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Original article

A comparison of intranasal fentanyl spray with oral transmucosal fentanyl citrate for the treatment of breakthrough cancer pain: an open-label, randomised, crossover trial

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Abstract

Objective:
The efficacy of intranasal fentanyl spray (INFS) was compared with that of oral transmucosal fentanyl citrate (OTFC) for the relief of cancer-related breakthrough pain (BTP) in an open-label, crossover trial.

Methods:
Adult cancer patients receiving stable background opioid treatment and experiencing BTP episodes were recruited from 44 study centres in seven European countries (Austria, France, Germany, Italy, Poland, Spain and the United Kingdom); of the 196 patients enrolled, 139 were randomised to receive INFS followed by OTFC, or vice versa. Patients were titrated to an effective dose of one agent (50, 100 or 200 μg INFS; 200, 400, 600, 800, 1200 or 1600 μg OTFC) to treat six BTP episodes, then titration and treatment were repeated with the other agent. The primary outcome was patient-recorded time to onset of 'meaningful' pain relief. Secondary outcomes included pain intensity difference (PID) at 10 and 30 minutes (PID_{10}, PID_{30}), sum of PID at 15 and 60 minutes ($SPID_{0–15}$, $SPID_{0–60}$), ease of administration, treatment preference and relationship between background opioid dose and effective INFS dose. Additional outcome measures included proportions of episodes with ≥33% and ≥50% pain intensity (PI) reduction, and PID at additional time points.

Clinical trial registration number:
NCT00496392.

Results:
Among the intention-to-treat population ($n = 139$), median time to onset of 'meaningful' pain relief was 11 minutes with INFS versus 16 minutes with OTFC; 65.7% of patients attained faster time to 'meaningful' pain-relief onset with INFS ($p < 0.001$). PID was statistically significantly greater for INFS than OTFC from 5 minutes post-dosing. Significantly more INFS-treated breakthrough pain episodes achieved clinically important pain relief (≥33% and ≥50% PI reduction) up to 30 minutes post-dosing. The proportions of episodes treated with INFS and OTFC achieving a PI reduction of ≥33% at 5 minutes were 25.3% versus 6.8% ($p < 0.001$), and at 10 minutes were 51.0% versus 23.6% ($p < 0.001$), respectively; the proportions of episodes treated with INFS and OTFC achieving a ≥50% PI reduction at 5 minutes were 12.8% versus 2.1% ($p < 0.001$), and at 10 minutes were 36.9% versus 9.7% ($p < 0.001$), respectively. Higher $SPID_{0–15}$ and $SPID_{0–60}$ scores were achieved with INFS ($p < 0.001$). More patients preferred INFS than OTFC ($p < 0.001$) and more patients found it very easy/easy to use. Both treatments were well tolerated. In the safety population ($n = 139$), 56.8% ($n = 79$) of patients experienced ≥1 AE during the trial. The only AE that occurred in ≥5% of patients in either treatment group was nausea. Among those patients who experienced serious AEs (13.7%, $n = 19$), none were considered to be related to either study medication. There was a weak correlation between effective INFS doses and background opioid doses.

Conclusion:
In this open-label, randomised, crossover trial, significantly more patients attained faster 'meaningful' pain relief with INFS than OTFC, and more patients preferred INFS to OTFC.

Introduction

During the past two decades cancer-related breakthrough pain (BTP) has become accepted as a discrete pain entity[1]. Although the term BTP is inconsistently used in clinical practice, the definition proposed by Portenoy *et al.* (2004)[2] is one of the most widely accepted. That is, BTP is a transitory exacerbation of pain experienced by the patient who has relatively stable and adequately controlled baseline (background) pain[2].

BTP episodes typically occur frequently, are of moderate-to-severe intensity, with a rapid onset (minutes), and a short duration (~30 minutes)[1,3–5]. BTP is associated with several causes (e.g., the cancer itself, anti-cancer treatment or concomitant illness), and pathophysiologies (e.g. nociceptive, neuropathic, mixed)[6]. As such, the clinical features of BTP vary between and within individuals, often reflecting the clinical features of the background pain[7,8]. Effective management of BTP has proved difficult to achieve, and is an important unmet need in the treatment of cancer patients. The presence of BTP decreases patient satisfaction with overall pain management, limits quality of life, increases the likelihood of physical, psychological and social complications, and places an economic burden on society and the healthcare system[3,8–11].

Fentanyl citrate, a synthetic opioid, has a rapid onset of effect and a short duration of action[12], matching the temporal characteristics of a BTP episode. The development of oral transmucosal fentanyl citrate (OTFC, Actiq*) was an important advance in BTP treatment, as it provides a non-invasive method of administration, and has demonstrated significant superiority over oral morphine (morphine sulphate immediate release) in the relief of BTP[13]. However, OTFC requires a 15-minute administration and reasonable saliva levels. Since salivary gland dysfunction and xerostomia are common in cancer patients[14,15], OTFC may be difficult to administer successfully[16]. This shortfall has led to the development of alternative formulations of fentanyl for the treatment of BTP, including intranasal fentanyl spray (INFS). The intranasal mode of administration has the advantage of bypassing the oral route and thus may be more acceptable to patients who experience nausea, vomiting, oral mucositis, impaired gastrointestinal function and xerostomia. Fentanyl's high lipophilicity, low potential for irritation and short duration of action, make it well suited for intranasal administration.

Intranasal fentanyl spray (INFS)† constitutes a promising new treatment option for BTP, having demonstrated a rapid onset of action (median 7 minutes) for the relief of dental post-operative pain[17], and a clinically important reduction in pain at 10 minutes post-administration in cancer patients with BTP[18,19]. Furthermore, INFS is well tolerated by cancer patients[18,19]. Here we report the results of an open-label, randomised, crossover trial, comparing the efficacy and tolerability of INFS with OTFC treatment for the relief of BTP in patients with cancer.

*Actiq is a registered trade name of Cephalon, USA.
†Instanyl is a registered trade name of Nycomed, Denmark.

Patients and methods

The trial was conducted during 2007–2008, in accordance with the Declaration of Helsinki[20], and Good Clinical Practice. Twelve different national and regional ethical committees from the seven countries involved approved the study. (Clinical trial registration number: NCT00496392.)

Patients

The trial included patients from seven European countries (Austria, France, Germany, Italy, Poland, Spain and the United Kingdom), recruited from 44 study centres.

Eligible patients were in- or outpatients with cancer, aged ≥18 years, with a life expectancy of ≥3 months, who were experiencing ≥3 BTP episodes per week, but ≤4 BTP episodes per day. In addition, all patients had received stable opioid treatment for background pain (oral morphine, oxycodone, hydromorphone or transdermal fentanyl) at a dose equivalent to 60–500 mg/day of oral morphine for ≥1 month prior to the study. This dose had to reduce background pain to a level of none or 'mild' (i.e., ≤4 on a validated 11-point numerical rating scale). If the level of background pain was too high during screening, adjustment of background pain medication was permitted. If the level of background pain could not be stabilised to ≤4 following such adjustment, the patient was discontinued from the trial.

Patient exclusion criteria were: recent therapy that could potentially reduce background opioid requirements and/or the frequency of BTP episodes to less than the inclusion criteria; radiotherapy within the last 3 weeks, or scheduled within the next 8 weeks; oral/nasal surgery or facial radiotherapy; pathological conditions of the nasal and/or oral cavity contraindicating INFS or OTFC; current use of drugs for nasal administration or use of a nasogastric tube; conditions significantly increasing the risk of raised intracranial pressure/impaired consciousness; impaired respiratory function that may severely increase the risk of clinically relevant respiratory depression by BTP fentanyl treatment; hypersensitivity to fentanyl or other opioids/their excipients; or recent treatment with monoamine oxidase inhibitor(s) (last 14 days), methadone (last 32 days) or buprenorphine (last 16 days). Additional exclusion criteria typical of clinical studies of this type also applied.

Study design

The study was an open-label crossover trial comparing the efficacy of INFS with OTFC. The trial comprised three distinct phases:

(1) *Screening*: ~1 week patient self-assessment of background pain intensity, BTP episodes, and use of rescue medication. On the last day of screening (baseline), eligible patients received a 50 μg test dose. Patients who did not develop clinically significant reactions to the test dose were randomised to receive INFS followed by OTFC, or vice versa, using block randomisation stratified by centre.

(2) *Titration phase*: a given dose of study drug was used to treat four BTP episodes, at least three of which had to be considered effectively treated by the patient and physician/researcher (efficacy and tolerability) for the given dose to be designated effective. If two treatments with a given dose were ineffective, the patient proceeded to the next dose (up or down) in the agreed titration schedule. The titration phase lasted up to 5 weeks for INFS and up to 8 weeks for OTFC.

(3) *Efficacy phase*: ≤2-week phase (per drug), during which six BTP episodes were treated with the identified effective INFS/OTFC dose. Time to onset of 'meaningful' pain relief, pain intensity and the use of rescue medication were recorded for each episode.

Following completion of the titration and efficacy phases with INFS or OTFC the patient repeated the titration and efficacy phases with the other study drug. Maximum duration of participation in the study was 26 weeks.

Treatment administration

Up to four episodes of BTP per day were treated with study medication, intranasal fentanyl spray (INFS), as described below.

Intranasal fentanyl spray has recently received marketing authorisation from the Committee for Medicinal Products for Human Use and will be launched under the trade name Instanyl (Nycomed, Denmark). Doses of 50, 100 and 200 μg fentanyl (using INFS solutions of 0.5 mg/ml, 1.0 mg/ml and 2.0 mg/ml, respectively) were taken as a single dose in one nostril. A second INFS dose was permitted 10 minutes after the first, if required, taken in the other nostril. Rescue analgesics were permitted 10 minutes after the second INFS administration if pain relief was still insufficient.

The comparator medication, oral transmucosal fentanyl citrate (OTFC) (Actiq, Cephalon, USA), was used at six doses: 200, 400, 600, 800, 1200 or 1600 μg in the form of single compressed lozenges with integral oromucosal applicators. One lozenge equalled one dose. OTFC was administered according to manufacturer's recommendations (15 minutes in the oral cavity between cheek and gum). A second OTFC dose was permitted 30 minutes after the first, if required. Rescue analgesics were allowed, as needed, 45 minutes (if a second OTFC dose was not taken) or 60 minutes (if a second OTFC dose was taken) after start of administration.

Primary outcome measure

The primary outcome measure was the time to onset of 'meaningful' pain relief, as defined/determined by the patient (no advice from healthcare professionals/researchers), recorded using a stopwatch. The stopwatch was started synchronously with the first INFS dose or the start of OTFC administration[21,22].

Secondary outcome measures

Pain intensity (PI) was assessed using a standard 11-point numerical rating scale, ranging from 0 = no pain to 10 = worst possible pain, at 0, 5, 10, 15, 20, 30 and 60 minutes after commencement of INFS/OTFC administration. If patients took rescue medication before 60 minutes post-dosing, the last PI value prior to dropping out/taking rescue medication was carried forward (last observation carried forward). Pain intensity difference (PID) at 10 minutes ($PID_{10} = PI_0 - PI_{10}$) and at 30 minutes ($PID_{30} = PI_0 - PI_{30}$), and the sum of pain intensity differences (SPID = area under the curve for PID/time interval in minutes) for the 0–15 minute interval ($SPID_{0–15}$) and the 0–60 minute interval ($SPID_{0–60}$), were also calculated.

The patient's general impression (GI) of drug efficacy was assessed at 60 minutes following the first administration of INFS, or the start of OTFC administration, using a 5-point verbal rating scale ranging from 0 = poor to 4 = excellent. Ease of drug administration was assessed by the patient at the end of each efficacy phase using a 5-point verbal rating scale ranging from 0 = very easy to 4 = very difficult. After the completion of both efficacy phases (i.e., INFS and OTFC), patients were asked to record which of the two medications they preferred, based upon pain relief and ease of administration. The relationship between the background opioid doses and the effective BTP doses of INFS was also explored.

Safety assessments included the incidence and nature of adverse events (AEs [MedDRA]) occurring during the trial (from point of consent to 2 days after last study dose), and any events that required follow-up.

Additional outcome measures

Additional analysis was performed for PID_5, PID_{15}, PID_{20} and PID_{60}. The proportion of episodes in which a ≥33% reduction in PI score (clinically important level of

pain relief[23]), and a ≥50% reduction in PI score were achieved, were also calculated for each treatment at 5, 10, 15, 20, 30 and 60 minutes post-dosing.

Statistical analysis

A projected sample size of 85 patients completing the study (ITT analysis set) was based on the primary endpoint, with a power of 95%, and a two-sided exact test for single proportion at 5% significance level. Two-sided tests with a significance of $\alpha = 5\%$ were used throughout, unless otherwise stated.

The intention-to-treat (ITT) dataset included all randomised patients. The per-protocol (PP) dataset was defined as patients who were treated, and who reported the time to onset of 'meaningful' pain relief for at least one BTP episode in each efficacy period, without violating any relevant inclusion/exclusion criteria. The safety dataset included all randomised patients exposed to INFS or OTFC.

The primary analysis was based on the proportion of patients having a faster onset of 'meaningful' pain relief on INFS as compared with OTFC. For each of the two treatment periods the patients registered the time to onset of 'meaningful' pain relief for up to six BTP episodes. Median times to onset of relief for each treatment period were compared within each patient. The proportion of patients having a shorter median time to onset with INFS as compared with OTFC was tested with an exact binomial test. The null hypothesis of no treatment effect (both proportions equal 0.5) was tested in this model. The analysis was performed for the ITT and PP datasets. The within study-drug median time to onset was descriptively reported and illustrated with a Kaplan–Meier plot. When the patient took rescue medication before time of onset, the recording was censored to 60 minutes. Only episodes with registered time to onset of 'meaningful' pain relief were included in the calculation of median time to 'meaningful' pain relief. For patients without time to onset of 'meaningful' pain relief on both study drugs, the endpoint was imputed for the ITT dataset according to the prespecified statistical analysis plan.

PID_{10}, PID_{30}, $SPID_{0–15}$, $SPID_{0–60}$ and GI were analysed using a mixed linear model[24], including treatment, country, period and baseline PI (except for GI) as fixed effects and patients as a random effect. Ease of administration was analysed using non-parametric Koch analysis for crossover trials[25]. The patient's preferred treatment was analysed in a similar fashion to the primary analysis. Secondary endpoints were analysed in two subsets: pain measurements and patients' impressions/opinions. Each was adjusted for multiple testing (to maintain overall significance level at 5%), using the false discovery rate procedure[26]. Additional analysis was performed for PID_5, PID_{15}, PID_{20} and PID_{60} with the same method as for PID_{10} above, with p values being adjusted by the Hochberg procedure[27]. The proportion of episodes in which a ≥33% and a ≥50% reduction in PI score was achieved was analysed using generalised estimating equation methods to account for intra-individual association.

The association between background opioid and rescue medication doses (INFS) was evaluated by a scatter plot and the Spearman correlation coefficient.

Efficacy analyses reported in this article refer to the ITT dataset, unless otherwise stated.

Results

Patients

Of the 196 patients enrolled, a total of 57 were discontinued prior to randomisation (for reasons, see Figure 1). The remaining 139 patients were randomised to the INFS/OTFC (71 patients) or OTFC/INFS (68 patients) treatment sequence, and comprised the ITT dataset. Fifty-three patients discontinued during the titration and efficacy phases, and 86 patients completed the study (Figure 1). Rates of withdrawal for all enrolled patients were similar for the two treatment groups. In total, 577 BTP episodes were treated with INFS and 577 BTP episodes were treated with OTFC.

Seventy-nine (56.8%) patients from the ITT dataset were male and 60 (43.2%) were female. The mean (±SD) age of the ITT dataset was 62.0 (±11.6), ranging from 22 to 94 years. All patients were Caucasian.

For INFS, efficacy data was obtained from 101 patients, and for OTFC, efficacy data was obtained from 100 patients. The majority of patients treated six BTP episodes with trial medication: 93.1% during INFS treatment, 92.0% during OTFC treatment.

Titration of INFS and OTFC

In total 85.1% and 87.9% of patients initiating titration reached an effective dose of INFS and OTFC, respectively.

Among these, 23 patients achieved an effective dose with INFS at strengths of 50 µg, 32 with 100 µg, and 40 with 200 µg, compared with 34 for 200 µg, 30 for 400 µg, 11 for 600 µg, and 5 each for 800 µg, 1200 µg and 1600 µg doses of OTFC.

There was a weak association between effective INFS doses and effective OTFC doses (Spearman correlation [95% CI] = 0.567 [0.410, 0.725]; two-sided p-value: <0.0001) – that is, patients on the higher INFS doses tended to titrate to the higher OTFC doses, while patients on lower INFS doses tended to titrate to lower OTFC doses.

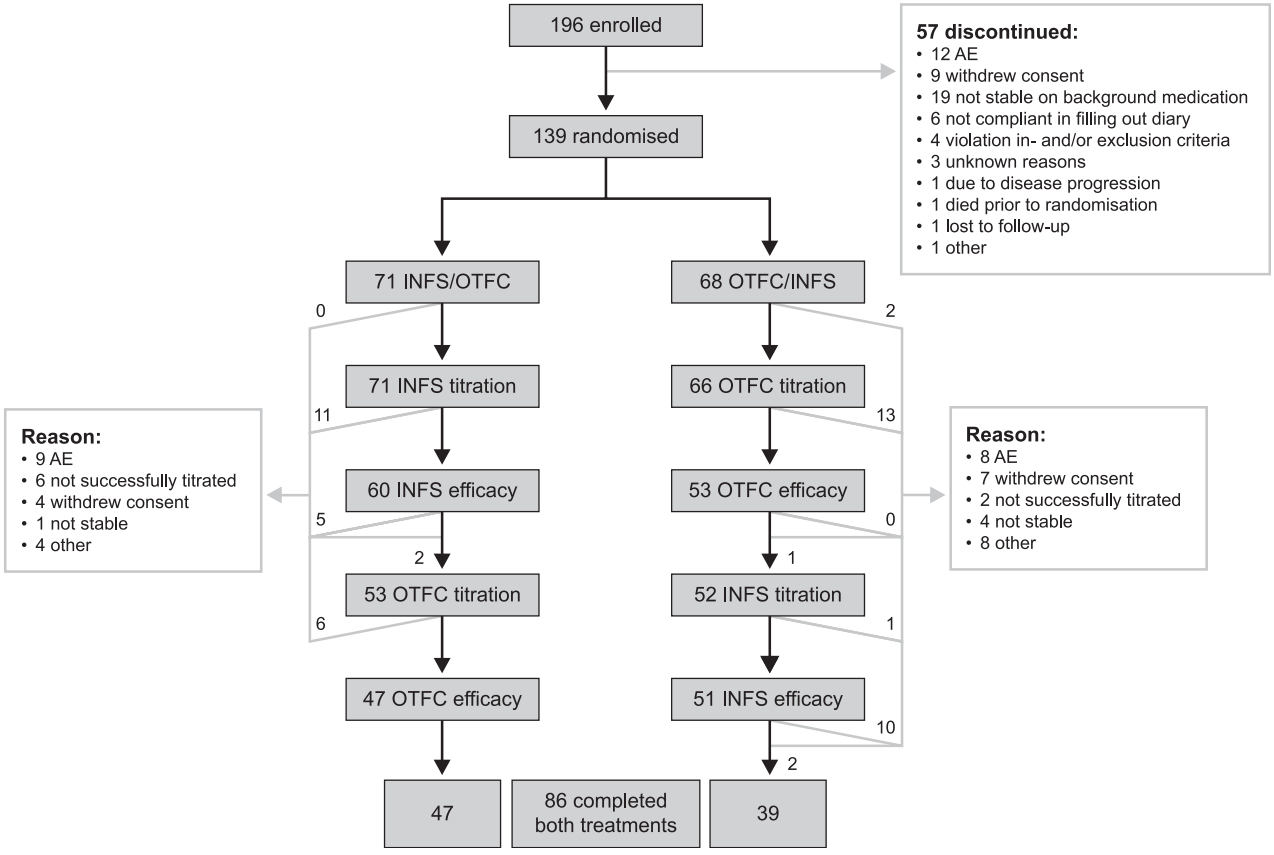

Figure 1. Flow chart of patient disposition assessed for the cross-over study participants receiving intranasal fentanyl spray (INFS) followed by oral transmucosal fentanyl citrate (OTFC), or vice versa, for the relief of breakthrough cancer pain.

Efficacy

In the primary efficacy endpoint analysis, the median time to onset of 'meaningful' pain relief was 11 minutes for INFS ($n = 101$) and 16 minutes for OTFC ($n = 100$). Figure 2 shows a Kaplan–Meier plot of the time to onset of 'meaningful' pain relief for INFS and OTFC. The proportion of the ITT dataset experiencing a faster onset of 'meaningful' pain relief with INFS compared with OTFC was 65.7%, which was significantly different to 50% as compared under the null hypothesis ($p < 0.001$). In the PP analysis set ($n = 72$), 73.6% of patients achieved pain relief more quickly with INFS than with OTFC.

The secondary efficacy measures of adjusted mean PID_{10} and PID_{30} scores were significantly greater for INFS than OTFC ($p < 0.001$; Table 1). In fact, following additional evaluations of PID at 5, 15, 20 and 60 minutes post-dose, a statistically significant separation between the two groups in favour of INFS was found as early as 5 minutes post-dosing. This separation was maintained until the final assessment at 60 minutes (Figure 3). INFS produced significantly superior adjusted mean $SPID_{0–15}$ and $SPID_{0–60}$ scores compared with OTFC ($p < 0.001$; Table 1).

The proportions of episodes with ≥33% and ≥50% PI reduction at each time point are shown in Figure 4. Statistically greater proportions of episodes treated with

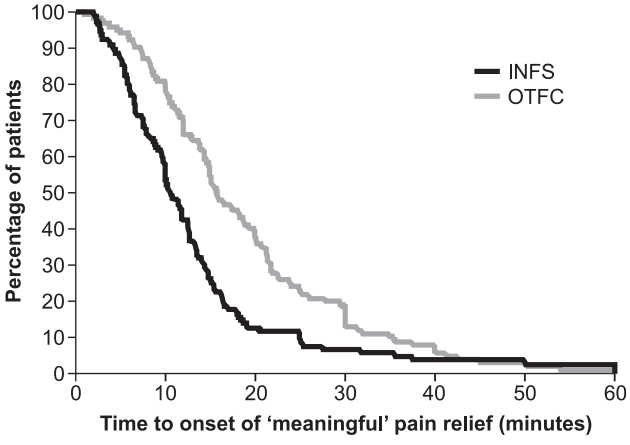

Figure 2. Kaplan–Meier plot of the within-patient-median time to onset of 'meaningful' pain relief for study participants receiving intranasal fentanyl spray (INFS) followed by oral transmucosal fentanyl citrate (OTFC), or vice versa, for the relief of breakthrough cancer pain: INFS ($n = 101$) versus OTFC ($n = 100$). The curve represents the proportion of patients at a given time point that have not yet experienced 'meaningful' pain relief in a median episode.

Table 1. Summary of pain intensity difference (PID) and sum of PID (SPID) scores for the crossover study population receiving intranasal fentanyl spray (INFS) followed by oral transmucosal fentanyl citrate (OTFC), or vice versa, for the relief of breakthrough cancer pain [95% CI: 95% confidence interval].

	Mean PI_0	Efficacy phase: Least squares mean (95% CI)			
		PID_{10}	PID_{30}	$SPID_{0–15}$	$SPID_{0–60}$
INFS ($n=101$)	6.36	2.27 (1.98, 2.56)	4.15 (3.82, 4.48)	1.66 (1.46, 1.87)	3.52 (3.26, 3.79)
OTFC ($n=100$)	6.37	1.08 (0.79, 1.36)	3.39 (3.06, 3.72)	0.85 (0.64, 1.05)	2.83 (2.56, 3.09)
Treatment difference	–	1.19 (1.04, 1.34)	0.76 (0.62, 0.90)	0.82 (0.72, 0.92)	0.70 (0.60, 0.80)
p-value	–	<0.001	<0.001	<0.001	<0.001

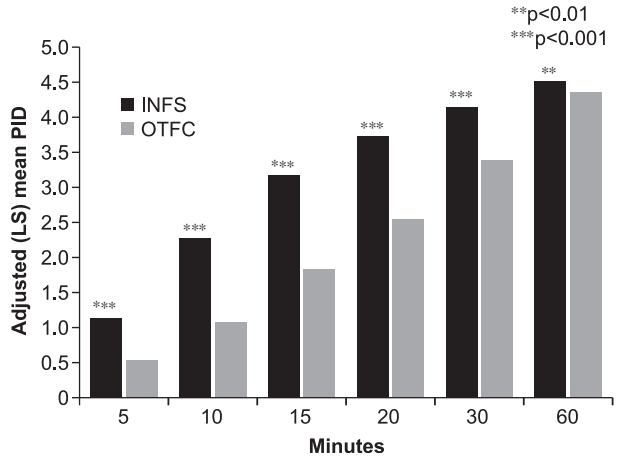

Figure 3. Summary of mean overall pain intensity differences (PIDs) in study participants receiving intranasal fentanyl spray (INFS) followed by oral transmucosal fentanyl citrate (OTFC), or vice versa, for the relief of breakthrough cancer pain. Adjusted (least squares) mean PID at 5, 10, 15, 20, 30 and 60 minutes for INFS ($n=101$) and OTFC ($n=100$).

INFS compared with OTFC achieved ≥33% and ≥50% PI reduction up to 30 minutes post-dosing. The proportion of episodes treated with INFS and OTFC achieving a PI reduction of ≥33% at 5 and 10 minutes were 25.3% versus 6.8% ($p<0.001$) and 51.0% versus 23.6% ($p<0.001$), respectively. This suggests a very fast onset of clinically important pain relief is provided by INFS compared with OTFC. The proportion of episodes treated with INFS and OTFC achieving a ≥50% PI reduction at 5 and 10 minutes were 12.8% versus 2.1% ($p<0.001$) and 36.9% versus 9.7% ($p<0.001$), respectively.

The adjusted mean GI score for treatment of the BTP episode as assessed by the patient at 60 minutes following the administration of INFS and start of OTFC use respectively was 2.1 (95% CI: 2.0–2.3) compared with 2.0 (95% CI: 1.9–2.1), with treatment difference of 0.2 (95% CI: 0.1–0.2), $p<0.001$.

Adverse events

The safety dataset comprised 139 patients. Due to the crossover design, where some patients did not receive both treatments, 122 patients received at least one dose of INFS and 118 patients received at least one dose of OTFC.

A summary of the AEs for the combined titration and efficacy phases is shown in Tables 2 and 3. In all, 56.8% ($n=79$) of patients experienced ≥1 AE during the trial. The only AE that occurred in ≥5% of patients in either treatment group was nausea (Table 3). The incidence of

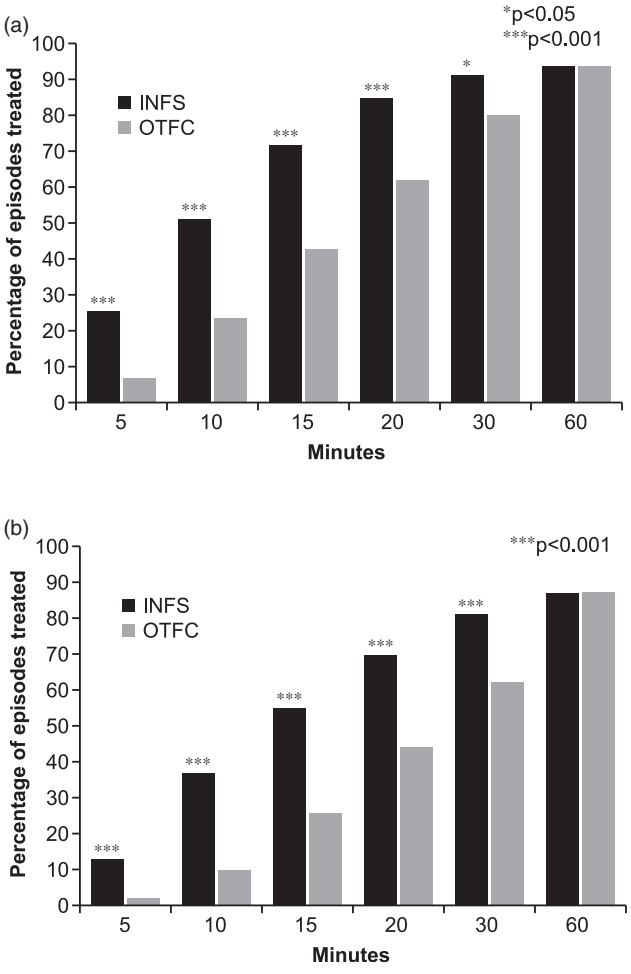

Figure 4. Percentage of episodes treated ($n=577$) with INFS and OTFC for the relief of breakthrough cancer pain, wherein (a) ≥33% and (b) ≥50% reduction in PI was achieved.

Table 2. Summary of adverse events (AEs): titration and efficacy phases combined for the safety population ($N=139$) receiving intranasal fentanyl spray (INFS) followed by oral transmucosal fentanyl citrate (OTFC), or vice versa, for the relief of breakthrough cancer pain.

	INFS ($N=122$)		OTFC ($N=118$)	
	Patients with ≥1 AE		Patients with ≥1 AE	
	n	%	*n*	%
Total AEs	56	45.9	41	34.7
Serious AE, SAEs (all)	13	10.7	6	5.1
Treatment-related SAEs*	0	0.0	0	0.0
Deaths (all)	5	4.1	0	0.0
Treatment-related deaths*	0	0.0	0	0.0
AE(s) leading to trial withdrawal	10	8.2	8	6.8

N = number of patients exposed to treatment; n = number of patients with event; % = number of patients with event as percent of patients exposed.
*Considered by the investigator to be probably or possibly related to the study drug.

Table 3. All adverse events (AEs) occurring in >2% of patients in either group during treatment for the safety population ($N=139$) receiving intranasal fentanyl spray (INFS) followed by oral transmucosal fentanyl citrate (OTFC), or vice versa, for the relief of breakthrough cancer pain.

MedDRA term	INFS ($N=122$)		OTFC ($N=118$)	
	n	%	*n*	%
Nausea	10	8.2	9	7.6
Vomiting	6	4.9	4	3.4
Constipation	5	4.1	4	3.4
Malignant neoplasm progression	5	4.1	0	0.0
Diarrhoea	4	3.3	3	2.5
Dizziness	4	3.3	2	1.7
Asthenia	4	3.3	2	1.7
Urinary tract infection	3	2.5	2	1.7
Pyrexia	3	2.5	2	1.7
Dyspnoea	2	1.6	4	3.4
Somnolence	2	1.6	3	2.5
Dysgeusia	1	0.8	3	2.5
Anxiety	0	0.0	3	2.5

N = number of patients exposed to treatment; n = number of patients with event; % = number of patients with event as percent of patients exposed.

local AEs of the nasal cavity was low, with only one event (nasal ulcer) in one patient being reported (described below).

The majority of AEs were considered not to be related to study medication; 33 patients (23.7%) experienced AEs that were reported as probably or possibly related to treatment (15 patients [12.3%] with INFS; 22 patients [18.6%] with OTFC).

Most AEs (85.5%) experienced by trial participants were mild to moderate in nature. Severe AEs were reported in more patients following INFS than OTFC treatment (13.1% versus 7.6%), although equal numbers of patients ($n=3$) were considered to be experiencing treatment-related severe AEs following both treatments. Severe, treatment-related nausea and vomiting were reported for one patient following INFS treatment (vomiting was reported twice in this patient) and for one patient following OTFC treatment. The remaining severe, treatment-related AEs were reported in one patient each: constipation, dysgeusia, and somnolence following OTFC; skin pain, and nasal ulcer following INFS. In the latter case, two small ulcers of the nasal mucosa (one in each nostril) developed 7 days after initiation of INFS treatment. INFS was discontinued and the patient recovered 9 days later.

Among the 19 patients (13.7%) who experienced serious AEs, none were considered to be related to either study medication. The five deaths that occurred in the trial were during an INFS treatment phase. All were attributed to progression of the underlying cancer disease and all were considered by the investigator not related to study medication.

A total of 15 patients discontinued from the study due to AEs. The treatment-related AEs most commonly leading to withdrawal were nausea and vomiting, resulting in withdrawal in two patients each following OTFC treatment and in one patient each following INFS treatment.

Other analyses

Out of the 86 patients completing the study, 84 patients were questioned on their preference for study medication. Of these, 77.4% favoured INFS compared with 22.6% for OTFC ($p<0.001$).

Patients' rating of the ease of use of the two treatments is shown in Figure 5. When compared with OTFC, more than twice as many patients found INFS easy/very easy to administer (90.1% versus 39.8%, respectively).

A correlation plot between the effective INFS doses for BTP treatment and corresponding background opioid

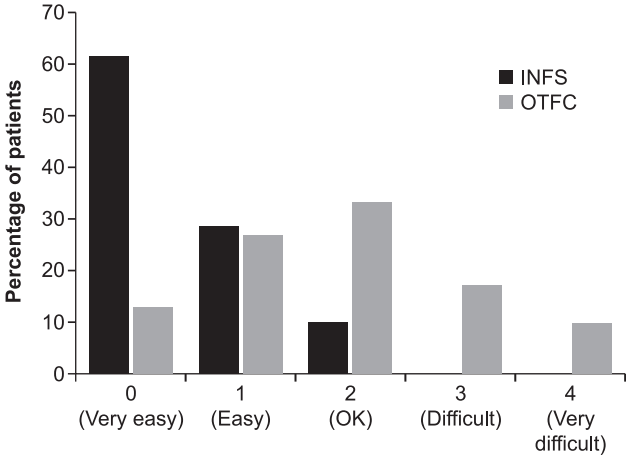

Figure 5. Patients' rating of ease of use. Patients (INFS $n=91$, OTFC $n=93$) were asked how easy the medication was to administer, after treating six BTP episodes, using a 5-point verbal rating scale where 0 = very easy, 1 = easy, 2 = OK, 3 = difficult and 4 = very difficult.

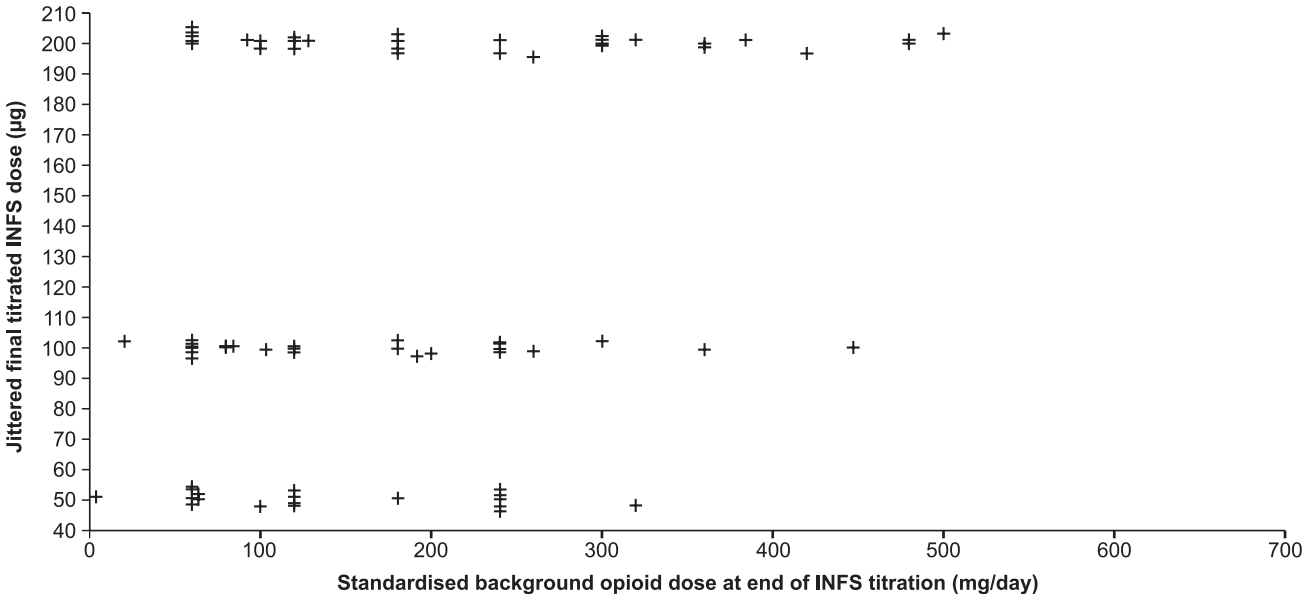

Figure 6. Correlation plot between effective dose of INFS and background opioid dose, by patient ($n = 95$). Data are displayed up to a 700 mg/day background opioid dose cut-off (three observations with 200 µg INFS dose and a standardised background opioid dose >1000 mg/day are not plotted). All original values formed part of the analysis: Spearman correlation coefficient (95% CI) = 0.352 (0.176, 0.528); corresponding two-sided *p*-value: $p < 0.001$.

medication doses by patient reveal a weak, but statistically significant, correlation (Spearman correlation = 0.352; $p < 0.001$) – Figure 6.

The proportion of treated BTP episodes that required rescue medication in the efficacy phases was generally low. This proportion after administration was 45/577 episodes (7.8%) with INFS, compared with 28/577 episodes with OTFC (4.9%).

Discussion

The reported study is the first investigation ever conducted to compare two products developed specifically for the treatment of BTP. The primary outcome of the study – time to onset of 'meaningful' pain relief – demonstrated that statistically significantly more patients experienced faster pain relief with INFS than with OTFC. Secondary and additional efficacy outcome measures also favoured INFS over OTFC, with comparisons already being both statistically significant and clinically important at 5 minutes.

BTP in cancer patients is a common problem, with patients typically experiencing severe episodes of pain lasting for ~30 minutes and occurring on average four times a day[1]. BTP is associated with significant morbidity, impaired quality of life and economic burden[3,8,10,11]. In light of these factors, the importance of effective BTP treatment should not be underestimated.

The optimal BTP treatment should mirror the rapid onset and short duration of the BTP episode itself, should produce clinically important/'meaningful' pain relief, and be well tolerated. Existing data on INFS, together with the results of this trial, show that INFS fits this profile. INFS, with pH 6.4, has been formulated to match closely the physiological environment of the nasal cavity[17], hence lowering the potential for local irritation. In addition, this nasal spray formulation is of sufficient concentration to deliver an 'analgesic dose' in a volume that does not exceed nostril capacity (~150 µl) and that can be adequately absorbed by the mucosa[28]. Christrup *et al.* (2008) demonstrated a rapid onset of pain relief with INFS, with a median time of 7 minutes in healthy individuals for the relief of dental post-operative pain, and a duration of effect of 56 minutes[17].

Farrar *et al.* (2000) described a ≥33% reduction in PI as clinically important pain relief[23]. In addition, PIDs greater than 2 are generally accepted as clinically significant[23]. According to these definitions, INFS has previously been shown to produce clinically important/significant pain relief 10 minutes post-administration in patients with cancer BTP[18,19]. These results are supported, and strengthened, by the results of the current study, which showed that INFS produced superior clinically important pain relief (≥33% PI reduction) versus OTFC as early as 5 minutes post-dosing.

In this study, rescue medication was used in more INFS-treated episodes than OTFC-treated episodes (8% versus 5%; all doses combined). However, rescue medication could be taken 20 minutes after the first INFS dose and 10 minutes after the second dose, whereas rescue medication could not be taken until 45 or 60 minutes after start of administration of the first OTFC dose (depending on whether one or two lozenges were administered). As such, the difference is not unexpected.

INFS has also been shown to be well tolerated by patients with cancer in this study, and in previous investigations[18,19]. In the present study, both INFS and OTFC were well tolerated, with reported AEs being typical of opioid treatment, such as nausea, vomiting and constipation. Both treatments had similar proportions of patients discontinuing due to AEs. Only one person (INFS treated) was reported to have a local AE. This low incidence is supported by data from previous INFS studies where no/low levels of acute and long-term local AEs were reported[17,19].

No randomised, blinded trial to date has been able to demonstrate a correlation between the dose of opioid needed to control background pain and the dose of OTFC needed to control BTP[13,29,30], although one open-label study suggested that OTFC doses proportional to the dose of background opioid were well tolerated and effective against BTP[31]. The current study reported in this article provides no clear association between the dose of BTP medication and the dose of background opioid taken by the patients. However, the correlation between INFS effective dose and background opioid dose was statistically significant, although the correlation was weak. As is evident from the correlation plot, the background opioid dose could not be used to determine BTP medication dose. On this basis, patients still need to be individually titrated[32], with the optimal dose for an individual patient being determined by the balance between efficacy and tolerability. Future studies with appropriate design (randomised, prospective) looking into the correlation between background opioid dose and optimal BTP dose are required.

Further, the study revealed a statistically significant, but only weak, correlation between effective INFS doses and effective OTFC doses. The lack of strong correlation suggests that doses that prove efficacious and well tolerated for one formulation, cannot be assumed to be efficacious and well tolerated for the other formulation – separate titration is required.

Two potential criticisms of this trial are related to its design and choice of comparator drug. The study was open-label to avoid the complexities of a double-dummy design, such as the difficulty in producing a convincing OTFC placebo. The chosen crossover design (in which individuals acted as their own controls) aimed to minimise confounding external factors that may have influenced the experience of pain, and also allowed patient preference and ease of use to be examined. The primary outcome of the study was time to onset of 'meaningful' pain relief, defined as meaningful to the patient, and measured by the patient using a stopwatch. This measure was selected as it was considered important to have a patient-centred primary outcome that would provide a clinically relevant endpoint measure. It has previously been suggested that this method of measuring pain relief provides a precise measurement of treatment response and a more sensitive method of detecting between-group differences than conventional pain assessments[21]. OTFC (rather than a more traditional BTP treatment, such as oral morphine) was chosen as the comparator for this study as it was considered to be the best BTP treatment available at the time that the study was designed. It was the only BTP-specific treatment with marketing authorisation, and in contrast to oral morphine, has pharmacodynamic properties that more closely match the temporal characteristics of BTP[12,33]. Double-blind, randomised trials have demonstrated a better pain relief compared with placebo and oral opioids[13,30,34].

The disadvantages of the oral transmucosal route of administration include the requirement for a 15-minute administration, and difficulty in use for patients with dryness of the mouth and those with oral discomfort – both of which are common problems in patients with advanced cancer[14–16]. INFS has the potential to overcome these problems, however, such a hypothesis was not directly assessed in the current study, and further investigations are required in this regard.

Potential issues relating to the intranasal administration include complications associated with nasal pathology. In a recent study of INFS in subjects with allergic rhinitis, only those subjects treated with the vasoconstrictor, oxymetazoline, experienced a lowered maximum fentanyl plasma concentration (C_{max}) following INFS treatment, whereas subjects not receiving vasoconstrictor were unaffected. However, total systemic exposure of fentanyl was not significantly affected for any of the subjects[35]. In a similar study in subjects with common cold, no change in the pharmacokinetic profile was found, suggesting no need for dose adjustment[36].

Walker *et al.* (2003) investigated the patient-perceived acceptability of different routes of administration of BTP medication. They reported that acceptability was affected by the severity of the pain[37]. Stigma associated with intranasal application did not appear to be an issue, although concerns over the transmucosal formulation appearing childlike were raised. For severe pain, transmucosal administration was unacceptable in 25% of patients, compared with only 18% of patients for intranasal application[37]. In the present study, significantly more patients preferred INFS to OTFC, and more than twice as many found it very easy/easy to use. Such aspects of patient-related outcomes are particularly relevant in terms of individual care, especially in those with advanced disease (as in this population), where patient comfort and quality of life are paramount.

Conclusion

INFS offers unique advantages over existing treatment options in cancer pain management. The

pharmacodynamic profile of INFS fits very closely with the temporal characteristics of breakthrough pain, and the present study has shown that 'meaningful' pain relief was obtained faster in patients treated with INFS than with OTFC. Pain intensity difference was significantly greater for INFS than OTFC from 5 minutes post-dosing, and clinically important pain relief (≥33% reduction in pain intensity) was seen 5 minutes after INFS treatment in a quarter of breakthrough pain episodes. Furthermore, INFS was easy to use, with the majority of patients preferring INFS over OTFC. It was well tolerated with a safety profile that is typical for this group of opioids. INFS represents a considerable improvement in the clinicians' armamentarium for the treatment of BTP.

Transparency

Declaration of funding

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Declaration of financial/other relationships

S.M. has disclosed receiving grant/research funding from Nycomed, Cephalon, Grünenthal, and Mundipharma and acting as a consultant/advisor for Nycomed, Cephalon, Grünenthal, Janssen, GW Pharmaceuticals, Mundipharma and Novartis. L.R. has disclosed acting as a consultant/advisor on Nycomed's German and International Advisory Boards. A.D. has disclosed receiving grant/research funding from Nycomed, acting as a consultant/advisor for Nycomed and speaking at one of their satellite symposia. P. Poulain has disclosed that he has no relevant financial/other relationships. T.S. has disclosed receiving sponsorship from Nycomed, Archimedes, Haupt, Mundipharma and ProStrakan and acting as a consultant/advisor for Nycomed, Grünenthal, Haupt, Archimedes, Jansen-Cilag and Fresenius-Kabi. P. Perkins has disclosed receiving (on behalf of: Sue Ryder Care Leckhampton Court Hospice) grant/research funding for enrolling patients in the present study. T.C. is an employee of Nycomed. M.A.C. has disclosed that he has no relevant financial/other relationships.

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