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Opioid Safety in Patients With Renal or Hepatic Dysfunction

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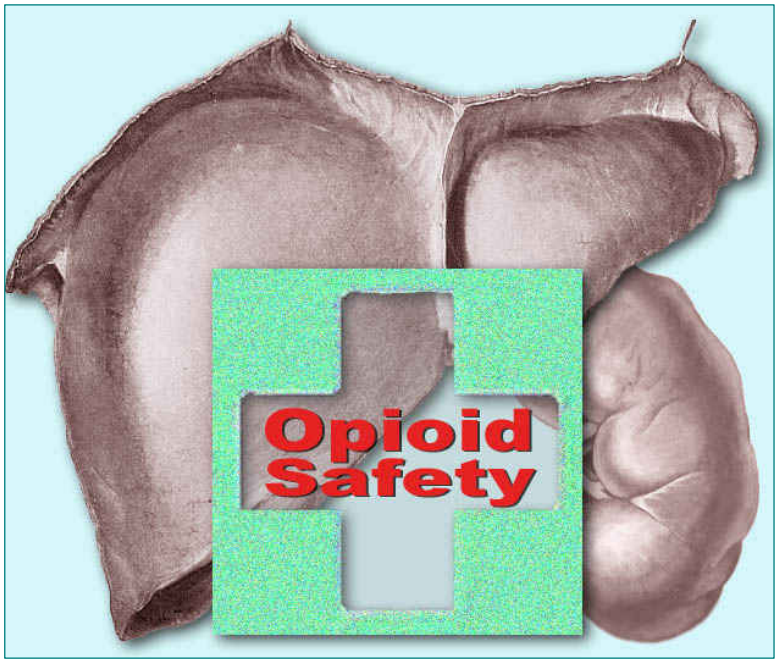


It has been estimated that up to one-third of patients with renal dysfunction (defined as creatinine clearance [CrCl] < 50 mL/min) also receive opioids to relieve pain [Davison 2003]. Use of opioids in these patients can present a challenge because adequate pain control is necessary while balancing the risk of overdose due to altered drug clearance and accumulation of the opioid parent drug and/or metabolites in the presence of renal dysfunction.

During dialysis, properties of the parent opioid drug and its metabolites, as well as physical properties of the dialysis equipment (eg, filter pore size), flow rate, the efficiency of the technique used, and dialysis method (intermittent versus continuous dialysis), must be considered to achieve effective pain relief without adverse effects. Similar problems exist for patients with hepatic dysfunction because the liver is responsible for metabolism of the parent opioid drug to active and inactive metabolites.

When patients with renal or hepatic dysfunction receive opioid analgesics, it is essential to understand and consider how opioid pharmacokinetics can be altered. This is necessary to ensure appropriate pain relief for the patient while limiting serious and *potentially preventable* adverse effects – such as respiratory depression, hypotension, or central nervous system (CNS) toxicity – from either the parent drug or its metabolites. This paper addresses considerations for the safe use of opioid agents in patients with renal and/or hepatic dysfunction.

It is essential to understand how opioid pharmacokinetics may be altered by kidney or liver disease to ensure appropriate pain relief for the patient, while limiting serious and potentially preventable adverse effects.

Opioid Use in Renal Dysfunction and Dialysis

See the text following these summary tables for further information.

Recommended Use of Selected Opioids in Patients with Renal Dysfunction [Aronoff 1999; Dean 2004]

Opioid	Recommended Use	Comment
Morphine	*Use cautiously*; adjust dose as appropriate. **	Metabolites can accumulate causing increased therapeutic *and* adverse effects.
Hydromorphone/ Hydrocodone	*Use cautiously*; adjust dose as appropriate. **	The 3-glucuronide metabolite can accumulate and cause neuro-excitatory effects.
Oxycodone	*Use cautiously* with careful monitoring; adjust dose if necessary.**	Metabolites and parent drug can accumulate causing toxic and CNS-depressant effects.
Codeine	*Do not use.*	Metabolites can accumulate causing adverse effects.
Methadone*	Appears safe.**	Metabolites are inactive.
Fentanyl*	Appears safe; however, a dose reduction is necessary.**	No active metabolites and appears to have no added risk of adverse effects; monitor with long term use.
Meperidine	*Do not use.*	Metabolites can accumulate causing increased risk of adverse effects.
Propoxyphene	*Do not use.*	Metabolites can accumulate, and use in renal dysfunction has been associated with hypoglycemia, cardiac conduction problems, and CNS and respiratory depression [Almirall et al. 1989; Davies 1996; Kurella 2003; Shah et al. 2006].

***** Negligible or no active metabolites; although, not considered first-line therapy. ****** See Table below for dosing recommendations.

Recommended Use of Selected Opioids in Dialysis Patients [Aronoff 1999; Dean 2004]

Opioid	Recommended Use	Comment
Morphine	*Use cautiously* and monitor patient for rebound pain effect or *do not use.*	Both parent drug and metabolites can be removed with dialysis; watch for “rebound” pain effect.
Hydromorphone/ Hydrocodone	*Use cautiously* and monitor patient carefully for symptoms of opioid overdose.	The parent drug can be removed, but metabolite accumulation is a risk.
Oxycodone	*Do not use.*	No data on oxycodone and its metabolites in dialysis.
Codeine	*Do not use.*	The parent drug and metabolites can accumulate causing adverse effects.
Methadone*	Appears safe.	Metabolites are inactive, but use caution because parent drug is not dialyzed.
Fentanyl*	Appears safe.	Metabolites are inactive, but use caution because fentanyl is poorly dialyzable.
Meperidine	*Do not use.*	Few data on meperidine and its metabolites in dialysis; risk of adverse effects.
Propoxyphene	*Do not use.*	Propoxyphene is not dialyzed. Metabolites can accumulate causing increased risk of hypoglycemia, cardiac conduction problems, and CNS and respiratory depression [Almirall et al. 1989; Davies 1996; Kurella 2003; Shah et al. 2006].

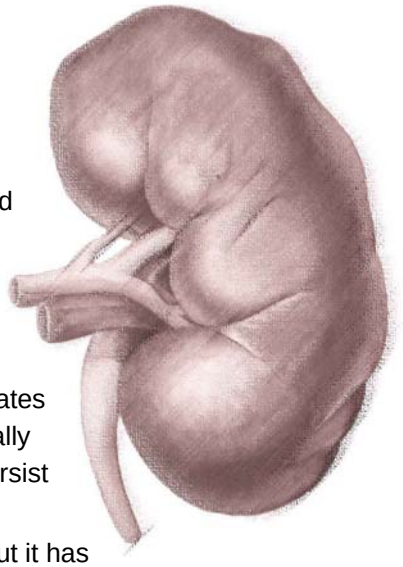
* Use caution because these drugs are not dialyzable.

Recommended Dosage Adjustments for Select Opioids in Renal Insufficiency [Aronoff 1999]

GFR (mL/min)	Morphine	Hydromorphone or Hydrocodone	Oxycodone	Methadone	Fentanyl
>50	100*	50 to100*	100*	100*	100*
10-50	50 to 75*	50*	50*	100*	75 to100*
<10	25 to 50*	25*	*Do not use*	50 to75*	50*

GFR = glomerular filtration rate. * = % of normal dose. Codeine, meperidine, and propoxyphene are not recommended for use.

Morphine [Aronoff 1999; Dean 2004; Duramorph PI 1994]



Metabolites:

- Morphine is metabolized in the liver to morphine-3-glucuronide (M3G, 55%), morphine-6-glucuronide (M6G, 10%), normorphine (4%), and codeine, all of which are renally excreted. In addition, a small portion of the parent compound (10%) is excreted unchanged.
- Morphine excretion is not altered significantly in renal insufficiency, but its metabolites can accumulate.
- M6G is an active metabolite that has more potent analgesic properties than the parent drug and can contribute to respiratory depression when it accumulates in renal dysfunction. M6G also crosses the blood-brain barrier slowly, potentially causing CNS effects such as somnolence, dizziness, and hallucinations to persist even after morphine discontinuation.
- M3G has a low affinity for opioid receptors, resulting in no analgesic activity, but it has been shown to stimulate respiration and cause behavioral excitation. This effect is magnified in patients with renal insufficiency due to M3G accumulation.
- M3G is thought to antagonize the potent effects of M6G.

Dialysis Implications:

- Morphine has low protein-binding and moderate water solubility, and it is likely to be removed during dialysis.
- M6G is removed by dialysis; however, its slow diffusion out of the CNS delays removal during dialysis.
- Removal of morphine (or any parent drug or metabolite) with high efficiency dialyzers may be so complete that its elimination from plasma exceeds the transfer of drug to other tissues, causing a “rebound” effect after dialysis. This may lead to unpredictable analgesia and sedation.

Because the predominant morphine metabolites are inactive and antagonize the effect of the active metabolite, morphine may be used in patients with renal insufficiency and in those on dialysis, but a lower than usual dose and less frequent dosing may be necessary to prevent adverse effects.

Hydromorphone and Hydrocodone [Aronoff 1999; Dean 2004; Durnin et al. 2001; Lurcott 1998]

Metabolites:

- Hydrocodone is metabolized to hydromorphone by CYP2D6. Poor metabolizers experience little or no analgesia [Lurcott 1998].
- Hydromorphone is metabolized in the liver to hydromorphone-3-glucuronide (H3G, 37%), 6-hydroxy metabolites (1.1%), as well as other metabolites in negligible amounts, all of which are renally excreted along with small amounts of free hydromorphone.

- H3G has no analgesic activity but possibly causes neuro-excitation in humans, as well as agitation, confusion, and hallucinations.
- Area under the curve for plasma concentration versus time is doubled for patients with moderate renal failure and increased 4-fold in patients with severe renal failure, suggesting *that lower doses or longer dosing intervals for patients with renal insufficiency may be a better starting point for initiation of hydromorphone therapy*.

When giving multiple doses of hydromorphone or hydrocodone, start with a lower dose or a longer dosing interval in patients with renal dysfunction. Proportionally higher doses of hydromorphone at the beginning of dialysis or re-dosing after dialysis may also be necessary.

Dialysis Implications:

- Hydromorphone is water soluble, with a small volume of distribution and low molecular weight, all of which contribute to easy dialysis. Studies have shown that plasma levels decreased by 60% of predialysis levels during hemodialysis [Durnin et al. 2001].

Oxycodone [Aronoff 1999; Dean 2004; Fitzgerald 1991; Foral et al. 2007; Lurcott 1998]

Metabolites:

- Oxycodone is metabolized to a combination of conjugated and free oxycodone (8% to 14%), noroxycodone, conjugated oxymorphone, and oxymorphone (the only active metabolite, but with negligible plasma levels). The elimination half-life is lengthened in patients with renal dysfunction, and excretion of metabolites is severely impaired.
- Oxycodone is metabolized by CYP2D6. Poor metabolizers will experience little or no analgesia [Lurcott 1998].
- CNS toxicity and sedation with usual doses of oxycodone in renal-failure patients have been published [Fitzgerald 1991].

Oxycodone may be used very cautiously in patients with renal insufficiency when the dose of the drug is reduced and it is monitored carefully. Its use is not recommended in dialysis patients due to the lack of data.

Dialysis Implications:

- Oxycodone has a large volume of distribution but is only 50% protein-bound, and is water soluble making it likely to be dialyzable based on its physical properties. No pharmacokinetic data on oxycodone use in dialysis patients have been published; however, one case report in the literature indicated that use of a 45-hour continuous infusion of naloxone was necessary to reverse the effects of oxycodone in a patient on chronic hemodialysis [Foral et al. 2007].

Codeine [Dean 2004; Gasche et al. 2004; Guay et al. 1988; Matzke et al. 1986; Talbott et al. 1997]

Metabolites:

- Codeine is metabolized via CYP2D6 to codeine-6-glucuronide (C6G, 81%), morphine (10%), normorphine (2%), M6G, and M3G, as well as other metabolites in negligible amounts. Both codeine and C6G are renally excreted, and renal clearance of codeine and its metabolites are significantly decreased in patients with moderate to severe renal failure.
- A report of respiratory arrest in a child with renal failure who received codeine was attributed to the M6G metabolite [Talbott et al. 1997]. Reports of profound narcolepsy in patients with renal failure on codeine have also been published [Matzke et al. 1986].
- Patients with ultrarapid CYP2D6 metabolism may experience intoxication due to accumulation of metabolites when renal dysfunction is present [Gasche et al. 2004].

If the use of codeine is necessary, lowering the usual dose is recommended for patients with renal insufficiency. However, it is best to avoid using codeine in patients with renal insufficiency and in those on dialysis.

Dialysis Implications:

- Codeine has a moderately large volume of distribution and molecular weight, suggesting that it will not be extensively dialyzed. It has been proposed, based on clinical studies, that chronic codeine dosing causes accumulation to toxic levels in two-thirds of hemodialysis patients [Guay et al. 1988].

Methadone [Dean 2004; Dolophine PI 2006; Furlan et al. 1999]

Metabolites:

- Methadone and its metabolites are excreted in the urine (20% to 50%) and feces (10% to 45% as the pyrrolidine metabolite).
- No reports of adverse effects related to methadone in patients with renal failure have been published.

Dialysis Implications:

- Methadone has high protein-binding and a large volume of distribution, suggesting poor removal by dialysis [Furlan et al. 1999].

Limited numbers of case reports indicate that methadone is safe in patients with mild to moderate renal insufficiency, and supplemental methadone doses are not needed following dialysis.

Fentanyl [Dean 2004]

Metabolites:

- Fentanyl is metabolized in the liver primarily to norfentanyl (>99%) and other inactive metabolites.
- A review of the literature indicated that fentanyl clearance is reduced in patients with moderate to severe uremia (BUN > 60 mg/dL), and that it depresses respiration post-operatively due to decreased clearance.

Dialysis Implications:

- Fentanyl has high protein-binding and molecular weight, a large volume of distribution, and low water solubility, causing it to be poorly dialyzable. However, fentanyl may be removed from the blood by some types of dialysis filters.

Limited case reports and pharmacokinetic data suggest that fentanyl can be used at usual doses in mild to moderate renal insufficiency and in dialysis patients with proper monitoring (eg, respiratory and cardiovascular status, blood pressure, heart rate).

Meperidine [Demerol PI 2002; Hassan et al. 2000; Szeto et al. 1977]

Metabolites:

- Meperidine is metabolized in the liver to various metabolites, primarily normeperidine, which is the most toxic and long-lasting. Meperidine and its metabolites are excreted by the kidney.
- Normeperidine has a half-life 5 to10 times longer than meperidine, and the half-life is significantly lengthened in patients with renal insufficiency.
- Normeperidine has less analgesic potency than meperidine, but it decreases seizure threshold and may induce CNS hyperexcitability and seizures [Hassan et al. 2000].
- Naloxone is not useful for reversal of CNS hyperexcitability and may actually worsen it [Hassan et al. 2000].
- The effects of normeperidine are more profound in uremic patients due to its excessive accumulation; however, meperidine and normeperidine can also be problematic even in patients with normal renal function.

Meperidine should not be used in patients with renal insufficiency, and while normeperidine can be removed by dialysis, meperidine should not be used during dialysis due to its risk of adverse events.

Furthermore, use of more than one dose of meperidine in patients with renal impairment is discouraged due to the risk for adverse events.

Dialysis Implications:

- Meperidine is very water soluble and has a small molecular weight, suggesting parent drug and its metabolites are removed by dialysis. Very few case reports and pharmacokinetic data are available pertaining to meperidine use in dialysis patients. One case report describes a patient with end-stage renal disease who received meperidine and subsequently developed a normeperidine-induced grand mal seizure. This report states that normeperidine was effectively cleared by hemodialysis, and the patient successfully recovered [Hassan 2000].

Propoxyphene [Almirall et al. 1989; Barkin et al. 2006; Bennett et al. 1987; Davies 1996; Kurella 2003; Li Wan Po et al. 1997; Mauer et al. 1975; Shah et al. 2006]

Metabolites:

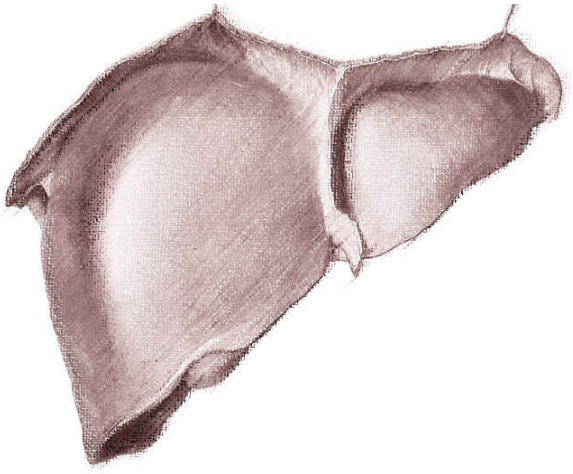
Due to risks for adverse events and poor efficacy in terms of pain relief, the use of propoxyphene in renal dysfunction is not recommended.

- Propoxyphene is mainly metabolized in the liver to norpropoxyphene and other minor metabolites [Barkin et al. 2006].
- Norpropoxyphene is an active metabolite that causes less CNS depression than the parent drug but has been associated with other adverse events such as hypoglycemia, respiratory depression, and cardiac conduction abnormalities.
- The half-life of the parent drug and the metabolites are prolonged in renal failure [Bennett et al. 1987].
- Propoxyphene, often used as a combination product with acetaminophen, has not been shown to be more effective than acetaminophen alone but may be associated with serious adverse effects [Li Wan Po et al. 1997].

Dialysis Implications

- Propoxyphene is not dialyzable in significant amounts [Mauer et al. 1975].

Opioid Use in Hepatic Dysfunction



The liver is the major site for transformation of opioids from parent compounds to active or inactive metabolites. In patients with liver failure, reduced metabolism usually results in accumulation of the parent drug in the body with repeated administration. ***In general, patients with severe liver disease should be prescribed lower doses of opioids, with extended dosing intervals when multiple daily doses of opioids are needed.***

Oxidation and other hepatocellular processes seem to be more affected by liver dysfunction than glucuronidation (which does not require hepatocellular enzymes), and most opioids undergo oxidation to the metabolites discussed previously. However, morphine is primarily transformed via glucuronidation [Duramorph PI 1994], and its accumulation has been problematic in some patients with hepatic failure. Hydromorphone and hydrocodone also may accumulate and should be used cautiously. Fentanyl appears to be more affected by reduced hepatic blood flow than by severe hepatic dysfunction [Duragesic PI 2003].

Codeine should be avoided since the liver is required for biotransformation of the drug into the active metabolite, morphine, so pain control could be compromised [Gasche et al. 2004].

Methadone is not advised in severe liver dysfunction [Dolophine PI 2006]. Meperidine should be avoided due to the potential for toxic metabolite accumulation. Propoxyphene has been associated with hepatotoxicity as a single agent or in combination with acetaminophen [Klein and Magida 1971; Propoxyphene PI 2005].

Recommended Use of Opioids in Hepatic Dysfunction
[Demerol PI 2002; Dolophine PI 2006; Guay et al.1988; Klein and Magida, 1971; Murphy 2005; Propoxyphene PI 2005; Tegeder et al. 1999]

Opioid	Recommended Usage	Comment	Dosing Recommendations*
Morphine	*Use cautiously* and monitor patient for sedation.	In severe hepatic impairment, the parent drug may not be readily converted to metabolites.	Increase the dosing interval by twice the usual time period.
Hydromorphone/ Hydrocodone	*Use cautiously* and monitor patient carefully for symptoms of opioid overdose.	In severe hepatic impairment, the parent drug may not be readily converted to inactive metabolites.	Decrease initial dose by 50% of the usual amount.
Oxycodone	*Use cautiously* and monitor patient carefully for symptoms of opioid overdose.	In severe hepatic impairment, the parent drug may not be readily converted to inactive metabolites.	Decrease initial dose by 1/2 to 1/3 of the usual amount.
Codeine	*Avoid use.*	In severe hepatic impairment, codeine may not be converted to the active metabolite, morphine.	—
Methadone	*Not advised.*	Not advised in severe liver failure due to risk of methadone accumulation.	—
Fentanyl	Appears safe, generally no dose adjustment necessary.	Decreased hepatic blood flow affects metabolism more than hepatic failure.	Dosing adjustment usually not needed.
Meperidine	*Do not use.*	Inactive metabolite is associated with risk of seizure.	—
Propoxyphene	*Do not use.*	Hepatotoxicity reported with or without acetaminophen component.	—

*Recommended dose in severe hepatic impairment.

Summary

In renal or hepatic dysfunction, usual or adjusted doses are appropriate for some opioids, while others should be avoided.

Knowledge of altered opioid metabolism and excretion in patients with renal and/or hepatic dysfunction is essential for adequate pain relief while minimizing adverse effects. Although these patients are at a high risk for opioid-related adverse effects, extensive clinical data supporting specific dosing recommendations are lacking. Opioids should be used cautiously in this patient population due to possible accumulation of the parent drug and/or metabolites. Usual or adjusted doses may be appropriate for certain opioids (eg, morphine, hydromorphone, hydrocodone). Oxycodone should not be used in dialysis patients, and others should be avoided at all times (eg, codeine, meperidine, and propoxyphene). Methadone and fentanyl are generally not first-line therapies, although they can be carefully used in patients with renal dysfunction or on dialysis, and methadone is not advised in severe liver failure. For most patients with renal or hepatic dysfunction, either morphine or hydromorphone could be a good starting therapy if an opioid agent is used.

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