Can Saliva and Plasma Methadone Concentrations Be Used for Enantioselective Pharmacokinetic and Pharmacodynamic Studies in Patients With Advanced Cancer?

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ABSTRACT

Purpose: Methadone is a potent analgesic used to treat refractory cancer pain. It is administered as a racemic mixture, with the l-enantiomer being primarily a μ-receptor agonist, whereas the d-enantiomer is an *N*-methyl-D-aspartate antagonist and inhibits serotonin and norepinephrine reuptake. Dose requirements vary greatly among patients to achieve optimal pain control and to avoid the risk of adverse effects. The relationship between plasma and saliva methadone enantiomer concentrations was investigated to determine if saliva could be a substitute for plasma in pharmacodynamic and pharmacokinetic studies for clinical monitoring and dose optimization of methadone in patients with advanced cancer.

Methods: Patients with advanced cancer who were prescribed varying doses of oral methadone for pain management were recruited to obtain paired plasma and saliva samples. Pain scores were recorded at the time of sampling. The total and unbound plasma and saliva concentrations of the l- and d-enantiomers of methadone were quantified by using an HPLC-MS/MS method. The relationship between plasma (total and unbound) and saliva concentrations were compared. The saliva-to-plasma concentration ratio was compared versus the dose administered and the time after dosing for both enantiomers. The association of methadone concentrations with reported pain scores was compared by using a Mann-Whitney *U* test for significance.

Findings: Fifty patients receiving a mean dose of 11mg/d of methadone provided 151 paired plasma and saliva samples. The median age of the population was 61 years with an interquartile range of 53-71 years with total body weight ranging from 59-88 kg. Median (interquartile) total plasma concentrations for l- and d-methadone were 50.78 ng/mL (30.6–113.0 ng/mL) and 62.0 ng/mL (28.7–116.0 ng/mL), respectively. Median (interquartile range) saliva concentrations for l- and d-methadone were 81.5 ng/mL (28.0–203.2 ng/mL) and 44.2 (16.2–149.7 ng/mL). No relationship could be established between plasma and saliva concentrations for l- and d-methadone (r^2 = 0.35 and 0.25). The saliva-to-plasma concentration analyzed with the methadone dose showed higher saliva concentrations at lower doses. Dose-normalized saliva concentrations followed a similar pattern over time compared with plasma concentrations. No correlation was found between l-methadone plasma, d-methadone plasma, l-methadone saliva, d-methadone saliva concentrations, and pain score.

Implications: Saliva concentration was not a better predictor of pain control than plasma concentration for dose optimization and monitoring studies of

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methadone in patients with cancer. Although the saliva-to-plasma ratio of the concentration of methadone enantiomers was stable across the dosing range, due to the variability in individual saliva-to-plasma ratios, saliva sampling may not be a valid substitute in pharmacokinetic studies of methadone in cancer. (*Clin Ther*. 2017;39:1840–1848)

Key words: cancer pain, enantiomers, methadone, pharmacokinetics, plasma, saliva.

INTRODUCTION

Cancer pain affects 60% to 70% of the cancer population.[1] Estimates of the prevalence of cancer-related pain vary greatly, owing to limitations in standardization of definitions of pain, assessment, diversity of nociceptive and neuropathic pain conditions, and heterogeneity of cancer diagnoses.[2] Methadone is a potent lipophilic synthetic opioid widely used in the treatment of cancer pain.[3] The properties of methadone include oral bioavailability, rapid onset of analgesic effect, long half-life, lack of active metabolites, low rate of tolerance induction, low cost, and perceived benefit in difficult pain control scenarios, especially in cases of neuropathic pain.[4] These characteristics favor its use in the management of pain in profoundly ill patients.[5–7] Opioid switching to oral methadone is proven to provide adequate pain relief and reduces the use of other adjuvant analgesic agents.[8] However, the pharmacokinetic and pharmacodynamic relationship of methadone dose, exposure, and pain control is still not well understood.

Large interindividual,[9] but lower intraindividual,[10] subject variability in methadone concentrations to achieve analgesia have been reported. Furthermore, comorbidity, concomitant medications, genomics, and lack of distinct equianalgesic dose ratio to other opioids[11] restricts its clinical use without previous knowledge of pharmacokinetic variables in individual patients. The same dose of methadone often results in markedly different plasma concentrations, with wide interindividual variation in pharmacodynamic[12] and pharmacokinetic[13] responses. Repeated blood samples are often required for pharmacokinetic studies; however, in patients with advanced cancer, noninvasive and easy sample collection is preferred by the study subjects and the investigators.[14,15]

Strong correlations between plasma and saliva concentrations for the analgesics paracetamol[16] and hydromorphone[17] have been reported previously. Factors influencing the concentration of a drug in saliva include the pKa of the drug and pH of the saliva, molecular weight, lipid solubility, and degree of protein binding.[18] Methadone has a pKa of 8.3 at the physiological pH of saliva of 7.4, with absolute bioavailability varying from 41% to 95%[19,20] after oral administration. Drug transport from plasma into the salivary duct is determined by the capability of the unbound drug molecule to traverse the cell membranes, and the lipophilicity of the drug facilitates this transport. Saliva is a complex fluid secreted as a result of different mechanisms, including passive diffusion, ultrafiltration, and active transport.[21] The possibility of an active transport system has not been clearly defined for disposition of methadone into saliva.[22] A review of the relationship between saliva and plasma methadone concentrations suggests that saliva concentrations may relate better to efficacy or toxicity compared with plasma concentrations.[23]

The goal of the present study was to investigate the relationship between plasma and saliva methadone enantiomer concentrations to explore the possibility of saliva samples being used in clinical monitoring and for dose optimization.

PATIENTS AND METHODS

Participants and Data

Adult patients (age ≥18 years) with cancer-related pain being cared for at the inpatient or outpatient oncology and palliative care service of the Mater Adults Hospital and St. Vincent's Private Hospital in Brisbane between 2013 and 2016 were eligible for recruitment to the study. Patients received methadone via the oral route, and methadone was not prescribed as breakthrough medication. Patients who were willing and able to provide saliva and blood samples, able to read and understand a patient information sheet, and able to provide written consent were included. Patients with oral mucositis, infection, or xerostomia were excluded. Sampling was performed at the convenience of the patients.

Saliva samples were obtained at the same time of plasma sampling by having the patients chew on a cotton dental bud supplied within a Salivette (Salivetter, Sarstedt, Nümbrecht, Germany). No specific time