

Secondary-peak profile of methadone in saliva after administration of multiple doses in patients with chronic pain

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ABSTRACT

The unique pharmacokinetics and pharmacodynamics of methadone make it a valuable option in the management of chronic pain. Saliva is a useful tool for monitoring this drug and studying a possible recirculation process. The objective of this study was to identify the recirculation process of methadone in patients with chronic pain using saliva as biological fluid. The concentration-time profiles of methadone in saliva in eight patients with chronic pain were obtained. Morning methadone dose was administered at 8:00 a.m. with 250 mL of water. Times of food ingestion were 4 hours (lunch) and 8 hours (tea) post-dose. Saliva samples were collected using Salivette[®] devices. Drug quantification in saliva was performed using a validated high performance liquid chromatography method. Immediately after sampling, the pH was measured using a portable pH meter with a semi-micro electrode. Two secondary peaks were observed at 6 and 10 hours post-dose (two hours after food intakes) in the mean concentration-time curve of methadone in saliva. No correlation between saliva pHs and salivary methadone concentrations was observed. Methadone was found to be subject to recirculation, probably via gastric secretion and intestinal reabsorption. Saliva proved to be a more useful tool than plasma to magnify this phenomenon.

KEYWORDS: methadone, saliva, secondary peaks, chronic pain

INTRODUCTION

Methadone is a synthetic opioid with potent analgesic effects. Although it is commonly associated with treatment of opioid addiction [1], its unique pharmacokinetics and pharmacodynamics make it a valuable option in the management of cancer pain [2] and chronic pain [3, 4]. Additionally, its increased efficacy in the setting of neuropathic pain is well demonstrated [5].

Methadone exerts its activity by binding to μ opioid receptors centrally and in the periphery. It also acts as a serotonin and norepinephrine reuptake inhibitor and as a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist [6-9]. These combined mechanisms are responsible for its efficacy in chronic and neuropathic pain. NMDA antagonism is also believed to attenuate tolerance [10, 11].

Methadone hydrochloride that is available in the market is a racemic mixture of two stereoisomers (R)- and (S)-methadone, both of which are responsible for its analgesic effect. The (R)-enantiomer exerts most of its opioid effect and it also acts as a NMDA antagonist. The (S)-methadone not only antagonizes NMDA-receptor but also inhibits serotonin and norepinephrine reuptake [12-14].

Methadone is a highly lipophilic compound (octanol/water partition coefficient of 117 at pH 7.4) with basic properties ($pK_a = 8.3$) [15].

Methadone taken orally and at steady-state is subjected to first-pass effect [16] and is observed in plasma 30 minutes after administration. It is also a substrate of P-glycoprotein (P-gp) [17]. Its

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bioavailability is variable, from 41 to 95% [18]. The average time needed to reach peak plasma concentrations (T_{MAX}) in patients is 4.4-6 hours [16, 18] whereas in healthy volunteers it is 2.8 hours [19]. Sixty to ninety percent of methadone is bound to plasma proteins, mostly to alpha-1-acid glycoprotein [16, 20]. Methadone is secreted in saliva, breast milk, amniotic fluid and umbilical cord plasma.

At steady-state, its elimination half-life is 22-25 hours. Due to induction of its own metabolism (CYP3A4 and/or P-glycoprotein induction), elimination half-life is longer after the first dose (36.7 hours) [19] than during maintenance treatment [16, 18]. Its long elimination half-life in comparison with other opioids such as morphine makes it a useful alternative for avoiding patient's withdrawal symptoms.

Methadone is stored in body tissues, where it accumulates and is then slowly released to plasma during the terminal elimination phase. This contributes to the prolonged elimination half-life of methadone. Cardiac and respiratory systems are vulnerable targets of the toxic action of this drug [16, 20].

Methadone is metabolized in the liver by the enzymes of the P450 cytochrome system (CYP3A4, CYP2B6, CYP2D6, CYP2C19 and other enzymes to a lesser extent) and in the gastrointestinal tract by CYP3A4, but excretion through the kidneys and feces is not negligible. As methadone is a basic drug, the urinary excretion of the drug is dependent on pH [16, 20] and is increased by urine acidification.

The main biotransformation that occurs in the two methadone enantiomers is N-demethylation by CYP3A4. This enzyme has no genetic polymorphism but the inter-individual difference in its expression in the gut is responsible for the variations of methadone bioavailability. Polymorphism in CYP2B6, CYP2D6 and CYP2C19 can affect its activity and is responsible for a more rapid or a slower elimination of methadone, with a consequent shortening or lengthening of methadone's half-life and a fall or rise in its levels in plasma [18].

Venous plasma drug concentrations are the ones usually determined in pharmacokinetic studies and in the clinical setting. However, drug concentrations in veins and arteries vary throughout time [21].

Arterial drug concentration is higher than the respective venous concentration during input of the active substance either after intravenous or oral administration. The opposite is observed when drug elimination predominates [22]. Hence, if enterohepatic or blood-gastrointestinal cycling processes are operating, sudden absorptions during the elimination phase could be inferred by higher arterial drug concentrations.

Despite being potentially important, measuring drug levels in artery is not a practical procedure. Our research group has been using saliva as biological fluid for several years [23-26]. Saliva collection is simple and non-invasive. Saliva is produced in the salivary glands by ultrafiltration of arterial plasma [22], and hence saliva drug concentration is more closely related to arterial free plasma drug concentration. This fact makes drug monitoring in saliva an interesting tool to assess enterohepatic or blood-gastrointestinal cycling processes. Elevated drug concentrations in saliva during the elimination phase could predict the re-entry processes. By using this methodology, enterohepatic circulation of paracetamol has been evaluated by our group [27].

Recommendations regarding the utility of saliva sampling for methadone have been contradictory [16, 28]. The influence of variable saliva pH on methadone excretion into saliva at the time of sampling could be the cause of such controversies. The poor correlations between salivary and plasma methadone concentrations observed by some authors [16] are partly related to the effect of variable saliva pH. However, as stated by these authors, saliva pH accounted only for 10%-36% of the total variation as they found weak inverse correlations between saliva pH and dose-adjusted trough methadone concentrations in saliva.

Studies indicate that significant enterohepatic circulation of unchanged methadone is unlikely [29, 30]. Some other authors [31] working with healthy volunteers and heroin addicts receiving methadone found that in the normal subjects about 2% of the administered dose was recovered in the gastric juice in 8 hours, whereas in the addicts about 7% was recovered evidencing the secretion of methadone in the gastric juice of humans. Moreover, the same authors found that in the addicts, salivary methadone concentrations were

often 10 times more than those recorded in the blood.

The aim of this work was to identify the recirculation process of methadone in patients with chronic pain using saliva as biological fluid.

PATIENTS AND METHODS

Subjects

Eight Caucasian outpatients (seven women and one man) with chronic pain diagnosed by the Interdisciplinary Pain Unit of the University Hospital (Montevideo, Uruguay) took part in the study. The diagnosis were degenerative disc disease, low lumbar pain, arthritis in femur head, post-surgery chronic lumbar pain, back pain, fibromyalgia and sciatica pain.

The demographic characteristics of the subjects are summarized in table 1. Eight subjects were studied during a 12-hour interdosing interval (twice daily dosing) at steady state. Each patient's usual daily dose of methadone (range: 10-30 mg/day) was administered as a tablet (the same brand of methadone for all patients) under supervision of the study personnel. The usual co-medication of the patients was not discontinued and consists of lamotrigine, pregabalin, gabapentin, paracetamol, quetiapine, duloxetine, morphine, tramadol and ibuprofen as pain relievers. Five out of eight patients were with omeprazole 20 mg/day.

The study protocol was approved by the Institutional Ethics Review Committee of the Faculty of Chemistry (Uruguay). Written informed consent was obtained from all the subjects before their entry into the study.

Table 1. Demographic characteristics of the subjects.

Number of patients	8
Age (years)	47 (31 - 59)
Sex (F/M)	7/1
Weight (kg)	74.4 (52 - 122)
Height (cm)	163.9 (155.0 - 178.0)
BMI (kg/m ²)	27.4 (21.7 - 38.6)

Data is presented as mean (range) when appropriate. BMI: body-mass index.

Sampling and chemical analysis

Saliva samples were collected using Salivette[®] devices. The Salivette consists of a conical tube with a suspended insert containing a cotton-wool swab. Patients were instructed to keep the swab in their mouth for about 1-3 minutes. After being soaked with saliva, the swab was reinserted in the tube and the device was closed. After centrifugation, clean saliva was obtained and was kept at -20 °C until analysis.

Immediately after sampling, the pH was measured using a portable pH meter with a semi-micro electrode (Thermo Scientific Orion Laboratory Products, USA).

All patients were under fasting conditions and saliva samples were scheduled at 0 (before dose intake) and 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours after dosing. Morning dose was administered at 8:00 a.m. with 250 mL of water. Times of food ingestion were 4 hours (lunch) and 8 hours (tea) post-dose.

Drug quantification in saliva was performed using a validated high performance liquid chromatography method [32]. The lower limit of quantification was 50.0 ng/mL and linearity was proven up to 1000 ng/mL. Intra- and inter-day precision and accuracy were < 8.3%.

Pharmacokinetic and statistical analysis

Mean concentration-time profile of methadone in saliva for the subjects was constructed considering a mean dose of 11 mg (5-15) every 12 hours.

Mean experimental maximum concentration (C_{MAX}) (\pm standard deviation) and median T_{MAX} (interquartile range) were computed. The area under the saliva concentration-time curve during the interdosing period was calculated using the trapezoidal rule (AUC_T). The average saliva concentration at steady-state (C_{AV}) was calculated as AUC_T/T , where T is the interdosing period. Saliva concentration at each sampling point of each individual (C_{SAL}) divided by C_{AV} (C_{SAL}/C_{AV}) was also computed in order to correlate them with salivary pHs.

RESULTS AND DISCUSSION

Figure 1 shows the mean concentration-time profiles of methadone in saliva. A mean C_{AV} of 141.9 (\pm 95.3) ng/mL corresponds to a mean dose of 11 mg every 12 hours. Mean saliva C_{MAX} was 326 (\pm 259) ng/mL and the median T_{MAX} was 3 (2-4) hours

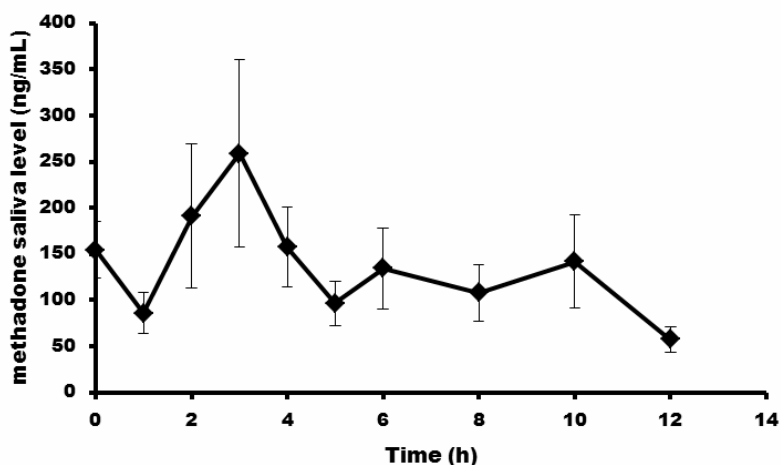


Figure 1. Mean saliva methadone concentration-time curve after administration of methadone dose with standard error in 8 patients.

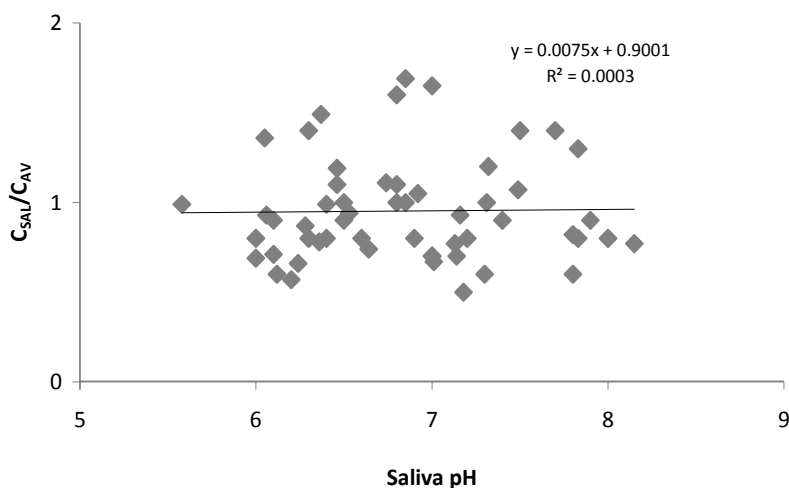


Figure 2. Relationship between C_{SAL}/C_{AV} and saliva pHs. The solid line represents the line of regression.

which is in accordance with previously published literature [16, 18]. Two secondary peaks were observed at 6 and 10 hours post-dose (two hours after food intakes).

Not all saliva pHs could be measured due to saliva sampling size. As can be observed in figure 2, no correlation between saliva pHs and C_{SAL}/C_{AV} was observed. Due to the pH gradient between plasma and saliva and because of the properties of methadone (weak base with a pKa of 8.3), a higher saliva methadone concentration with a lower saliva pH must be expected. However, our findings showed

that the secondary peaks observed could not be attributed to saliva pH changes occurred at those peak times. This fact is in accordance with Shiran *et al.* [15], who found a significant but weak correlation between saliva pH and methadone saliva concentration ($R^2 = 0.27$).

A plausible explanation for the appearance of these peaks is that methadone may be secreted into the gastric juice to a greater extent once a meal was taken, and subsequently reabsorbed from the gastrointestinal tract. Such secretions could be attributed to both the pH gradient between plasma (pH 7.4) and the gastric

juice (pH 1.2), and the increased blood flow rate and gastric fraction of the cardiac output that take place after food intake. This phenomenon of secretion was reported by several authors who measured methadone concentrations in gastric juice via a nasogastric tube and found a higher methadone concentration in this fluid in comparison with the respective blood levels [31]. Salivary methadone concentrations were also measured by these authors. Their findings revealed that salivary methadone concentrations were 10 times more than those recorded in blood. Due to the favorable pH-related transportation that methadone has from blood to saliva, and due to the closer relation between saliva and arterial drug concentration, each entry or reentry of methadone could be enhanced by drug monitoring in saliva.

Several factors have to be taken into account in these patients. Methadone itself delays gastric emptying and gastric motility. Some patients were also receiving tramadol or morphine; both these drugs can potentiate the delay in the gastrointestinal transit. Moreover, under the influence of omeprazole it is evident that the gastric secretion of methadone could be diminished due to an increase in gastric pH. This could result in the reduction or elimination of the secondary peaks.

Amitriptyline taken by some patients can also influence gastric emptying and acid secretion into the stomach due to its anticholinergic properties [33]. This could lead to a considerable delay in the appearance of the peaks.

Apart from the aforementioned effect, the pylorus constitutes a flow resistance from the stomach into the duodenum and vice versa. Many factors affect the pyloric tone and flow resistance. Food intake is one of them and it contributes to the interruption of the passage to the intestine, slowing the gastric emptying. The stomach would press mixed meals against a tight pyloric orifice in order to complete digestion. Hence, taking into consideration all these factors, the abrupt fall after food intake is due to pyloric closure, and the first significant increase in methadone salivary levels observed two hours after lunch intake (6 hours post-dose) could be because of pyloric re-opening and a delayed absorption of methadone dose in the duodenum and not entirely to drug reabsorption.

However, the second increase in salivary levels 10 hours post-dose is unlikely to be due to remaining dose. In this case, a secretion of methadone into the stomach, stimulated by the acid secretion after meal intakes, together with an increased blood flow to the stomach during digestion may be occurring. Once at the intestine, the drug could re-enter generating the peak.

Perhaps more or enhanced drug re-entries could have been operating but co-medication itself (inhibitors of acid secretion) did not enable us to observe them.

Methadone recycling can have a significant impact on pharmacokinetics not only by increasing drug elimination half-life, but also by affecting drug arteries/venous plasma ratio leading to increased arterial drug concentration during the reabsorption process. For a lipophilic molecule such as methadone with rapid distribution from blood to tissues, the result would be an increase in the tissue to plasma ratio, which explains the methadone toxicity in certain tissues and the lack of correlation found between adverse effects and methadone venous concentration [16].

The knowledge on methadone gastric secretion could also have a practical significance in the clinical setting in case of methadone intoxication. The administration of activated charcoal could interrupt methadone re-entries leading to a more rapid drug elimination rate and thus a reduction in methadone exposure.

CONCLUSION

Methadone was found to be subject to recirculation, probably via gastric secretion and intestinal reabsorption. The finding of this study can be extremely valuable to determine the importance of blood-gastrointestinal cycling in the disposition of basic drugs. Saliva proved to be a more useful tool than plasma to magnify this phenomenon not only because of its lower pH, but also because salivary drug concentrations are more related to arterial plasma concentrations.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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