

P & T News

Published by the Pharmacy and Therapeutics Subcommittee of the University Hospital
Advisory Committee and the Department of Pharmaceutical Care

Volume 27 Number 4

March/April 2007

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Opioid Use in Patients with Renal and Hepatic Dysfunction

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It has been estimated that up to one-third of patients with renal dysfunction receive opioids to relieve pain.¹ Use of opioids in renal dysfunction can present a challenge because adequate pain control is necessary while balancing the risk of opioid overdose due to altered drug clearance and accumulation of the parent drug and/or metabolites of the opioid in the presence of renal dysfunction. A similar problem exists for patients with hepatic dysfunction, since the liver is responsible for metabolism of the parent drug to, in many situations, inactive metabolites. When patients with renal or hepatic dysfunction receive opioid analgesics, it is essential to understand how opioid pharmacokinetics have been altered to ensure appropriate pain relief for the patient, while limiting serious, potentially preventable adverse effects, such as respiratory depression, hypotension, and central nervous system (CNS) toxicity from either the parent drug or its metabolites. In addition, during dialysis, properties of the parent drug and its metabolites as well as physical properties of the dialysis equipment (filter pore size, flow rate, and the efficiency of the technique used) and dialysis prescription (intermittent dialysis versus continuous dialysis) must be considered in order to achieve effective pain relief without adverse effects. Considerations for the use of opioid agents and their use in patients with renal dysfunction and dialysis, as well as use in hepatic dysfunction, are discussed in this article.

Opioid Use in Renal Dysfunction and Dialysis²

Morphine³

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.

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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 with high efficiency dialysis machines may be so efficient that the elimination of morphine from the plasma exceeds the transfer of drug to other tissues, causing a "rebound" effect after dialysis. The rebound effect may lead to unpredictable analgesia and sedation.

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

Hydromorphone and Hydrocodone²

Metabolites:

- ✧ Hydrocodone is metabolized to hydromorphone by CYP2D6. Poor metabolizers of CYP2D6 experience little or no analgesia.⁴
- ✧ 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 increased by two times for patients with moderate renal failure [creatinine clearance (CrCl) 40-60 mL/min] and by four times in patients with severe renal failure (CrCl <30 mL/min), suggesting that lower doses or increased dosing intervals for patients with renal insufficiency may be a better starting point for initiation of hydromorphone therapy.

Dialysis Implications:

- ✧ Hydromorphone has a small volume of distribution, water solubility, and low molecular weight, all of which contribute to easy dialyzability of hydromorphone. Studies have shown that plasma levels decreased by 60% of pre-dialysis levels during hemodialysis.

When giving multiple doses of hydromorphone or hydrocodone, start with a lower dose or an increased 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.

Oxycodone²

Metabolites:

- ✧ Oxycodone is metabolized to conjugated and free oxycodone (8 to 14%), noroxycodone, conjugated oxycodone, 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.⁴
- ✧ Case series detailing experience with CNS toxicity and sedation with usual doses of oxycodone in renal failure patients have been published.⁵

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 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.⁶

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.

Codeine²

Metabolites:

- ✧ Codeine is metabolized to codeine-6-glucuronide (C6G) (81%), morphine (10%), normorphine (2%), M6G, and M3G as well as other metabolites in negligible amounts via CYP2D6. Both codeine and C6G are renally excreted. Renal clearance of codeine and its metabolites are significantly decreased in patients with advanced renal failure.
- ✧ A report of respiratory arrest in a child with renal failure who received codeine was attributed to the M6G metabolite. Reports of profound narcolepsy in patients with renal failure on codeine have also been published.⁷
- ✧ Patients with ultrarapid CYP2D6 metabolism may experience intoxication due to accumulation of metabolites when renal dysfunction is present.⁸

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.⁹

Lowering the usual dose is necessary in most patients with renal dysfunction who are receiving codeine. Codeine should be avoided in patients with renal insufficiency and patients on dialysis.

Methadone²

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.¹⁰

The 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.

Fentanyl⁸

Metabolites:

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

Dialysis Implications:

- ◇ Fentanyl has high protein-binding, a high molecular weight, a large volume of distribution, and low water solubility, causing it to be poorly dialyzable. Fentanyl may be able to 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 dialysis patients with proper monitoring (e.g., respiratory and cardiovascular status, blood pressure, heart rate).

Meperidine¹¹

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 to 10 times longer than meperidine; this 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.
- ◇ The effects of normeperidine are more profound in uremic patients due to excessive normeperidine accumulation; however, meperidine and normeperidine can also be problematic even in patients with normal renal function.

Dialysis Implications:

- ◇ Meperidine is very water soluble and has a small molecular weight, suggesting meperidine 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.¹²

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 without renal impairment is discouraged due to the risk for adverse events.

Table 1. Recommended Usage of Selected Opioids in Patients with Renal Dysfunction^{2,13}

Opioid	Recommended Usage	Comment
Morphine	Use cautiously, dose adjust as appropriate. **	Metabolites can accumulate, causing adverse effects.
Hydromorphone/ Hydrocodone	Use cautiously, dose adjust as appropriate. **	The 3-glucuronide metabolite can accumulate and cause neuro-excitatory effects.
Oxycodone	Use cautiously with careful monitoring, dose adjust 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.

* Negligible or no active metabolites; not considered first-line therapy

** See Table 3 for dosing recommendations

Table 2. Recommended Usage of Select Opioids in Dialysis Patients^{2,13}

Opioid	Recommended Usage	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 parent drug is not dialyzed.
Fentanyl*	Appears safe.	Metabolites are inactive, and it is not dialyzed.
Meperidine	Do not use.	Few data on meperidine and its metabolites in dialysis; risk of adverse effects.

* Use caution because these drugs are not dialyzable

Table 3. Recommended Dosage Adjustments for Select Opioids in Renal Insufficiency¹³

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

*% of normal dose

GFR = glomerular filtration rate

Opioid Use in Hepatic Dysfunction^{14, 15}

The liver is the major site for transformation of the opioids from the parent compound to the active or inactive metabolite. Most opioids undergo oxidation to the metabolites discussed previously, although morphine is primarily transformed via glucuronidation.³ The oxidation and other hepatocellular processes seem to be more affected in liver dysfunction than glucuronidation (glucuronidation does not require hepatocellular enzymes); however, morphine accumulation has been problematic in patients with hepatic failure. Fentanyl appears to be more affected by reduced hepatic blood flow, not by severe hepatic dysfunction.¹⁶

In patients with liver failure, reduced metabolism usually results in accumulation of the parent drug in the body with repeated administration. Patients with severe liver disease should be administered lower doses of opioids and extended dosing intervals when multiple daily doses of the opioid are needed. Codeine should be avoided since the liver is required for biotransformation of the drug into the active metabolite, morphine, thus pain control could be compromised.⁶ Methadone is contraindicated in severe liver dysfunction.¹⁷ Fentanyl does not appear to be affected by severe hepatic dysfunction.^{16, 9}

Naloxone for Reversal of Opioid Overdose¹⁸

Naloxone is a pure opioid antagonist that works through competitive inhibition of the opioid receptor. Naloxone is used to counteract the symptoms of opioid overdose, most commonly respiratory depression. The goal of reversal should be to improve spontaneous ventilation, so that the patient is alert while still maintaining pain control. Complete arousal of the patient is not necessary. Unless the person is in respiratory distress, more conservative methods should be considered. These methods include holding the opioid until the respiratory rate increases, giving oxygen through a nasal canula, or providing physical stimulation. Conservative methods may be more useful if the patient received an opioid with a short half-life as opposed to an opioid with a long half-life (e.g., methadone or controlled-release morphine).

If naloxone is deemed necessary, it is important to dose it correctly. Excessive dosing of naloxone may result in increased pain; once the opioid receptors are blocked, it may be difficult to control the pain with additional opioid drugs. The recommended dosage of naloxone for opiate-induced respiratory depression is 0.1 to 0.2 mg in adults (or 0.005 mg to 0.01 mg in children) to be given every 2 to 3 minutes until the desired response is attained. Naloxone must always be diluted before injection. The recommended dilution is 1 mg of naloxone in 100 mL of normal saline; 2 mL of the dilution should be administered IV push over 1 to 2 minutes and repeated as long as the respiratory rate remains below 8 per minute. The lowest reasonable doses should be used to prevent opioid withdrawal side effects.

If a patient who is dependant on opioids receives too much naloxone, side effects such as profound withdrawal, seizures, arrhythmias, and severe pain may result. Large doses of an opioid may then be required to counteract the withdrawal symptoms. For drugs with a long half-life (e.g., methadone), naloxone should be given as a continuous intravenous infusion after the boluses are given. The continuous infusion can be prepared as 0.5 mg in 250 mL of normal saline. The rate of administration is titrated to patient response.

Summary

Patients with renal and/or hepatic dysfunction are at a high risk for opioid-related adverse effects, but clinical data supporting specific dosing recommendations are lacking. Opioids should be used cautiously in these patients due to accumulation of the parent drug or metabolites. Usual doses or dosage adjustments may be appropriate for some opioids (e.g., morphine, hydromorphone, hydrocodone, oxycodone, methadone, and fentanyl) while others should be avoided at all times (e.g., codeine and meperidine). Knowledge of altered opioid metabolism and excretion in renal and hepatic dysfunction is essential for adequate pain relief without adverse effects.

Table 4. Recommended Usage of Opioids in Hepatic Dysfunction^{9, 14, 15, 16, 17}

Opioid	Recommended Usage	Comment	Dosing Recommendations*
Morphine	<i>Use cautiously</i> and monitor patient for sedation.	In severe hepatic impairment, the parent drug may not be readily converted to metabolites.	Increase the dosing interval by 2 times the usual interval.
Hydromorphone/ Hydrocodone	<i>Use cautiously</i> 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 dose.
Oxycodone	<i>Use cautiously</i> 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 dose.
Codeine	<i>Do not use,</i>	In severe hepatic impairment, codeine may not be converted to the active metabolite, morphine.	---
Methadone	<i>Do not use.</i>	Contraindicated in liver failure.	
Fentanyl	Appears safe, generally no dose adjustment necessary.	Decreased hepatic blood flow seems to affect the metabolism more than hepatic failure.	Dosing adjustment not needed.
Meperidine	<i>Do not use.</i>	Decreased analgesic activity does not warrant risk of accumulation of the parent drug; in- active metabolite is associated with risk of seizure.	---

*Recommended dose for severe hepatic impairment

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PHARMACY AND THERAPEUTICS SUBCOMMITTEE ACTIONS

DRUGS ADDED TO STOCK

COLISTIMETHATE

Colistimethate (Coly-Mycin®) is used by inhalation for the treatment of pseudomonas infections in cystic fibrosis patients.

Note: Restricted to prescribing by Adult and Pediatric Pulmonary physicians.

DARUNAVIR

Darunavir (Prezista® - Tibotec/Ortho Biotech) tablets is a protease inhibitor indicated for co-administration with ritonavir and other antiretroviral agents for the treatment of HIV infection.

DASANTINIB

Dasatinib (Sprycel® - BMS) is indicated for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib (Gleevec®). It is also indicated for the treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL).

DECITABINE

Decitabine injection (Dacogen® - MGI Pharma) is indicated for the treatment of myelodysplastic syndromes.

ETONOGESTREL

Etonogestrel implants (Implanon® - Organon) are subdermally implantable contraceptive devices that are effective for 3 years post-insertion.

GADOBENTATE DIMEGLUMINE

Gadobentate dimeglumine injection (MultiHance® - Bracco) is a paramagnetic agent indicated for use in MRI of the central nervous system to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine and associated tissues.

IBUPROFEN

Ibuprofen lysine injection (Neoprofen® - Ovation) is indicated for the closure of clinically significant patent ductus arteriosus in premature infants.

Note: The prescribing of ibuprofen injection is restricted to Pediatrics.

IDURSULFASE

Idursulfase injection (Elaprase® - Shire) is indicated for the treatment of Hunter Syndrome.

Note: The prescribing of idursulfase is restricted to Pediatrics.

LUBIPROSTONE

Lubiprostone capsules (Amitiza® - Takeda) are indicated for the treatment of chronic idiopathic constipation in adults.

MOMETASONE FUROATE

Mometasone inhalation powder (Asmanex® Twisthaler - Schering) is indicated for the maintenance treatment of asthma in patients 12 months of age and older.

DRUGS ADDED TO STOCK (Continued)

PANITUMUMAB

Panitumumab injection (Vectibix® - Amgen) is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma with progression with fluorouracil-, oxaliplatin-, and irinotecan-containing regimens.

POSACONAZOLE

Posaconazole oral liquid (Noxafil® - Schering) is an antifungal agent that is useful in treating infections resistant to other agents.

Note: Due to the potential for the development of resistant organisms, serious adverse effects, and drug interactions, the prescribing of posaconazole is restricted to the Infectious Diseases Service.

RANOLAZINE

Ranolazine tablets (Ranexa® - CV Therapeutics) are indicated for the treatment of chronic angina in patients who have not had an adequate response with other antianginal agents.

Note: The initial order/prescription for ranolazine is restricted to Cardiology.

ZOSTER VACCINE

Zoster vaccine injection (Zostavax® - Merck) is indicated for the prevention of herpes zoster (shingles) in patients ≥ 60 years of age.

ADDITIONAL ACTIONS

CIPROFLOXACIN

The injectable dosage form was added to stock.

IBANDRONATE (Boniva® - Roche)

The injectable dosage form was added to stock.

LEVETIRACETAM (Keppra® - UCB)

The injectable dosage form was added to stock.

NICOTINE POLARCILEX

Oral lozenges (Commit® - GSK) have been added to stock.

PREDNISOLONE

An orally disintegrating tablet (Orapred ODT®) was added to stock.

THERAPEUTIC INTERCHANGE OF HFA INHALERS FOR CFC INHALERS

To decrease the depletion of the ozone layer, the FDA has determined that all metered dose inhalers (MDI) containing CFC (chlorofluorocarbons) propellants must be withdrawn from the US market by Dec. 31, 2008. Therefore, manufacturers are discontinuing the production of CFC inhalers and converting to inhalers with HFA (hydrofluoroalkane) propellants. Because the CFC and the HFA versions of the inhalers deliver the same amount of medication, the Pharmacy and Therapeutics Subcommittee has determined that they can be used interchangeably. Therefore, when supplies of currently stocked CFC inhalers are exhausted, the HFA version will be dispensed.

PHARMACY AND THERAPEUTICS SUBCOMMITTEE ACTIONS (CONTINUED)

DRUGS DELETED FROM STOCK

ALUMINUM HYDROXIDE CAPSULES (Alu-caps®)

Discontinued by the manufacturer. Aluminum hydroxide oral suspension is available.

DURASPHERE® INJECTION

Discontinued by the manufacturer.

PHENTERMINE RESIN CAPSULES (Ionamin®)

Discontinued by the manufacturer. Orlistat is available.

QUININE 200 mg CAPSULES

Only FDA-approved quinine products (325 mg strength) can remain on the market.

Note: The prescribing of quinine is now restricted to the treatment of malaria.

DRUGS DELETED FROM STOCK (CONTINUED)

TEGRESS® URETHAL IMPLANT

Discontinued by the manufacturer.

TRIAMCINOLONE ACETONIDE ORAL INHALER (Azmacort®)

Deleted due to low use. Mometasone, fluticasone, and beclomethasone inhalers are available.

VITAMIN E 26.7 units/ml ORAL LIQUID (Liqui-E®)

Discontinued by the manufacturer. Aquasol-E® is available.

Note: The cost following each monograph is the inpatient acquisition cost.

Compounded Topical Medications for Pain Management

Questions have recently been raised by UIHC care providers regarding the use of extemporaneously compounded topical preparations to provide analgesia. The questions posed along with the results of an extensive literature search are outlined below. Based on the lack of efficacy and stability data - and the potential for adverse effects - the Pain Management Section and the Pharmacy and Therapeutics Subcommittee have determined that these preparations should not be used at UIHC

What data are available to support the use of compounded topical medications for pain management?

There are numerous case reports and case series (open-label trials) that report positive outcomes. Most of the information is for ketamine alone or ketamine in combination with amitriptyline. Efficacy data on other combinations are lacking.

There are two, randomized, placebo-controlled trials evaluating ketamine in combination with amitriptyline in varying concentrations. One trial found no difference from placebo (*Anesthesiology* 2005;203:140-6); the other found no difference in the placebo-controlled portion of the trial, but analgesia was reported in the open-label part of the trial (*Clin J Pain* 2003;19:323-8).

Are compounded topical medications currently part of guidelines for the management of postherpetic neuralgia or complex regional pain syndrome?

They are not listed in current review articles (*PLoS Med* 2005;2(7):e164., *Clin J Pain* 2006;22:425-9.) Topical agents recommended in these articles include lidocaine and/or capsaicin.

Are there any standard drugs and/or drug concentrations that are used in compounded topical medications for pain management?

- Drugs and concentrations vary widely.
- Ketamine is the most widely cited drug; concentrations range from 0.25% to 15%.
- Ketamine (range 0.5% to 10%) and amitriptyline (range 1% to 2%) have been used in combination.
- Additional agents that have been prepared by compounding pharmacies in varying combinations and concentrations (sometimes with ketamine and amitriptyline) include gabapentin, baclofen, clonidine, lidocaine, ketoprofen, nifedipine, and capsaicin.

Have any of these compounded topical medications been tested for stability?

No, therefore it is unknown if potency decreases or at what rate it decreases over time.