The Pearls of Pharmacotherapy in Palliative Care: Pain Management and Beyond

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Disclosure

I have no real or potential conflict(s) to disclose.
Objectives

• By the end of the presentation, the audience should be able to....
  • Define palliative care
  • Understand approach for opioid dosing in palliative care
  • Describe pharmacotherapeutic approach to other symptom management in palliative care
Outline

1. Pain Management
   1. Specific Properties of Opioids
   2. Principles in Opioid Usage (Rotation, Titration, Toxicity)

2. Sedation

3. Respiratory Depression

4. Nausea and Vomiting

5. Constipation
Palliative Care

• Optimizes the **quality of life** of **patients** with incurable life-limiting illness and **their families**

• Acknowledges dying as a normal process

• **Neither prolongs nor shortens life**

http://www.who.int/cancer/palliative/defintion/en/
Pain Control
Causes of Pain in Palliative Care

• **Metastases**
  • Treatment side effects
    • Radiation
    • Chemotherapy (contributing to peripheral neuropathies)
    • Surgery
  • In advanced disease
    • **Tumor infiltration**
      • bone
      • soft tissue
      • nerves
      • ligaments
      • fascia
Pain Classification

• Nociceptive
  • Physical tissue destruction
  • Somatic:
    • Sharp, well-localized, worsened by pressure in the area or movement
  • Viseral:
    • Dull, poorly-localized, could be described as cramping.

• Neuropathic
  • Nerve tissue damage
  • Burning/radiating/tingling/ stinging
Pain Assessment

- **PQRST** (Provoke, Quality, Radiate, Severity, Time)
- **Understanding**: What do you feel caused it? How has it affect you and your family?
- **Values**: What is your goal for the symptoms? What is a tolerable level?
- Common tools
  - Verbal Rating Scale
  - Visual Analog Scale

Breakthrough Pain

- Caused by:
  - Pain fluctuation
    - Idiopathic, spontaneous
  - End of dose failure
- Different compared to incident pain
  - Predicted pain caused by
    - Movement
    - Nursing care
      - Dressing change


BJU Int. 2007;99(5 Pt B):1305-12.
Pearls of Individual Opioid Properties
WHO Cancer Pain Ladder

Mild Pain 1-3/10

- ASA, Tylenol, NSAIDS

Moderate Pain 4-6/10

- Weak opioids +/- non-opioids (e.g. Tylenol #3®)
- Tramadol

Severe Pain 7-10/10

- Potent opioids (e.g. morphine) +/- non-opioids

It is acceptable to start at any point on the ladder

Adapted from www.who.int
Pain 1995; 63: 65–76
Weak Opioids

• Tramadol
• Codeine

Key concept: Controversy exists for use of weak opioids in cancer related pain because of ceiling effect and lack of definitive proof for efficacy in pain
Tramadol

• Synthetic analog of codeine with MAOii properties
  • Neuropathic pain

• Demethylation by CYP2D6 as active metabolite
  • Drug interactions
  • Lack the isoenzyme $\rightarrow$ decreased analgesic effect

• Ceiling of 400 mg a day
  • Seizures
  • Serotonin syndrome

References:
European Journal of Palliative care 14: 879-923
Cochrane Database Syst Rev. 3. CD003726
Emergency Medicine Australasia 17. 73-83
American Journal of Human Genetics 60:284-295
Pain. (suppl.5):S377
Annuals of Oncology 5:141-146.
Codeine

• CYP 2D6 demethylation $\rightarrow$ morphine
  • Responsible for analgesic effect
  • Genetic polymorphism CYP2D6
    • Drug interactions
    • 1-3 % of Asians this enzyme is not active $\rightarrow$ No analgesic effects

• Not recommended in palliative care
  • Ceiling effect
    • No more than 240 mg in 24 hours
  • NNT= 16 for 50% pain relief
    • Some studies - no better than placebo
Strong Opioids

• Morphine
• Hydromorphone
• Oxycodone
• Fentanyl
• Methadone

Key concept: Opioids with less active metabolites are chosen for frail elders and those with renal impairment
Morphine

• Available as IR, SR, ER and injectable forms

• Undergoes first pass metabolism in the liver

• Renal excretion
  • Avoid in renal impairment and the elderly

(M3G) 😞 No analgesic activity
Neurologic adverse effects

(M6G) ❤️ Active metabolite

doi: 10.1046/j.1365-2125.2002.01554.x
Hydromorphone

• Available IR, SR and injectable forms
  • Hydromorphone contin (capsule)
    • Open and sprinkled on food for ease of administration

• Undergoes first pass metabolism
  • Metabolite hydromorphone-3-gluronide (H3G)
    • Renal excreted
    • No analgesic properties
    • 2.5 X as potent as M3G as a neurotoxin
      • Reports of neurotoxicity with renal failure
      • Side effect profile in renal failure better than morphine in palliative patients

Pain 1992;51:260-261
European Journal of Palliative Care 2001;8:142-146
J Opioid Management 2008;4(6);335 -344
Oxycodone

- Available as IR and SR form
- Metabolized to oxymorphone and noroxycodone via CYP
  - Oxymorphone =10X as potent as morphine
- Renal excretion
  - Avoid in renal disease

Fentanyl

• Top 10 drug of potential medication errors
• Lipophilic
• Available as a transdermal patch
  • Applied to skin every 72 hours
    • Fast metabolizers → patches changed every 48 hrs.
• Inactive metabolites
• Should never be used on opioid naïve individuals
• Transdermal difficult to titrate for non-stable pain

Pain 2009;29:969-971
Br J Pharmacol. 2015 May; 172(9): 2179–2209
Fentanyl

• Heat increases absorption of the patch
  • fever, diaphoresis
• Reduced absorption in cachectic and obese patients
• 28% to 84% of the active ingredient found in used patch!

### Fentanyl

<table>
<thead>
<tr>
<th>Morphine PO (mg per day)</th>
<th>Hydromorphone PO (mg per day)</th>
<th>Fentanyl Patch (mcg per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45-134</td>
<td>9-26</td>
<td>25</td>
</tr>
<tr>
<td>135-224</td>
<td>27-44</td>
<td>50</td>
</tr>
<tr>
<td>225-314</td>
<td>45-62</td>
<td>75</td>
</tr>
<tr>
<td>315-404</td>
<td>63-80</td>
<td>100</td>
</tr>
<tr>
<td>405-494</td>
<td>81-98</td>
<td>125</td>
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<tr>
<td>495-584</td>
<td>99-116</td>
<td>150</td>
</tr>
<tr>
<td>585-674</td>
<td>117-134</td>
<td>175</td>
</tr>
<tr>
<td>675-764</td>
<td>135-152</td>
<td>200</td>
</tr>
<tr>
<td>765-854</td>
<td>153-170</td>
<td>225</td>
</tr>
<tr>
<td>855-944</td>
<td>171-188</td>
<td>250</td>
</tr>
<tr>
<td>945-1034</td>
<td>189-206</td>
<td>275</td>
</tr>
<tr>
<td>1035-1124</td>
<td>207-224</td>
<td>300</td>
</tr>
</tbody>
</table>

Compendium of Pharmaceuticals and Specialties 2015
Methadone

• Additional neuropathic pain
  • NMDA receptor and monoamine reuptake inhibition

• Metabolized by CYP3A4
  • No active metabolite
    • Less neurotoxic potential than hydromorphone and morphine
  • Excreted via the gut
    • Useful in those with renal impairment

• May prolong the QT interval at high doses
Methadone

• Can be given as sublingual and buccal
  • Off-label option if PO, PR, parenteral not possible
  • buccal=lining of the cheek and the upper and lower lips
    • Thinner mucosa
    • Use if aspiration risk
  • < 1 mL per dose to avoid aspiration
    • Concentrated liquid, 10mg/mL or 40 mg/mL

Methadone

- Conversion ratio is dose dependant
- Large variation of conversion ratios
- Divide daily methadone into q8h frequency

<table>
<thead>
<tr>
<th>Daily Oral Morphine Equivalents (mg)</th>
<th>Conversion Ratio Morphine to Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>3:1</td>
</tr>
<tr>
<td>101-300</td>
<td>5:1</td>
</tr>
<tr>
<td>301-600</td>
<td>10:1</td>
</tr>
<tr>
<td>601-800</td>
<td>12:1</td>
</tr>
<tr>
<td>801-1000</td>
<td>15:1</td>
</tr>
<tr>
<td>1001-5000</td>
<td>20:1</td>
</tr>
<tr>
<td>5000-10000</td>
<td>30:1</td>
</tr>
<tr>
<td>&gt; 10000</td>
<td>60:1</td>
</tr>
</tbody>
</table>

Methadone

Maximum effect will vary from about 35 to 325 h (13.5 days)
Edmonton Palliative Care Methadone Method

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC “X”</td>
<td>100%</td>
<td>60%</td>
<td>30%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>ATC Meth. (Target)</td>
<td>0%</td>
<td>30%</td>
<td>60%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>PRN</td>
<td>10% of “X” daily dose</td>
<td>10% of “X” daily dose</td>
<td>10% of “X” daily dose</td>
<td>10% of “X” daily dose</td>
<td>10% of “X” daily dose</td>
</tr>
</tbody>
</table>

- Note: If pain severe, or fast rotation necessary, then cross-titration in the span of 3 days instead of 5
Pearls of Opioid Usage (Rotation, Titration, Toxicity)
## Opioids: Starting doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral Dose</th>
<th>Parenteral Dose</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10 mg</td>
<td>5mg SC/IV</td>
<td>Every 2-4 hrs</td>
</tr>
<tr>
<td>Codeine</td>
<td>60-100mg</td>
<td>30-50mg SC/IV</td>
<td>Every 4-6 hrs</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>5-7.5mg</td>
<td>2.5-3.75mg SC</td>
<td>Every 4-6 hrs</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2mg</td>
<td>1mg SC/IV</td>
<td>Every 2-4 hrs</td>
</tr>
</tbody>
</table>

Note: Elderly patients start at half dose

Opioids Titration

1) Start with regular q4h + prn dosing with IR opioids
2) Allow opioid to reach steady state before increasing regular dosing
   • Dosing reassessed every 48-72 hours
3) Increase the regular dose until there is adequate relief throughout each q4h period
   • If >3 prn doses used
   • Increase by fix percentage or using PRN amounts
4) Replace q4h dose with q12h dose (i.e. SR formulation) once stable
Opioid Breakthrough Dose

• Use immediate release opioid
  • Give 10% of the 24 hour dose
    • Remember to increase breakthrough doses when ATC doses increase!
  • Should be dosed every 1-2 hours
    • Peak analgesic effect correlates with the peak plasma concentration

Patient Case A

• 80 y.o. Female breast cancer with bone mets and severe pain
  • Progressive multiorgan failure

• Morphine 10mg PO q4hr ATC, and 6mg PO q1 hr prn initiated
  • 4 BTA in last 24hr

• In 36 hours she has become more confused and delirious

• No clinical changes with exception of Opioid addition
Opioid Toxicity

- Opioid Induced neurotoxicity (OIN)
  - Nightmares, hallucinations (visual, tactile, auditory), confusion, myoclonus

- Opioid induced hyperalgesia (OIH)
  - Hyperalgesia (increased perceived intensity of painful stimulus)
  - Allodynia (non-painful stimulus experience as painful)
Opioid Toxicity

• Often secondary to accumulation of opioids and/or its metabolites
  • Dehydration, renal impairment can contribute.

• Management:
  • Hydration
  • Opioid rotation
    • Most common after hydration
  • Opioid reduction
    • Often not an option
Opioid Rotation

1. Calculate the total daily dose of current opioid (ATC doses + PRN doses)
2. Calculate equianalgesic dose of alternate opioid
3. Decrease dose by 20-30% to account for incomplete cross tolerance between opioids
4. Calculate regular dose
5. Calculate breakthrough dosing
6. Daily follow up

Victoria Hospice Society Learning Centre for Palliative Care; 2006. p. 189-251.
Equianalgesic Doses: Opioid Analgesics

<table>
<thead>
<tr>
<th>DRUG</th>
<th>PO DOSE</th>
<th>SC/IV DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Codeine</td>
<td>100 mg</td>
<td>50 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>5-7.5 mg</td>
<td>2.5-3.75 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2 mg</td>
<td>1 mg</td>
</tr>
</tbody>
</table>

Downy, Wainwright, “Medical Care of the Dying”, 2006
1. **ATC Dose** = 10mg X 6 times daily = 60mg
   **PRN dose** = 6mg X 4 doses = 24mg
   **Morphine total daily dose** = 60 + 24 = 84 mg

2. Convert morphine to hydromorphone using equianalgesic chart
   • 84 ÷ 5 = 16.8mg hydromorphone

3. Reduce by 30% to account for incomplete cross tolerance
   • 16.8mg X 0.7 = 11.76mg daily hydromorphone

4. Divide daily dosing by 6 for q4h hydromorphone dosing
   • 11.76 ÷ 6 = 2mg q4H ATC

5. Calculate breakthrough dosing
   1) PRN dose = 10% daily dose = 11.76 X 0.1 = 1mg
   2) 1mg PO q1hr prn
Pearls for Other Symptoms
Sedation

- Multifactorial
  - Not always opioids!
    - Disease progression
    - Insomnia

- Opioids sedation threshold builds up over time
  - Do not over react!
  - Monitor respiratory status

- Goal to balance sedation vs pain relief
Respiratory Depression

- Tolerance develops quickly and pain is a natural antagonist
- Uncommon with appropriate dosing
Naloxone
• Palliative care indication
  • Pinpoint pupils
  • Unrousable
  • RR<8
  • Not actively dying
• Majority of uses of naloxone are inappropriate for palliative patients
  • Health professionals often over react and give when there is a hint of sedation

J Pain Symptom Manage. 1996 Feb;11(2):131-4
http://www.noperi.org/ems.html
Naloxone

• Considerations:
  • Exacerbation of pain
  • Withdrawal syndrome
    • More severe than abrupt discontinuation of opioids
  • Catecholamine-mediated cardiac arrhythmias and vasoconstriction
  • Reserve for respiratory depression

• Naloxone 0.4mg in 9mL NS for slow IV push
  • Give 1ml IV q 5-10 minutes until RR>8

Nausea

• Reversible causes
  • Corticosteroids – decrease gut edema
  • Hypercalcemia – hydration and bisphosphonates
  • Uremia – rehydration
  • Gastritis – PPI
  • Infection – ABX
  • Constipation – laxatives
  • Emotions – anxiolytics
## Nausea: Management

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid induced nausea</td>
<td>Metoclopramide, domperidone or haloperidol</td>
</tr>
<tr>
<td>Malignant bowel obstruction</td>
<td>Haloperidol (1&lt;sup&gt;st&lt;/sup&gt; line), or dimenhydrinate or 5HT3 antagonist (2&lt;sup&gt;nd&lt;/sup&gt; line)</td>
</tr>
<tr>
<td>Chemotherapy or radiotherapy induced</td>
<td>5HT3 antagonist (1&lt;sup&gt;st&lt;/sup&gt; line), cannabinoids (2&lt;sup&gt;nd&lt;/sup&gt; line), corticosteroids, metochlopramide</td>
</tr>
<tr>
<td>Anticipatory or anxiety related</td>
<td>Benzodiazepine anxiolytic</td>
</tr>
<tr>
<td>Motion sickness</td>
<td>Dimenhydrinate, prochlorperazine or hyosine hydrobromide</td>
</tr>
</tbody>
</table>
Nausea

• If the nausea is most likely secondary to opioids
  • Haloperidol 0.5 mg q12h regular or
  • Metoclopramide 10mg qid

• If the nausea is present only with movement dimenhydrinate may be appropriate.
Constipation

- Occurs frequently in terminally ill patients
- Complications:
  - Increased pain
  - Abdominal distention & discomfort
  - Nausea & vomiting
  - Overflow diarrhea
  - Hemorrhoids & anal fissures
  - Pseudo bowel obstruction
  - Urinary retention
  - Increased anxiety
Constipation

- Often multi-factorial
  - Drugs: anticholinergics, antiemetics, diuretics, anticancer agents, OPIOIDS
  - Decreased hydration
  - Malnutrition
  - Reduced activity level
  - Increased fatigue & weakness
  - Hypercalcemia & hypokalemia
Constipation in Advanced Cancer Patients

• Start laxatives early when opioids are started
  • Key Concept: PROACTIVE is key

• First Line:
  • Sennosides 24mg PO BID
  • PEG 17g PO bid
  • Bisacodyl 10mg suppository and/or fleet enema q3days

• Second Line:
  • Lactulose 30mL PO bid
  • Oral phosphates sodium PO 45mL
  • Oil retention enema

• Newest Agent:
  • Peripheral Opioid Antagonist, Methylnaltrexone (RelistorTM)
    • Reserved use
Conclusion

• Palliative care focuses on living, not dying
• The choice of opioids must be individualized to the situation and the person
  • Strong opioids have no ceiling
  • Opioids rotation may be necessary to manage adverse effects
• Respiratory depression is uncommon if the opioid is dosed appropriately
  • Caution should be exercised by considering naloxone
• Consideration of the factors that are contributing to nausea is important when selecting an antiemetic
• Constipation is an ongoing concern and necessitates proactive use of bowel regimen
Questions?

Never believe that a few caring people can't change the world. For, indeed, that's all who ever have.

(Margaret Mead)
Extra Cases
Opioids Use in Palliative Care

- Pain
- Dyspnea
- Cough

BJU Int. 2007 May;99(5 Pt 8):1305-12.
Patient Case B

- Mr. B: metastatic lung cancer, liver and bone metastases.
- He is currently taking Morphine Contin 60 mg bid, and Codeine 30mg q4hr prn
  - States breakthrough not helping to alleviate pain
Case B (Breakthrough Opioid)

• Morphine Contin 60mg bid = 120mg daily
• 10% 120mg = 12 mg Morphine Breakthrough
• Convert to Codeine 20mg Po Morphine = 130-200mg Codeine
• 12 mg Morphine = 80-90mg Codeine

1) The patient was on Codeine 30mg q4h prn
   • Way below the 10% breakthrough
2) This patient was on two different opioids
   • Not recommended practice
Patient Case C

• 64 y.o with prostate cancer with bone mets
  • Hydromorphone
    • 6 mg po q4h Around the Clock (ATC)
    • 1 mg po q1h prn
    • Taking 5 breakthrough analgesia (BTA) daily

• Pain uncontrolled
  • Neuropathic component
Patient Case C

• Calculate **MORPHINE EQUIVALENT DAILY DOSE (MEDD):**
  • ATC dose = 6mg X 6 times daily = 36mg
  • PRN dose = 3 mg x 5 doses = 15 mg
  • Total hydromorphone daily = 51 mg
  • conversion to morphine (5:1)
  • MEDD = 255 mg
Patient Case C

• Calculate target dose of methadone
  • MEDD 101-300 mg: use 5:1 ratio = 51 mg methadone
  • Reduce by 20 – 30 % for incomplete cross-tolerance 51 x 70% = 36 mg/day
  • Calculating for q8h dose = 13 mg po q8h

• Calculate the breakthrough dose
  • = 10% of total daily dose (36 mg)
  • = 3 mg po q1h prn

• Check daily for pain control & toxicities
  • Titrate as necessary (calculating BTA doses)
  • Titrate slowly because of unpredictable kinetics
# Patient Case C

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATC HM</strong></td>
<td>100% 6 mg po q4h</td>
<td>67% 4 mg po q4h</td>
<td>33% 2 mg po q4h</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>ATC Meth</strong></td>
<td>0</td>
<td>33% 3 mg po q8h</td>
<td>67% 8 mg po q8h</td>
<td>100% 12 mg po q8h</td>
<td>100% 12 mg po q8h</td>
</tr>
<tr>
<td><strong>PRN</strong></td>
<td>3 mg HM po q1h prn</td>
<td>3 mg HM po q1h prn</td>
<td>3 mg HM po q1h prn</td>
<td>3 mg HM po q1h prn</td>
<td>3 mg MD q1h prn</td>
</tr>
</tbody>
</table>