Original Article

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.

Key Words

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

Introduction

Breakthrough cancer pain (BTcP) 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] BTcP is a heterogeneous condition,[2,3] and so, management needs be individualized; the management of BTcP 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.[1] Nevertheless, the cornerstone of the management of BTcP 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

Accepted for publication: November 9, 2015.

0885-3924/$ - see front matter
http://dx.doi.org/10.1016/j.jpainsymman.2015.11.018

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.[1] 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.[2,3] 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.[1,4]

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."[5] 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[5] 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[6] 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,[7,8] and cancer patients.[9] 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.[10] Salivary gland hypofunction may amend absorption through the oral mucosa.[11] 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)[12,13] 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[11,14]). Moreover, saliva is essential for the dissolution of such oral transmucosal formulations.[15]

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)[14]; 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.[12] The normal range for the UWSFR is 0.3–0.4 mL/min, and a rate of <0.1 mL/min is considered abnormal[14]; the normal range for the SWSFR is 1–2 mL/min, and a rate of <0.5 mL/min is considered abnormal.[14] 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.