The Influence of Low Salivary Flow Rates on the Absorption of a Sublingual Fentanyl Citrate Formulation for Breakthrough Cancer Pain

Andrew Davies, FRCP, Gill Mundin, BSc (Hons), Joanna Vriens, MRCP, Kath Webber, PhD, Alison Buchanan, RGN, and Melanie Waghorn, RGN
Royal Surrey County Hospital (A.D., K.W., A.B., M.W.), Guildford, Surrey; Mundipharma Research Ltd. (G.M.), Cambridge, Cambridgeshire; and Princess Alice Hospice (J.V.), Esher, Surrey, United Kingdom

Abstract

Context. Salivary gland hypofunction may affect the absorption of drugs through the oral mucosa, which in turn may affect their clinical efficacy (e.g., onset of action).

Objectives. The aim of this study was to assess the pharmacokinetics of a sublingual fentanyl orally disintegrating tablet (Abstral®, Prostrakan Inc.) in a group of cancer patients with salivary gland hypofunction.

Methods. Nine cancer patients with salivary gland hypofunction underwent a series of three pharmacokinetic studies with the sublingual fentanyl orally disintegrating tablet. In the first phase, the patients received no pretreatment; in the second phase, the patients were allowed to moisten the oral cavity before dosing; in the third phase, the patients were given pilocarpine hydrochloride (saliva stimulant) before dosing. Fentanyl concentrations were measured using a method of high-performance liquid chromatography with validated tandem mass spectrometric detection.

Results. The Tmax was longer, the Cmax was lower, the AUC0-30 lower, and the AUClast lower in the phase involving no pretreatment; the Tmax/Cmax/AUC0-30/AUClast were similar in the phase involving moistening of the oral cavity and the phase involving giving pilocarpine hydrochloride.

Conclusion. The pharmacokinetics of the sublingual fentanyl orally disintegrating tablet appear to be negatively affected by the presence of salivary gland hypofunction, although the moistening of the oral cavity before dosing results in a pharmacokinetic profile similar to that seen with the giving of pilocarpine hydrochloride. J Pain Symptom Manage 2016;51:538–545. © 2016 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.

Key Words
Breakthrough cancer pain, opioid analgesic, fentanyl, oral transmucosal route, salivary gland hypofunction

Introduction

Breakthrough cancer pain (BTPcP) has been defined as “a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain.”1 BTPcP is a heterogeneous condition,2 and so, management needs be individualized; the management of BTPcP includes treatment of the underlying cause of the pain, avoidance/treatment of the precipitating factors of the pain, modification of the background analgesic regimen/“around-the-clock medication,” use of “rescue medication,” nonpharmacological interventions, and interventional techniques.3 Nevertheless, the cornerstone of the management of BTPcP is the use of rescue medication; in most cases, the most appropriate rescue medication will be an opioid, rather than a nonopioid or an adjuvant analgesic.1

Address correspondence to: Andrew Davies, FRCP, Royal Surrey County Hospital, Guildford, Surrey GU2 7XX, United Kingdom. E-mail: adavies12@nhs.net

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Rescue medication is taken as required, rather than on a regular basis; in the case of spontaneous or nonvolitional incident subtypes of BTcP, the treatment should be taken at the onset of the pain; in the case of volitional incident or procedural subtypes of BTcP, the treatment should be taken before the relevant precipitant of the pain. Traditionally, the most common form of rescue medication has been the oral “normal-release” (“immediate-release”) formulations of morphine and other relevant opioid analgesics. However, the pharmacokinetic/pharmacodynamic profiles of oral opioids do not tend to mirror the temporal characteristics of many BTcP episodes. Thus, the slow onset of action (onset of analgesia: 20–30 minutes; peak analgesia: 60–90 minutes) results in delayed/ineffective analgesia, whereas the prolonged duration of effect (3–6 hours) results in ongoing adverse effects.

Abstral® (ProStrakan Group Plc, Galashiels, UK) is a sublingual fentanyl orally disintegrating tablet, which is indicated for the “management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain.” Thus, the sublingual fentanyl orally disintegrating tablet should only be prescribed to patients who are already taking regular opioids for moderate-to-severe pain (i.e., morphine-equivalent daily dose ≥ 60 mg). The tablet should be placed under the tongue and allowed to spontaneously dissolve; it should not be sucked, chewed, or swallowed. The Summary of Product Characteristics for the sublingual fentanyl orally disintegrating tablet state that “in patients who have a dry mouth water may be used to moisten the buccal mucosa before taking [the drug],” whereas the Patient Information Leaflet states “if your mouth is dry, take a sip of water to moisten it. Spit out or swallow the water.”

The pharmacokinetics of the sublingual fentanyl orally disintegrating tablet have been investigated in normal volunteers, and cancer patients. However, there appears to be no data on the pharmacokinetics of sublingual fentanyl orally disintegrating tablets, or indeed other oral transmucosal opioids, in patients with salivary gland hypofunction. Salivary gland hypofunction may amend absorption through the oral mucosa. Salivary gland hypofunction is associated with a decrease in oral pH (which should increase the ionized fraction of the fentanyl, which in turn should reduce the lipophilicity of the fentanyl) and is also associated with a variety of oral mucosal disorders (which may result in either atrophy or hypertrophy of the oral mucosa, which in turn may result, respectively, in increased permeability or decreased permeability of the oral mucosa). Moreover, saliva is essential for the dissolution of such oral transmucosal formulations.

The aim of this exploratory study was to assess the pharmacokinetics of the sublingual fentanyl orally disintegrating tablet in cancer patients with salivary gland hypofunction.

Methods

The study was conducted at the Royal Surrey County Hospital, and the Royal Marsden Hospital in the U.K. The study was sponsored by Imperial College London, and approved by the South West London Research Ethics Committee, and the Medicines and Healthcare Products Regulatory Agency. Patients were given a standard information sheet, time to consider the study, opportunity to discuss the study (with researchers/others) and asked to provide formal written consent before enrollment.

Subjects were recruited from the inpatient wards, and the outpatient clinics at the two institutions; any patient who fulfilled the entry criteria was eligible for inclusion into the study. The inclusion criteria for the study were as follows: 1) age > 18 years; 2) diagnosis of cancer; 3) regular prescription of opioid for moderate-to-severe pain (“strong opioid”); 4) morphine-equivalent daily dose ≥ 60 mg; 5) low unstimulated whole salivary flow rate (i.e., < 0.1 mL/min); and 6) stimulated whole salivary flow rate greater than unstimulated whole salivary flow rate. The exclusion criteria for the study were as follows: 1) estimated prognosis less than 2 weeks; 2) any prescription of fentanyl in the previous 48 hours (i.e., regular or as required); 3) radiotherapy to head and neck region; 4) surgery to oral cavity; 5) oral mucositis; 6) other significant oral pathology; and 7) inability to give informed consent.

The study schedule involved three assessments, with each assessment being at least 72 hours apart from the previous/subsequent assessment (Fig. 1):

1) Assessment 1: The subjects were screened for eligibility to enter the study, and demographic/other relevant data collected (e.g., prescribed medication). Unstimulated whole salivary flow rate (UWSFR) and then stimulated whole salivary flow rate (SWSFR) were measured using a standard technique. The normal range for the UWSFR is 0.3–0.4 mL/min, and a rate of < 0.1 mL/min is considered abnormal; the normal range for the SWSFR is 1–2 mL/min, and a rate of < 0.5 mL/min is considered abnormal. After 60 minutes of being nil by mouth, 200 mcg of sublingual fentanyl orally disintegrating tablet was administered sublingually, and venous blood collected for analysis at 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 120, and 180 minutes after administration.
2) Assessment 2: The protocol was essentially the same as assessment 1, except the patients were allowed to moisten their mouth with water immediately before the administration of the tablet (as per the Summary of Product Characteristics for the sublingual fentanyl orally disintegrating tablet).

3) Assessment 3: The protocol was essentially the same as assessment 1, except the patient was given pilocarpine hydrochloride (Salagen; Novartis Pharmaceuticals UK Ltd., Frimley, UK) 5 mg 1½ hours before the measurement of the salivary flow rates. Pilocarpine is a salivagogue, which has a marketing authorization for treatment of salivary gland hypofunction associated with Sjogren’s syndrome and head and neck radiotherapy; pilocarpine also has been used to treat drug-induced salivary gland hypofunction. It should be noted that the sublingual fentanyl orally disintegrating tablet was only administered if the UWSFR was >0.1 mL/min (post pilocarpine); patients who failed to stimulate with pilocarpine 5 mg were later rechallenged with pilocarpine 10 mg.

The assessments were not done in a random order, as pilocarpine was shown to have a prolonged effect (carry-over effect) in a previous cross-over study comparing artificial saliva and pilocarpine in the management of xerostomia in patients with cancer.

The venous blood samples were mixed and centrifuged, and the plasma was separated from the cells and stored at −80°C (before the fentanyl analyses). Fentanyl concentrations were measured using a method of high-performance liquid chromatography.
with validated tandem mass spectrometric detection. The fentanyl analyses were performed by the GLP/GCP compliant laboratory of Analytical Services International Ltd. (based at St. George’s, University of London).

The maximum observed plasma concentration (Cmax) and the time to maximum observed plasma concentration (Tmax) were obtained from the fentanyl concentration-time data sets. The area under the plasma concentration-time curve from the time of dosing to 30 minutes (AUC0-30) and from the time of dosing to the last measurement (AUClast) were calculated using the linear trapezoidal method. The pharmacokinetic data were analyzed using Phoenix WinNonlin, version 6.2 (Pharsight, Princeton, NJ). The bioequivalence of the different interventions (i.e., no treatment, sip of water, pilocarpine) was further assessed by calculating the ratio and 90% confidence interval (of the ratio) for relevant pharmacokinetic parameters (i.e., Cmax, Cmax0-30, AUC0-30, and AUClast): the ratios were calculated for no treatment versus a sip of water, no treatment versus pilocarpine, and a sip of water versus pilocarpine.

One subject (Patient 4) had two plasma concentrations in the middle of the sequence that were below the lower level of quantification (i.e., <50 pg/mL). It was deemed unlikely that these were true observations (based on the preceding/succeeding observations), although it was unclear what the reason may have been for these anomalous observations. In view of the anomalous observations, the various pharmacokinetic parameters were calculated both including these two results, and excluding these two results. The pharmacokinetic parameters were similar whether the anomalous data were included or excluded (see the following).

### Results

Nine patients completed all three phases of the study. The median age of the patients was 58 years

<table>
<thead>
<tr>
<th>Patient</th>
<th>UWSFR (mL/min)</th>
<th>SWSFR (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>&lt;0.01</td>
<td>1.55</td>
</tr>
<tr>
<td>Patient 2</td>
<td>0.04</td>
<td>0.75</td>
</tr>
<tr>
<td>Patient 3</td>
<td>&lt;0.01</td>
<td>0.15</td>
</tr>
<tr>
<td>Patient 4</td>
<td>&lt;0.01</td>
<td>0.47</td>
</tr>
<tr>
<td>Patient 5</td>
<td>&lt;0.01</td>
<td>2.00</td>
</tr>
<tr>
<td>Patient 6</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Patient 7</td>
<td>0.05</td>
<td>3.00</td>
</tr>
<tr>
<td>Patient 8</td>
<td>0.06</td>
<td>1.90</td>
</tr>
<tr>
<td>Patient 9</td>
<td>&lt;0.01</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Unstimulated whole salivary flow rate (UWSFR < 0.10 mL is considered abnormal). Stimulated whole salivary flow rate (SWSFR < 0.50 mL is considered abnormal).
(range 47–71 years), and there were five women and four men. The cancer diagnoses were prostate (n = 3), gastrointestinal (n = 3), breast (n = 2), and melanoma (n = 1); the performance statuses were Eastern Cooperative Oncology Group (ECOG) 0 (n = 1), ECOG 1 (n = 5), and ECOG 2 (n = 3). It should be noted that all the recruited patients had advanced (i.e., locally advanced, metastatic) cancer, with no expectation of a so-called “complete response” from their ongoing anticancer treatment.

The UWSFR/SWSFR measurements from assessment 1 are summarized in Table 1. (The salivary flow rates were stable during the study period.) All the patients had an “abnormal” UWSFR (<0.1 mL/min), although only three patients had an “abnormal” SWSFR (i.e., <0.5 mL/min). Of note, all the patients were prescribed drugs that are known to cause salivary gland hypofunction; the median number of drugs was four (range 2–6). The drug classes were opioid analgesics (n = 9), proton pump inhibitors (n = 7), antidepressants (n = 4), hormone therapies (n = 3), nonsteroidal anti-inflammatory drugs (n = 3), antipsychotics (n = 2), corticosteroids (n = 2), calcium channel blockers (n = 2), and miscellaneous other drugs (n = 3). The drug regimens were stable during the study period.

The pharmacokinetic parameters from the three phases are summarized in Table 2, and the plasma concentration-time profiles for the whole time period and the first 30 minutes are shown in Figs. 2 and 3. The bioequivalence data for the whole period and the first 30 minutes are summarized in Table 3; the data including the anomalous results were similar to the data excluding the anomalous results (data not shown).

**Discussion**

This appears to be the first published pharmacokinetic study of an oral transmucosal opioid formulation...
in patients with salivary gland hypofunction. The data suggest that salivary gland hypofunction negatively affects the pharmacokinetics of sublingual fentanyl orally disintegrating tablet, that is, results in a longer Tmax, a lower Cmax, a lower AUC0-30, and a lower orally disintegrating tablet, that is, results in a longer effect on the pharmacokinetics of sublingual fentanyl.

BTcP is common in patients with advanced cancer, although it may occur at any stage of the disease. Equally, salivary gland dysfunction is common in this group of patients, with a reported prevalence of xerostomia (subjective sensation of dryness of the mouth) of 78%—82%, and a reported prevalence of salivary gland hypofunction (objective reduction in salivary flow rate) of 82%—83%. Thus, many patients with BTcP have salivary gland hypofunction.

Oral transmucosal opioid formulations are an established intervention for BTcP. The rationale for the use of oral transmucosal opioid formulations is the more rapid onset of action of the drug as a result of the more rapid absorption of the drug (compared with oral opioid formulations). The sublingual fentanyl orally disintegrating tablet has been shown to be an effective treatment for BTcP, and relatively more effective than oral morphine. However, the fentanyl's efficacy is dependent on rapid/good absorption through the mucosa of the floor of the mouth.

In this study, the use of a saliva substitute (water) and the use of a saliva stimulant (pilocarpine) were equally effective in terms of optimizing the absorption of the sublingual fentanyl orally disintegrating tablet. Thus, patients with salivary gland hypofunction may be advised to moisten the oral mucosa before dosing with the sublingual fentanyl. However, such patients should probably be treated with saliva stimulants rather than saliva substitutes, as these drugs are overall much more effective in managing salivary gland hypofunction.

The study data suggest that successful treatment of salivary gland hypofunction may necessitate retitrination of oral transmucosal fentanyl opioid formulations. Indeed, we have previously reported a case of a patient with salivary gland hypofunction, who was treated with bethanechol chloride (a saliva stimulant), and who then required a dose reduction of oral transmucosal fentanyl citrate; the patient himself reported quicker dissolution of the product, and quicker onset of analgesia, after treatment of salivary gland hypofunction.

It is likely that salivary gland hypofunction affects the pharmacokinetics of other oral transmucosal opioids. Indeed, salivary gland hypofunction affects the pharmacokinetics/clinical efficacy of other oral transmucosal drugs. However, the results of this study cannot be extrapolated to other oral transmucosal opioid formulations. Thus, saliva substitutes have a short duration of effect, and so, the use of saliva substitutes may not be as effective with other oral transmucosal opioid formulations as they tend to take longer to dissolve. For example, it is stated to take 15 minutes to dissolve oral transmucosal fentanyl citrate (Actiq®, TEVA UK Ltd., Castleford, UK), and 14—25 minutes to dissolve a fentanyl buccal tablet (Effentora®, TEVA UK Ltd.).

The major limitation of the study is the number of patients enrolled; the predetermined sample size was somewhat pragmatic, as we anticipated (correctly) that recruitment would be challenging because of the involvement of patients with cancer pain/other morbidities (as opposed to the involvement of healthy volunteers). Indeed, our results need to be confirmed by other investigators.

**Table 3**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference Intervention</th>
<th>Intervention</th>
<th>Ratio</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>No treatment</td>
<td>Sip water</td>
<td>116.98%</td>
<td>95.17—143.79%</td>
</tr>
<tr>
<td></td>
<td>No treatment</td>
<td>Pilocarpine</td>
<td>119.77%</td>
<td>97.44—147.22%</td>
</tr>
<tr>
<td></td>
<td>No treatment</td>
<td>Pilocarpine</td>
<td>102.39%</td>
<td>83.30—125.85%</td>
</tr>
<tr>
<td>Cmax(0—30)</td>
<td>No treatment</td>
<td>Sip water</td>
<td>138.66%</td>
<td>107.41—179.01%</td>
</tr>
<tr>
<td></td>
<td>No treatment</td>
<td>Pilocarpine</td>
<td>155.14%</td>
<td>120.17—200.28%</td>
</tr>
<tr>
<td></td>
<td>Sip water</td>
<td>Pilocarpine</td>
<td>111.88%</td>
<td>86.66—144.44%</td>
</tr>
<tr>
<td>AUC0-30</td>
<td>No treatment</td>
<td>Sip water</td>
<td>150.20%</td>
<td>106.30—212.23%</td>
</tr>
<tr>
<td></td>
<td>No treatment</td>
<td>Pilocarpine</td>
<td>206.53%</td>
<td>146.16—291.82%</td>
</tr>
<tr>
<td></td>
<td>Sip water</td>
<td>Pilocarpine</td>
<td>137.50%</td>
<td>97.31—194.29%</td>
</tr>
<tr>
<td>AUClast</td>
<td>No treatment</td>
<td>Sip water</td>
<td>107.34%</td>
<td>90.09—127.89%</td>
</tr>
<tr>
<td></td>
<td>No treatment</td>
<td>Pilocarpine</td>
<td>107.93%</td>
<td>90.38—128.60%</td>
</tr>
<tr>
<td></td>
<td>Sip water</td>
<td>Pilocarpine</td>
<td>100.55%</td>
<td>84.39—119.80%</td>
</tr>
</tbody>
</table>

Cmax = maximum concentration; Cmax (0—30) = maximum concentration 0 minutes to 30 minutes; AUC0-30 = area under curve 0 minutes to 30 minutes; AUClast = area under curve 0 minutes to 180 minutes (last sample).
that seen with the use of a saliva stimulant (and resulting in a normal unstimulated whole salivary flow rate).

Disclosures and Acknowledgments

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References


