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Opioids in Renal and Hepatic Dysfunction

Mary Lynn McPherson, PharmD, MA, MDE, BCPS

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PALLIATIVE CARE

Pain Assessment

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Learning Objectives

1

Describe the prevalence of pain in renal and hepatic impairment.

2

Given a simulated patient with renal impairment, select the most favorable opioid to minimize adverse effects.

3

Given a simulated patient with hepatic impairment, select the most favorable opioid to minimize adverse effects.

Pain in Chronic Kidney Disease (CKD)

- Pain is a common experience in CKD
  - 40-60% of patients on renal replacement therapy
  - 60-70% of patients with pre-end-stage kidney disease
  - Nearly 100% of patients hospitalized with CKD
- Types of pain
  - Musculoskeletal (60-70%)
  - Neuropathic pain (15%) [due to diabetes and ischemic pain]
- Severity of pain
  - 2/3 of patients rate pain as > 5/10
- Approximately 50% of patients on dialysis will receive an opioid

Davison et al. *Semin Dial*. 2014;27:188-204.

PROs and CONs of Opioid Therapy

- Opioid may infer protection against ischemic reperfusion injury (a common cause of acute kidney injury)
- Morphine may injure parts of the glomerulus
  - Albuminuria and increased albumin-creatinine ratio seen
- Long-term opioid therapy (LTOT; continuous opioid therapy 90 days) associated with increased mortality for patients on dialysis
  - Possibly LTOT is a marker for greater co-morbidities and more severe disease
  - Patients with GFR $\leq$ 40 ml/min on opioids > 60 MME have a 3.9 fold greater risk of dying

Pham et al. *NDT Plus*. 2009;2:111-8.
Davison et al. *Semin Dial*. 2014;27:188-204.
Erkilic et al. *Drug Des Devel Ther*. 2017;11:677-683.
Kimmel et al. *J Am Soc Nephrol*. 2017;28:3658-3670.

General Conclusions on Opioids in Renal Impairment

- Opioids with 30% dependence on creatinine clearance or have active metabolites derived through the CYP2D6 or 3A are considered “less safe” or “unfavorable.”

Favorable Opioids
Buprenorphine
Fentanyl
Hydromorphone
Methadone
Nalbuphine
Tapentadol

Unfavorable Opioids
Codeine
Dihydrocodeine
Hydrocodone
Morphine
Oxycodone
Tramadol

Coluzzi et al. Safe use of opioids in chronic kidney disease and hemodialysis patients: tips and tricks for non-pain specialists. *Ther Clin Risk Manage*. 2020;16:821-837.

Opioid Dosing Strategies in Renal Impairment

- Dose reductions relative to stand dosing should be used in the opioid naïve
- SR opioids and around the clock dosing should be avoided, especially with "unfavorable" opioids; using an "as needed" strategy with immediate release product is likely safer
- There is a poor correlation between GFR and drug clearance
- CKD influences nonrenal clearance of medications

Hirata. [Appropriate pharmacotherapy in patients with chronic kidney disease – new approach.] *Yakugaku Zasshi*. 2012;132:461-470.

Renal Dialysis and Opioids

- Dialysis influences opioid clearances, particularly hydrophilic opioids
- Methadone, buprenorphine, fentanyl and nalbuphine serum levels are not significantly influenced by dialysis
- Type of dialysis has an impact
  - High efficiency (hyperpermeable) continuous renal replacement > standard hemodialysis > peritoneal dialysis

Bodd et al. Morphine-6-glucuronide might mediate the prolonged opioid effect of morphine in acute renal failure. *Hum Exp Toxicol*. 1990;9:317-321.

Favorable Opioids in Renal Impairment

Buprenorphine

- High first pass hepatic clearance, then metabolized sequentially by CYP3A4 to norbuprenorphine, then conjugated principally by UGT2B7
  - Glucuronidated parent drug and metabolite are largely inactive
- Buprenorphine clearance in patients with normal and impaired renal function is similar
- Buprenorphine has a ceiling effect on respiratory depression and is well tolerate in the elderly
- Levels are stable on hemodialysis

Dahan et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. *Br J Anaesth*. 2006;96:627-632.
Pergolizzi et al. Opioids and the management of chronic severe pain in the elderly; consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). *Pain Pract*. 2008;8:287-313.

Fentanyl

- Metabolized to the inactive metabolite, norfentanyl, by CYP3A4
  - Less than 1% excreted in the urine
- Fentanyl clearance is reported to be impaired in severe renal failure and the critically ill
- Around-the-clock dosing leads to accumulation in muscle and fat; prolonged clearance with discontinuation
- Transdermal and transmucosal fentanyl products are not approved for opioid-naïve patients
- Fentanyl is not dialyzed

Davies et al. Pharmacokinetics of opioids in renal dialysis. *Clin Pharmacokinet*. 1996;31:410-422.
Koehntop et al. Fentanyl pharmacokinetics in patients undergoing renal transplantation. *Pharmacotherapy*. 1997;17:746-752.
Huhn et al. Protracted renal clearance of fentanyl in persons with opioid use disorder. *Drug Alcohol Depend*. 2020;214:108147.

Hydromorphone

- Conjugated by UGT2B7 to hydromorphone-3-glucuronide (HM-3-G)
  - No analgesic effect; neurotoxic compound
- Hydromorphone serum levels increase in renal failure
- HM-3-G accumulates between dialysis treatments but is removed by HD
- Dose reduce with renal impairment

Durnin et al. *Proc West Pharmacol Soc*. 2001;44:81-82.
Davison et al. *J Opioid Manag*. 2008;4:335-336, 9-44.
Dean. *J Pain Sympt Manag*. 2004;28(5):497-504.

Methadone

- Metabolized by multiple CYP enzymes; primarily 2B6 to an inactive metabolite (EDDP)
- Methadone and EDDP are compensatorially excreted in stool as kidneys fail to function
- Methadone has a long and variable elimination half-life
- Prolongs QTc, may cause Torsades de Pointe
- Associated with MANY drug interactions; patients with advanced CKD have polypharmacy
- Start LOW and increase SLOWLY

Vodoz et al. *Praxis* (Bern 1994). 2003;92:1748-1750.
McKillop. *J Ren Care*. 2013;39:200-207.
www1.health.gov.au/internet/publications/publishing.nsf/Content/drugtreat-pubs-meth-toc~drugtreat-pubs-meth-s1.
Ahmad. *Biochem Pharmacol*. 2018;153:196-204.
Sommer. *Drugs Aging*. 2020;37(5):359-372.

Other Favorable Opioids

- Nalbuphine
  - MOR antagonist and kappa opioid receptor partial agonist
  - Metabolized by UGT2B7 to an inactive glucuronide metabolite
  - Better tolerated than morphine and has a ceiling on respiratory depression
- Tapentadol
  - Glucuronidated to inactive metabolites
  - Safe to use in renal failure; no adjustment needed for mild to moderate CKD
  - No data available in severe CKD or dialysis
  - Likely dialyzed to some extent due to low protein binding, low molecular weight, average water solubility

Zeng et al. A comparison of nalbuphine with morphine for analgesic effects and safety: meta-analysis of randomized controlled trials. *Sci Rep*. 2015;5:10927.
Vieira et al. [Opioids for cancer pain and its use under particular conditions: a narrative review]. *Acta Med Port*. 2019;32:388-399.
Coluzzi et al. Safe use of opioids in chronic kidney disease and hemodialysis patients: tips and tricks for non-pain specialists. *Ther Clin Risk Manage*. 2020;16:821-837.

Unfavorable Opioids in Renal Impairment

Morphine

- Metabolized by UGT2B7 to:
  - Inactive metabolite morphine-3-glucuronide (M3G)
  - Active metabolite morphine-6-glucuronide (M6G)
- Both metabolites are largely excreted in urine and serum levels increase with loss of renal function
- M6G binds to MOR1 more efficiently
  - M6G is more active at MOR2 subtype receptors
  - MOR2 is responsible for opioid related respiratory depression and GI side effects
  - IT M6G is a much more potent analgesic than morphine
- Reports of morphine toxicity in renal failure is due to M6G – guilt by association? Low doses probably acceptable

Portenoy et al. *Clin Pharmacol Ther*. 1992;52:422-431.
Frances. *Prog Clin Biol Res*. 1990;328:477-480.

Other Unfavorable Opioids

- Codeine
  - Metabolized by UGT2B7 to codeine-6-glucuronide
  - Metabolized by CYP3A4 to norcodeine
  - Metabolized by 2D6 to morphine
  - Severe toxicity and respiratory arrest seen with codeine in advanced CKD
  - AVOID!
- Hydrocodone
  - Metabolized by hydromorphone through CYP2D6
  - Avoid in CKD
- Dihydrocodeine
  - Little evidence to guide decision-making

Guay et al. Pharmacokinetics and pharmacodynamics of codeine in end-stage renal disease. *Clin Pharmacol Ther*. 1988;43:63-71.
Monte et al. The effect of CYP2D6 drug-drug interactions on hydrocodone effectiveness. *Acad Emerg Med*. 2014;21:879-885.

Oxycodone

- Oxycodone
  - Metabolized by CYP2D6 to active metabolite oxymorphone
  - Metabolized by CYP3A4 to noroxycodone and noroxymorphone
  - Conjugated to glucuronide metabolites
  - Noroxycodone and noroxymorphone are the major metabolites
  - Oxycodone is removed by hemodialysis
  - Recommendations for using oxycodone vary significantly (do not use to use with caution)

Dean. Opioids in renal failure and dialysis patients. *J Pain Symptom Manage*. 2004;28:F636-645.
Leuppi-Taegtmeyer et al. Pharmacokinetics of oxycodone/naloxone and its metabolites in patients with end-stage renal disease during and between haemodialysis sessions. *Nephrol Dial Transplant*. 201;34:692-702.
Foral et al. Oxycodone accumulation in a hemodialysis patients. *South Med J*. 2007;100:212-214.

Tramadol

- Weak MOR agonist and inhibits reuptake of serotonin and norepinephrine
- O-des-methyltramadol is derived through CYP2D6
- Also metabolized to inactive metabolites N-desmethyltramadol through CYP 3A4 and 2B6
- 90% excreted in urine, accumulate with GFR < 30 ml/min
- Accumulation can lead to respiratory arrest, seizures, serotonin syndrome
- Limit dose to 100 mg twice daily and with dialysis limit to 50 mg twice daily

Raffa et al. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an “atypical” opioid analgesic. *J Pharmacol Exp Ther*. 1992;260:275-285.
Kitson et al. Tramadol and severe serotonin syndrome. *Anaesthesia*. 2005;60:934-935.
Labate et al. Tramadol and new-onset seizures. *Med J Aust*. 2005;182:42-43.
Pham et al. Clin Kidney J. 2017;10(5):688-697.

Dialysis and Opioid Management

Opioid	Recommendation
Buprenorphine	No change in dosing
Fentanyl	Generally safe, start with low doses and go slow
Methadone	No change in dose
Nalbuphine	No change in dose
Tapentadol	No change in dose
Hydromorphone	Generally, start at lower doses; can give around the clock
Morphine	Use cautiously, dosing strategy unknown in CKD; use low dose or PRN is used
Oxycodone	Best to avoid
Tramadol	Best to avoid

Case 1

- MJ is a 72 year old man admitted to hospice with a diagnosis of colon cancer with metastasis to the spine.
- His persistent pain seems a mix of nociceptive and neuropathic pain so his prescriber started methadone, and dexamethasone with good success.
- Unfortunately MJ has stage 4 CKD, and his prescriber is unsure whether to use an additional methadone dose for breakthrough pain, or to go with the opioid he usually prescribes for breakthrough pain – morphine.
- How would you advise the prescriber?

Self-Assessment!

- Which of the following opioids should be AVOIDED in patients with renal impairment?

A. Buprenorphine
B. Fentanyl
C. Codeine
D. Methadone
E. Hydromorphone

Self-Assessment!

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D. Methadone
E. Hydromorphone

Pain in Liver Impairment

- "Liver disease" – what are we referring to?
- Acute liver disease
  - Drug or alcohol toxicity or a viral infection
- Chronic liver disease
  - Alcohol use, autoimmune hepatitis, genetic disorders, viral hepatitis B or C
- Hepatocellular carcinoma (HCC), often a result of cirrhosis
- Pain is a common symptom in chronic liver disease or cirrhosis; 30-79%
- HCC is the third most likely cause of cancer-related deaths worldwide
  - 80% have underlying liver disease or cirrhosis; 90% report pain
- Opioids commonly used to treat pain

Sarin S et al. Global burden of liver disease: a true burden on health sciences and economies! 2021.
Soleimanpour et al. Opioid drugs in patients with liver disease: a systematic review. *Hepat Mon*. 2016;16(4):e32636.

PROs and CONs of Opioid Therapy

- Majority of patients with cirrhosis or HCC report visceral abdominal pain
- Opioids may have direct and indirect effects on liver causing injury
- Liver is the primary site of biotransformation of opioids from parent drug to one or more metabolites (may or may not be pharmacologically active)
  - Opioids are metabolized by the CYP450 system in the liver or undergo glucuronidation via UGT2B7 in the liver
  - Oxidation more affected by liver impairment
  - Glucuronidation more preserved in liver disease

Peng et al. Symptom prevalence and quality of life of patients with end-stage liver disease: a systematic review and meta-analysis. *Palliat Med*. 2019;33(1):24-36.
Klinge et al. The assessment and management of pain in cirrhosis. *Curr Hepatol Rep*. 2018;17(1):42-51.

PROs and CONs of Opioid Therapy

- Opioids with a high “first pass” hepatic extraction (morphine, fentanyl) may have higher bioavailability in advanced liver disease
- Oxycodone, hydromorphone, hydrocodone, codeine are metabolized to active metabolites (required CYP450) – effect reduced/absent in advanced liver disease
- Difficult to classify the degree of hepatic impairment
  - Child-Pugh system; MELD system
- Rule of thumb – start an opioid at a reduced dose, allow a longer period of time between dosage

Verna, Schluger, Broan. Opioid epidemic and liver disease. *JHEP Reports*. 2019;1:240-255.
Bergasa et al. Up-regulation of central mu-opioid receptors in a model of hepatic encephalopathy: a potential mechanism for increased sensitivity to morphine in liver failure. *Life Sci*. 2002;70:1701-1708.
Moon et al. Opioid prescriptions are associated with hepatic encephalopathy in a national cohort of patients with compensated cirrhosis. *Aliment Pharmacol Thera*. 2020;51:652-660.

General Conclusions on Opioids in Liver Impairment

Category	Opioids
Preferred	Fentanyl Remifentanil
Use with caution	Buprenorphine Hydrocodone Hydromorphone Methadone Morphine Oxycodone Tapentadol Tramadol
Avoid	Codeine Meperidine

www.mypcnow.org/fast-fact/opioid-use-in-liver-failure/

Preferred Opioids in Liver Disease

- Fentanyl
  - Lipid-soluble, highly protein bound
  - Metabolized by CYP3A4 to inactive metabolites
  - Considered acceptable in hepatorenal syndrome (caution with continuous infusion)
  - Transdermal fentanyl has not been adequately studied in liver failure
- Remifentanil
  - Ultra-short-acting synthetic opioid agonist
  - Does not undergo hepatic metabolism; metabolized by plasma and tissue esterase, which is not affected by liver dysfunction

Bosilkovska et al. Analgesics in patients with hepatic impairment. Pharmacology and clinical implications. *Drugs.* 2012;72(12):1645-1669.
Habeter et al. Fentanyl pharmacokinetics in anaesthetized patients with cirrhosis. *Br J Anaesth*. 1982 Dec;54(12):1267-1270.

Use with Caution

- Buprenorphine
  - Partial mu-opioid agonist, metabolized by CYP450
  - Buprenorphine and norbuprenorphine further glucuronidated
  - Liver damage has been reported, and may see increase in liver enzymes
- Hydrocodone
  - Metabolized by CYP450 to hydromorphone and other metabolites
  - Metabolism may be reduced in liver disease, and clearance may be reduced with a prolonged half-life of elimination
  - Start at a lower dose and longer dosing interval
  - Often with acetaminophen – Yikes!

Zuin et al. Acute liver and renal failure during treatment with buprenorphine at therapeutic dose. *Dig Liv Dis*. 2008;41(7):e8-e10.
Donaher et al. Managing opioid addiction with buprenorphine. *Am Fam Physician*. 2006;73(9):1573-1578.

Use with Caution

- Hydromorphone
  - Undergoes significant first pass effect; reduced in cirrhosis (greater BAB)
  - Half-life same with moderate hepatic impairment; prolonged half-life with severe liver disease
- Methadone
  - Metabolized by CYP450 3A4, 2B6; metabolites not associated with toxicity
  - Mild-to-moderate alcoholic liver disease – methadone disposition similar to controls
  - Severe liver disease – longer half-life

Bosilkovska et al. Analgesics in patients with hepatic impairment. Pharmacology and clinical implications. Drugs. 2012;72(12):1645-1669.
Durnin et al. Pharmacokinetics of oral immediate-release hydromorphone (Dilaudid IR) in subjects with moderate hepatic impairment. *Proceed Western Pharmacol Soc*. 2001;44:83-84.
Novick et al. Effect of severe alcoholic liver disease on the disposition of methadone in maintenance patients. *Alcohol Clin Exp Res*. 1985;9(4):349-354.
Novick et al. Methadone disposition in patients with chronic liver disease. *Clin Pharmacol Ther*. 1981;30(3):353-363.

Use with Caution

- Morphine
  - Metabolized by glucuronidation to M3G and M6G
  - Glucuronidation usually preserved despite reduced liver function; morphine clearance prolonged by up to 60% in cirrhosis
  - Oral bioavailability significantly higher in liver disease
- Oxycodone
  - Metabolized by CYP3A4 and 2D6; reduced production in liver disease
  - Maximum oxycodone serum level may be increased by up to 40%, AUC increased 90%, elimination half-life prolonged by 2 hours

Hasselstrom et al. The metabolism and bioavailability of morphine in patients with severe liver cirrhosis. *Br J Clin Pharmacol*. 1990;29:289-297.
Kotb et al. Pharmacokinetics of controlled release morphine (MST) in patients with liver cirrhosis. *Br J Anaesth*. 1997;79(6):804-806.
Kaiko. Pharmacokinetics and pharmacodynamics of controlled-release opioids. *Acta Anaesthesiol Scand*. 1997;41(1 Pt 2):166-174.

Use with Caution

- Tapentadol
  - Dual action analgesic; oral bioavailability about 30% (increases with liver disease)
  - Primarily metabolized by conjugation; lesser effect from CYP450
  - AUC with mild and moderate hepatic impairment are 1.4 and 2.5 times normal
  - No data on use in severe impairment
- Tramadol
  - Dual mechanism analgesic
  - Metabolized by CYP2D6; diminished in liver impairment
    - Analgesic effects may be primarily derived from the monoaminergic modulation
  - Bioavailability higher in liver disease

Nucynta Prescribing Information.
Kotb HIM et al. Pharmacokinetics of oral tramadol in patients with liver cancer. *J Opioid Manage.* 2008;4(2):99-104.

Opioids to Avoid in Liver Disease

- Codeine
  - Weak opioid agonist; most of analgesic activity is conversion of 10% parent drug to morphine
  - CYP2D6 activity is diminished in liver impairment; less morphine produced
- Meperidine
  - Synthetic opioid with a neurotoxic metabolite – normeperidine
  - In patients with cirrhosis there is a significant reduction in meperidine clearance and doubling of elimination half-life

Case 2

- JP is a 58 year old man with hepatocellular carcinoma and wide-spread metastasis. He also has advanced cirrhosis.
- Dr. Jones, JP's prescriber, is concerned about using acetaminophen due to the patient's liver issues, and the patient is at high risk for bleeding, so the prescriber doesn't want to use a NSAID.
- Dr. Jones also knows all the opioids are metabolized by the liver, so what's left – chew on a stick?
- Dr. Jones would really like to use methadone – but the pharmacokinetics are tricky and it's got that LONG half-life…sigh.
- What would you advise Dr. Jones do in this case?

Conclusion

- When selecting an opioid for a specific patient, consider
  - Patient-related variables
  - Drug-related variables
- Consider pharmacokinetic and pharmacodynamic changes of opioid therapy in renal and/or hepatic impairment
- Dose adjust or carefully select opioids

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