Original Article

Opioid Concentrations in Oral Fluid and Plasma in Cancer Patients With Pain

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Abstract

Context. Measuring opioid concentrations in pain treatment is warranted in situations where optimal opioid analgesia is difficult to reach.

Objectives. To assess the usefulness of oral fluid (OFL) as an alternative to plasma in opioid concentration monitoring in cancer patients on chronic opioid therapy.

Methods. We collected OFL and plasma samples from 64 cancer patients on controlled-release (CR) oral morphine, CR oral oxycodone, or transdermal (TD) fentanyl for pain. Samples were obtained on up to five separate days.

Results. A total of 213 OFL and plasma samples were evaluable. All patients had detectable amounts of the CR or TD opioid in both plasma and OFL samples. The plasma concentrations of oxycodone and fentanyl (determination coefficient $R^2 = 0.628$ and 0.700, respectively), but not morphine ($R^2 = 0.292$), were moderately well correlated to the daily opioid doses. In contrast to morphine and fentanyl (mean OFL/plasma ratio 2.0 and 3.0, respectively), the OFL oxycodone concentrations were significantly higher than the respective plasma concentrations (mean OFL/plasma ratio 14.9). An active transporter could explain the much higher OFL vs. plasma concentrations of oxycodone compared with morphine and fentanyl.

Conclusion. OFL analysis is well suited for detecting the studied opioids. For morphine and fentanyl, an approximation of the plasma opioid concentrations is obtainable, whereas for oxycodone, the OFL/plasma concentration relationship is too variable for reliable approximation results. J Pain Symptom Manage 2015;50:524–532.

Key Words

Opioid, oral fluid, plasma, concentration

Introduction

The use of opioids for the treatment of pain has rapidly increased in Europe and in the U.S. in the last decade.[1,2] Opioids are the mainstay of treatment for cancer pain. In some other types of chronic pain, for example, neuropathic pain, opioids are recommended as an alternative treatment after trials of antidepressants and antiepileptics.[3] Development of tolerance may complicate long-term opioid use as the opioid dose has to be gradually increased to maintain satisfactory analgesia. The high plasma opioid concentrations reported in clinical studies on opioid-tolerant cancer pain patients[4,5] are close to concentrations seen in fatal opioid overdoses.[6,7]

In the clinic, measuring plasma opioid concentrations in pain treatment is warranted in problematic situations where optimal opioid analgesia is difficult to attain. Plasma opioid concentrations are typically widely variable.[5,8] Although opioid doses and plasma opioid concentrations may be poorly correlated,[8]

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opioid concentration monitoring can demonstrate treatment adherence, that is, that an opioid has been ingested, and indicate patients with very low plasma opioid concentrations. Low plasma opioid concentrations may be caused by poor oral or transdermal (TD) opioid absorption or a drug interaction affecting opioid elimination. Of the so-called strong opioids, oxycodone, fentanyl, and methadone are most susceptible to drug interactions. For example, coadministration of the antituberculotic agent rifampin with oxycodone leads to decreased oxycodone plasma concentrations because of CYP3A4 induction and increased oxycodone metabolism.[9]

Oral fluid (OFL) is an alternative matrix for urine and plasma in monitoring drug use. Drugs are transferred into the OFL through the salivary gland membranes by passive diffusion, by active transport or, for small molecules, by filtrating through pores in the membrane.[10] Factors that may affect the passive diffusion of a drug through the salivary gland membranes are the pH of OFL and plasma and drug properties (lipid solubility, acid-base properties, and protein binding). OFL sampling is an easy, noninvasive, and inexpensive method of sample collection, where the disadvantages of blood and urine sampling (e.g., discomfort, risk of infection) are avoided, although different sampling procedures may cause some variation in the results. Outside the clinic, other applications for opioid testing are, for example, roadside drug testing for drivers to improve traffic safety,[11] workplace drug testing,[12] and monitoring illicit drug use in drug treatment programs.[13]

Therapeutic drug monitoring by OFL concentration analysis is possible for drugs with good correlation between OFL and plasma concentrations, such as phenytoin and theophylline.[14,15] There are few studies on the OFL/plasma concentration ratios of opioids.[16–18] The OFL and plasma concentrations of codeine were significantly correlated in 19 healthy volunteers.[17] In pediatric patients on intravenous morphine for sickle cell crisis, no correlation was found between OFL and plasma morphine concentrations.[18] A study on cancer pain patients on chronic oxycodone therapy reported poor correlation between OFL and plasma oxycodone concentrations.[19] No studies have been published on the OFL/plasma concentration relationships of fentanyl.

The aim of this study was to examine the OFL/plasma opioid concentration relationships for morphine, oxycodone, and fentanyl and to study whether OFL is a possible alternative for plasma sampling in cancer patients on chronic opioid therapy.

Methods

Sixty-four adult cancer patients treated at the Pain Clinic of the Helsinki University Central Hospital provided written informed consent to participate in the study. The study protocol was approved by the Institutional Review Board of the Helsinki University Central Hospital (T10200066). Patients on any dose of controlled-release (CR) oral morphine, CR oral oxycodone, or TD fentanyl were recruited. All patients were using other medications besides the opioid for pain and other symptoms during the study. Use of CYP3A4-inducing drugs was recorded separately.

OFL and blood plasma samples were collected on up to five separate days during outpatient visits at the pain clinic or during an inpatient stay on the hospital ward. Samples were not obtained before the opioid steady state was achieved (i.e., at least five times the elimination half-life of each opioid from the latest dose increase). The samples were taken two to 10 hours after a scheduled oral opioid dose or 12 to 60 hours after TD fentanyl patch application. The patients were allowed to use an immediate-release (IR) opioid formulation for rescue medication during the study. When possible, the IR opioid was changed to an opioid other than the CR opioid before the study. If patients continued using the same IR and CR opioids, only samples taken at least 12 hours after the latest IR opioid dose were analyzed.

The OFL samples were collected by drooling using 50 mL wide-mouthed sampling tubes (Sarstedt AG & Co., Nümbrecht, Germany). Approximately 1 mL of OFL was collected for each sample. When the patient was finished with the OFL collection, a venous blood sample was collected from an antecubital vein into a 10 mL ethylenediaminetetraacetic acid tube. The blood samples were centrifuged at 3000 rpm for 10 minutes. Plasma and OFL were immediately frozen in polypropylene tubes at −70°C. The samples were stored at −70°C for one to 22 months before analysis.

A simultaneous sensitive quantification of morphine, oxycodone, and fentanyl as trimethylsilylated derivatives was obtained by gas chromatography-mass spectrometry in selected ion monitoring mode modified from the previous methodologies.[20,21] The limits of quantification (LOQs) were 1.0, 0.5, and 1.0 ng mL^{-1}, respectively, for both plasma (1 mL) and OFL (0.5 mL) samples. All compounds fulfilled internationally accepted validation criteria for quantitative performance.[22]

Statistical Analysis

All calculations were made with PASW Statistics 18.0.0 (IBM Corporation, Armonk, NY) software. Evaluation of correlation of OFL and whole blood drug concentrations was made by examination of the scatter plots. In addition, the linear relationship of drug concentrations between OFL and whole blood was evaluated by the results of linear regression analysis. Inter- and intrapatient variations in opioid plasma concentrations and dose as well as in OFL and plasma