Pain Management in Hepatic and Renal Dysfunction

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Objectives

- Review the pharmacologic basis for medications used in pain management
- Identify pain medications which should be avoided in patients with hepatic dysfunction
- Identify pain medications which should be avoided in patients with renal dysfunction
- Determine the most appropriate pain regimen if given a patient with hepatic and/or renal dysfunction
Definitions of Pain

- **Chronic**
  - Lasting longer than 6 months
- **Nociceptive**
  - Pain coming from injured body tissues
- **Neuropathic**
  - Pain involving damage to the nervous system
- **Mixed**
  - Combination of nociceptive and neuropathic

Principles of Pain Management

- Symptom Relief
- Disease Specific Tx
- Patient Education
- Specialist Referral
- Psychology
- Occupational and Physical Therapy

WHO Analgesic Ladder

1. Mild
   - Non-opioid
     +/− adjuvant

2. Mild-Moderate
   - Opioid
     +/− non-opioid
     +/− adjuvant

3. Moderate-Severe
   - Opioid
     +/− non-opioid
     +/− adjuvant
Hepatic Dysfunction

- Liver is the major site of metabolism for most opioids
- Oxidation is the major metabolic pathway for most opioids
  - Reduced in hepatic dysfunction
    - Decreased drug clearance
    - Increased oral bioavailability (reduced 1st pass metabolism)
- Glucuronidation occurs in a few opioids
- Generally managed by reducing dose or extending dosing intervals
Renal Dysfunction

- Analgesic therapy is commonly prescribed for people with renal disease
- 37-50% of hemodialysis patients experience chronic pain of which 82% is moderate – severe pain
- Pain is often multi-factorial
- Differentiate nociceptive versus neuropathic pain

### Causes of Pain in Dialysis Patients

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoarthritis + osteoporosis</td>
<td>31%</td>
</tr>
<tr>
<td>Inflammatory arthritis</td>
<td>7%</td>
</tr>
<tr>
<td>Renal osteodystrophy</td>
<td>5%</td>
</tr>
<tr>
<td>Peripheral polyneuropathy</td>
<td>13%</td>
</tr>
<tr>
<td>Carpel tunnel</td>
<td>2%</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>9%</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>2%</td>
</tr>
<tr>
<td>Related to dialysis procedure</td>
<td>14%</td>
</tr>
<tr>
<td>Not yet diagnosed</td>
<td>18%</td>
</tr>
<tr>
<td>Other (trauma, calcium phosphate, etc)</td>
<td>18%</td>
</tr>
</tbody>
</table>

Many patients have more than 1 cause for their pain

Non-Opioids
Acetaminophen

- Analgesic and antipyretic
- Metabolized by the liver
  - Dose reduction or avoidance in liver disease
- Does not require dosage adjustment in chronic kidney disease (CKD) or end-state renal disease (ESRD)
- Non-narcotic of choice for mild to moderate pain in patients with CKD

NSAIDs

- Can increase bleeding risk
  - Decrease platelet function and gastrointestinal mucosa
- Generally avoid in liver disease
- Should be used for precise indications and a limited time in ESRD (ie, gout flare)
- Can exacerbate HTN and lead to edema
- Reversible reduction in GFR
  - Highest risk in patients with CHF, cirrhosis, elderly, dehydrated, or receiving diuretic therapy

Normal Non-Opioid Dosing

- Acetaminophen
  - 325-650 mg q4-6 hrs prn
  - 1 gm 3-4 x daily
  - Max dose: 4gm/24hr

- ASA
  - 325-650 mg q4-6 hrs prn
  - 500 mg q3hr prn
  - 1000 mg q6hr prn
  - Max dose: 4 gm/24hr

- Ibuprofen
  - 400 mg q4-6 hr prn
  - Max dose: 3200 mg/24 hr

- Naproxen
  - 250-500 mg BID prn
  - Max dose: 1500 mg/24 hr

- Celecoxib
  - 200 mg/day or 100 mg BID

Adjuvants
TCAs

- Indicated for neuropathy pain
- Undergoes primary hepatic metabolism
- Amitriptyline is converted to nortriptyline in the liver
- Little data to indicate dose reduction in renal dysfunction
- TCAs have been associated with acute liver failure (2-10% increase in LFTs)
- In hepatic dysfunction contraindicated
Carbamazepine

- Indicated in neuropathic pain
- Inducer of hepatic enzymes
- Undergoes primary hepatic metabolism
- Less than 1% excreted unchanged in the urine
- Contraindicated in severe hepatic dysfunction

Gabapentin

- Indicated for neuropathic pain
- Primary renal excretion
- $T\frac{1}{2}$ extended in ESRD (up to 132 hrs)
- Cleared by hemodialysis
- Dose reduction required in renal failure
- Safe to use in hepatic dysfunction

Dosing Recommendations

- APAP
  - Renal
    - EstCrCl 10-50 ml/min: Administer q6hr
    - EstCrCl < 10 ml/min: Administer q8hr
  - Hepatic
    - Avoid if possible
    - < 2 gm/24hr
- TCAs
  - Renal
    - Not dialyzable
  - Hepatic
    - Contraindicated
Dosing Recommendations

- Carbamazepine
  - Renal
    - No dosing change
  - Hepatic
    - Contraindicated in severe dysfunction
- Gapapentin
  - Renal
    - EstCrCl ≥60 ml/min: 300-1200 mg 3 times/day
    - EstCrCl >30-59 ml/min: 200-700 mg twice/day
    - EstCrCl >15-29 ml/min: 200-700 mg/day
    - EstCrCl <15 mL/minute: 100-300 mg/day
  - Hepatic
    - No dosing change
Opioids
Morphine

- Primary site of metabolism is the liver
  - Glucoronidation
  - Principle metabolite is morphine-3-glucuronide (M3G) – no opioid agonist activity
  - Morphine-6-glucuronide is a metabolite highly cleared through kidneys
- Extrahepatic metabolism contributes to 40% of total body clearance
- About 10% of morphine excreted unchanged in the urine

Morphine

- $T_{1\frac{1}{2}}$ of M6G can be prolonged from 2.1 hrs up to 27 hrs in ESRD
- Oral doses will cause more accumulation than parenterally administered doses
- Metabolites can be removed via hemofiltration (47-100%) and hemodialysis (24-84%) in ESRD

Hydromorphone

- Semi-synthetic derivative of morphine
- Metabolized to hydromorphone-3-glucuronide (H3G)
- H3G can accumulate in renal failure (4 fold increase)
- May be safe in renal dysfunction
  - Dose reduce and extend dosing interval
- Undergoes 1st pass metabolism
  - Increased bioavailability in hepatic disease
Methadone

- Not the best choice for acute pain
- Utility in controlling chronic pain
- High bioavailability of 80%
- 20% renally excreted as unchanged
- In renal dysfunction
  - Initiate lower starting dose
- Contraindicated in hepatic dysfunction

Fentanyl

- Subject to high hepatic extraction ratio
  - Decreased clearance in altered hepatic blood flow
- No active metabolites
- Ideal agent for use in renal failure
  - Exception is presence of uremia
    - Prolonged clearance (requires ½ of usual dose)
- Hepatic failure is likely to impair clearance
  - Requires dose reduction

Tramadol

- Metabolized in liver to active metabolite (O-demethyl tramadol) which is excreted renally
- T½ is increased x 2 in CKD patients (10 hours)
- Reports of respiratory depression in CKD patients
- Avoid concomitant administration with SSRIs

Codeine

- Mainly metabolized in liver
- 10% metabolized to morphine
- Case reports of prolonged CNS depression in ESRD
- Use with caution in ESRD (reported $T\frac{1}{2}$ up to 27 hrs)
- Not recommended to use in hepatic or renal dysfunction

Hydrocodone

- Greater potency than codeine
- Commonly combined with APAP
- Combo products limit dose titration
  - APAP and risk of hepatotoxicity
  - Limit APAP to 2gm/day max in liver disease

Oxycodone

- Metabolized to noroxycodone and oxymorphone
- Less than 10% excreted unchanged in urine
- T½ prolonged in ESRD
- In renal dysfunction
  - Initiate low dose and titrate cautiously
- Decreased metabolism in liver disease
  - Initiate low dose and titrate cautiously

## Routes of Administration

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intravenous</th>
<th>Oral</th>
<th>Transdermal</th>
<th>Rectal</th>
<th>Spinal</th>
<th>Subcutaneous</th>
<th>Sublingual</th>
<th>Transmucosal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowel obstruction, vomiting, dysphagia</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Breakthrough pain</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>++(^{\dagger})</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Coagulation disorders, immunosuppression</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>-(^{+\dagger})</td>
<td>-(^{+\dagger})</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Cognitive failure (sedation)</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Colostomy, hemorrhoids, anal fissures</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Frequent dose change</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Generalized edema</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Initial titration</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

+, May be indicated; ++, indicated; -, contraindicated. *Short-release formulation only. \(^{\dagger}\)Patient-controlled analgesia. \(^{+\dagger}\)May cause bleeding.

Opioid Pharmacokinetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>F (%)</th>
<th>PB (%)</th>
<th>CL (ml/min)</th>
<th>V₅₀ (L)</th>
<th>t₁/₂β (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfentanil</td>
<td>88-92</td>
<td></td>
<td>300-500ᵃ</td>
<td>30-70ᵃ</td>
<td>1.5-2</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>50-55ᵇ</td>
<td>~96</td>
<td>650-1300</td>
<td>200-400</td>
<td>3-6 (-23ᶜ)</td>
</tr>
<tr>
<td>Codeine</td>
<td>50-55</td>
<td>4-7</td>
<td>210-350ᵃ</td>
<td></td>
<td>2.5-3.5</td>
</tr>
<tr>
<td>C-Demethyl-tramadol</td>
<td>~9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dextropropoxyphene</td>
<td>30-70</td>
<td>80</td>
<td>600-1200</td>
<td>700-1800</td>
<td>11-16</td>
</tr>
<tr>
<td>Dilaudid (codeine)</td>
<td>12-34</td>
<td></td>
<td>80-90ᵃ</td>
<td></td>
<td>3.3-4.5</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>80-86</td>
<td></td>
<td>600-1000</td>
<td>200-560ᵃ</td>
<td>3-4 (-15ᵈ)</td>
</tr>
<tr>
<td>Methadone</td>
<td>41-99</td>
<td>70-90</td>
<td>50-200</td>
<td>240-330ᵃ</td>
<td>19-58</td>
</tr>
<tr>
<td>Morphine</td>
<td>15-50</td>
<td>20-35</td>
<td>800-2000</td>
<td>70-330</td>
<td>1.5-4.5 (-2)</td>
</tr>
<tr>
<td>Morphine-3-glucuronide</td>
<td>150-190</td>
<td></td>
<td>8-30</td>
<td></td>
<td>1.2</td>
</tr>
<tr>
<td>Norpethidine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12-24</td>
</tr>
<tr>
<td>Norpropoxyphene</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>23-37</td>
</tr>
<tr>
<td>Nortilidine</td>
<td>99</td>
<td></td>
<td></td>
<td></td>
<td>3.3-4.9</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>&lt;20</td>
<td></td>
<td>1200-1700</td>
<td>350-500</td>
<td>2-5 (-10ᶠ)</td>
</tr>
<tr>
<td>Pethidine (meperidine)</td>
<td>48-56</td>
<td>60-80</td>
<td>470-730ᵃ</td>
<td>260-320ᵃ</td>
<td>3-7</td>
</tr>
<tr>
<td>Remifentanil</td>
<td></td>
<td></td>
<td>3000-5000</td>
<td>25-40</td>
<td>10-20 min</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>91-93</td>
<td></td>
<td>700-1500ᵃ</td>
<td>120-380ᵃ</td>
<td>2.5-3.5 (-12.8⁰)</td>
</tr>
<tr>
<td>Tilidine</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>65-75</td>
<td></td>
<td>440-490</td>
<td>200-300</td>
<td>5-6</td>
</tr>
</tbody>
</table>

# Normal Opioid Dosing

<table>
<thead>
<tr>
<th>Agent</th>
<th>Oral analgesic daily dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>15–60 mg every 4–6 hours</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>10–40 mg every 12 hours (controlled-release dosage formulation; 7.5 mg every 6 hours immediate-release dosage formulations)</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>5–10 mg every 4–6 hours prn or 10–20 mg every 6 hours prn in opioid-naive patients; maximum of 20 mg per dose</td>
</tr>
<tr>
<td>Oxymorphone extended-release (ER)</td>
<td>5, 10, 20, or 40 mg PO every 12 hours</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>65 mg every 4 hours prn, not to exceed 360 mg/day (HCl salt); 100 mg every 4 hours prn, not to exceed 600 mg/day (napsylate salt)</td>
</tr>
<tr>
<td>Morphine</td>
<td>10–30 mg every 4 hours prn</td>
</tr>
<tr>
<td>Fentanyl (transdermal-dose semipermeable membrane patch)</td>
<td>12–25 μg/hour, initial dose every 72 hours; adjust dose as needed</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2 mg every 4–6 hours prn, up to 4 mg every 4–6 hours prn for severe pain</td>
</tr>
<tr>
<td>Methadone</td>
<td>2.5–10 mg every 3–4 hours prn for well-selected patients (black-box warning for arrhythmias)</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>2–3 mg every 6–8 hours, not to exceed 6–12 mg/24 hours</td>
</tr>
<tr>
<td>Tramadol</td>
<td>50–100 mg every 4–6 hours, not to exceed 400 mg/day; 37.5–75 mg/day when combined with acetaminophen formulation; 100–300 mg/day (extended-release dosage formulation)</td>
</tr>
</tbody>
</table>

Prn, as needed; PO, orally.

*All doses are designed to meet patient-specific needs, and there is no ceiling dose on most opioids.

Five Essentials of Opioid Dosing

- “By mouth”
  - Give orally whenever possible
- “By the clock”
  - Schedule doses over 24 hrs on a regular basis
- “By the ladder”
  - WHO analgesic ladder
- “For the individual”
  - The “right” dose is the dose that relieves pain without causing unacceptable side effects
- Attention to detail
  - Pain changes over time; Assess; Reassess

# Opioid Selection in Hepatic Disease

<table>
<thead>
<tr>
<th>Not Recommended</th>
<th>Use with Caution</th>
<th>Safest in Liver Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>Morphine</td>
<td>Fentanyl</td>
</tr>
<tr>
<td>Codeine</td>
<td>Oxycodone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydromorphone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tramadol</td>
<td></td>
</tr>
</tbody>
</table>

# Opioid Selection in Renal Failure

<table>
<thead>
<tr>
<th>Not Recommended</th>
<th>Use with Caution</th>
<th>Safest in Renal Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meperidine</td>
<td>Hydromorphone</td>
<td>Fentanyl</td>
</tr>
<tr>
<td>Codeine</td>
<td>Oxycodone</td>
<td>Methadone</td>
</tr>
<tr>
<td>Morphine</td>
<td>Oxymorphone</td>
<td></td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>Tramadol</td>
<td></td>
</tr>
</tbody>
</table>

Dosing Recommendations

- Morphine
  - Renal (Avoid if possible)
    - EstCrCl 10–50 ml/min: 75% normal dose
    - EstCrCl < 10 ml/min: 50% normal dose
  - Hepatic
    - Severe dysfunction reduce dose

- Oxycodone
  - Renal
    - Severe dysfunction reduce dose
  - Hepatic
    - Severe dysfunction reduce dose
Dosing Recommendations

- Hydromorphone
  - Renal
    - Severe dysfunction reduce dose
  - Hepatic
    - Severe dysfunction reduce dose
- Codeine
  - Renal (Avoid if possible)
    - EstCrCl 10- 50 ml/min: 75 % normal dose
    - EstCrCl < 10 ml/min: 50% normal dose
  - Hepatic
    - Contraindicated in severe dysfunction
Dosing Recommendations

- Fentanyl
  - Renal
    - No adjustment needed
  - Hepatic
    - No adjustment needed
- Methadone
  - Renal
    - EstCrCrl < 10 ml/min: 50-75% normal dose
  - Hepatic
    - Contraindicated in severe dysfunction
Dosing Recommendations

- Meperidine
  - Renal
    - Contraindicated
  - Hepatic
    - Reduce dose in severe dysfunction
- Propoxyphene
  - Renal (Avoid if possible)
    - Contraindicated if EstCrCl < 10 ml/min
  - Hepatic
    - Reduce dose in severe dysfunction
Dosing Recommendations

- **Tramadol**
  - **Renal**
    - EstCrCl < 30 m/min: 50-100 mg po q12h (max 200 mg/day of IR formulation)
    - ER formulation contraindicated if EstCrCl < 30 ml/min
  - **Hepatic**
    - Cirrhosis: 50 mg po q12h (IR formulation)
    - ER formulation contraindicated in severe (Child-Pugh Class C) hepatic dysfunction.