# SHORT COMMUNICATION

# Renal failure and opioids

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**ABSTRACT**

The review literature on the metabolism of many commonly used opioids and the known activities of its metabolites is reviewed in this article. The impact of renal failure on these medicines' and their metabolites' pharmacokinetics is then discussed. Finally, a review is given of how renal dialysis affects opioid medications and their metabolites. Based on the analysis, it is advised that methadone and fentanyl/sufentanil appear to be safe to use, whereas morphine and codeine should be avoided in patients who are on dialysis or have renal failure. Hydromorphone or oxycodone should also be taken with caution and strict monitoring. The "safe" medications for renal failure are also the least dialyzable, it is noted.

**Key Words:** *Opioids; Metabolism; Renal failure; Renal dialysis; Peritoneal dialysis*

## INTRODUCTION

The pharmacokinetics of many medications are impacted by renal insufficiency, and opioids are no exception. Individual opioids are affected differently by renal failure, and for many opioids, one must take into account both the parent molecule of the drug and its metabolites. Other issues relating to the mechanics of the dialysis operation come into play if the renal failure patient is receiving dialysis. An overview of the literature on opioid metabolism is provided in this article, along with information on how renal failure and/or dialysis affect the clinical effects of both the parent drug and its metabolites. The terms opioids, kidney failure, dialysis, oxycodone, codeine, morphine, hydromorphone, fentanyl, and methadone were used in a database search. The rate of elimination of any drug is, in theory, proportional to the Glomerular Filtration Rate in the absence of tubular secretion or reabsorption (GFR). However, because opioids are weak organic bases, changes in urine pH can have an impact on tubular processing and the connection between renal elimination and GFR. The ability of such formulas to predict pharmacokinetic profiles for the majority of medications has not been established, however formulas for estimating GFR can be used to predict drug pharmacokinetics. However, some writers have suggested adjusting the opioid dosage based on the GFR, even if the methodology for calculating the dose reduction is not always clear. The GFR approximates the renal excretion of several medications. Elimination may be hampered if several drugs are fighting for the same renal route [1].

## RENAL FAILURE AND DRUG METABOLISM

### Morphine

The majority of research has been done on morphine. In people with normal renal function, it is metabolized in the liver to morphine-3-glucuronide (M3G) (55%), morphine-6-glucuronide (M6G) (10%), and normorphine (4%), all of which are eliminated through the kidneys along with around 10% of the parent molecule. Researchers discovered that the kidney is actively secreting substances because the renal clearance of morphine and M6G was greater than creatinine clearance. M6G is a Central Nervous System (CNS) depressant and an analgesic, however it is unclear how these effects would affect breathing. The analgesic action of M6G was validated in a recent review by Andersen et al., who also summarized the literature and highlighted that its potency has not yet been determined. The varied respiratory action of this metabolite may be brought on by the diminished binding of M6G at the mu-2 receptor, which is the primary mediator of respiratory depression. It has been noted that M6G, when it builds up in renal failure, mediates respiratory depression [2]. Morphine clearance in subjects with renal failure is

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not significantly different from clearance in subjects who are not renally compromised, although glucuronide metabolites are excreted renally and accumulate in patients with renal failure. Patients with impaired renal function have high serum levels of M6G, and although it crosses the blood-brain barrier slowly, once it enters the Central Nervous System (CNS), its effects may last for a long time. There may be two types of M6G: one that is folded and more lipophilic and found in tissues with low levels of water, and the other that is stretched and hydrophilic. Because of this, the CNS effects may last for a while after stopping morphine or dialyzing to remove the M6G as the M6G gradually re-equilibrates across the blood-brain barrier and back into the systemic circulation [3].

**Hydromorphone**

M3G has no analgesic effect and just a weak affinity for opioid receptors. When administered intra-cerebroventricularly, M3G has been demonstrated by some authors to counteract the analgesic effects of morphine and M6G, but other studies have found no effect at the spinal level or a lengthening of the analgesic effect. It has been demonstrated that M3G stimulates respiration, however it is unclear whether this is due to direct stimulation or antagonism of the actions of morphine and M6G. In addition to hyperesthesia and allodynia, it can excite behavioral responses in rodents like rats and mice. There is disagreement over whether an opioid antagonist like naloxone can stop the excitatory behavior. In addition to dihydromorphine (0.1%), dihydroisomorphine (1.0%), hydromorphone-3-glucuronide (36.8%), and trace amounts of norhydromorphone and nordihydroisomorphone, hydromorphone is metabolized in the liver. All metabolites and a little amount of free hydromorphone are eliminated through the kidneys. Although researchers have proposed additional conversion of the dihydro-forms to hydromorphone-6-glucuronide. The excretion of such a chemical in urine was not seen by researchers. Additionally, they investigated the pharmacokinetics of hydromorphone in volunteers with various degrees of renal impairment and normal renal function. They discovered that for individuals with normal renal function, moderate renal failure (creatinine clearance (Ccl) 40-60mL/min), and severe renal failure (Ccl 30mL/min), respectively, the area under the curve for the plasma concentration/time plot rose in a ratio of 1:2:4. Despite being a single-dose study, they advised closer monitoring for both groups, lower starting dosages for moderate renal failure, and longer dosing intervals for severe renal failure.

**Oxycodone**

However, they did not provide data for the other metabolites they discovered, including noroxycodone, conjugated oxycodone, conjugated oxymorphone, and oxymorphone. Researchers discovered that 8%–14% of oxycodone is excreted as conjugated and free oxycodone. The single active metabolite, oxymorphone, had very little effect on plasma levels. In uremic individuals, oxycodone's elimination half-life is prolonged and metabolite excretion is substantially compromised.

**Codeine**

Norcodeine (2.16%), codeine-6-glucuronide (81.0%), morphine (0.56%), morphine-3-glucuronide (2.10%), morphine-6-glucuronide (0.80%), and normorphine (2.44%) are all pro-ducts of the metabolism of codeine. Codeine and codeine-6-glucuronide are both eliminated by the kidneys. In a single-dose study, researchers discovered that patients with advanced renal failure had significantly reduced renal clearance of codeine, codeine glucuronide, morphine, and morphine glucuronide. However, other pharmacokinetic parameters were not significantly different, likely due to the high interpatient variability in the renal failure group. A kid with renal failure who received codeine for post-operative pain has been reported to have experienced respiratory arrest, which has been linked to the morphine-6-glucuronide metabolite. Earlier studies have also linked codeine to significant narcolepsy in three patients with renal failure.

**Methadone**

The main products of methadone's metabolism are pyrrolidine and pyrroline, both of which can be hydroxylated. Pyrrolidone and the potentially active methadol metabolites may be produced by minor mechanisms. Typically, methadone or its metabolites account for 20 to 50% of urine excretion, and the pyrrolidine metabolite accounts for 10 to 45% of feces excretion. In one trial, an anuric patient excreted virtually all of the dose in the feces, but still only 3% of it was unmodified methadone. An oliguric subject expelled 15% of the daily dose in the feces, of which 3% was unchanged methadone. The author comes to the conclusion that patients with renal impairment can safely utilize methadone [4].

**Fentanyl and sufentanil**

Lesser amounts of despropionylfentanyl, hydroxyfentanyl, and some duodenal metabolism to norfentanyl are also produced during fentanyl metabolism in the liver (>99%). None of these metabolites appear to have any active properties. A patient with intestinal obstruction and renal failure was given a fentanyl infusion over the course of two days, and the results showed good pain management and no negative side effects. In ten patients undergoing renal transplantation, they investigated the utility of a six-hour sufentanil infusion. The authors note that even though the study's conclusion was that no dosage adjustments are required in renal failure, the fact that all of the patients had a working kidney at the end of the six-hour period may suggest that their findings are not applicable to chronic renal failure.

**Dialysis**

Dialysis has a very intricate role in the clearance of a medication and/or its metabolites. Along with technical aspects of the dialysis method, it is necessary to take into account the parent drug's qualities as well as those of its metabolites. The total of a drug's renal and non-renal clearances is known as "plasma clearance." As a result, dialysis won't have much of an impact on a drug's clearance if non-renal mechanisms—usually the liver—clear the majority of the substance. Any molecule's likelihood of being removed from blood by dialysis depends on its molecular weight, water solubility, and volume of distribution. The amount of protein binding in the molecule influences its dialyzability as well, however the amount of protein binding can change with uremia.

**Morphine**

In patients who are uremic and anephric, morphine's poor protein

binding is moderately and dramatically diminished, respectively. Due to its moderate water solubility, most dialysis processes are likely to remove it. Although reports have verified this, further research has revealed that hemofiltration and hemodiafiltration remove far less morphine due to their significantly slower (40 times less) flow rates. Hemodialysis also removes morphine-6-glucuronide, but because it leaves the CNS relatively slowly, the effect of the dialysis is delayed. A more recent study in patients with chronic renal failure receiving continuous ambulatory peritoneal dialysis found that only about 12% of the parent substance and its glucuronide metabolites are removed per exchange [5]. Earlier research in patients with acute renal failure found that morphine and the glucuronides were cleared by peritoneal dialysis. According to extrapolation of these findings, morphine would not build with prolonged administration, but the glucuronides would.

**Hydromorphone**

Low molecular weight, high water solubility, and low volume of distribution characterize hydromorphone. The usual sources of information on protein binding were inaccessible for this information. However, some reports indicate that hemodialysis lowers plasma levels to 40% of pre-dialysis levels.

**Oxycodone**

In comparison to hydromorphone, oxycodone is more widely distributed and has a higher protein binding and water solubility percentage. Despite the lack of information on oxycodone dialysis, its physicochemical characteristics indicate that it is probably dialyzable to some degree.

**Codeine**

When researchers compared a group of healthy participants with a group receiving hemodialysis, they discovered substantial changes in the pharmacokinetics of codeine. Although this was a single-dose trial, he extrapolated the findings to claim that two-thirds of the hemodialysis patients would accumulate to hazardous levels with chronic treatment. When two of the six hemodialysis patients experienced significant adverse responses to a single dosage of codeine, plans to continue the trial to evaluate repeat dosing were scrapped. They come to the conclusion that some uremic patients on codeine may require dosage adjustment [6].

**Methadone**

Low molecular weight, high volume of distribution, moderate water solubility, and high protein binding are all characteristics of methadone. The first two characteristics would imply that it is ineffectively eliminated by dialysis, and one patient report has demonstrated this to be the case, while the author expresses concern about the possibility of patient variability. The less active, more water-soluble metabolite is eliminated more easily, but there are no negative clinical effects.

**Fentanyl and sufentanil**

Fentanyl has a high volume of distribution, a somewhat high molecular weight, high protein binding, and limited water solubility. As a result, it would not be expected to be dialyzable, and this is supported by the reports. However, one of the reports speculated that a specific kind of dialysis filter (CT 190) might remove fentanyl by adsorbing it onto its surface because fentanyl appeared to be removed from the blood but did not show up in the dialysate solution. Although there are no data on sufentanil and dialysis, one might anticipate that it wouldn't be dialyzable given that it shares pharmacokinetic characteristics with fentanyl.

## RECOMMENDATIONS

Even while some writers have suggested cutting back on opioid dosage based on the computed GFR value, the rationale behind these suggestions is not totally obvious. Based on the review that came before, an alternative strategy is provided here. Although many studies employ serum BUN or creatinine levels, the degree of renal failure should ideally be assessed in terms of GFR (and/or creatinine clearance). Additionally, the trials have a very varied design and primarily use volunteers or patients who have never used opioids. The issue of opiate use leading to the development of renal failure has not been addressed. Based on the facts, one may infer that as renal failure progresses, the parent drug's and/or its metabolites' excretion would decline, and a progressive buildup would take place, with accompanying clinical effects. There are no reports in the literature comparing the signs and symptoms of an opioid overdose in a patient with impaired renal function to those in a person with normal renal function.

**Renal failure**

Morphine

Due to the challenge of controlling the complex adverse effects of the metabolites, do not use.

Hydromorphone

Use with caution. Hydromorphone has been used in renal failure patients without any negative side effects, despite the 3-glucuronide metabolite being neuro-excitatory and having the potential to accumulate in the condition.

Oxycodone

To make a recommendation, there are not enough data. If utilized, take extreme caution and close supervision when administering. Although it is produced in very small quantities, the active metabolite, free oxymorphone, does accumulate in renal failure along with the parent medication. Its toxic and CNS-depressant effects have been anecdotally reported in patients with renal failure [7].

Codeine

Do not apply. In renal failure, the active metabolites build up, and patients have been reported to experience severe negative effects.

Methadone

Seems secure. The original chemical and the metabolites are excreted into the gut in renal failure, and the metabolites are reportedly inactive. These findings come from trials involving a fairly limited number of people, thus subject variability is conceivable. It is unclear why some writers advise dose reduction in cases of severe renal failure (GFR 10 mL/min). The standard safety measures for prescribing methadone should still be followed.

**Fentanyl**

Safe, at least in the near future. The parent molecule has been reported to accumulate in cases of renal failure, although clinical experience has shown that there are no side effects. However, it is advised to carefully monitor the pharmacodynamic effects when used over an extended period of time in patients with renal failure [8].

**Dialysis**

Morphine

Dialysis can remove both the parent substance and the metabolites, but watch out for "rebound" as medicines and/or metabolites re-equilibrate between the CNS and plasma. Between dialysis sessions, metabolites would build up, necessitating further dose either during or after dialysis. In dialysis patients, it is advisable to avoid morphine because there are better options available.

Hydromorphone

Use with caution and keep an eye on the patient. Patients on dialysis have used hydromorphone without experiencing any negative effects. Dialysis partially removes the parent medication, but there are no data on the metabolites; buildup of metabolites is a problem [9].

Oxycodone

On the dialysis of oxycodone and its metabolites, there is no information. It is advised to avoid using oxycodone in dialysis patients until such data are obtained.

Codeine

Do not apply. Renal failure causes the metabolites to build up, and codeine has been linked to serious side effects in dialysis patients.

Methadone

It is not dialyzed and the metabolites are inactive. Patients on dialysis do not need any dose modifications. The standard safety measures for prescribing methadone should still be followed.

**Fentanyl**

Appears secure, at least temporarily. Although there is some worry that the parent molecule may accumulate in renal failure, the metabolites are inactive, and it is unclear what this means clinically. It is not dialyzed, so patients on dialysis typically don't need to change their dose. But fentanyl might adhere to a particular kind of filter, in which case switching to a different filter is advised. If that is not possible, switching to methadone is advised [10].

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