Saliva versus Plasma for Pharmacokinetic and Pharmacodynamic Studies of Fentanyl in Patients with Cancer

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ABSTRACT

Purpose: Fentanyl is widely used to relieve cancer pain. However there is great interpatient variation in the dose required to relieve pain and little knowledge about the pharmacokinetic and pharmacodynamic (PK/PD) relationship of fentanyl and pain control. Patients with cancer are fragile and there is reluctance on the part of health professionals to take multiple plasma samples for PK/PD studies. The relationship between plasma and saliva fentanyl concentrations was investigated to determine whether saliva could be a valid substitute for plasma in PK/PD studies.

Methods: One hundred sixty-three paired plasma and saliva samples were collected from 56 patients prescribed transdermal fentanyl (Durogesic, Janssen-Cilag Pty Limited, NSW, Australia) at varying doses (12–200 μg/h). Pain scores were recorded at the time of sampling. Fentanyl and norfentanyl concentrations in plasma and saliva were quantified using HPLC-MS/MS.

Findings: Saliva concentrations of fentanyl (mean = 4.84 μg/L) were much higher than paired plasma concentrations of fentanyl (mean = 0.877 μg/L). Both plasma and saliva mean concentrations of fentanyl were well correlated with dose with considerable interpatient variation at each dose. The relationship between fentanyl and norfentanyl concentrations was poor in both plasma and saliva. No correlation was observed between fentanyl concentration in plasma and saliva (r^2 = 0.3743) or free fentanyl in plasma and total saliva concentrations (r^2 = 0.1374). Pain scores and fentanyl concentration in either of the matrices were also not correlated.

Implications: No predictive correlation was observed between plasma and saliva fentanyl concentration. However the detection of higher fentanyl concentrations in saliva than plasma, with a good correlation to dose, may allow saliva to be used as an alternative to plasma in PK/PD studies of fentanyl in patients with cancer. (*Clin Ther*. 2015;37:2468–2475)

Key words: cancer pain, fentanyl, opioid, pharmacokinetics, plasma, saliva.

INTRODUCTION

Fentanyl is a synthetic, highly selective opioid agonist that acts primarily at the μ-opioid receptor, with minor activity at the Δ and κ receptors.[1] Fentanyl is widely used in patients with cancer along with morphine and oxycodone. The transdermal patch is the most common means of delivery of fentanyl to patients with cancer. Fentanyl has a large volume of distribution (3.5–8 L/kg; mean = 6 L/kg), a high total body clearance of 30 to 72 L/h,[2] and a long elimination half-life of 3 to 8 hours.[3] Fentanyl is

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primarily (>75%) metabolized[4,5] by CYP3A4[6] and likely CYP3A5 to the inactive[7] norfentanyl that does not have relevant pharmacologic activity.[4]

Fentanyl has been reported to be a substrate for the P-glycoprotein efflux transporter. In addition to passive diffusion, active transport systems have also been described for fentanyl uptake into the central nervous system (CNS).[8] Therefore, because fentanyl and its metabolites are known to be actively transported into various body fluids, it is reasonable to assume that its passage into saliva may also be assisted. Given our previous report of active transport of oxycodone into saliva,[9] we also tested the hypothesis that fentanyl may be transported into saliva by a similar mechanism to that occurring in the CNS. If so, we postulated that saliva concentrations of fentanyl may provide better predictive relationships than plasma concentrations. This approach has been exploited for phenytoin, where saliva concentrations correlate better with cerebrospinal fluid concentration than with serum concentrations.[10] Strong correlations between plasma and saliva concentrations for the analgesics acetaminophen[11] and hydromorphone[12] have been described. A review of the relationship of saliva and plasma drug concentrations suggests that saliva concentrations may relate better to efficacy and/or toxicity than plasma concentrations.[13] Just as drugs must pass through cellular membranes to enter saliva, they also must pass through membranes to reach their site of action in the CNS. It is therefore possible that the pharmacokinetic (PK) and pharmacodynamic relationship of saliva concentrations of fentanyl will be of greater utility in dose adjustment than plasma concentrations.

In the only study of its kind reported to date, Silverstein et al[14] attempted to quantify fentanyl and norfentanyl in saliva and urine to detect and monitor abuse in 7 female patients receiving intravenous fentanyl. In that small study, neither fentanyl nor norfentanyl was detected in saliva at any time of sampling and the authors' conclusion was that saliva testing does not appear to be a viable alternative to urine testing. Our initial work suggested that it was possible to measure fentanyl in saliva after transdermal delivery. The aim of our study was to determine if saliva was a valid substitute for plasma in determining drug concentrations of fentanyl. If this relationship could be established, it could be a significant advantage to frail cancer patients who are reluctant to provide regular plasma samples for clinical observations.

METHODS

Participants

All patients had malignant disease and were inpatients or outpatients of an oncology/palliative care service. All were receiving fentanyl at a range of doses, via the transdermal route (Durogesic, Janssen-Cilag Pty Limited, NSW, Australia). Patients had to be willing and able to provide paired saliva and blood sample(s) on more than 1 occasion. Patients were excluded if they had oral mucositis, infection and/or xerostomia (such that it was painful or not possible to collect a saliva sample), or were using fentanyl for breakthrough analgesia. The study was conducted in compliance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. The study was approved by the Mater Health Services Human Research Ethics Committee and Human Research Ethics Committee of Griffith University.

Documentation

Patient age, height and weight, recent blood tests (to assess renal function and liver function), fentanyl dose, duration of treatment, site of placement, timing of samples in relation to timing of fentanyl patch change, and concomitant medications were documented. Body mass index and body surface area were determined at baseline. At the time of sampling, participants were asked to complete a numerical rating scale for "pain right now" ranging from 0 (no pain) to 10 (worst possible pain). Similarly a visual and descriptive 5-point scoring system (FDA 2010)[36] for adhesion of transdermal patches was used to grade the degree of patch adhesion at the time of sampling that ranged from 0 (completely adhered) to 4 (completely detached). This patch adhesion scale has been validated[15] for use in clinical practice.

Sample Collection and Storage

Blood samples (3–4 mL) were collected in standard 5 mL EDTA tubes without a serum separator plug. Samples were centrifuged within 1 hour of collection and the plasma stored at −70°C until analysis. Saliva samples were obtained by having the participant chew a dental bud (noncitrated) that was supplied to them in a Salivette (a dental bud is supplied in a plastic tube designed for saliva collection) (Sarstedt, Nümbrecht, Germany). Thorough rinsing of the mouth was required at least 5 minutes before specimen collection to avoid contamination by