rapidly absorbed fentanyl products (RAFs), is based on an initial titration to effect phase followed by a maintenance phase. For FPNS, treatment is initiated at a dose of 100 µg and then titrated (up to 800 µg) based on patient reported efficacy in the absence of safety concerns. Once patient satisfaction had been achieved, patients maintain that dose of FPNS for all future episodes of BTPc. In the Phase 3 program, ~ 50% of patients were maintained on 100 or 200 µg, while ~ 50% used doses of 400 or 800 µg. Furthermore, > 90% of patients did not require any change in dose over time [14]. This approach to dose selection, titration to effect, and then maintenance of that titrated dose for future events, makes an underlying assumption that the uptake of fentanyl will not change over time nor be affected by clinical conditions that might modify absorption. For example, fentanyl absorption can be increased from oral cavity administered fentanyls when a patient develops mucositis, a not uncommon clinical event in patients being treated for cancer [22]. By contrast, oral mucositis would not affect absorption of fentanyl from FPNS, but nasal conditions might have an impact. The general literature suggests that nasal pathologies (e.g., coryza and allergic rhinitis) have no impact on drug absorption [23, 24]. However, there is a report that nasal absorption of fentanyl from a nasally administered aqueous solution (Instanyl®; Takeda Pharmaceuticals International GmbH, Zurich, Switzerland) is reduced by co-administration of a vasoconstrictor [25, 26]. In that study, the effect of rhinitis was not assessed, but prior administration of oxymetazoline delayed the absorption (t_{max} increased from 21 to 46 minutes), and lowered peak concentration (C_{max}

decreased by over 50%) of fentanyl although the overall extent of absorption (AUC) was not significantly affected.

In this study with FPNS, the impact of both rhinitis alone and rhinitis treated with oxymetazoline were independently assessed. All subjects in the study demonstrated at least moderate symptoms associated with allergen exposure. Rhinitis alone did not affect the absorption of fentanyl during either overall or the early phase, which is crucial for early analgesia. Co-administration of oxymetazoline slightly reduced the overall extent of absorption of fentanyl; but, more importantly it delayed the absorption of fentanyl (t_{max}) and reduced its early absorption (C_{max} and AUC_t).

The clinical implications of these data are that patients who suffer from rhinitis, but who do not use a vasoconstrictor, can continue to use the same dose of FPNS without regard to season and the emergence of symptomatic rhinitis. Oxymetazoline is not used chronically; if oxymetazoline is added to manage rhinitis symptoms in a patient already taking FPNS there will likely be a reduction in C_{max} and t_{max} will be delayed. This might translate into reduced analgesia, but that would need to be assessed on an individual patient basis. However, when the oxymetazoline is stopped there is a potential for increased fentanyl levels that might have safety implications, especially if the dose of FPNS had been increased when the oxymetazoline was initiated.

Conclusion

This study demonstrates that the pharmacokinetics of FPNS is not affected by the presence of allergic rhinitis, but that the co-administration of oxymetazoline slows the absorption of fentanyl. Patients should be advised of this interaction and would benefit from added observation when oxymetazoline is initiated (assures adequate analgesia) and stopped (assures safety).

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