

Absorption and tolerability of fentanyl buccal soluble film (FBSF) in patients with cancer in the presence of oral mucositis

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Purpose: Fentanyl buccal soluble film (FBSF) consists of a small, bilayered, water-soluble polymer film that adheres to the buccal mucosa and rapidly delivers fentanyl into the systemic circulation. The purpose of this study was to evaluate the absorption of fentanyl from FBSF in patients with cancer, with and without grade 1 oral mucositis, and to assess the tolerability of FBSF in this patient population.

Patients and methods: In an open-label, single-dose study, two groups of opioid-naive patients (ie, not receiving opioids on a regular basis) with cancer received a 200 µg dose of FBSF. Patients in cohort I (n = 7) had grade 1 mucositis, and patients in cohort II (n = 7) were age- and gender-matched controls without mucositis. The FBSF dose was placed on the area of mucositis in cohort I and on a matching location in cohort II. Blood samples were collected up to 4 hours after administration, and safety assessments were made throughout the study.

Results: Peak plasma concentration and area under the concentration–time curve from time 0 to 4 hours post-dose values of patients in the grade 1 mucositis cohort were lower than those observed in patients without mucositis. There was no application site irritation reported in any patient, regardless of mucositis status. Mild somnolence was reported by two patients with mucositis. There were no deaths or serious adverse events reported in this study.

Conclusion: The results of this study indicate that application of FBSF to an area of grade 1 mucositis does not result in increased fentanyl exposure or irritation of the mucosa. The 200 µg dose of FBSF was well tolerated.

Keywords: breakthrough cancer pain, clinical study, application site pain

Introduction

Oral mucositis is defined as the inflammation and ulceration of the oral mucosa. In patients with cancer, it can be induced by chemotherapy and/or radiation therapy.^{1–4} Although the incidence of mucositis varies depending on the location of the tumor and the course of treatment, occurrence of the condition is highest among patients with cancers of the head and neck, with approximately 80% of these patients developing mucositis.^{5,6}

The presence of mucositis has a number of clinical implications in patients with cancer. Development of oral mucositis may ultimately impede a patient's ability to drink, eat, and swallow if it progresses to more severe stages.⁷ In addition, the likelihood of developing infections of the mouth due to damaged oral mucosa and impaired immunity resulting from chemotherapy and radiation is greater in patients with mucositis. Oral mucositis may also impact the tolerability and efficacy of chemotherapeutic agents.⁸ Furthermore, patients may experience pain from mucositis

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alone, or they may experience cancer breakthrough pain (BTP) that is related to their persistent cancer pain.

Transmucosal delivery of fentanyl is a common practice in the treatment of BTP, the transitory flare of pain that occurs in otherwise stable, persistent pain.⁹ Treatments for BTP include oral transmucosal fentanyl citrate (OTFC),¹⁰ fentanyl buccal tablet (FBT),¹¹ and fentanyl buccal soluble film (FBSF).¹² The diffusion of fentanyl through the buccal mucosa may be altered in patients with mucositis. This is a significant clinical issue as the absorption of fentanyl from these treatments may be impacted by the presence of mucositis.

Absorption of fentanyl delivered via FBT in the presence of oral mucositis has been studied previously.¹³ Fentanyl release from FBT occurs as the effervescent tablet dissolves between the buccal mucosa and the upper gum.¹⁴ In a pharmacokinetic study to evaluate the exposure of FBT in patients with and without mild mucositis, the treatment was well tolerated, and overall exposure of fentanyl after FBT dosing was higher in the patients with mucositis compared with those without mucositis.¹³

FBSF was approved in the United States in 2009 as an opioid analgesic for the treatment of BTP in opioid-tolerant patients with cancer, 18 years of age and older.¹² FBSF consists of a small, bilayered, water-soluble polymer film that adheres to the buccal mucosa and rapidly delivers fentanyl into the systemic circulation.¹⁵ In a pharmacokinetic study conducted to determine the absorption of fentanyl from FBSF,¹⁶ volunteers were administered different formulations of fentanyl including FBSF administered as a single film and as four separate films. After dosing, the two FBSF doses were bioequivalent and both had an absolute bioavailability of 71%, with 51% of an administered dose absorbed through the oral mucosa.

As changes in the oral mucosa may affect the absorption of fentanyl from FBSF in patients with cancer and mucositis, this study was undertaken to evaluate the absorption of fentanyl from FBSF in patients with and without grade 1 oral mucositis, and also to assess the tolerability of FBSF in that patient population.

Materials and methods

This was a Phase I, open-label, single-dose study in patients with cancer, conducted in the United States between February and August 2007. The study protocol, amendments, and informed consent forms were reviewed and approved by a regional institutional review board (Western Institutional Review Board, Olympia, WA). This study was conducted

in accordance with the ethical principles that have their origins in the Declaration of Helsinki and the Code of Federal Regulations, Title 21, Part 50. Written informed consent to participate in the study was obtained from each subject at the screening visit prior to the conduct of any investigational procedures.

Patients

A complete oral examination was performed by a qualified clinician, and mucositis was graded according to the National Cancer Institute system.¹⁷ In this system, grade 1 mucositis is characterized by painless ulcers, erythema, or mild soreness, and the patient is able to eat solids. Grade 2 mucositis is identified by the presence of painful erythema, edema, or ulcers, and the patient can eat or swallow. Patients with grade 3 mucositis have painful erythema, edema, or ulcers requiring intravenous hydration. Patients with grade 4 mucositis experience severe ulcerations or require parenteral or enteral nutritional support or prophylactic intubation.

Seven patients with grade 1 oral mucositis (cohort I) secondary to radiation or chemotherapy treatment of cancer and 7 age- and gender-matched control patients without oral mucositis (cohort II) were selected for participation in this study. Both cohorts included males and non-pregnant females aged 18 years or older. Patients were excluded if, in the opinion of the investigator, cardiopulmonary disease would increase the risk of respiratory depression, moderate or severe (grade 2–4) oral mucositis was present, the patient reported use of transdermal or transmucosal fentanyl for pain management within 7 days prior to the study period, and if the patient had a history of intolerance to fentanyl. Exclusion criteria for cohort II included any patient with grade 1 or greater oral mucositis. Females could only participate in the study if they were not lactating and were either surgically sterile, postmenopausal, or using a highly effective method of contraception, and had a negative urine beta-human chorionic gonadotropin test result prior to administration of the study drug.

FBSF administration

Eligible patients received a single 200 µg dose of FBSF (Meda Pharmaceuticals Inc, Somerset, NJ), which was applied by study personnel to either the area of the mucosa that met the requirements for grade 1 oral mucositis (patients with mucositis; cohort I) or to a location of the mucosa similar to the site used for the matched patient with mucositis (patients without mucositis; cohort II). Opioid tolerance was not an inclusion criterion. As the minimum

dose of FBSF available was used, oral naltrexone was not coadministered to block the respiratory depressive effects of fentanyl.

Pharmacokinetic analyses

Bioanalytical methods

The bioanalytical methods used in this study were reported previously.¹⁸ Venous blood samples (7 mL) were collected in K₃-ethylenediaminetetraacetic acid (EDTA) Vacutainer[®] tubes (Becton Dickinson, Franklin Lakes, NJ) for measurement of fentanyl plasma concentrations just prior to each FBSF dose and at the following times after drug administration: 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, and 4.0 hours. Blood sample tubes were inverted gently 10 times to mix the anticoagulant and then placed on ice. Within 30 minutes of collection, blood samples were centrifuged and the plasma fraction was transferred to two polypropylene screw-cap cryogenic storage tubes and frozen at -20°C until analysis for fentanyl. Plasma samples were analyzed for fentanyl using a validated liquid chromatography with tandem mass spectrometry procedure with a lower limit of quantification of 0.025 ng/mL and upper limit of 5.00 ng/mL based on the analysis of 0.500 μL of EDTA human plasma.¹⁸

Pharmacokinetic data analysis

Fentanyl plasma concentrations that were below the limit of quantification (BLQ) (<0.025 ng/mL) were assigned a value of zero if occurring from time zero up to the first measurable concentration. BLQ concentrations occurring in the terminal phase, elimination phase, or after peak concentrations were treated as missing. All pharmacokinetic and statistical analyses were performed using unrounded concentration data.

The pharmacokinetic parameters determined for each patient and each treatment included the following: peak plasma concentration (C_{max}), time to reach C_{max} (t_{max}), and area under the plasma concentration–time curve from time 0 to 4 hours post-dose, calculated by the linear trapezoidal rule (AUC_{0-4}). C_{max} and t_{max} were determined from the individual patient's concentration–time profiles. Plasma concentration–time data for each patient were analyzed by non-compartmental analysis using WinNonlin version 4.0 (Pharsight Corporation, Mountain View, CA). Pharmacokinetic calculations were based on actual sampling times.

FBSF residence time assessment

FBSF residence/dissolution was assessed just after application and at 15, 30, 45, and 60 minutes after application.

Safety evaluations

Adverse events (AEs) were monitored throughout the study. Pain and/or local irritation at the FBSF application site were measured on a 4-point scale (none, mild, moderate, or severe) just before application and at 0.5, 1.0, 2.0, 3.0, and 4.0 hours after application. The number and percentage of patients reporting a response at each time point were summarized per cohort.

Measurements of vital signs were performed at designated times throughout the study, and changes in respiratory rates were assessed through standard vital sign measurements.

Statistical analysis

Descriptive statistics were calculated to summarize the pharmacokinetic parameters for patients with mucositis and without mucositis. Inferential statistical testing of these results was not the primary intent of this study and was not performed.

Results

Study population

The demographic data of the patients included in this study are presented in Table 1. Fourteen patients (10 males and 4 females) with a median age of 61.5 years were included. All patients completed the study. No AEs leading to premature discontinuation were reported. Only one patient had a history of head and neck cancer (in cohort I), and no patient was treated for head and neck cancer at the time of this study. All patients in the mucositis group had examination findings consistent with mucositis at entry; five patients reported mild pain, one reported moderate pain, and one had severe baseline mucositis pain. Of the six patients with mild or moderate mucositis pain at baseline, five became pain free within 1 hour of FBSF administration, and one became pain free within 2 hours of dosing. The patient with severe pain at baseline became pain free 1 hour after dosing, and

Table 1 Patient characteristics

Variable	Cohort I patients with mucositis (n = 7)	Cohort II patients without mucositis (n = 7)
Sex, n (%)		
Male	5 (71)	5 (71)
Female	2 (29)	2 (29)
Race, n (%)		
Caucasian	6 (86)	4 (57)
Hispanic	1 (14)	3 (43)
Age, years ^a	65 (45–77)	57 (47–75)
Height, cm ^a	178 (152–185)	175 (165–183)
Weight, kg ^a	89.5 (55.5–145.1)	90.5 (67.0–103.4)

Note: ^aMedian (range).

then mild pain returned through 4 hours. Pain at the site of application was determined to be due to mucositis, and not related to FBSF (Table 2).

Pharmacokinetic assessments

Pharmacokinetic parameters for FBSF for the two cohorts are presented in Table 3. C_{max} of fentanyl after FBSF administration was achieved in 1 hour in both cohorts (Figure 1). The mean AUC_{0-4} (ie, from time 0 to 4 hours post-dose) was 1.14 h-ng/mL in the oral mucositis cohort and 1.29 h-ng/mL in the cohort without oral mucositis. Thus, mean AUC_{0-4} for patients in both cohorts was similar, with patients in the oral mucositis cohort having a mean AUC_{0-4} of 88% of the value observed for those patients without oral mucositis. The range of maximum fentanyl concentrations was narrower in patients with mucositis compared with patients without mucositis. In addition, the maximum plasma fentanyl concentration observed in the mucositis cohort was 73% of the value reported in the cohort without oral mucositis (1.13 ng/mL

Table 2 Application site pain and/or irritation assessment

Scheduled time points/ pain and/or irritation severity, n (%)	Cohort I patients with mucositis (n = 7)	Cohort II patients without mucositis (n = 7)
Pre-dose		
None	0 (0)	7 (100)
Mild	5 (71)	0 (0)
Moderate	1 (14)	0 (0)
Severe	1 (14)	0 (0)
0.5 hours post-dose		
None	3 (43)	7 (100)
Mild	3 (43)	0 (0)
Moderate	1 (14)	0 (0)
Severe	0 (0)	0 (0)
1.0 hour post-dose		
None	6 (86)	7 (100)
Mild	1 (14)	0 (0)
Moderate	0 (0)	0 (0)
Severe	0 (0)	0 (0)
2.0 hours post-dose		
None	6 (86)	7 (100)
Mild	1 (14)	0 (0)
Moderate	0 (0)	0 (0)
Severe	0 (0)	0 (0)
3.0 hours post-dose		
None	6 (86)	7 (100)
Mild	1 (14)	0 (0)
Moderate	0 (0)	0 (0)
Severe	0 (0)	0 (0)
4.0 hours post-dose		
None	6 (86)	7 (100)
Mild	1 (14)	0 (0)
Moderate	0 (0)	0 (0)
Severe	0 (0)	0 (0)

Table 3 Pharmacokinetics of fentanyl buccal soluble film in opioid-tolerant patients with cancer, with and without mucositis

Parameter	Cohort I patients with mucositis (n = 7)	Cohort II patients without mucositis (n = 7)
C_{max} , ng/mL	0.33 (0.19–1.13) Mean (SD): 0.47 (0.32)	0.57 (0.13–1.55) Mean (SD): 0.69 (0.54)
AUC_{0-4} , h-ng/mL	0.98 (0.47–2.60) Mean (SD): 1.14 (0.71)	1.12 (0.39–2.97) Mean (SD): 1.29 (0.87)
T_{max} , hours	1 (0.45–3.92) Mean (SD): 1.46 (1.15)	1 (0.50–1.50) Mean (SD): 1.04 (0.33)

Note: Data are median (range), unless otherwise indicated.

Abbreviations: AUC_{0-4} , area under the concentration–time curve from time 0 to 4 hours; C_{max} , peak plasma concentration; SD, standard deviation; T_{max} , time to C_{max} .

versus 1.55 ng/mL, respectively). Finally, the median and mean C_{max} values in the oral mucositis cohort were 58% and 68% of the median and mean C_{max} values, respectively, observed in the group without oral mucositis.

FBSF residence time assessment

No FBSF residence time was collected for the first seven patients (with mucositis) in this study. Fifteen minutes after application, four of the remaining seven patients had $\geq 10\%$

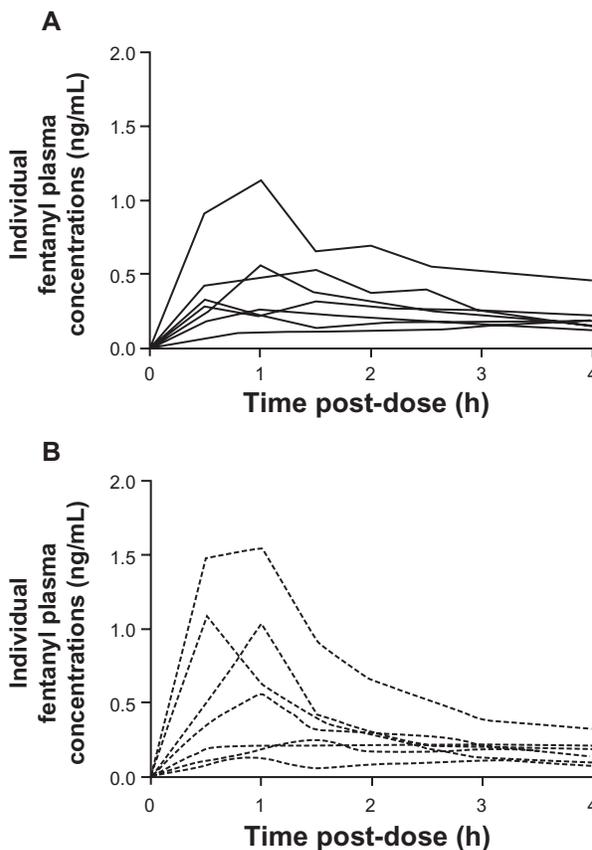


Figure 1 Individual plasma concentrations of fentanyl following administration of fentanyl buccal soluble film in patients with cancer with oral mucositis (A) and without oral mucositis (B).

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and <50% of the film remaining, and three of the seven patients had $\geq 50\%$ and <100% of the film remaining. After 30 minutes, one patient had trace amounts of the film present. There was no evidence of a relationship between C_{\max} and film residence time.

Safety

There was no application site irritation in any patient, regardless of oral mucositis status. Two patients with mucositis reported mild somnolence following FBSF application. No treatment was administered, and both of these events resolved within 2 hours of reporting. No other AEs, serious AEs, or deaths were reported. Two patients with oral mucositis and six patients without oral mucositis had a post-baseline decrease in either systolic or diastolic blood pressure of ≥ 15 mmHg; however, none of these patients had symptoms associated with significant changes in blood pressure. There were no clinically meaningful changes in respiratory rates, with the maximum decrease being two breaths per minute.

Discussion

The effects of oral mucositis can impair the quality of life of patients with cancer and may limit the effectiveness and tolerability of cancer treatments.^{1-4,19-21} The objective of this study was to assess the absorption and tolerability profile of FBSF in patients with cancer with and without oral mucositis. The results of this study indicate that, although the presence of grade 1 oral mucositis may influence the absorption of FBSF, in contrast to FBT, bioavailability is decreased rather than increased. Time to maximum plasma fentanyl concentration was nearly 50% greater in the mucositis population (1.46 hours versus 1.00 hour), while maximum fentanyl concentration and overall exposure were lower in the mucositis population, suggesting the edema of the mucosa had a greater effect on mucosal drug absorption than local irritation. This finding is of practical importance: If the absorption of fentanyl in patients with mucositis was substantially greater, unexpectedly rapid rises in fentanyl plasma levels may lead to opioid-related AEs. In this study, film dissolution in most patients occurred in less than 30 minutes, irrespective of the buccal mucosa status, and there was no evidence of any relationship between C_{\max} and dissolution times. Also, after administration of FBSF, no AEs relating to the oral mucosa were reported. Finally, all patients with mucositis at the beginning of the study became mucositis pain free.

The pharmacokinetics of FBT in the presence of mucositis were evaluated previously.¹³ The study included

eight patients with mucositis and eight patients without mucositis. Patients were instructed to place the tablet in the least inflamed area of the mucosa but not an area that was unaffected. Of the patients who participated in the FBT study, all of the patients in the group with mucositis had clinical grade 1 mucositis (ie, experienced erythema of the mucosa). Of those patients, only one experienced mucositis with a functional grade of 2 (ie, patient experienced the symptoms of mucositis but was able to consume a modified diet, and the respiratory symptoms observed did not impact the daily activities of the patient). After treatment with FBT, there was no difference in C_{\max} values after a 200 μg dose of FBT (1.14 ng/mL versus 1.21 ng/mL). Overall systemic exposure (AUC_{0-8}) of fentanyl after FBT dosing was 32% higher in the patients with mucositis compared with those without mucositis (2.05 ng-hr/mL versus 1.55 ng-hr/mL). Although the difference in exposure was not statistically significant, this may have been due to the small sample size or the variability in the AUC measurement. As only one patient had grade 2 mucositis, no conclusion could be drawn about the impact of a more severe disease level on the absorption of fentanyl from FBT.¹³ The study of OTFC was limited to the tolerability of the application and did not examine the influence of severe mucositis on the absorption of fentanyl from OTFC.²² In the present study, the lower fentanyl exposure after FBSF dosing in the presence of mucositis suggests that alterations to the oral mucosal in patients with cancer with grade 1 mucositis membrane do not lead to an uncontrolled increase in the absorption of fentanyl. A possible clinical implication for this finding is that patients with cancer who are also experiencing mucositis may require slightly higher doses of FBSF than patients with cancer without mucositis.

When considering the difference in systemic exposure of fentanyl in patients with and without mucositis, the process of drug absorption via the oral mucosa and physiological changes to the oral mucosa in the presence of mucositis should be taken into account. Drug absorption via the oral mucosa occurs through a process of passive diffusion.²³ The rate of passive diffusion and amount of drug absorbed are influenced by a number of factors including a drug's lipophilicity, the free drug concentration, the surface area associated with drug application, the length of time the drug is in contact with the oral mucosa, and the thickness of the oral mucosa.^{23,24} The oral mucosa consists of mucus, an epithelium, the basal lamina, and connective tissue comprised of the submucosa and the lamina propria.²³ The epithelium (~150–250 μm) protects the underlying connective tissues

from damage.²⁵ During the primary damage response and signal amplification phase of mucositis, the epithelium thins. In addition to epithelium thinning, edema has also been observed in patients with cancer with mucositis during radiation and chemotherapy.²⁶ Decreases in epithelial thickness have also been observed in animal mucositis models.^{27,28} Our results indicate that the changes occurring in the buccal epithelium at the early stages of mucositis do not increase the passive diffusion of fentanyl, suggesting that fentanyl absorption is more influenced by parameters such as the absorption surface area and the duration of the absorption process than by the thickness of the epithelium.

Some limitations related to the study population and trial design should be considered in evaluating the results. Study limitations include the use of an open-label study design and the minimum dose of FBSF available (200 µg). Another limitation was the presence of mucosal pain in each of the patients with mucositis, which suggests that the severity of mucositis was higher than grade 1. The restriction of measurements of fentanyl concentrations to the interval of 0.5 to 4.0 hours was another limitation. Although the sample size was comparable to the number of patients included in similar studies, the number of patients included in this study was small.^{13,22} In addition, collection of film residence times in controls was a study limitation. Finally, statistical analyses were not performed to compare the pharmacokinetic parameters.

Conclusion

The results of this study show that application of FBSF to an area of grade 1 mucositis does not result in increased fentanyl absorption. Use of the film did not produce local irritation, and the 200 µg dose of FBSF was well tolerated in patients with cancer with and without grade 1 mucositis.

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