Pain management in chronic kidney disease: The pharmacokinetics and pharmacodynamics of hydromorphone and hydromorphone-3-glucuronide in hemodialysis patients

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ABSTRACT

Objective: To describe the pharmacokinetics of hydromorphone (HM) and its primary metabolite hydromorphone-3-glucuronide (H3G) both on and off dialysis in relation to the pharmacodynamic measurements of pain.

Design: Prospective, open-label, observational study.

Setting: Canadian, university-based renal program.

Participants: Twelve anuric bimodialysis patients with chronic pain, established on immediate-release HM.

Main Outcome Measures: HM and H3G plasma concentrations were measured during and between hemodialysis treatments using a reverse-phase high-performance liquid chromatography assay with liquid chromatography/mass spectrometer/mass spectrometer detection. The McGill Pain Questionnaire (MPQ) and a Visual Analogue Scale (VAS) were used to measure pain. Noncompartmental analyses were conducted. Adverse effects were recorded.

Results: HM did not substantially accumulate (accumulation factor R = 2.7 (1.6)), most likely due to the rapid conversion to H3G. Conversely, H3G accumulated between dialysis treatments (R = 12.5 (12.1)) but appeared to be effectively removed during hemodialysis (1.8 (0.7), p = 0.03). HM resulted in >65 percent reduction in pain over dosing intervals. Mean MPQ pain scores decreased from 39.8 (18.2) to 12.3 (16.2) on dialysis and from 35.0 (18.5) to 15.5 (13.6) between dialysis treatments. Mean VAS pain scores decreased from 7.5 (2.5) to 3.0 (1.5) on dialysis and from 5.9 (3.2) to 4.4 (1.6) between dialysis treatments. No clinically significant opioid toxicity was observed. The accumulation of H3G between hemodialysis treatments was associated with greater sensory-type pain (r = 0.76, p < 0.0001) and reduced duration of analgesia.

Conclusions: HM may be a safe and effective opioid for use in selected hemodialysis patients.

Key words: kidney failure, dialysis, opioids, hydromorphone, hydromorphone-3-glucuronide, pharmacokinetics, pharmacodynamics, chronic pain

INTRODUCTION

Fifty to 63 percent of dialysis patients report a problem with chronic pain; 42-55 percent of these patients rate their pain as severe.1,2 This is not surprising given that the average age of patients starting dialysis is 62.7 years, and the majority have significant comorbidity.3,4 While dialysis sustains life, underlying systemic diseases such as diabetes mellitus and vascular disease continue to progress leading to painful syndromes such as ischemic limbs and peripheral neuropathies. In addition, there are painful syndromes unique to chronic kidney disease (CKD) such as calcific uremic arteriolopathy and renal osteodystrophy.

Undertreatment of pain in CKD is in large part due to the reluctance to use opioids as CKD patients are more likely to experience opioid toxicity. The World Health Organization has published guidelines that are effective for the management of malignant and nonmalignant pain.5,6 These rely on the step wise approach to nonopioid and opioid analgesics. Management of pain in dialysis patients is not consistent with these guidelines: only 14.9-18.0 percent of dialysis patients use opioids and only 9-7 percent of dialysis patients with pain receive strong opioids.1,8 In fact, up to 75 percent of dialysis patients with moderate to severe chronic pain are not prescribed any analgesics.8 No opioids have been systematically studied in CKD, but clinical experience suggests that hydromorphone (HM) may be relatively well tolerated in patients with CKD.9 However, until the pharmacokinetics and pharmacodynamics of opioids in CKD are better understood, their use will likely remain limited in these patients. The purpose of this study was to describe the pharmacokinetics of HM and its primary metabolite hydromorphone-3-glucuronide (H3G) both on and off dialysis in relation to the pharmacodynamic measurements of pain.
METHODS

Patient selection

This is a prospective, open-label, observational study of anuric hemodialysis patients at the University of Alberta, Canada, conducted between July 2004 and January 2006. Eligible patients were consecutively invited to participate in the study. Eligibility criteria included patients who were established on immediate-release HM for chronic pain (defined as greater than 3 months of duration); on chronic HD ≥ 3 months; and older than 18 years of age. HM doses were established by their attending physician. Ethics approval was obtained from the University of Alberta Health Research Ethics Board, and written informed consent was obtained from all participants.

Outcome measures

Data were collected following HM administration on a nondialysis day during a 2-day break and again following HM administration at the beginning of a dialysis treatment. Venous blood samples and pain scores were collected at the time of HM administration (time 0) and 0.5, 1, 2, 2.5, 3, 3.5, 4 hours after administration. During the dialysis study, time 0 coincided with the start of hemodialysis. All participants received 4-hour hemodialysis treatments three times a week using an F8 Fresenius dialysis membrane.

Bioanalysis. Concentrations of HM and H3G were measured using a reverse-phase high-performance liquid chromatography (HPLC) assay with liquid chromatography/mass spectrometer/mass spectrometer (LC/MS/MS) detection. The assay was a modification of the one by Chen et al. and the protein precipitation extraction was a modification of the method published by Somers et al. Briefly, thawed frozen plasma (100 μL) from the study participants was pipetted into glass tubes. To this, 400 μL of HPLC grade methanol containing 25 mg/mL morphine internal standard was added. Samples were capped, vortexed for 15 seconds, then allowed to sit for 10 minutes. After this, samples were revorketed for 15 seconds, and then centrifuged at 3,300 rpm for 10 minutes. The supernatant was transferred to autosampler vials that were capped and stored at room temperature prior to analysis. An Agilent 1100 series LC was equipped with a quaternary pump, a solvent degasser, an autosampler, and a temperature-controlled column compartment. The column temperature was controlled at 25°C, and an injection volume of 5 μL was used. Compounds of interest were separated using an acetonitrile (ACN)/water (+10 mM ammonium acetate) solvent system on a Phenomenex Luna 3u Silica (2) column (100Å, 2.0 × 50 mm²). A silica presaturator (Upchurch Perisorb A, 2 × 20 mm²) was used to prevent column degradation. The LC program was 0.5 mL/min isocratic at 80 percent ACN for 4 min, then stepped to 50 percent ACN for 3 minutes, then regenerated for 3 minutes at 80 percent ACN prior to the next injection. Tandem MS detection was done using an ABI-Sciex API3,000, equipped with a TurboSpray interface. A turbogas temperature of 550°C and an ionspray voltage of +1,500 V were found to provide optimal results. Multiple reactions monitoring mode was used to monitor for parent/fragment ions for morphine (261.1/165.0), HM (286.1/185.0), and H3G (462.1/286.1). Detection limits were 0.3 ng/mL for HM and 1 ng/mL for H3G. PK analyses were also initially performed on the metabolite hydro- morphone-6-glucuronide (H6G), but this metabolite was present in trace amounts only and therefore these analyses were discontinued.

Pain measures. The McGill Pain Questionnaire (MPQ) and a 0-10 Visual Analogue Scale (VAS) were used to measure pain. These are well-validated pain measurement tools that have been used extensively in a variety of acute and chronic pain studies in different patient populations across cultural and linguistic backgrounds in North America and Europe. Both the MPQ and the VAS were collected with each blood sample. All adverse effects including constipation, nausea, vomiting, dry mouth, gastroesophageal reflux symptoms, somnolence, restless legs, pruritus, symptomatic hypotensive episodes during dialysis, respiratory depression, and decreased level of consciousness were recorded. Blood pressures are routinely recorded during hemodialysis treatments. If a patient felt nauseated or lightheaded, blood pressure would be measured. For this study, hypotension was defined as a greater than 20 mmHg drop in systolic blood pressure and/or a 10 mmHg drop in diastolic blood pressure from their predialysis blood pressure.

Pharmacokinetic-pharmacodynamic analyses. Descriptive statistics were used to describe noncompartmental pharmacokinetic and pharmacodynamic parameters using WinNonlin Professional v 4.1 (Pharsight Software, CA). Primary pharmacokinetic parameters were as follows: maximum concentration (Cmax), time of maximum concentration (Tmax), terminal elimination rate (λz), half-life of terminal elimination (t1/2), area-under-the-curve (AUC), clearance after extravascular administration (CL/F), and the apparent volume of distribution after extravascular administration (Vd/F). Drug accumulation (R) for HM was calculated using the following formula: R = AUC / tmax. This same calculation was used as a surrogate for H3G accumulation. This is a surrogate only since H3G was not directly administered but rather was formed from the parent drug HM.

Pharmacodynamic parameters were time to maximum analgesic effect (TEmax), maximum analgesic effect (Emax), and percent time (of the 4-hour dosing interval) the VAS...
was below the baseline score as a measure of duration of analgesia. PK-PD relationships were explored graphically plotting drug concentration against pain scores. To normalize for differences in pain scores at baseline, percent change from baseline scores were used. Regression analysis was used to explore the relationship between drug/metabolite concentrations and pain scores using Pearson’s correlation (r). Data collected while on dialysis and between dialysis treatments were compared directly using t-tests or Wilcoxon Rank Sum where appropriate. A p < 0.05 was considered statistically significant.

Sample size. Opioid-pain studies in anesthesia and in cancer patients have demonstrated that pharmacokinetic variability is often less than pharmacodynamic variability, but individual patient pharmacodynamics are still reproducible. Holding the probability of a Type I error at \( \alpha = 0.05 \) using a two-tailed test, and the power \( 1-\beta \) at 80 percent, and assuming that the true change in the dependent variable (eg, pain score) is at least two standard deviations per one standard deviation change in the independent variable (eg, drug concentration), a total of six patients are required to complete each of these studies. To minimize the effect of higher interpatient variability in the pharmacokinetic data that may be present in dialysis patients, 12 patients were recruited. Variability in pharmacokinetic data from other chronic pain studies such as cancer pain were used to calculate a variation inflation factors which demonstrated that eight data points per patient is optimal.

RESULTS

Twelve patients completed the study. Patient characteristics are summarized in Table 1. Mean (SD) HM dose was 5.2 (4.0) mg every 6.3 (2.8) hours. Patients had been on HM for a mean of 8.7 (9.8) months (range one to 27 months).

Pharmacokinetic results

The mean plasma concentrations of HM and H3G are depicted graphically in Figure 1a and 1b, respectively. Multiple peaks were observed for both HM and H3G, consistent with the characteristic sawtooth pattern indicative of enterohepatic circulation commonly observed with opioids. Corresponding noncompartmental pharmacokinetic parameters are summarized in Table 2. The \( t_{1/2} \) of HM was 3.2 (2.0) hours on hemodialysis and 5.9 (3.4) hours between dialysis treatments. Based on the accumulation factors (R) 1.8 and 2.7 during and between dialysis, respectively, there was no significant drug accumulation (p = 0.05). While on dialysis, the \( t_{1/2} \) of H3G was not prolonged (3.3 (2.1) hours), and the accumulation factor (R) was low at 1.8 (0.7). However, between dialysis treatments, the \( t_{1/2} \) of H3G was substantially prolonged (33.3 (31.8) hours, p = 0.02), with an accumulation factor of 12.5 (12.1), p = 0.02.

Pharmacodynamic results

The mean baseline MPQ and VAS pain scores were 39.8 (18.2) and 7.5 (2.5), respectively, prior to dialysis and decreased to 12.3 (16.2) and 3.0 (1.5) during the dosing interval while on dialysis. The second dosing interval to be studied was between dialysis treatments: the mean baseline MPQ and VAS pain scores between dialysis treatments were 35.0 (18.5) and 5.9 (3.2), respectively, and decreased to 15.5 (13.6) and 4.4 (1.6) over the dosing interval. The percent change in total MPQ and VAS scores following HM administration are superimposed graphically on both the HM and H3G concentration time curves in Figure 1. A negative percent change in pain score indicates analgesia. These data demonstrate an association between HM drug concentration and analgesia with a sawtooth pattern similar to that seen for the pharmacokinetic data.
Table 3. Noncompartmental pharmacodynamics: Analgesia as percent change of visual analogue scale and McGill pain questionnaire scores from baseline

<table>
<thead>
<tr>
<th>Phase</th>
<th>( \text{TE}_{\text{max}} ), mean (range), hours</th>
<th>( \text{E}_{\text{max}} ), percent (SD)</th>
<th>Percent time VAS below baseline score, percent (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysis</td>
<td>1.8 (0.5-4.0)</td>
<td>68.8 (37.5)</td>
<td>66.3 (40.1)</td>
</tr>
<tr>
<td>Between dialysis</td>
<td>3.0 (0.5-4.0)</td>
<td>65.5 (43.3)</td>
<td>40.2 (31.8)</td>
</tr>
</tbody>
</table>

\( \text{TE}_{\text{max}} \) = Time to maximum percent reduction in VAS score; \( \text{E}_{\text{max}} \) = Maximum percent reduction in VAS score; percent time VAS below baseline score = percent duration of analgesia over the 4-hour dosing interval; VAS: 0-10 Visual Analogue Scale.

\*t-test.

\dagger Wilcoxon Rank Sum.

Noncompartmental parameters are summarized in Table 3. Pain scores decreased from 65.5 percent to 68.8 percent following HM administration \( \text{E}_{\text{max}} \) regardless of whether HM was administered while on hemodialysis or between hemodialysis treatments. However, the median time to maximal analgesia \( \text{TE}_{\text{max}} \) was significantly shorter when patients were on dialysis compared with a nonhemodialysis day (1.8 hours vs 3.0 hours, \( p = 0.045 \)).

Figure 2 demonstrates the association between H3G concentration and the sensory MPQ subscale, a measure of

Table 2. Noncompartmental pharmacokinetics for hydromorphone and hydromorphone-3-glucuronide

<table>
<thead>
<tr>
<th>Phase</th>
<th>( t_{1/2} ), mean (SD) (hours)</th>
<th>( T_{\text{max}} ), range (hours)</th>
<th>( C_{\text{max}} ), mean (SD) (ng/mL)</th>
<th>AUC, mean (SD) (ng.h/mL)</th>
<th>R, mean (SD)</th>
<th>Vd/F, mean (SD) (L)</th>
<th>CL/F, mean (SD) (L/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydromorphone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis</td>
<td>3.2 (2.0)</td>
<td>1.0 (0.0-2.0)</td>
<td>11.8 (7.0)</td>
<td>41.6 (20.3)</td>
<td>1.8 (0.8)</td>
<td>709.9 (495.7)</td>
<td>163.9 (91.8)</td>
</tr>
<tr>
<td>Between dialysis</td>
<td>5.9 (3.4)</td>
<td>1.0 (0.5-2.5)</td>
<td>9.2 (6.0)</td>
<td>33.9 (27.3)</td>
<td>2.7 (1.6)</td>
<td>1847.6 (2068.3)</td>
<td>184.0 (83.9)</td>
</tr>
<tr>
<td>p value*</td>
<td>0.079</td>
<td>ns</td>
<td>0.33</td>
<td>0.34</td>
<td>0.05</td>
<td>0.09</td>
<td>0.57</td>
</tr>
<tr>
<td>Hydromorphone-3-Glucuronide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Dialysis</td>
<td>3.3 (2.1)</td>
<td>0.25 (0.0-3.5)</td>
<td>1,572.7 (1,111.1)</td>
<td>3,243.9 (2,768.0)</td>
<td>1.8 (0.7)</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Between dialysis</td>
<td>33.3 (31.8)</td>
<td>1.0 (0.0-4.0)</td>
<td>1,260.0 (696.2)</td>
<td>4,229.9 (2,975.4)</td>
<td>12.5 (12.1)</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>p value*</td>
<td>0.02*</td>
<td>0.13\†</td>
<td>0.42*</td>
<td>0.41*</td>
<td>0.02*</td>
<td></td>
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\*t-test.

\† Wilcoxon Rank Sum.
data suggest that patients with renal failure are particularly susceptible to the toxic effects of morphine.\textsuperscript{15-19} Nausea, vomiting, myoclonus, seizures, sedation, and respiratory depression have been reported with morphine in patients suffering from renal failure.\textsuperscript{15-19} There are several hypotheses for this including increased enterohepatic circulation of morphine and accumulation of large quantities of the active metabolites including morphine-6-glucuronide (M\textsubscript{6G}),\textsuperscript{20} which is more potent than the parent compound.\textsuperscript{21-24} Because of these difficulties, morphine is contraindicated for the management of chronic pain in stage 4 and 5 CKD,\textsuperscript{25} and alternative strong opioids are recommended.

Clinical experience suggests that HM may be better tolerated in patients with advanced CKD.\textsuperscript{9} HM is a hydroxylated ketone of morphine with approximately five times the narcotic analgesic effect of morphine.\textsuperscript{26} The pharmacodynamics and pharmacokinetics of HM have been well studied in individuals with normal renal function and has recently been reviewed.\textsuperscript{26} HM produces significant and rapid pain relief following oral administration,\textsuperscript{27-29} and, in general, population has a similar side effect profile to morphine.\textsuperscript{30} However, despite having a chemical structure very similar to morphine, the minor structural differences impact metabolism. HM is extensively metabolized by the liver with approximately 62 percent of the oral dose eliminated on first pass.\textsuperscript{31} Unlike morphine, which has an analgesically active 6-glucuronide metabolite, H\textsubscript{6G} is present in trace amounts only.\textsuperscript{32} HM is metabolized principally to a 3-glucuronide, H\textsubscript{3G} in conjunction with very small amounts of other renally excreted, water-soluble metabolites and unconjugated HM.\textsuperscript{32} The plasma concentration of H\textsubscript{3G} at steady state after oral administration is approximately 25-30 fold greater than the plasma concentrations of the parent drug HM.\textsuperscript{33}

Our data suggest that the pharmacokinetics of the active parent HM are not substantially altered by CKD. The identical numerical values of HM total body clearance following oral administration (CL/F) during and between hemodialysis treatments supports the observation that dialysis does not have a significant role in the clearance of the parent HM. In addition, because AUC and $C_{\text{max}}$ in the multidose and dialysis phases are numerically very close, the rate and extent of HM absorption do not appear to be greatly altered by hemodialysis. Even though HM does not appear to be effectively removed by hemodialysis, it does not accumulate to any considerable extent. Presumably this is because it is metabolized rapidly by uridine diphosphate glucuronosyl transferase to H\textsubscript{3G}. The normal elimination half-life of HM in a healthy population has been reported to be 2.64 (0.88) hours.\textsuperscript{29} This is very similar to the elimination rate we observed during hemodialysis. The elimination half-life and accumulation factor were only slightly prolonged between dialysis treatments. Although a larger study may make

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{H3G concentration vs McGill pain questionnaire sensory scale: All study phases.}
\end{figure}

pH described as “tingling,” “itchy,” “sharp,” or “lancinating.” These words may be indicative of central nervous system excitation. The sensory MPQ scale was highly correlated with H3G concentration, both on dialysis and between dialysis runs ($r = 0.76$, $p < 0.001$), with higher H3G concentrations predicting higher pain scores. The sensory scale baseline score was at its highest immediately prior to dialysis, a time when H3G levels were also at their highest.

No episodes of central nervous system or respiratory depression were observed. All 12 patients had stable dialysis runs without symptomatic hypotensive episodes. Dry mouth, gastroesophageal reflux symptoms, nausea, and pruritus were reported in four, three, two, and four of the patients, respectively. While these symptoms can be caused or exacerbated by opioids, these are symptoms common to dialysis patients. All symptoms were reported as mild. With the exception of dry mouth, patients felt that symptom intensity had not changed since initiating opioid therapy, and that symptoms were not associated with opioid dosing. Five patients reported constipation. For four of these patients, the constipation started with the initiation of opioid therapy. All patients were adequately managed with bowel regimens.

**DISCUSSION**

A poor understanding of the pharmacokinetics and pharmacodynamics of opioids in kidney failure remains a substantial barrier to the effective management of chronic pain for dialysis patients. Opioids and their metabolites are excreted by the kidneys. Renal failure, therefore, has a substantial effect on the clearance of these drugs, with potentially important clinical consequences. This study is the first, to our knowledge, of combined pharmacokinetic and pharmacodynamic data of HM in CKD.

Most of the information about opioid use in CKD patients comes from experience with morphine. Clinical

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{H3G concentration vs McGill pain questionnaire sensory scale: All study phases.}
\end{figure}
these differences statistically significant, our data suggest that accumulation of HM in CKD between hemodialysis treatments is minimal. Hemodialysis did, however, impact the volume of distribution of HM. $V_{z}\over F$ was dramatically smaller during dialysis compared to between dialysis treatments suggesting that dialysis was more effective at removing fluid than removing HM. This could explain the slightly greater AUC observed during dialysis, with HM being slightly concentrated due to ultrafiltration.

The only published data of HM in CKD reported that hemodialysis reduced plasma levels of HM to 40 percent of predialysis levels in two patients after a single-dose study. However, the methodology was not outlined and the elimination half life was identical to that of H3G in our study, suggesting that they may have measured glucuronide metabolites and not the parent compound HM.

Unlike HM, the more polar and water soluble H3G is significantly altered by CKD and dialysis. The increased AUC, $t_{1/2}$, and $R$ for H3G between dialysis treatments demonstrated accumulation of the metabolite. This is consistent with the literature that has reported a plasma ratio of 100:1 (H3G:HM) in one patient with CKD (Cr 327 µmol/L) who had received HM 24 mg daily. However, in comparison, the significantly lower $t_{1/2}$ and accumulation factor during dialysis suggests H3G is effectively removed during hemodialysis.

The accumulation of H3G between hemodialysis treatments may have pharmacodynamic implications. H3G lacks analgesic activity: the modification of HM at the third position prevents binding to the $\mu$-opioid receptor. Animal studies, however, have demonstrated that H3G evokes a range of excitatory behaviors including myoclonus, ataxia, and tonic-clonic convulsions, and antagonize HM analgesia through a non-$\mu$-receptor mediated mechanism, potentially similar to those postulated for M3G. These animal studies are supported by clinical observations in the literature where HM administration to patients with CKD results in high levels of glucuronides and cognitive impairment, myoclonus, seizures, and allostynia. However, there are no controlled trials supporting an important neuroexcitatory action of H3G in a therapeutic context. Thus, clinically relevant neuroexcitatory effects of HM remain speculative. Although both neurotoxicity and antagonism of analgesia have been ascribed to M3G, recent clinical data do not support these effects. Clinical data from 103 cancer patients on oral morphine, only 10 of whom had abnormal renal function, found no association between M3G:M6G ratio and analgesia or toxicity, suggesting that in cancer patients with normal renal function, M3G is either devoid of significant toxicity or is of such low potency as to only be problematic at very high concentrations such as encountered with significant renal dysfunction.

Despite the lack of clinical evidence for a role on M3G in opioid toxicity, our data are suggestive for a role of H3G in antagonism of HM analgesia in patients with CKD. H3G, at the elevated concentrations seen in this study between dialysis treatments, were associated with decreased time to maximal analgesia. Therefore, the percent of the time below baseline pain score, which is indicative of the duration of analgesia, was greater during dialysis than between dialysis treatments (66.3 vs 40.2) although this only approached statistical significance ($p = 0.09$).

The elevated H3G concentrations in this study between dialysis treatments were also associated with increased sensations measured in the sensory scale of the MPQ by descriptive words such as tingling, itchy, sharp, and lancinating. Overall pain scores were also highest immediately prior to dialysis when H3G levels would be the greatest. The clearance of H3G during hemodialysis likely has an important role in enhancing analgesia and potentially minimizing the risk of HM toxicity. An important clinical implication of these findings is that while HM may be well tolerated in patients being dialyzed, it may not be as effective or as well tolerated in patients during the final days of life following withdrawal from dialysis or in patients with stage 5 CKD being managed conservatively without dialysis or yet to start dialysis. Alternatives such as methadone, fentanyl, or short-acting opioids such as alfentanil may be better choices in these situations. However, with careful monitoring, HM may be safely and effectively used in selected hemodialysis patients.

Although not assessed in this study, it is possible that anxiety and anticipatory pain associated with dialysis may play a role in the higher pain levels immediately prior to dialysis. It has been reported that 13.6 percent of dialysis patients that perceive themselves as having chronic pain attribute this pain to the recurrent symptoms associated with the dialysis procedure such as needling, cramping, and headaches.

Limitations

There are several limitations to this study. The timing of data collection on the nondialysis day varied slightly between patients likely leading to an increase in variability of the pharmacokinetic data. The sawtooth pattern observed for HM can introduce inaccuracies in the determination of elimination $t_{1/2}$ if there are not three data points clearly defined in the elimination phase. CL/F in this study is confounded by oral bioavailability and dialysate clearance, neither of which was formally assessed. Future studies would benefit from a formal assessment of oral bioavailability and dialytic clearance.

The accumulation factor calculated for H3G is a surrogate only since H3G was not administered directly, but rather was formed from the parent drug, HM.

While the sample size in this study is small, these data represent the largest pharmacokinetic sample size in
dialysis patients to date and this is the only study to our knowledge which correlates pharmacokinetic and pharmacodynamic data.

These patients received considerable analgesia with HM therapy without experiencing significant adverse effects. This study does not address the appropriateness or effectiveness of HM for chronic pain management in all hemodialysis patients. There are currently no published controlled trials studying the effectiveness of HM in chronic pain in CKD. Further research in this area is clearly necessary to elucidate the complexities of HM pharmacokinetic-pharmacodynamic relationships and the overall effectiveness of HM for management of chronic pain in patients with advanced CKD. However, these data will support the creation of treatment algorithms and management strategies using HM that can be systematically tested for effectiveness in future studies.

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ACKNOWLEDGMENTS

The authors gratefully acknowledge Dr Russell Handy for help with the bioanalysis and Medical Services Incorporated (MSI) for the funding of this study. This study was funded by a competitive grant from the MSI Foundation, Grant # 813.

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