Analgesic Prescribing with Renal or Liver Impairment for Palliative Care Patients

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Learning Objectives

- Understand the impact of renal and liver impairment on analgesic prescribing in palliative care
- Learn about referral options for patients with renal and liver impairment on the NW Coast
Outline the Session

- What are the issues with Kidney / Liver Impairment and using Analgesics?

- Clinical Scenario with Renal Impairment
- Renal Impairment
- Available Analgesics in Renal impairment

- Clinical Scenario with Liver Impairment
- Liver Impairment
- Available Analgesics in Liver impairment

- Referral Options in NW Tasmania

- MCQ x 3
History:
57 years old Mr R with Metastatic Prostate Carcinoma with Bony metastasis. Had DXT; now on Hormone therapy. Stable disease (PSA = 23) 3/12 ago.

He is admitted with 2/52 history of drowsiness, jerks & ache in back & legs. Unable to walk with movement related pain. Previously, he was reasonably active (AKPS = 90%) and admitted with poor functional-status (AKPS = 40%).

Investigations: B/L Hydronephrosis; eGFR = 25 & Cr = 234 & PSA = 210.

Current Pain Medications:
He is on MS Contin 60 mg BD + Endone (5mg x 2) prn + Panamax 2 tab tds

• What are the issues you find in this patient?

• What is your immediate management?

• What are the next step of management?
What are the issues you find in this patient?

- Prostate cancer disease progression leads to B/L Hydronephrosis.
- B/L Hydronephrosis ➔ renal impairment ➔ Accumulation of opioid metabolites ➔ His usual opioid dose become toxic ➔ Toxic Symptoms
- Increased pain despite of current medications
How do we manage Opioid Toxicity?

Opioid Toxicity

Toxic Symptoms & No Pain
- Reduce the current Opioid by 30-50%

Toxic Symptoms & Increasing Pain
- Opioid Switch
What is the aim of immediate management in this patient?

- Pain Control
- Use renal friendly opioid and prevent further Renal damage ➔ It helps in ↓ Toxicity, ↓ Drowsiness & Improve AKPS

How are you going to do?

- Opioid Switch
Available renal friendly opioids for this patient’s eGFR (= 25) are:

- **Hydromorphone** - oral } Short acting drug
  - sub cut Inj }
  - Syringe Driver over 24 hours

- **Fentanyl** - Patch (long Acting)  - Durogesic Patch
  - Lozenge (Short Acting)  - Actiq Lozenge
  - Injection (short acting)

- **Alfentanyl Injection** (only form) - Syringe Driver for 24 hour
  - Sub cut Inj (short acting - prn)

- **Weekly Norspan patch** ➔ Max dose: 40mcg / hour;
  if more than 40mcg/hr required, we switch to fentanyl patch!
How to do the Calculation for this patient?

The equivalent dose is……

- MS Contin 60mg po BD = Total of 120mg Morphine (Oral)

- Hydromorphone [120mg / 6] = Total 20mg Hydromorphone (Oral)
  = Total of 7mg Hydromorphone in the Syringe Driver over 24 hours (3:1)

- Alfentanyl [120mg / 30] = Alfentanyl 4mg sc in syringe Driver

- Fentanyl [90mg Morphine = 25mcg/hr Fentanyl patch]
  = Fentanyl Patch approx. 33.3mcg/hr
  (Next available patch is 25 +12 mcg/hr)

Why NOT Norspan Patch Here?
The required Norspan patch exceed 40mcg/hr
How to Calculate the Patch dose....?

- **Transdermal Fentanyl patch and oral Morphine**
  
  **Conversion Ratio:** Transdermal Fentanyl patch : Oral Morphine = 1 : 150  
  *(Ratio varies from 100 to 150 But taken as 150; Reference: APM; European Pall Care guidelines)*

  E.g.: Patient is on 25 mcg/hr Fentanyl patch; What is the equivalent Morphine?

  \[
  = \frac{25 \text{ [mcg / hour patch]} \times 24 \text{ [hours]} \times 150 \text{ [conversion ratio]}}{1000 \text{ [to make milligrams]}} = 90 \text{ mg Oral Morphine}
  \]

- **Transdermal Buprenorphine patch and oral Morphine**
  
  **Conversion Ratio:** Transdermal Norspan patch : Oral Morphine = 1 : 60  
  *(Ratio varies from 60 to 100 But taken as 60; Reference: APM; European Pall Care guidelines)*

  E.g.: Patient is on 10 mcg/hr Norspan patch; What is the equivalent Morphine?

  \[
  = \frac{10 \text{ [mcg / hour patch]} \times 24 \text{ [hours]} \times 60 \text{ [conversion ratio]}}{1000 \text{ [to make milligrams]}} = 14.4 \text{ mg Oral Morphine}
  \]
Next step of management for this patient...

- Opioid Titration – to achieve better pain control

- Using adjuvant medications according to opioid response

- Contact Oncology Team; inform the admission symptoms; Patient’s functional status & his PSA level on this time! for further active treatment....?
Drug Metabolism

The liver is the primary organ for clearance of most drugs. Non-polar, lipid-soluble drugs are converted to more polar and water-soluble compounds.

Water soluble drugs are excreted unchanged in the kidneys by glomerular filtration and/or renal tubular secretion.

Drug metabolism in Liver is classified in two phases:

- **Phase I:** reactions involve oxidative, reductive or hydrolytic reactions that are commonly catalysed by the mixed function oxidase system. The cytochrome P450 is the major enzyme system for oxidation of drugs.

- **Phase II:** reactions "conjugate" a water soluble entity, forming a more polar and water soluble metabolite that can be more easily excreted in the urine and/or bile.
Drug Metabolism

- Drug molecule
  - Phase I: More hydrophilic metabolite
  - Phase II: Conjugate
  - De-conjugation and reuptake (entero-hepatic cycling)

- Kidney
  - Urine

- Intestines
  - Bile
  - Faeces
In patients with liver failure, reduced metabolism usually results in accumulation of the parent drug in the body with repeated administration.

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 CNS toxicity from either the parent drug or its metabolites.
Vicious Cycle of Opioid-Induced Neurotoxicity

- Opioid tolerance
- Mild myoclonus (e.g.: with sleeping)
- Severe myoclonus
- Seizures, Death

- Delirium
- Agitation
- Opioids Increased
- Misinterpreted as Pain

- Hyperalgesia
- Opioids Increased
- Misinterpreted as Disease-Related Pain
ANALGESIC USE IN RENAL IMPAIRMENT
How to measure Renal function?

- Traditionally serum Creatinine has been used as a measure of renal function. This is inaccurate as patients may have a clinically significant deterioration in renal function while still having a serum Creatinine within the normal reference range. (Lamb et al)

- Glomerular filtration rate (GFR) is a preferable measure of renal function. There are two generally accepted methods of estimating GFR:
  1. Cockcroft + Gault equation
  2. 4 variant modification of diet in renal disease equation (4vMDRD)

- Both methods are inaccurate at extremes of age and body weight.

- Estimated GFR (eGFR) is now provided with biochemistry results and is based on the 4vMDRD calculation. (It will not have been adjusted for body total surface area).
### eGFR classification of Renal impairment

<table>
<thead>
<tr>
<th>Degree impairment</th>
<th>Chronic Kidney Disease (CKD) stage</th>
<th>eGFR ml/min/1.73m²</th>
<th>Creatinine Clearance ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal renal function</td>
<td>1</td>
<td>&gt;90</td>
<td>120</td>
</tr>
<tr>
<td>Mildly reduced renal function in presence of renal disease. In absence of renal disease eGFR &gt; 60 is considered normal</td>
<td>2</td>
<td>60-89</td>
<td>20-50</td>
</tr>
<tr>
<td>Moderately reduced renal function</td>
<td>3</td>
<td>30-59</td>
<td>10-20</td>
</tr>
<tr>
<td>Severely reduced renal function</td>
<td>4</td>
<td>15-29</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Very severe. Established (end-stage) renal failure</td>
<td>5</td>
<td>&lt;15</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>
Renal failure can make patients more susceptible to adverse effects of drugs.

- **In particular...**, it causes:
  - An increased bleeding tendency, therefore the risks of NSAIDs and anticoagulants are increased.
  - Increased blood-brain barrier permeability, therefore increased sensitivity to CNS side effects of drugs e.g. sedation.

- **Renal failure can change analgesic pharmacokinetics** in the following ways:
  - Reduced excretion of drug or metabolites
  - Altered drug distribution: especially if drug is plasma protein bound
  - Reduced oral absorption: vomiting diarrhoea or mucosal oedema
Analgesics can still be prescribed according to the WHO analgesic ladder.
STEP 1 - ANALGESICS in Renal Impairment

Paracetamol:

- **GFR 20-50** = no dose adjustment (1gram Qid)
- **GFR 10-20** = no dose adjustment (1gram Qid)
- **GFR <10** = Reduced dose (500mg-1g tds)

**NSAIDs:**

Should be avoided even in mild renal impairment.
**STEP 2 ANALGESICS in Renal Impairment**

**Codeine / Panadeine / Panadeine forte**
(Half life significantly prolonged in chronic renal failure).
- **Mild RF** – maintain normal dose
- **Moderate RF** – 75% dose
- **Severe RF** – 50% dose

**Tramadol**: (Usually, not recommended in Palliative care!)
(Active metabolite excreted via kidney)
- **Mild RF** - normal dose 50-100mg Qid
- **Moderate RF** – increase dosing interval 50-100mg bd
- **Severe RF** – avoid

**Buprenorphine**:  
Metabolised in the liver to inactive norbuprenorphine;  
Therefore, safe to use in patients with renal impairment.  
**No dose adjustments** in Transdermal preparations.  
(Reduce dose of SL buprenorphine by 25% in severe renal impairment).
Morphine:

Morphine and its metabolites accumulate in renal failure and should therefore be avoided.

(In my Practice, I monitor patient’s renal impairment (up to eGFR =40-50 with morphine; If they are clinically deteriorated or showing toxic symptoms ➔ I switch the opioids. Another set of patients with mild renal impairment & on morphine are comfortable / pain-free & eGFR is stable at the same level ➔ we continue the morphine but monitor them carefully with periodical check of eGFR).

Oxycodone:

Half life shown to be mildly prolonged. Suggest use with great caution in severe renal failure

- \( \text{GFR} 20-50 \) = no dose adjustment
- \( \text{GFR} 10-20 \) = no dose adjustment but avoid MR- Release
- \( \text{GFR} < 10 \) = avoid
Fentanyl:
Metabolised to norfentanyl and inactive metabolites. Theoretical and clinically observed reduction in toxicity in renal failure. Although metabolites are inactive there is some concern that the parent drug may accumulate in moderate-severe renal impairment hence the recommendation to reduce dose:

- GFR 20-50 = normal dose
- GFR 10-20 = 75% dose
- GFR<10 = 50% dose

Alfentanil:
Similar pharmacologically to fentanyl. Inactive metabolites. 30 times as potent as oral morphine. Can be administered via CSCI and is safe even in severe renal impairment. No dose adjustment is required.

Methadone:
Renal impairment does not affect methadone clearance. Can be used in severe renal failure but dose adjustment required.

- GFR 20-50 = no dose adjustment
- GFR 10-20 = no dose adjustment
- GFR <10 = 50% dose reduction
ADJUVANT ANALGESICS in Renal Impairment -1

**Amitriptyline:**
Starting dose needs no adjustment but must be titrated carefully to avoid sedation / hypotension.

**Gabapentin:** Requires significant dose reduction!
- GFR 20-50 = 300mg bd maximum
- GFR 10-20 = 300mg od maximum
- GFR <10 = 300mg alternate days maximum

**Pregabalin:** Require significant dose reduction!
- GFR 20-50 = starting dose 75mg od (Max 300mg/day in divided doses)
- GFR 10-20 = starting dose 25-50mg od (Max 150mg/day in divided doses)
- GFR <10 = starting dose 25mg od (Max 75mg od)
Sodium Valproate:
Start with normal dose but titrate carefully.
Beware increased sedation in renal failure.

Dexamethasone:
Does not require dose adjustment but may be complicated by fluid retention

Clonazepam:
No dose adjustment required but beware increased risk of sedation.
Ketamine:

Inactive metabolites. Safe in renal failure.
No dose adjustments required
Clinical Scenario with Liver Impairment
55 years of Mrs W admitted with confusion / drowsiness, Constant RUQ pain and back pain for 3/52 duration. She is a known patient with carcinoma of the colon. The last staging scan (3 months ago) revealed liver & peritoneal metastasis.

**Examination:** Palpable Tender Liver, Ascites, B/L leg Oedema noted.

**Investigations:** Bilirubin = 39; ALT = 112; δ-GT = 583; Alkaline Phos = 291; Albumin = 20; eGFR = 85; Cr = 109; K+ = 4.2 & Na+ = 143

**Current Medications:**
Kapanol (Morphine SR) 40mg BD + Ordine Suspension 5mg prn + Paracetamol 1 gr Oid

- What are the issues you find in this patient?
- What is your immediate management?
- What are the next step of management?
What are the issues you find in this patient?

- Liver impairment with pain
- Tender Liver indicate Liver Capsular pain
- Opioid of choice cause more symptoms
- Wrong prn dose of Ordine Suspension
What is your immediate pain management?

- Either we can reduce the opioid dose or do an opioid switch; considering her drowsiness / confusion and still having pain, I will consider switching the opioid in this case.
  - I will try Fentanyl patch

- What is the dose? & Why?

- What medication you consider as prn dose? Why? and What is the dose?
What are the next step of management?

• Confused ‘liver impairment patients’
  Management of encephalopathy is usually straightforward if you remember the checklist!
    ➢ Check for sepsis
    ➢ Lactulose
    ➢ Fluids
    ➢ Replace electrolytes
    ➢ Check drug chart
    ➢ Do not sedate them!!

• Contact the Gastro - team
ANALGESIC USE IN LIVER IMPAIRMENT
Opioid Use in Hepatic Dysfunction -1

• 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.
Opioid Use in Hepatic Dysfunction

- Oxidation and other hepatocellular processes seem to be more affected by liver dysfunction than glucuronidation which does not require hepatocellular enzymes.

- However, morphine is primarily transformed via glucuronidation [Duramorph PI 1994], and its accumulation has been problematic in some patients with hepatic failure.

- Hydromorphone 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].
## Recommended Use of Opioids in Hepatic Dysfunction

Demerol PI 2002; Dolophine PI 2006; Guay et al. 1988; Klein and Magida, 1971; Murphy 2005; Tegeder et al. 1999

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Recommended Usage</th>
<th>Comment</th>
<th>Dosing Recommendations*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Use cautiously and monitor patient for sedation.</td>
<td>In severe hepatic impairment, the parent drug may not be readily converted to metabolites.</td>
<td>Increase the dosing interval by twice the usual time period.</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Use cautiously and monitor patient carefully for symptoms of opioid overdose.</td>
<td>In severe hepatic impairment, the parent drug may not be readily converted to inactive metabolites.</td>
<td>Decrease initial dose by 50% of the usual amount.</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Use cautiously and monitor patient carefully for symptoms of opioid overdose.</td>
<td>In severe hepatic impairment, the parent drug may not be readily converted to inactive metabolites.</td>
<td>Decrease initial dose by 1/2 to 1/3 of the usual amount.</td>
</tr>
<tr>
<td>Codeine</td>
<td>Avoid use.</td>
<td>In severe hepatic impairment, codeine may not be converted to the active metabolite, morphine.</td>
<td>——</td>
</tr>
<tr>
<td>Methadone</td>
<td>Not advised.</td>
<td>Not advised in severe liver failure due to risk of methadone accumulation.</td>
<td>——</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Appears safe, generally no dose adjustment necessary.</td>
<td>Decreased hepatic blood flow affects metabolism more than hepatic failure.</td>
<td>Dosing adjustment usually not needed.</td>
</tr>
</tbody>
</table>
Referral System

- In the community (Home +N/homes), GPs are responsible for patients and in the hospitals, the relevant medical team.

- **Examples:**
  - **In the Hospital:** If you find, poor renal functions and patient is on inappropriate opioids, you can raise the concerns, talking to the team, express your concerns!

- **Community:** Quite Challenging! But still, if I were you, I will talk to the relevant GP & express my concerns!
1. Mr JB is on MS Contin 30mg po BD; Achieved Good pain control & no B/Ts needed. He renal functions rapidly declined with cancer progression with B/L Hydronephrosis (eGFR = 25 now); What is the appropriate Hydromorphone dose / 24 hours
   (1) 40mg (2) 30mg (3) 20mg (4) 10mg

2. Mrs S is on Gabapentin 300mg po BD for her cancer related neuropathic pain. She developed renal impairment (eGFR=30). What her current ‘safe Gabapentin dose’ at present?
   (1) 300mg BD (2) 300mg OD (3) 100mg BD (4) 50mg BD

3. Mr B is on OxyContin 30mg BD for his cancer pain. His liver functions deteriorated with cancer spread to the liver (moderate to severe dysfunction) & he is getting more pain now. What is your choice of analgesics?
   (1) Convert to Methadone (2) Keep the same opioid drug/dose
   (3) Stop opioids & start a NSAID + Steroids (for liver capsular pain)
   (4) Reduce the 24 hr dose by half and consider ‘steroid trial’
References:

- Davies G, Kingswood C and Street M. Pharmacokinetics of opioids in renal dysfunction. Clinical Pharmacokinetics. 1996; Dec 31(6) 410-422
- Devaney A, Ashley C, Tomson C. How the reclassification of kidney disease impacts on dosing adjustments. Pharmaceutical journal 2006; 277:403-405


