PAIN® 154 (2013) 2794–2800

PAIN®

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Intradialytic clearance of opioids: Methadone versus hydromorphone

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

ARTICLE INFO

Article history:
Received 22 April 2013
Received in revised form 14 August 2013
Accepted 15 August 2013

Keywords:
Chronic pain
Dialysis
Hydromorphone
Methadone
Pharmacokinetics

ABSTRACT

Opioids are commonly prescribed to patients with chronic pain associated with end-stage renal disease requiring hemodialysis. The stability of opioid analgesia during dialysis may vary among different opioids. No studies to date have corroborated this clinical observation by directly comparing plasma concentrations of different opioids during dialysis. We compared changes in peridialysis plasma concentrations of 2 pharmacokinetically distinct opioids, methadone and hydromorphone (HM). Fourteen dialysis patients with chronic pain received either methadone or HM for at least 2 weeks before beginning the study. Blood samples were obtained immediately before, during, and after hemodialysis in 2 separate dialysis sessions, 1 week apart, and were analyzed for opioid concentrations. Methadone plasma concentrations were more stable during hemodialysis compared to HM: the mean percent change of methadone plasma levels was 14.9% ± 8.2% (±SD) compared with 55.1% ± 8.1% in the HM treatment group, a difference of 40.2% (95% confidence interval 17.14 to 63.14). The mean plasma clearance of methadone was 19.9 ± 8.5 mL/min (±SD) compared with 105.7 ± 8.3 mL/min for HM, a difference of 85.7 mL/min (95% confidence interval 61.9 to 109.1). There were no differences between the 2 opioid groups in pain scores, side effect profile, and quality of life. Methadone therapy was not associated with an increased rate of adverse events. If confirmed by larger clinical studies, methadone could be considered as one of the opioids of choice in dialysis patients.

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1. Introduction

End-stage renal disease is defined as the deterioration in renal function to the point where dialysis or transplantation is required for maintenance of life [4]. In the last decade, the number of Canadians living with end-stage renal disease has risen by 57%, half of whom require chronic dialysis treatment [9,44]. More than 30% of patients undergoing dialysis also suffer from chronic pain [17]. Pharmacological treatment, including both nonopioid and opioid analgesic medications, is the mainstay therapy in most patients [10].

Most available opioids are not ideal for use in patients undergoing chronic dialysis: morphine, meperidine, dextropropoxyphene, codeine, and oxycodone each show unpredictable levels of analgesia, accumulation of toxic metabolites, significant adverse effects, or extensive removal of both parent compounds and active metabolites by the dialysis filter [1,3,11,24,25,27,34]. Although probably safer, fentanyl could be directly adsorbed onto specific dialysis filters, resulting in reduced plasma levels [11,27]. Similarly, hydromorphone (HM) is probably safe in patients undergoing hemodialysis, although its principal metabolite (hydromorphone-3-glucuronide) could accumulate between dialysis sessions [10,39] and may result in hyperalgesia, cognitive impairment, myoclonus, ataxia, and tonic-clonic convulsions [2,31,46,49]. Equally important is the fact that HM is effectively dialyzed due to its low volume of distribution (l.22 L/kg) and serum protein binding (19%), high water solubility, and low molecular weight [35,45,47]. Consequently, postdialysis plasma concentrations of HM have been shown to decrease by 60% compared with predialysis values [14]. Patients treated with HM could therefore be at higher risk for increased levels of pain and opioid withdrawal symptoms after dialysis.

In contrast, methadone has several properties that could make it superior to most other opioids in dialysis patients, including high oral bioavailability (>80%), lipophilicity, volume of distribution (4.1 to 6.7 L/kg), and protein binding capacity (60% to 90%) [11,21,23].

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http://dx.doi.org/10.1016/j.pain.2013.08.015

In addition, in anuric individuals, methadone is exclusively eliminated via the fecal route [30]. These characteristics would suggest reduced removal by dialysis, reduced fluctuations in plasma concentrations, and more stable analgesia. To date, however, there have been only 2 case reports, each describing a single patient in whom methadone was found to be poorly removed from the plasma during hemodialysis [18,28]. Other case reports showed that methadone is safe in renal insufficiency and that supplemental methadone doses are not required after dialysis [11,18,22,28,30]. At the Montreal General Hospital, HM is the oral opioid of choice in dialysis patients with pain necessitating opioid therapy. Methadone is used more sporadically in specific pain conditions such as resistant neuropathic pain and when HM must be discontinued due to intolerance or serious side effects.

To our knowledge, no previous controlled trials have been conducted comparing plasma concentrations of methadone and HM in patients undergoing hemodialysis. Therefore, in the current study, the intradialytic changes in plasma concentrations of these 2 opioids were compared. We hypothesized that plasma concentrations of methadone would be less affected by dialysis compared with HM.

2. Methods

The study was approved by the Institutional Ethics Board and conducted in accordance with Good Clinical Practice and applicable Canadian regulatory requirements. Written informed consent was obtained from all participants. This was an open-label, prospective, 4-week trial conducted in a single dialysis unit at the Montreal General Hospital. The primary outcome of the study was the change in opioid plasma concentrations during dialysis in patients treated with methadone or HM.

2.1. Study participants

The study included outpatients, 18- to 85-year-old women and men with end-stage renal disease, requiring intermittent hemodialysis. Patients were allocated to either the methadone or HM groups based on the following criteria: (1) Opioid-naive patients and patients receiving opioids other than methadone or HM who reported average pain levels $\geqslant$4 of 10 (Numerical Pain Scale) in the week preceding enrolment were allocated to receive either methadone or HM. (2) Patients already treated with methadone or HM continued the same therapy during the study if reporting average pain levels <4 of 10 with no major side effects or symptoms associated with opioid withdrawal during dialysis. Patients treated with methadone or HM were converted to the other study opioid if they reported average pain level $\geqslant$4 of 10 during the previous week or significant side effects were noted with the current opioid. Inclusion criteria were end-stage renal disease necessitating chronic hemodialysis and chronic pain necessitating opioid therapy. Exclusion criteria were opioid therapy via a nonoral route; prolonged QT_c (>470 ms in men and >450 ms in women); known allergies to methadone, HM, or acetaminophen; pregnancy; and regular use of benzodiazepines.

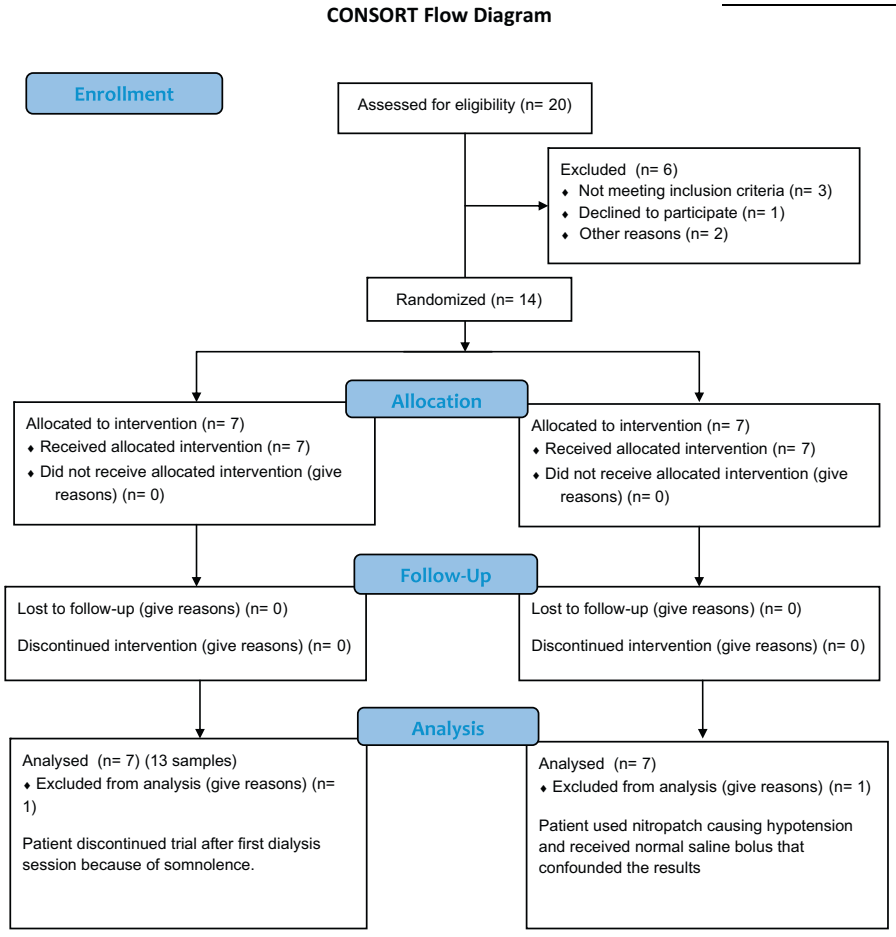

Table 1
Demographic data.

Patient no.	Age (years)	Sex	BMI	Pain etiology
1	70	F	20.2	Colon cancer
2	56	M	37.3	Chronic low back pain
3	66	M	21.1	Chronic low back pain
4	38	M	34	Chronic low back pain
5	84	F	19.5	Osteoarthritis
6	60	M	32.6	Peripheral vascular disease
7	70	M	29	Polyneuropathy
8	81	M	24.6	Chronic low back pain
9	41	F	46.8	SLE myopathy/neuropathy
10	71	F	26.6	Rhabdomyosarcoma
11	84	M	25.3	Chronic low back pain
12	65	M	30.3	Postthoracotomy pain
13	63	M	25.5	Osteoarthritis
14	55	M	25.8	Osteoarthritis

BMI = body mass index; F = female; M = male; SLE = systemic lupus erythematosus.

2.2. Opioid management

Methadone was supplied in a 0.1% liquid form (1 mg/1 mL) and HM was supplied in a 1-mg, 2-mg, or 4-mg pill form. Dose escalation was based on the individual patient's needs as determined by the treating team. In opioid-naive patients the initial dose of methadone was 1 mg twice daily and that of HM was 1 mg 3 times daily. The duration of the transition period to the study opioids in patients who were not opioid-naive depended on the type and dose of the prestudy opioid. Conversion to the study opioid was done under close supervision of the research team during scheduled visits to the dialysis clinic and by telephone consultations between dialysis sessions. For the purposes of this study, methadone and HM were considered equipotent and 6-fold more potent than morphine [7,31]. A ceiling dose of 30 mg/day was set for both methadone and HM.

2.3. Plasma opioid sampling and analysis

After enrolment, patients entered a 2-week period of opioid therapy optimization. The initial opioid blood sampling was done during the first scheduled dialysis session after these 2 weeks. To ensure that plasma opioid concentrations were measured during the elimination phase, patients taking HM and methadone were instructed to take the last dose approximately 1.5 and 6 hours before the beginning of dialysis, respectively. This schedule ensured that the time to maximum concentration (T_{max}) and maximum concentration (C_{max}) of both drugs were reached at the time of blood sampling, enabling accurate assessment of the elimination with minimal influence from absorption or redistribution [10,42,43].

Adhering to routine clinical procedures, patients were cannulated and connected to a single dialysate delivery system (Fresenius Medical Care North America, Waltham, MA) by a double needle access to an arteriovenous fistula or central catheter. The Fresenius hemodialysis unit uses a high-flux dialyser with a Diasafe Plus filter (Fresenius Medical Care North America, Waltham, MA). This system features a constant dialysate flow rate of approximately 500 mL/min, allowing a rate of blood flow entering the dialyser of approximately 250 to 400 mL/min and an ultrafiltration rate not exceeding 1500 mL/hour. The ultrafiltration rate of all study patients was determined at the beginning of each dialysis session and remained unchanged throughout the entire treatment session. Patients did not receive additional or breakthrough doses of opioids during dialysis. If needed, patients received acetaminophen 325 to 650 mg as a rescue medication.

Blood samples were obtained during 2 different dialysis sessions 1 week apart for measurement of opioid concentrations. Four blood samples, 3 venous and 1 arterial, were collected in each session shortly before dialysis started (venous), at mid-dialysis, approximately 2 hours after commencement (venous and arterial), and immediately after dialysis (venous). To accurately obtain a blood sample, the nurse turned off the ultrafiltration, slowed the blood pump to 100 mL/min for 10 seconds, and then stopped the pump. Five to 10 mL of blood were placed in Ethylenediaminetetraacetic acid (EDTA) tube, mixed gently, and centrifuged at 3000 rpm for 10 minutes at 4°C. After 10 minutes, the plasma was transferred to plastic 2 × 3-mL sterile tubes (Symport #T310-3A) and then stored at −80°C until analysis. Quantification of methadone and HM concentrations was accomplished by using liquid chromatography tandem mass spectrometry (Appendix 1). Coefficient of variation and accuracy for all standards were within the acceptable range, which was 20% of the lower limit of quantification and 15% of other standards and quality control samples. Linearity was achieved in the analytical ranges of 0.5 to 300 ng/mL and 0.2 to 20 ng/mL for methadone and HM, respectively. These values were chosen based on the limited existing pharmacokinetic data of the 2 tested opioids [10,18,22]. For all calculations, the measured opioid concentrations of an individual time point of the first and second dialysis sessions were combined and averaged. The intradialytic extraction ratio of plasma opioids was measured by simultaneously sampling arterial (inflow) and venous (outflow) plasma opioid concentration and then dividing the difference by the arterial concentration (Appendix 2) [12,42]. This method was selected because of its simplicity and reduced number of blood samples required, compared with constructing a full pharmacokinetic profile in a known anemic and fragile patient population. Because the ultrafiltration rate during the entire dialysis session was maintained constant, a single point estimate of extraction could be extrapolated to the entire dialysis session. Point estimation of opioid dialytic clearance was then done by multiplying the extraction ratio by blood flow.

2.4. Secondary outcomes

Pain intensity levels were assessed using a 100-mm visual analogue scale (VAS; 0: no pain; 100: worst pain ever). This is a well-validated tool both in English and in French [38]. VAS score was obtained immediately before the dialysis session, when patients marked their current pain level, and immediately after dialysis before disconnecting the patient from the dialysis machine. Opioid-associated side effects were recorded using the Edmonton Symptom Assessment Scale before and at the end of each dialysis session [5]. This questionnaire consists of nine 100-mm VAS assessing adverse symptoms including activity, nausea, depression, anxiety, drowsiness, appetite, shortness of breath, and general well-being. Quality of life was determined using the Short Form Health Survey SF-12 [13,48]. This multipurpose 12-question health survey assesses 8 aspects of health status using a 4-week recall period. Patients completed the form at the beginning of the study and 4 weeks later when it ended.

2.5. Statistical analysis

Sample size calculation was based on the primary study outcome, ie, the peridialysis percent change in plasma opioid concentrations. Calculation was done assuming that the average postdialysis HM plasma concentration will be 40% of its predialysis concentration (a 60% change) and that the peridialysis change in plasma methadone concentrations will be at least 50% lower compared to HM (ie, the methadone group will change at most from 100% to 70%, a 30% change) [14]. Assuming a standard deviation of 20% in each group and 95% confidence interval [CI], 7 subjects

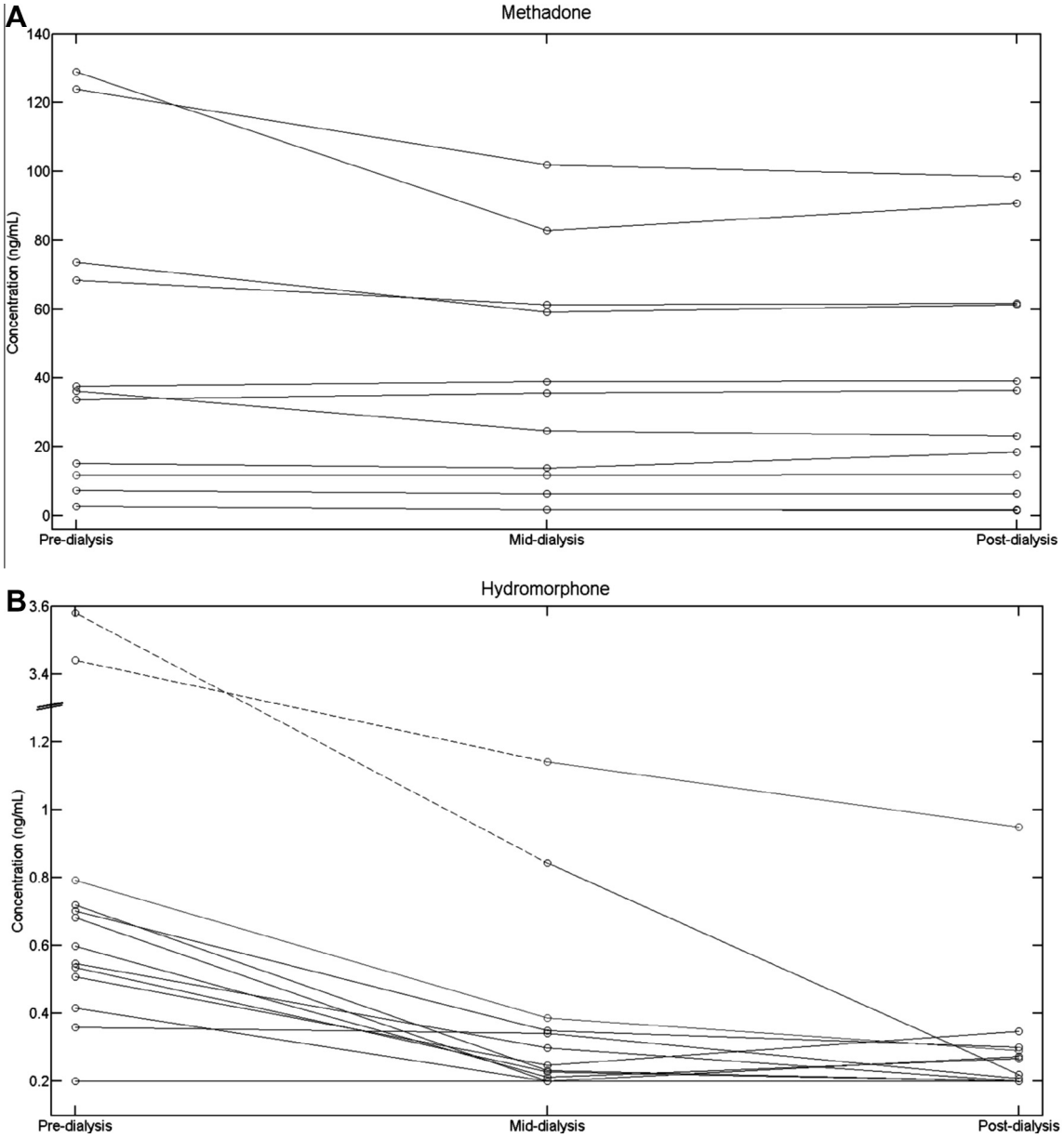

Fig. 1. Peridialysis change in methadone and hydromorphone plasma concentrations. (A) Methadone. (B) Hydromorphone. Blood and dialysate flow rates and ultrafiltration rate were similar among all patients.

Table 2
Mean changes ± SD in opioid pharmacokinetics during dialysis.

	Hydromorphone	Methadone
Concentration change (%)	55.1 ± 8.1	14.9 ± 8.2
Extraction (%)	40.3 ± 3.8	4.8 ± 3.9
Clearance (mL/min)	105.7 ± 8.3	19.9 ± 8.5

per group were needed to fulfill these criteria. Descriptive statistics were compiled for each variable of interest (age, body mass index [BMI], gender, and pain diagnosis) using means and standard deviations for continuous outcomes, and proportions for dichotomous outcomes, as appropriate. Statistics were compiled for both groups separately, and overall. Between-group comparisons of the main outcomes were based on a Bayesian hierarchical model to account for the repeated-measures structure of the data and to adjust for imbalances owing to potential missing data. At the first level of this hierarchical model, the outcome of each individual, at each time point, followed a linear regression model with an individual specific intercept and regression coefficients for drug group (HM vs methadone) and BMI. BMI was considered a possible confounding variable because it was the only unevenly distributed variable between the treatment groups. At the second level of the hierarchy, individual subject intercepts were assumed to follow a normal distribution. The mean of this density represents the average value across patients, adjusted for BMI and drug group, wherea the variance represents the between-subject variability. Noninformative prior densities were used across all unknown parameter values, allowing the data to drive the final inferences.

3. Results

Patient demographics and type of pain are summarized in Table 1. Of the 20 patients that were considered as candidates for the study, 2 refused to participate and 4 did not fulfill the inclusion/exclusion

criteria. In total, 14 patients with an average age of 64.6 years (range 38 to 84 years) were enrolled in the study, 7 patients per opioid group. Six of the 7 patients treated with methadone were switched from hydromorphone because their pain was not adequately controlled, and 1 patient continued his current methadone therapy. In the hydromorphone group, 4 of 7 patients were already receiving it and 3 were opioid-naïve before the study. One patient who received methadone was excluded from the study after the first hemodialysis session due to drowsiness. Because this was discovered only before the second blood sampling session, the first set of samples was included in the study. Although the patient did not report other side effects, it was decided for safety reasons that methadone administration to this patient be discontinued. Blood samples of another methadone-treated patient that were collected during the second dialysis session were not included in the final analysis because of an episode of hypotension during dialysis, requiring treatment with a 1-litre bolus of normal saline. It was determined that the hypotensive event was due to the vasodilating effects of an overlooked high nitroglycerin transdermal patch, resulting in dialysis-induced hypovolemia.

3.1. Opioid measurement

The average last dose of HM and methadone taken before dialysis was 2.3 ± 2.1 mg and 2.6 ± 1.9 mg (±SD), respectively. Plasma concentrations of both opioids declined during dialysis, with HM concentrations more affected than methadone (Fig. 1, Table 2). The mean percent change of methadone plasma concentrations was 14.9%, compared with 55.1% in the HM treatment group, corresponding to a difference of 40.2% between the 2 opioid groups (95% CI 17.14 to 63.14). The mean plasma clearance of methadone was 19.9 ± 8.5 mL/min compared with 105.7 ± 8.3 mL/min for HM (±SD; Fig. 2). The mean difference between the opioid clearance levels during dialysis was 85.7 mL/min (95% CI 61.9 to 109.1). The extraction percent ratio of methadone was almost 10-fold lower compared to HM: 4.8% vs 40.3%, respectively. The difference in the mean extraction ratio of the 2 opioids was 35.5% (95% CI 24.5 to 46.2).

3.2. Secondary outcomes

Methadone mean predialysis VAS score was 20.1 ± 5.0 (±SD), and it changed to 26.4 ± 32.5 after it. Hydromorphone predialysis VAS score was 34.9 ± 32.5, and it changed to 46.3 ± 63.3 after it. The mean postdialysis VAS scores of patients receiving methadone and HM increased by 6.4 ± 4.4 mm and 11.4 ± 4.3 mm (±SD), respectively. The mean difference was 4.9 mm (95% CI −9.0 to 18.1; inconclusive owing to wide confidence intervals). The mean difference in the Edmonton Symptom Assessment Scale score was 1.1 (95% CI −11.4 to 14.7; inconclusive owing to wide confidence intervals). Similarly, the Mental Health composite score results of the Quality of Life scale were not different between the 2 groups (data not shown), although the Physical Health Composite scale scores showed a trend toward improvement in methadone users by 22.8% (95% CI −4.3 to 51.3).

4. Discussion

Few studies to date have examined the pharmacological implications of renal impairment, specifically dialysis therapy, on opioid dosing requirements and potential dose adjustments [11]. No previous trials have comparatively evaluated the magnitude of change in opioid plasma concentrations during dialysis. The major finding of this study was that methadone plasma concentrations remained significantly more stable during hemodialysis compared to HM: mean methadone concentrations declined by 14.9%, compared to a 55.1% decline of HM concentrations. In accordance with this finding, the peridialysis methadone clearance and extraction from the plasma were 5- and 10-fold lower than HM, respectively. The different kinetic profiles of these 2 opioids during dialysis is not surprising considering their different physicochemical properties and the results of previous case reports [14,18,28]. This difference could probably explain our anecdotal observations in HM, but not methadone-treated patients developing peridialysis symptoms compatible with acute opioid withdrawal (unpublished data). Evidently, compounds such as methadone with a high volume of distribution, increased lipophilicity, and tissue binding are less available for clearance from the plasma by dialysis [15,21,36]. The effectiveness of dialysis in drug elimination has been traditionally determined by the differences in predialysis and postdialysis plasma concentrations [36]. However, declining plasma concentrations during dialysis could also be explained by other nonrelated mechanisms, especially if a medication has significant alternative routes of elimination (eg, via the liver) [11]. By assessing differences in plasma concentrations at the start and end of hemodialysis, along with determination of a midpoint extraction ratio, we were able to attribute changes in plasma concentrations to the hemodialysis procedure itself.

Although primarily a kinetic study, our results nevertheless merit further clinical discussion because they suggest a possible advantage of methadone over HM in dialysis patients. Prescribing methadone to this high-risk patient group could be regarded as controversial considering the heated debate surrounding opioid use in patients with noncancer pain in general, and the specific role of methadone in this patient population. In addition to its primary use in opioid maintenance programs, methadone has been traditionally prescribed as an analgesic medication in cancer and palliative-care patients. Its use in patients with noncancer pain has, however, increased significantly in the last decade and has probably been associated with an increased mortality rate, alerting both health authorities and providers to its potential hazards [29]. It should be remembered, though, that the increased mortality of patients treated with methadone may be attributed to either medical ignorance and/or the concomitant use of other potent centrally acting medications such as benzodiazepines, other opioids, antidepressants, and alcohol [6]. Indeed, its safe use in children and

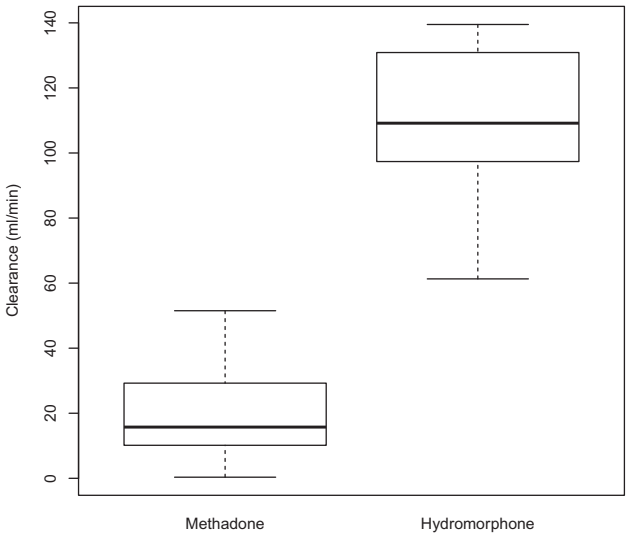

Fig. 2. Clearance (mL/min) estimates during hemodialysis. Each box plot analysis demonstrates the minimum and maximum values (whiskers), median clearance (thick black line), and middle 50% of the data sample (within the box itself).

adults with acute and chronic noncancer pain has been previously documented [19,20,26,37,40,41]. Furthermore, methadone has been advocated as the possible opioid of choice in patients with severe liver and kidney disease [8,28,32,33]. In the current study, methadone users showed a tendency toward improvement in all secondary clinical measurements compared with patients receiving HM. Together with previous clinical data and the kinetic findings of the current study, the results suggest that methadone is a viable therapeutic alternative to HM in patients undergoing dialysis. Drawing definite clinical conclusions is, however, premature; the current study was primarily designed as a kinetic and not a clinical study, and the number of required participants for this study was therefore calculated solely based on kinetic considerations. Consequently, the relatively small number of patients resulted in wide confidence intervals in all clinical measures, thus reducing our ability to draw definite clinical conclusions.

This study has a few potential limitations. Firstly, we did not generate a full pharmacokinetic model, which would necessitate taking a relatively large number of blood samples. This is not as difficult with the short-acting HM, whose time to maximum concentration (T_{max}) is only 30 minutes to 1 hour, making it easier to correctly capture its maximum concentration (C_{max}) period. Methadone, however, has a longer half-life with a variable T_{max} (1 to 6 hours), making it difficult to determine its C_{max} [16]. Therefore, significantly more blood samples would need to be taken from methadone-treated patients. We considered that obtaining so much blood from this frail and anemic population was potentially dangerous and even unethical. Secondly, no real randomization was done in selecting patients for the 2 study groups. This could potentially create a selection bias with regard to the secondary outcomes of this study, ie, its clinical measures. However, opioid plasma concentrations, being the primary outcome of this study, could not have been affected by the mode of randomization. In addition, we measured the plasma concentrations of only the parent opioid, but not its metabolites. Although metabolite concentrations could be clinically relevant during dialysis, especially for HM, whose metabolites could accumulate and become toxic, they bear no direct relevance to the main study outcome. Finally, patients recruited for this study consumed relatively low doses of both HM and methadone—the maximal daily doses of HM and methadone were 20 mg and 17 mg, respectively. Although there is no evidence suggesting that the peridialysis kinetics of HM or methadone could be different when used at higher doses, extrapolating the results of this study to a clinical scenario of high opioid consumption should be done cautiously.

We conclude that peridialysis fluctuations in plasma concentrations of methadone are smaller compared with HM. The stability of methadone during dialysis is probably explained by its higher lipophilicity, greater volume of distribution, and enhanced protein-binding capacity. Combined with the limited available clinical data, these results suggest that methadone may be a useful alternative opioid in patients with chronic pain and end-stage renal disease requiring hemodialysis. Larger clinical studies are necessary to determine whether methadone may in fact be the most suitable opioid in dialysis patients suffering from chronic pain. Given that the majority of patients with end-stage renal disease present with other medical comorbidities requiring diverse pharmacotherapy, similar kinetic studies should be considered for optimizing further medication dosages, improving clinical efficacy, and avoiding unnecessary adverse effects.

Acknowledgements

The authors are grateful to the Louise and Alan Edwards Foundation for their generous support of both this research and of Dr. Hili Giladi; to the nursing team of the dialysis unit at the Montreal General Hospital for their support and superb patient care; to Samir Nassr and Eliapharma Services Inc. (Laval, Quebec) for their technical expertise and advice; and to Dr. Sameena Iqbal for critically reviewing the manuscript. Dr. Shir received consulting fees from McKesson Canada Corporation. No conflict of interest is declared by the other authors.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pain.2013.08.015.

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