Efficacy and Tolerability of Intranasal Fentanyl Spray in Cancer Patients With Breakthrough Pain

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ABSTRACT

Purpose: The aims of this study were to explore the efficacy of intranasal fentanyl spray* (INFS) 400 μg to evaluate 12-week tolerability of the nasal mucosa and to explore safety data for all dose strengths of INFS in patients with cancer-related breakthrough pain (BTP).

Methods: Patients received a test dose of INFS 50 μg, followed by a titration phase. Those patients with doses titrated to 200 or 400 μg entered a randomized, double-blind, cross-over efficacy phase, in which 8 episodes of BTP were randomly treated with INFS 400 μg (6 episodes) and placebo (2 episodes), followed by a tolerability phase. Patients with doses titrated to 50 or 100 μg entered the tolerability phase directly. Primary outcome was measured by pain intensity difference at 10 minutes, analyzed using ANCOVA, and presented as least square mean difference. Examination of the nasal cavity was conducted at inclusion and after 12 weeks of treatment by an otorhinolaryngologist.

Findings: Forty-six patients were included. Thirty-eight patients' doses were titrated to an effective dose of INFS; 50 μg (n = 8), 100 μg (n = 9), 200 μg (n = 9), and 400 μg (n = 12); 15 patients entered the efficacy phase and 31 entered the tolerability phase. In the efficacy phase, 88 and 29 episodes of BTP were treated with INFS 400 μg and placebo, respectively. Pain intensity difference at 10 minutes least square mean for INFS 400 μg was 2.5 (95% CI, 1.42−3.49) ($P < 0.001$) and least square mean difference between INFS 400 μg and placebo was 1.1 (95% CI, 0.41−1.79) ($P = 0.002$). Runny nose (10%) and change in color of the mucosa (9%) were the most frequent findings of nasal examination, and nausea and dizziness were the most frequent treatment-related adverse events. One serious adverse event (ie, respiratory depression) was considered related to INFS.

Implications: INFS 400 μg is effective and nasal tolerability and overall safety profile is acceptable during 12 weeks of use. ClinicalTrials.gov identifier: NCT01429051. (*Clin Ther*. 2015;37:585–596)

Key words: breakthrough pain, cross-over efficacy phase, Instanyl, intranasal fentanyl spray, pain intensity difference.

INTRODUCTION

More than 50% of cancer patients suffer from cancer-related pain,[1] despite improved guidelines and treatment alternatives.[2]

The term *breakthrough pain* (BTP) was introduced by Portenoy and Hagen in 1989.[3] Prevalence varies from 40% to 80%, according to setting and definition,[4] and characteristics are typically described as a median of 3 BTP episodes per day, time to peak intensity of 5 to 10 minutes, and duration of untreated episodes of 45 to 60 minutes. The majority of patients report their BTP as severe.[5]

*Trademark: Instanyl® (Takeda Pharmaceutical Company Limited, Zurich, Switzerland).

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Immediate-released (IR) morphine taken orally on demand in addition to slow-released morphine is commonly used and recommended in the treatment of BTP.[2] This is despite IR morphine's delayed onset of analgesia (30–60 minutes).[6,7] Rapid-acting fentanyl preparations have been introduced as an alternative approach to IR morphine for the treatment of BTP.[8] Rapid-acting fentanyl exists in a variety of administration forms.[9] Most studies of these products are placebo controlled and show favorable analgesic effect in the treatment of BTP compared with placebo. Analgesic effect is typically achieved within 10 to 30 minutes and adverse effects are similar to other opioids.[9]

Pharmacokinetic studies of nasal administration of opioids show rapid uptake and action.[10,11] Two drugs for treating BTP are available for nasal administration; intranasal fentanyl spray* (INFS) and fentanyl pectin nasal spray.† INFS is available as 50, 100, and 200 μg/dose, and pharmacokinetic studies have found a median T_{max} value between 12 and 15 minutes[12] and a bioavailability of 89%.[13] The efficacy of INFS has been reported in several studies, showing rapid time to analgesic effect,[14] superior pain intensity difference at 10 minutes (PID_{10}) compared with placebo,[15] and that onset of meaningful pain relief is experienced earlier compared with oral transmucosal fentanyl citrate.[16] Indirectly compared with other fast-acting fentanyl components, INFS has provided the greatest PID compared with placebo at 15 minutes and 30 minutes post baseline.[9] Adverse effects of INFS are typically opioid related, such as nausea, vertigo, dizziness, and myoclonus,[15,16] but nasal ulcers have been observed,[16] and a systematic evaluation of the nasal cavity in long-term use is required.

Optimal treatment of BTP is an unmet need among cancer patients. Clinical experience has found that 10% to 20% of patients are in need of a higher dose of INFS than that approved and on the market today. INFS 400 μg has therefore been developed. Pharmacokinetic studies in healthy subjects have indicated dose linear increase in the exposure in the dose range of 200 μg to 2 × 400 μg.[17]

In the present trial, the efficacy of INFS 400 μg is compared with placebo, and the nasal tolerability and general adverse effects during 12 weeks of follow-up for all dose strengths of INFS are evaluated.

†Lazanda® (Archimedes Development Limited, Bedminster, New Jersey).

METHODS

The present placebo-controlled, double-blind, randomized, cross-over efficacy study was conducted from August 2011 until January 2013 in 11 European centers (Norway, 2 sites; Hungary, 7 sites; and Russia, 2 sites). After a test dose of INFS 50 μg, the patients' doses were titrated to an effective dose of INFS for their BTP. Patients with doses titrated to 50 μg and 100 μg proceeded directly to a tolerability phase lasting for 3 months. Patients with doses titrated to 200 or 400 μg INFS were included in the efficacy phase, in which 8 episodes of BTP were treated with INFS 400 μg (6 episodes) and placebo (2 episodes). Having completed the efficacy phase, these patients continued into the tolerability phase. An examination of the nasal cavity was conducted by an otorhinolaryngologist at baseline and after 12 weeks of INFS treatment, and patient-assessed tolerability was evaluated during all phases of the study (**Figure 1**).

Patients

Cancer patients aged ≥18 years with BTP episodes between 3 times per week and 4 times per day, and life expectancy of more than 3 months were eligible for this study. Both inpatients and outpatients were included. Use of oral opioids or transdermal fentanyl (morphine equivalent doses of 60–1000 mg/24 h) for treatment of stable and controlled background pain (BGP), defined as a mean ≤4 on an 11-point Numeric Rating Scale (NRS), were required. The exclusion criteria were history of abuse, severe hepatic impairment (alanine aminotransferase or aspartate aminotransferase >3 × upper normal range), severe renal impairment (serum creatinine ≥3.0 mg/dL [265 μmol/L]), and severe impairment of respiratory function, which might increase the risk of relevant respiratory depression. In addition, patients having concomitant conditions resulting in runny nose (eg, rhinitis), patients who had been at some point treated with facial radiotherapy, and patients treated with nasal surgery within the last 30 days before screening were excluded. Patients with head injury, primary brain tumor, or other pathologic conditions that could significantly increase the risk of elevated intracranial pressure or impaired consciousness were also excluded. Any kind of drugs for intranasal administration or the use of a nasopharyngeal probe were not allowed, and patients having recurrent episodes of epistaxis were excluded. Intake of