Postoperative pain management

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Joseph Park, MD, FRCP (C), FIPP
Clinical Assistant Professor, Director of pain fellowship
McMaster University, Hamilton
Objectives

• At the conclusion of the presentation resident will be able to
  • Define drug addiction, tolerance, physical dependence, pseudo addiction, central hypersensitization, incomplete tolerance, and opioid induced hyperalgesia.
  • Be familiar with “multimodal” or “balanced analgesia” in postoperative pain management.
  • Know the advantages and disadvantages of IV PCA and epidural analgesia.
  • Know the common complications of postoperative pain management with IV PCA and epidural analgesia.
  • Know the equianalgesic table for opioids and its pitfalls.
  • Know how to convert from IV to oral opioids or vice versa.
  • Know the common side effects of opioids and NSAID’s.
Postoperative factors that may delay recovery

- Pain
- PONV-Ileus
- Organ dysfunction-surgical stress
- Hypoxemia, sleep disturbances
- Immobilisation
- Semi-starvation
- Fatigue
- Traditions (drains, tubes etc.)
- Specific postoperative factors
Definitions and terms in pain
Definition of pain by IASP

Pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”
Chronic pain

- > 3-6 months (> 3 month by IASP)
- Pain lasting longer than the expected time to tissue healing or resolution of underlying disease process
- Prevalence
  - 17 % of adult Canadians
  - 2.5 % of adult Canadians have severe chronic pain (Millar WJ. Chronic pain, Statistics Canada. Health Rep 1996;7:47-53).
Tolerance

- Is a state in which escalating doses of drug are needed to maintain an analgesic effect.
- Develop tolerance to the side effects
  - Euphoria, somnolence, respiratory depression, and nausea develop readily
- Such acquired tolerance usually takes 2 to 3 weeks to develop with analgesic doses of morphine (anesthesia literature)
- Tolerance to the opioid is quickly lost during withdrawal.
Cross tolerance

- Tolerance to one opioid leads to tolerance to other opioid.
- However it produces incomplete tolerance.
Physical dependence

- Characterized by onset of acute signs and symptoms of withdrawal reactions when opioid is suddenly stopped.
- Withdrawal reactions
  - Coryza, tremor, sweats, chills, lacrimation, abdominal cramps, arthralgias, myalgias, vomiting, and diarrhea
- Withdrawal reaction - not life threatening
- Usually requires 25 days to develop physical dependence for morphine?
Signs and symptoms of opioid withdrawal

- Yawning
- Diaphoresis
- Tremor
- Lacrimation
- Coryza
- Tachycardia
- Abdominal cramps
- Nausea and vomiting

Mostly sympathetic signs and symptoms
## Time course of opioid withdrawal S & S

<table>
<thead>
<tr>
<th></th>
<th>Onset</th>
<th>Peak intensity</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>6-18 hr</td>
<td>36-72 hr</td>
<td>7-10 days</td>
</tr>
<tr>
<td>Meperidene</td>
<td>2-6 hr</td>
<td>8-12 hr</td>
<td>4-5 days</td>
</tr>
<tr>
<td>Fantanyl</td>
<td>2-6 hr</td>
<td>8-12 hr</td>
<td>4-5 days</td>
</tr>
<tr>
<td>Methadone</td>
<td>24-48 hr</td>
<td>3-21 days</td>
<td>6-7 wks</td>
</tr>
</tbody>
</table>
Definition of addiction
by APS, ASPM, and ASAM in 2001

• “a primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations.”

• Biopsychosocial disorder characterized by one or more of the following 4C’s
  • Impaired control over drug
  • Compulsive use of substance
  • Continued use of opioid despite physical, emotional, social and economic harm
  • Craving

• Development of iatrogenic addiction is rare when opioids are carefully prescribed for the relief of acute or cancer pain
Addiction

Incidence of addiction

Pain medicine Fishbain et al 2008;9:4:444-459

- 3.27% of chronic pain patients (CPP) developed abuse or addiction
- 0.19% of CPP who did not have previous history of abuse/addiction developed abuse or addiction
- 11.5% of CPP (2466 pts in 17 studies) developed drug related aberrant behavior
- 0.59% of CPP (2644 pts in 17 studies) who never had history of abuse/addiction developed aberrant drug related behavior
Aberrant behaviours


- Used additional opioids than those prescribed
- Used additional opioids than those prescribed more than once
- Forged prescription
- Sold prescription
- Admitted to seeking euphoria from opioids
- Admitted to wanting opioids for anxiety
- Overdose and death
- Injected drug
- Abnormal urine/blood screen
- Abnormal urine/blood screen positive for 2 or more substances
- Solicited opioids from other providers
- Unauthorized ER visits

- Concurrent abuse of alcohol
- Unauthorized dose escalation
- Resisted therapy changes/alternative therapy
- Reported lost or stolen prescriptions
- Canceled clinic visit
- Requested early refills
- Requested refills instead of clinic visit
- Abused prescribed drugs
- Was discharged from practice
- No show or no follow-up
- Third party required to manage patient’s medications
Pseudo addiction

- Drug seeking behaviour as addiction
- Pt may take extraordinary steps to maintain an adequate supply of medication
- Due to inadequate prescription of analgesics for pain control
- Escalation of analgesic demands by pt
- A crisis of mistrust between the pt and the health care team
- Providing more analgesics lead to cessation of addiction behavior and cause no harm
Central hypersensitization

• ‘wind up’: repetitive stimulation of C fibers produces exaggerated discharge of WDN
  • It increases subsequent neural response to low threshold afferent input (allodynia)
  • It increases response generated by a given noxious afferent input (hyperalgesia)
• Enlarges receptive field in the spinal cord (neuroplasticity) → secondary hyperalgesia
Opioid induced hyperalgesia

- State of nociceptive sensitization caused by exposure of opioids causing increasing pain despite of increasing dose of opioids.

  - Former opioid addicts on MMT
  - Perioperative exposure to opioids in patients undergoing surgery especially remifentanil
  - Healthy human volunteers after acute opioid exposure
Pain mechanism
Pain pathways

Ascending pain pathways

Descending pain pathways
Increased spinal neuronal activity

(Philip J. et al. Chapter 23 pg 685 in Neural blockade-3rd edition)
Central hypersensitization
(Philip J. et al. Chapter 23 pg 680 in Neural blockade-3rd edition)
Types of pain

- Somatic
- Visceral
- Neuropathic
- Bone
# Visceral and somatic pain

<table>
<thead>
<tr>
<th></th>
<th><strong>Somatic</strong></th>
<th><strong>Visceral</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site</strong></td>
<td>Well localized</td>
<td>Poorly localized</td>
</tr>
<tr>
<td><strong>Radiation</strong></td>
<td>May follow distribution of somatic nerve</td>
<td>Diffuse</td>
</tr>
<tr>
<td><strong>Character</strong></td>
<td>Sharp and definite</td>
<td>Dull and vague (may be colicky, cramping, squeezing, etc.)</td>
</tr>
<tr>
<td><strong>Relation to stimulus</strong></td>
<td>Hurts where the stimulus is; associated with external factors</td>
<td>May be ‘referred’ to another area; associated with internal factors</td>
</tr>
<tr>
<td><strong>Time relations</strong></td>
<td>Often constant (sometimes periodic)</td>
<td>Often periodic and builds to peaks (sometimes constant)</td>
</tr>
<tr>
<td><strong>Associated symptoms</strong></td>
<td>Nausea usually only with deep somatic pain owing to bone involvement</td>
<td>Often nausea, vomiting, sickening feeling</td>
</tr>
</tbody>
</table>
Convergence of visceral and somatic nociceptive afferents

(Siddall et al. Chapter 23. Pg 691 in Neural blockade-3rd edition)
Viscera and their segmental nociceptive nerve supply

(Philip J. et al. Chapter 23 pg 692 in Neural blockade-3rd edition)

<table>
<thead>
<tr>
<th>Viscus</th>
<th>Spinal segments of visceral nociceptive afferents$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>T1–T5</td>
</tr>
<tr>
<td>Lungs</td>
<td>T2–T4</td>
</tr>
<tr>
<td>Esophagus</td>
<td>T5–T6</td>
</tr>
<tr>
<td>Stomach</td>
<td>T6–T10</td>
</tr>
<tr>
<td>Liver and gall bladder</td>
<td>T6–T10</td>
</tr>
<tr>
<td>Pancreas and spleen</td>
<td>T6–T10</td>
</tr>
<tr>
<td>Small intestine</td>
<td>T9–T10</td>
</tr>
<tr>
<td>Large intestine</td>
<td>T11–T12</td>
</tr>
<tr>
<td>Kidney and ureter</td>
<td>T10–L2</td>
</tr>
<tr>
<td>Adrenal glands</td>
<td>T8–L1</td>
</tr>
<tr>
<td>Testis, ovary</td>
<td>T10–T11</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>T11–L2</td>
</tr>
<tr>
<td>Prostate gland</td>
<td>T11–L1</td>
</tr>
<tr>
<td>Uterus</td>
<td>T10–L1</td>
</tr>
</tbody>
</table>

$^a$ These travel with sympathetic fibers and pass by way of sympathetic ganglia to the spinal cord. However, they are not sympathetic (efferent) fibers. They are best referred to as visceral nociceptive afferents. **Note:** Parasympathetic afferent fibers may be important in upper abdominal pain (vagal fibers, celiac plexus).
Sclerotome chart
Effects of regional analgesia and pain management on surgical outcome
Best postoperative pain management

- **Pre-emptive analgesia** (Katz et al. Anesthesiology 1992;77:439)
  - Prevention of acute pain by minimizing afferent nociceptive input from injured tissue by preinjury intervention with LA or opioids.
  - Use of regional analgesia with LA have been shown to reduce postoperative pain and the need for postoperative opioid. (Schulze S et al. Surgery 1988;103:321)

- **Multimodal (balanced) analgesia** (Kehlet H et al. A & A1993;77:1048)
  - Enhance analgesia by targeting different levels of injury response by combining medications and analgesic techniques for possible additive or synergistic effects.
  - It may decrease side effects due to reduced analgesics
  - But needs to be incorporated with physical and mental rehab postoperatively for better postoperative outcomes.
Pre-emptive analgesia
Multimodal (balanced) analgesia

Analgesia is targeted at four different sites along the nociceptive pathway.
Multimodal (balanced) analgesia

- Additive or synergistic analgesic effects
- Reduce side effects (e.g., opioid sparing effects) such as N & V by ↓ required analgesics.
Advantages of regional anesthesia for postoperative pain management

- Better postoperative pain management
- Inhibit the stress response in elective procedures in the lower part of the body.
  - ↓ post surgical catabolic and hypermetabolism
- Reduce intra-operative blood loss
  - Mostly ortho, gyne, distal vascular surgeries
  - By 30 %
  - Mostly with spinal and epidural anesthesia
- Reduce thromboembolic complications
  - Mostly due to increased blood flow to the lower extremities and a favourable change in coagulation and fibrinolysis, and inhibition of thrombocyte aggregation.
Pathophysiology of pain
(Liu et al. Anesthesiology 1995;82:1474)

- **Cardiovascular effects**
  - ↑ myocardial oxygen demand (↑ HR, BP, and contractility) resulting from sympathetic efflux and catecholamine.

- **Coagulative effects**
  - Hypercoagulable state caused by stress response and pain.
  - DVT associated with postop bed rest

- **Pulmonary effects**
  - Pneumonia and atelectasis caused by pain, ↓ diaphragmatic function, ↑ expiratory intercostal and abdominal muscle tone till 7-14 days.

- **GI effects**
  - Postoperative N & V
  - Postoperative ileus as a result of pain stimulated reflex arc.

- ↑ surgical stress
Clinical effects of postoperative epidural analgesia

- Lower extremity vascular surgery
  - Decreased thromboembolic morbidity by intraoperative epidural anesthesia

- Thoracic surgery
  - Inconclusive for pulmonary outcome.
  - Epidural LA attenuate diaphragmatic dysfunction

- Abdominal surgery
  - Improve postoperative pulmonary function
  - Decrease postoperative ileus
  - Early discharge (Liu et al. Anesthesiology 1995;83:757)

- Regional anesthesia for orthopedic surgery
Early recovery of postoperative GI function with epidural analgesia

(Liu et al. Anesthesiology 1995:83:757)

<table>
<thead>
<tr>
<th></th>
<th>EPID MORPH + BUP</th>
<th>EPID MORPH</th>
<th>EPID BUP</th>
<th>IV PCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time until first flatus (h)</td>
<td>43 ± 4*</td>
<td>71 ± 4</td>
<td>40 ± 2*</td>
<td>81 ± 3</td>
</tr>
<tr>
<td>Time until discharge criteria fulfilled (h)</td>
<td>67 ± 8*</td>
<td>102 ± 13</td>
<td>62 ± 5*</td>
<td>96 ± 7</td>
</tr>
<tr>
<td>Time until actual hospital discharge (h)</td>
<td>199 ± 71</td>
<td>130 ± 14</td>
<td>101 ± 11</td>
<td>122 ± 9</td>
</tr>
</tbody>
</table>

Note: Values are mean ± standard error.
*Different from groups EPID MORPH and IV PCA (P < 0.005).
†Value after exclusion of incorrectly enrolled subjects. After exclusion, groups EPID MORPH and EPID MORPH + BUP are different from groups EPID MORPH and IV PCA (P < .04).
Advantages of regional anesthesia/analgesia for postoperative pain management

- May reduce postoperative cardiac morbidity
  - Coronary vasodilation, decrease SVR
- May reduce postoperative pulmonary complications
  - Efficient postoperative analgesia
  - May impair reflex diaphragmatic dysfunction in postoperative period
  - 0.5% epidural bupivacaine has been shown to improve diaphragmatic function after upper abdominal surgery. (Anesthesiology 1988;68:379)
  - Epidural analgesia with LA does not inhibit GI motility. Therefore earlier enteral feeding is possible, thus reducing the possibility of compromising the mucosal barrier of the intestine.
  - Concomitant administration of opioids with LA will result in an opioid induced delay in gastric emptying and a prolongation of paralytic ileus time.
- It has beneficial effects on the healing of intestinal anastomoses primarily due to increased splanchnic blood flow.
  - Pre-emptive use of spinal, LA may eliminate the phenomena associated with NMDA receptor activation.
The incidence of respiratory complications following abdominal surgery according to the type of analgesia

<table>
<thead>
<tr>
<th>References</th>
<th>No of patients</th>
<th>Parenteral analgesia</th>
<th>Epidural analgesia with LA (%)</th>
<th>Epidural analgesia with opioids (%)</th>
<th>Type of complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hjortso et al. Acta Anes Scan 1985;29(8):790</td>
<td>100</td>
<td>28</td>
<td>20</td>
<td></td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Hendolin H et al. Acta Anest Scan 1987;31:645</td>
<td>100</td>
<td>50</td>
<td>27*</td>
<td></td>
<td>Atelectasis</td>
</tr>
<tr>
<td>Jary C et al. Surgery 1988;104:57</td>
<td>150</td>
<td>51</td>
<td></td>
<td>66</td>
<td>atelectasis</td>
</tr>
</tbody>
</table>

*: Significant difference
# Postoperative pain relief and GI function: stomach and small intestine

<table>
<thead>
<tr>
<th></th>
<th>Epidural local anesthetics</th>
<th>Epidural opioids</th>
<th>Systemic opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric emptying</td>
<td>Normal</td>
<td>Delayed</td>
<td>Delayed</td>
</tr>
<tr>
<td>Orocecal transit time</td>
<td>Normal</td>
<td>Delayed</td>
<td>Delayed</td>
</tr>
<tr>
<td>Incidence of N &amp;V</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Facilitate enteral feeding</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Postoperative ileus time</td>
<td>Decreased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Increased pressure after neostigmine</td>
<td>+</td>
<td>(?)</td>
<td>(?)</td>
</tr>
<tr>
<td>Increased splanchnic blood flow</td>
<td>+</td>
<td>(?)</td>
<td>(?)</td>
</tr>
</tbody>
</table>
Common postoperative pain management
Common postoperative pain management

- Intermittent IV opioid + NSAIDS
- IV PCA
  - Morphine
  - Dilaudid
  - Fentanyl
- Epidural epimorph
- Intrathecal epimorph
- Epidural analgesia
  - Continuous infusion with LA + opioids
  - PCEA
- Peripheral nerve block
IV PCA

- Types of opioids
  - Morphine, Hydromorphone (Dilaudid), and Fentanyl

- Parameters of IV PCA
  - Dose: Morphine: 30 µg/kg, Hydromorphone: 0.1-0.5 mg, Fentanyl: 5-25 µg
    - Reduce PCA dose by 25-50% for elderly
  - Lockout interval: 5-10 min
  - 4 hr maximal limit
  - Continuous infusion: usually no

- Adjunct analgesics
  - NSAIDs-Ketorolac 15 mg IV q 6 h x 72 h or Ibuprofen 600 mg q 6 hr x 72 h
  - oral Tylenol or Oxycontin 5-10 mg po q 12 h

- Treatments for side effects
  - N & V: Ondansetron (Zofran) 1 mg IV q8 h prn → Dimenhydrinate (Gravol) 25 mg IV q 4 h prn
  - Pruritus: Naloxone IV infusion-0.25 µg/kg/hr x 24 h (0.4 mg in 100 ml NS) → Diphnyhydramine (Benadryl 25 mg IV q 4 h prn)
IV PCA for pediatric patient

- Dose of opioids:
  - Morphine: 10-30 µg/kg,
  - Morphine infusion: 10-40 µg/kg/h, 50-75 µg/kg for breakthrough pain q 3 h
  - Hydromorphine: 3-5 µg/kg,
  - Fentanyl: 0.5-1 µg/kg

- Adjunct analgesics
  - NSAIDs-Ketorolac 0.5 mg/kg (max:15 mg)
  - Ibuprofen- 5-10 mg/kg
  - Codeine-1 mg/kg (max:60 mg)
  - Acetaminphen-10-15 mg/kg

- Treatments for side effects
  - N & V: Ondansetron (Zofran) 0.05 mg-0.1 mg/kg (max:1 mg)
  - Dimenhydrinate (Gravol) 0.5-1 mg/kg (max: 25 mg)
  - Pruritus: Diphnhydramine (Benadryl) 0.5-1 mg/kg (max:25 mg)
IV PCA

- Monitoring
  - Respiratory rate and sedation score - q 2 h x 48 h → q 4 h
  - Vitals-BP, pulse, saturation, and pain score
    - Q 4 h or
    - Q 15 min x 2 if PCA setting was changed
    - Q 4 h x 1 once PCA is stopped

- When to call APS
  - RR < 10 /min
  - Saturation < 92 %
  - Sedation score is 3
  - Pain > 4/10 and patient is not satisfied
IV PCA monitoring

- Pain scale:
  - 0: no pain 10: worst pain

- N/V and Pruritus scale
  - 0: none, 1: mild, 2: moderate, 3: severe, treatment is not effective

- Sedation scale
  - 0: alert, 1: occasionally drowsy, 2: frequently drowsy, 3: somnolent, difficult to arouse, 4: normal sleep, easy to arouse
Common side effects of postoperative IV PCA opioids

- Pruritis
- N & V
- Sedation
- Respiratory depression
Epidural analgesia
Clinical properties of epidural opioids
(Sinatra. Chapter 26 in Neural blockade third edition)

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Lipid solubility</th>
<th>Onset of action</th>
<th>Duration of action</th>
<th>Loading dose</th>
<th>Conversion ratio from IV to epidural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine (Epimorph)</td>
<td>1.42</td>
<td>45 min</td>
<td>6-24 hr</td>
<td>2-4 mg</td>
<td>4-10:1</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>813</td>
<td>5-10 min</td>
<td>1-2 hr</td>
<td>30-100 µg</td>
<td>1-3:1</td>
</tr>
<tr>
<td>Hydromorphone (Dilaudid)</td>
<td>11.36</td>
<td>15 min</td>
<td>5-12 hr</td>
<td>0.5-1.5 mg</td>
<td>2-7:1</td>
</tr>
</tbody>
</table>
Comparison between clinical properties of lipophilic and hydrophilic opioid

<table>
<thead>
<tr>
<th></th>
<th>Highly lipophilic opioids</th>
<th>Poorly lipophilic (hydrophilic) opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example</td>
<td>Fentanyl</td>
<td>Morphine</td>
</tr>
<tr>
<td>Onset</td>
<td>Faster</td>
<td>Slower</td>
</tr>
<tr>
<td>Duration of action</td>
<td>Shorter</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Dermatormal spread of analgesic effect</td>
<td>Segmental distribution</td>
<td>More extensive cephalad spread</td>
</tr>
<tr>
<td>Side effects</td>
<td>Less, shorter</td>
<td>More, prolonged</td>
</tr>
<tr>
<td>Conversion ratio from IV to epidural</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Delayed respiratory depression</td>
<td>Less</td>
<td>More</td>
</tr>
</tbody>
</table>
Common side effects of epidural opioids

- Pruritus
- N & V
- Sedation
- Dizziness
- Urinary retention
- Delayed respiratory depression with epimorph up to 12 hr: 0.1 % (Rawal wt al. BJA 1987;5:791)
  - Due to rostral spread of opioid to the respiratory centre in the floor of the fourth ventricle in CSF
Risk factors for delayed respiratory depression with epidural opioids

- Thoracic surgery
- Increasing age
- Opioid naive patient
- Concomitant use of systemic opioids and sedatives
Epidural LA for postoperative pain management

- **Advantages**
  - Provide excellent postoperative analgesia
  - Block the metabolic endocrine stress response better than systemic pain control

- **Disadvantages**
  - Potential hypotension
  - Inability to ambulate if lumbar epidural
  - Intravascular injection?

- **Types**
  - Thoracic vs lumbar

- **Solutions**
  - LA
    - Bupivacaine: 0.08 %- 0.125-0.25 % or lidocaine
  - Opioid concentration and bolus
    - Fentanyl: 2 -5 µg/ml, 10-25 µg bolus for breakthrough pain
    - Epimorph: 0.05 mg/ml
    - Hydromorphone: 8-32 µg/ml
Thoracic epidural analgesia for postoperative pain

- **Indications**
  - Thoracic, upper abdominal > lower abdominal surgery, Nephrectomy,

- **Advantages**
  - Block visceral pain
  - Block somatic pain
  - Spares lower extremity motor function (Allow ambulation)

- **Disadvantages**
  - May be technically challenging
  - Potentially more risks and complications – direct spinal cord trauma, pneumothorax, dural puncture, bleeding, infection etc.
Advantages of combination of epidural opioid and LA

- Multimodal analgesia
  - Synergic effect acting at two distinct sites
  - Reduce side effects of opioids and LA
- Rapid onset
Multidomal studies and results of postoperative recovery
Panchal et al. Tech in RA and PM. April 2002;6 (2):72

<table>
<thead>
<tr>
<th>Study, Year, Reference</th>
<th>No. of Patients</th>
<th>Surgical Procedure</th>
<th>Multimodal Components of Care</th>
<th>Length of Stay/Recovery Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collier, 1995 (100)</td>
<td>186</td>
<td>Carotid endarterectomy</td>
<td>Preoperative patient education, local anesthesia—infiltration</td>
<td>1-2 days, reduced morbidity</td>
</tr>
<tr>
<td>Bardram et al, 1995 (101)</td>
<td>8</td>
<td>Laparoscopic colectomy</td>
<td>Preoperative patient education, early mobilization and nutrition, multimodal analgesia</td>
<td>2 days</td>
</tr>
<tr>
<td>Michaloliakou et al, 1996 (102)</td>
<td>49</td>
<td>Laparoscopic cholecystectomy</td>
<td>Multimodal analgesia</td>
<td>Ambulatory, reduced pain and nausea</td>
</tr>
<tr>
<td>Rasmussen et al, 1998 (103)</td>
<td>60</td>
<td>Meniscetomy</td>
<td>Multimodal analgesia, early mobilization</td>
<td>Ambulatory, reduced pain</td>
</tr>
<tr>
<td>Coveney, 1998 (104)</td>
<td>145</td>
<td>Mastectomy</td>
<td>Paravertebral block</td>
<td>Reduced pain, less than 24-hour stay</td>
</tr>
<tr>
<td>Tovar et al, 1998 (105)</td>
<td>10</td>
<td>Thoracotomy/lobectomy</td>
<td>Preoperative education, multimodal analgesia</td>
<td>1-2 days</td>
</tr>
<tr>
<td>Macario et al, 1998 (106)</td>
<td>560</td>
<td>Knee replacement</td>
<td>Revised clinical pathway, epidural analgesia</td>
<td>4-5 days, reduced cost</td>
</tr>
<tr>
<td>Worwag et al, 1998 (107)</td>
<td>100</td>
<td>Prostatectomy</td>
<td>Preoperative education, multimodal analgesia</td>
<td>1.3 days</td>
</tr>
<tr>
<td>Callesen et al, 1999 (108)</td>
<td>48</td>
<td>Herniorraphy</td>
<td>Preoperative education, local infiltration anesthesia</td>
<td>Short-stay ambulatory, reduced morbidity</td>
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<tr>
<td>Kehlet et al, 1999 (109)</td>
<td>16</td>
<td>Open colectomy</td>
<td>Preoperative education, early mobilization and nutrition, multimodal analgesia</td>
<td>2 days</td>
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</tbody>
</table>
Physiologic effects of epidural neural blockade with LA

- **Sympathetic block (efferent)**
  - Central sympathetic block (T1-T4): Blockade of
    - Cardiac sympathetic outflow: ↓HR, ↓CO
    - Cardiac sympathetic reflexes at segmental level
    - Vasoconstrictor fibers to head, neck, and arms: vasodilation of upper limbs
  - Adrenal medullary sympathetic block (T6-L1): Blockade of splanchnic nerves
    - Vasoconstrictor fibers to abdominal viscera
    - Adrenal medullary catecholamine secretion
  - Peripheral sympathetic block (T10-L2): Blockade of vasoconstrictor fibers to lower limbs

- **Visceral pain block (afferent)**

- **Somatic block**
  - Sensory block
  - Motor block
Factors determine type epidural block

- Dermatomal level of surgical incision
- Level of visceral pain
  - Thoracic-
  - Upper abdominal-above T10
  - Lower abdominal-below T10
  - Perineal-Lower lumbar
  - Lower extremity-lumbar
- Postoperative ambulation
# Nerve supply to viscera

(Siddall et al. Chapter 23. pg 692 in Neural blockade by Cousins-3rd edition)

<table>
<thead>
<tr>
<th>Viscus</th>
<th>Spinal segments of visceral nociceptive afferents</th>
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<tr>
<td>Heart</td>
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<td>Testis and ovary</td>
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<td>Urinary bladder</td>
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<td>Prostate</td>
<td>T11-L1</td>
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<tr>
<td>Uterus</td>
<td>T10-L1</td>
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</tbody>
</table>
Common side effects of epidural LA

- Hypotension
- Difficulty ambulation due to motor and/or sensory block of lower extremity
- Urinary retention
- Neurological damage - rare
- Epidural hematoma - rare
- Epidural abscess - rare
How to assess postoperative pain

• History
  • Know the type of surgery
  • Assess the side and location of pain and location of epidural site
    • Upper or lower
    • Bilateral vs unilateral (R/O unilateral block)
  • Assess the type of pain
    • Somatic - skin incision
    • Visceral
    • Bone
    • Neuropathic
  • Assess the intensity of pain - VAS
  • Assess the type of pain control
    • IV PCA
    • Epidural-thoracic vs lumbar
  • Assess the side effects of pain control - sedation, respiratory depression, hypotension, N & V etc.
  • R/O withdrawal S & S of premeds - Benzo, opioids, EtOH
How to assess postoperative pain

- Physical exam
  - VS: hypotension?, tachcardic?, sedated,? severity of pain
  - Any S & S of withdrawal?
  - Location, side (unilateral vs bilateral) of pain
  - Check the epidural site
  - Sensory exam for blocks
  - Motor exam for blocks
How to assess postoperative pain

- Consider any surgical complications for persistent, severe pain refractory to pain control - infection, abscess, perforation etc.
- Not all hypotension is due to epidural analgesia. Consider any surgical complications - dehydration (third space loss), sepsis etc.
Opioid withdrawal

- Signs and Symptoms
  - Tremor, diaphoresis, lacrimation, coryza, tachycardia, abdominal cramps, nausea, vomiting, yawning
- Withdrawal symptoms within 6-18 hr with morphine, 2-6 hr with fentanyl, 24-48 hr with methadone.
- Withdrawal reaction-not life threatening

Mostly sympathetic signs and symptoms
Withdrawal reaction of TCA’s

- Abrupt discontinuation of TCA → mild withdrawal reactions such as
  - Malaise
  - Chills
  - Coryza
  - Skeletal muscle aching
SSRI Discontinuation Syndrome

- Abrupt discontinuation has been associated with disequilibrium, N/V, fatigue, lethargy, myalgias, paresthesias, tremor, migrainelike auras and insomnia, as well as anxiety, over-agitation, irritability, overactivity, depersonalization, poor concentration, lowered mood, confusion, memory problems and vivid dreams.

- Occurs more often if the drug has a short half-life and increased anticholinergic effects (e.g. paroxetine).
Postoperative respiratory depression

APS catastrophic data of HHS from Feb. 2002 till Sept., 2005

- >15,000 postoperative patients from Feb, 02-Sept., 05
- Most common critical incidents
  - Severe hypotension: 1.37 %
  - Respiratory depression: 0.48 %
    - IV PCA (0.43 %) vs epidural morphine (0.27 %)
  - Error in pump programming: 0.19 %
  - No epidural abscess, no spinal hematoma
Peripheral nerve blocks for regional anesthesia and postoperative pain management

- Types of nerve blocks
  - The brachial plexus block
    - Interscalene, axillary, suprascapular, infraclavicular
  - The lumbar plexus
    - Sciatic, femoral nerve, obturator nerve, psoas compartment
  - The sacral plexus
- Tech of peripheral nerve blocks
  - With nerve stimulator
  - With ultrasound
- Indications
  - Upper and lower extremity surgery
- Advantages
  - Less concern for neuroaxial block complications
Peripheral nerve blocks for postoperative pain management
Challenging cases of postoperative pain management
Challenges of postoperative pain management

- Patients with:
  - Chronic pain patients-high dose of opioid
  - History of opioid abuse
  - Multiple risk factors for addiction
  - Ongoing addiction problem
  - Patient with history of drug diversion
  - Methadone maintenance
Chronic pain

- > 15% of Canadian has chronic pain
- High percentage of chronic pain patients has **no identifiable underlying specific disease**.
- In some cases, a recognized disease is **not treatable** and pain **become self generating**.
- However there are objective biochemical and structural mechanisms of peripheral and central sensitization.
Chronic pain patients

- Sleep disturbance
- Anxiety disorder
- Depression
- Fear-avoidance behaviour
- Pain behaviors?
- Psychosoical issues
The evidence for the use of opioid therapy

- A multispecialty committee of the CPSO performed a systemic review from 1996-1998 and concluded the following.
  - Significant pain relief can be achieved
  - Low risk of psychological dependence or addiction
  - Cognitive impairment can be minimized or eliminated
Reasons for undertreatment

- Fear of addiction
- Fear of diversion
- Fear of regulatory scrutiny
- No obvious cause for underlying chronic pain
- Medicalization of pain promotes dysfunctional pain behaviour?
- Inadequate knowledge
Position statement on pain relief by the Canadian Pain Society in 1997

- Almost all acute and cancer pain can be relieved and many patients with chronic non-malignant pain can be helped.
- Patients have the right to the best pain relief possible.
“To leave a person in avoidable pain and suffering should be regarded as a serious breach of fundamental human rights”

Somerville (Bioethicist, Health Care Analysis 1995;3:12)
Postoperative pain management of chronic pain patients

- Recognize chronic pain as a disease
- Self sustaining
- Maladaptive behaviour
- Different approach
  - Do not look for underlying disease for chronic pain
- Conservative approach for drug switch from oral to IV
- Our main concern is pain control
- Patient’s right to pain relief
- Not a time to worry about addiction, tolerance, diversion
Postoperative pain management of chronic pain patients

- Consider combining IV and neuroaxial pain management
- Be aware of withdrawal symptoms
  - When changed from oral to neuroaxial opioids
- Our reluctance
  - Not based on facts
  - Rather our comfort
- Pain management is essential for good surgical outcome.
- Requires change in attitude toward chronic pain
Risk factors for abusing opioids

- A previous history of substance abuse or dependence
- Family history of alcohol, drug abuse or significant psychiatric illness
- History of physical, sexual or emotional abuse
- Borderline, antisocial or psychopathic personality disorders
- A person living in a high-risk environment (others involved in drug misuse)
- A previous diagnosis of social phobia, BAD, psychotic disorder, ADHD.
Postoperative pain treatment of patients with multiple risk factors for addiction

- Treat pain first
- More vigilance
  - In assessing, prescribing, and monitoring
- Very rare to develop addiction in presence of postoperative pain
Postoperative pain treatment of ongoing addiction problem

- Patient’s right to pain treatment.
- Be aware of CPS and APS consensus.
- We are here to treat pain.
Patient with history of diversion of opioid for illicit use

- Patient came for surgery, not to divert opioids.
- One can not detect willful and deceptive behavior for opioid diversion.
- It is our responsibility to treat postoperative pain adequately. It is not our primary goal to detect opioid diversion behavior in postoperative setting.
- Strategies to discourage should not take precedence over effective pain management
Diversion of opioid for illicit use

“physicians who are practicing medicine in good faith and who use reasonable medical judgment regarding the prescription of opioids for the treatment of pain should not be held responsible for the willful and deceptive behaviour of patients who successfully obtain opioids for nonmedical purposes”

- Canadian Society of Addiction Medicine public policy statement
Postoperative pain treatment of methadone maintenance

- Treat postoperative pain
- Continue oral methadone treatment
  - Use NG if possible. Convert oral methadone to IV methadone: 1:1 (However some hospitals do not have IV methadone)
Case # 1: Postoperative pain management of chronic pain patient

- Ms. C.
  - 24 yr old female
  - for elective subtotal colectomy & ileostomy
  - Hx of U.C, depression, obsessive compulsive D
  - Chronic abdominal pain
  - Med: oral dilaudid 24 mg/day, amitriptyline 75 mg od, celexa 60 mg

Postoperative course: anxious and agitated
Case # 1: Postoperative pain management of chronic pain patient

- Ms. C.
  - Postoperative pain management
    - PACU
      - Thoracic epidural analgesia (Bup 0.125 % with fentanyl 5 ug/ml
      - IV dilaudid: 6 mg
      - IV PCA dilaudid: 0.25 mg/hr-0.5 mg-8 min
      - POD 0-1: pt. very anxious and agitated
      - Elavil and celexa started
Case # 2: Postoperative pain management of patient with previous drug addiction

- Mr. D.
  - 27 yr old male
  - For laparotomy, LOA, loop ileostomy for small bowel obstruction
  - Hx of Crohn’s D, multiple abdominal surgeries, seizures, chronic abdominal pain, previous drug abuse/addiction (IV use of Oxycontin and dilaudid from streets), cocaine use
  - Med: dilaudid PO 12 mg bid—15 mg IV q 2 hr prn, oxycontin 160 mg tid, fentanyl patch
Case # 2: Postoperative pain management of patient with previous drug addiction

- Mr. D.
  - Preop anesthesia consult
  - Postoperative pain management
  - PACU:
    - Thoracic epidural analgesia with bup. 0.125 % with dilaudid 10 ug/ml max: 12 ml/hr
    - Dilaudid 45mg (15 mg IV x 3) → IV PCA dilaudid 3 mg/hr + 1 mg q 8 min
    - IV PCA dilaudid continuous infusion 5 mg/hr
    - IV PCA for > 20 days
    - Postoperative pain—always wanted more opioids, pain is almost never under control
Case # 3: Postoperative pain management of patient with methadone

- **Mr. M.**
  - 33 yr old male
  - For laparotomy, resection of recurrent small bowel obstruction due to recurrent strictures
  - Hx of Crohn’s D, multiple abdominal surgeries, seizures, chronic abdominal pain
  - On methadone 36 mg po od x > 1yr, other opioids for breakthrough pain prn
Case # 3: Postoperative pain management of patient with methadone

- Mr. M.
  - Postoperative pain management
  - PACU:
    - Thoracic epidural analgesia with bup. 0.125 % with epimorph
    - IV Dilaudid > 30 mg → IV PCA Dilaudid 0.3 mg q 8 min
  - On ward
    - IV PCA dilaudid
    - Thoracic epidural analgesia at 14 ml/hr
    - Oral methadone through NG
Postoperative pain management of chronic pain patients

- Recognize chronic pain as a **disease**
- Self sustaining
- Maladaptive behaviour
- Different approach
  - Do not look for underlying disease for chronic pain
- Conservative approach for drug switch from oral to IV
- Our main concern is pain control
- Patient’s right to pain relief
- Not a time to worry about addiction, tolerance, diversion
Opioid
Opium-Phenanthrene

Figure 3-1. Phenanthrene alkaloids.
Central and peripheral opioid receptors

- Receptors located centrally and peripherally
- μ opioid receptor - principal receptor involved in pain management
- High concentrations of opioid receptors in the GI tract
Opioids

- More effective in continuous, dull pain > sharp, intermittent pain
- More effective for visceral, skeletal, joint, and integmental pain
Actions of opioids

- CVS
  - No myocardial depression
  - Bradycardia
    - (vagal stimulation in the medulla)
    - Direct stimulation at SA and AV node

- RESP
  - $\mu_2$ receptors on brain stem (ventral medulla) ventilation centres
  - Death from an opioid overdose is almost invariably attributed to depression of ventilation.
  - Cough suppressant due to depression of ciliary activity in the airways.
Actions of opioids

- CNS
  - Caution in head injury patient
    - Damage to BBB → increased CSF morphine
    - Miosis-Edinger Westphal nucleus of oculomotor nerve
  - Skeletal muscle rigidity
  - Myoclonus
Actions of opioids

- CNS
  - Cognitive dysfunction
  - Mood-Drowsiness, euphoria or dysphoria
  - N&V-due to CTZ stimulation & increased vestibular sensitivity
  - Temperature regulation- slight hypothermia
  - Neuroexcitatory symptoms-
    - Hallucinations
    - Hyperalgesia
    - Nystagmus to seizures
- Skeletal muscle rigidity
- Myoclonus
Actions of opioids

• Biliary tract
  • Opioid induced spasm of sphincter of Oddi intraop. may appear as bile duct stone due to radiological sharp constriction at the distal end of common bile duct.
  • 3 % of patients receiving fentanyl → spasm of the sphincter of Oddi
• Rx:
  • 2 mg IV glucagon (does not reverse analgesic effect of opioid)
  • Naloxone
• More common with fentanyl > morphine > meperidine
Actions of opioids

- **GIT**
  - Spasm of the GI smooth muscles
    - Delayed gastric emptying
    - Biliary colic
    - Decreased intestinal peristalsis
  - Constipation
    - Due to increased colonic absorption of water due to delayed passage of intestinal contents
Action of opioids

- Urinary retention

- Mechanism of action
  - Opioid acting on opioid receptors in the sacral spinal cord
    --> Promotes inhibition of sacral parasympathetic nervous system
    --> Detrusor muscle relaxation + Increased bladder capacity

Actions of opioids

- N & V due to
  - Direct stimulation of chemoreceptor trigger zone in the floor of fourth ventricle
  - Ileus
  - Increased GI secretion
- Skin- flushing due to cutaneous blood vessel dilation and histamine release
- Pruritus
Actions of opioids

- Newborns
  - Placenta give no barrier to transfer of opioids from mother to fetus
    - Depression of newborn as a consequence of opioid use in mother
    - More depression with morphine than meperidine
  - Is use of naloxone safe on newborn of mother who has been using opioid chronically?
    - Chronic maternal use of an opioid can result in the development of physical dependence in the fetus. Subsequent administration of naloxone to the neonate can precipitate a life-threatening neonatal abstinence syndrome
Pharmacokinetics of morphine

- Onset: 15-30 min after IM administration
- Peak effect: 45 -90 min
- Duration of action: 4 hr
- The principal pathway of metabolism
  - Conjugation with glucuronic acid
- Site of metabolism
  - Hepatic and renal
- Metabolites
  - M3G (morphine 3 glucuronide): inactive, 75-85 %
  - M6G: 5-10 %
    - active
  - Normorphine and codeine: < 5 %
- Elimination
  - renal
Effect of morphine in cirrhotic or renal failure patients

- Hepatic failure (cirrhosis) patient
  - Usually do not affect morphine metabolism (Bodenham et al 1989, Sear 1991)

- Renal failure patient
  - Impaired elimination → accumulation of metabolites and unexpected ventilatory depressant effects of small dose of opioids
  - Smaller Vd → higher plasma and CSF concentration of morphine and metabolites than normal patients.
Morphine-6-Glucuronide

- Duration of action of M6G: greater than morphine
- Comparable affinity to µ opioid receptors
- Analgesic potency: higher than morphine
- Therefore it is possible that majority of analgesic activity attributed to morphine is actually due to M6G esp. with long term administration of morphine
Meperidine

- Metabolites
  - Normeperidine
    - 50% as effective as meperidine
    - CNS stimulant: myoclonus and seizure, delirium
    - Elimination half life: 15 hr

- Cardiac effects
  - Orthostatic hypotension - more frequent and profound than morphine
  - Myocardial depression
  - Rarely bradycardia but tachycardia

- Clinical uses
  - Postoperative shivering (stimulation of kappa receptors)
Methadone

- Synthetic opioid
- Available over 40 yrs
- Bioavailability: 80 % (41-90%)
- Highly protein bound (AAG-alpha 1 acid glycoprotein): 60-90 %
- ↑ in AAG in cancer pts ⇒ ↓ free active methadone in plasma
- Duration of action
  - Single use: 4-6 hr
  - Chronic use: longer due to high volume of distribution
- Elimination half life: 15-60 hr
Methadone

• Advantages
  • tid
  • No known active metabolites
  • Possess noncompetitive NMDA receptor antagonist activity
  • Inhibit the re-uptake of norepinephrine and serotonin, neurotransmitters involved in afferent nociceptive impulses
  • Inexpensive

• Disadvantages
  • Long and unpredictable half-life and tissue accumulation
  • Unclear equianalgesic conversion
  • Therefore requires highly individual, time-intensive therapy
Three ways that methadone kills


Scenario #1: Single dose

- The first dose is a fatal overdose. This is most often seen in accidental ingestion in an opioid naïve patient, or in previously tolerant users who have had interruptions in their use of methadone.

- A clinically significant loss of tolerance to opioids may occur as quickly as three days without methadone.

- Therefore restart with 50% reduced dose.
Three ways that methadone kills

Senario # 2: Accumulated toxicity

- Doses accumulate over several days and toxicity develops. Today’s dose isn’t lethal, tomorrow’s dose isn’t lethal, but the entire third day dose plus half of the second and one quarter of the first dose accumulate to a lethal level.

- This is commonly seen in overly aggressive initiation protocols.
Three ways that methadone kills

Senario # 3: Drug-Drug Interaction

Methadone can be lethal when used with sedatives, other opioids or alcohol. In these cases, neither methadone nor the sedative drug alone is lethal, but in combination, death results. This is most commonly seen in the ‘stable’ methadone patient who periodically abuses sedative drugs such as benzodiazepines and/or alcohol. Drugs, which inhibit certain enzymes within the cytochrome system, can also result in methadone accumulation and toxicity.
Tramadol

- Centrally acting analgesic
- Mechanism of action
  - Binds to opioid receptors (atypical weak opioid)
  - Inhibit NA and 5 HT neuronal uptake in CNS and spinal cord level
  - Low affinity for μ receptors
  - 5-10 time less potent than morphine as analgesic (Egger and Power 1995)
- High incidence of N & V
- Advantages
  - No development of tolerance or addiction
Tramadol

- To avoid S/E, commence with low dose and increase dose gradually, titrating patient response against dose
- Start at 25 mg OD x 3 days and increase over several days to 50 mg q 4 to 6 h
- Max dose of 400 mg per day (300 mg in patients older than 60 years)
Tramadol

- 50 mg generally produces analgesia equal to acetaminophen 300 mg with codeine 30 mg
- Tramacet is a combination of tramadol 37.5 mg and acetaminophen 325 mg
- Consider tramadol for mild to moderate pain in patients who cannot tolerate NSAIDs and opioids and for whom acetaminophen is not effective
Need for opioid rotation

- Poor analgesic efficacy
- Side effects
- Requirement for more potent opioid
- Opioid side effects
  - Hyperalgesia, myoclonus, mental status changes, excessive sedation, N/V, and constipation
NSAIDs
MOA of NSAIDs

- Inhibition of cyclooxygenase $\rightarrow$ ↓ PG
- ↓ inflammatory response
- ↓ peripheral nociception and pain reception

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<tr>
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<th>Platelet aggregation</th>
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I, increased; D, decreased; NC, no change.
Action of NSAIDs

- Anti-inflammatory
  - Reduction of PGE2 and prostacyclin
- Analgesic
  - Reduction of PG in periphery ➔ decreased sensitization of nociceptors
  - Reduction of central hypersensitization (reduction in PG in spinal cord)
- Antipyretic
  - Reduction of PG in hypothalamus
NSAID mediated suppression of PG and TxA2

- Stomach (PGE 2 and PGI 2): gastric mucosal protection
- Kidneys (PGE2): vasodilation
- Platelets (TxA2 and PGI2): bleeding
- NSAID induced bronchospasm
- Suppression of new bone formation
Adverse effects of NSAIDs

- Inhibition of platelet aggregation
  - Postoperative bleeding (T & A)
- Gastric ulceration
  - Dyspepsia (most common SE)
- Renal dysfunction
- Asthma exacerbation
- Mild hypertension
- Allergic reactions
- Tinnitus
- Urticaria, erythema multiforme
- Aseptic meningitis
Drug interactions with NSAIDs

- Anticoagulant
- Interference with antihypertensives
  - Beta blockers, diuretics, ACE inhibitors,
- Potassium sparing diuretics $\rightarrow$ hyperkalemia
- ↓ clearance of certain drugs- dig, lithium, aminoglycosides
Contraindication to use of NSAIDS

- Asthma
- Renal failure (pre renal failure)
- PUD
- Allergy to aspirin
COX 2 inhibitors

- COX 2
  - is normally present in only few concentration
  - COX-2 is constituitively expressed in brain and spinal cord and is up-regulated after persistent noxious inputs (Important mechanism for reducing post injury hyperalgesia)
  - induced peripherally under conditions of inflammation.
Cox 2 inhibitors

- Celecoxib (Celebrex)—sulfonamide
- 100 mg po bid (ceiling effect)
- Works at spinal cord level
- Decrease opioid requirement by 20-50%
- Maintenance of normal blood flow and induction of appropriate thrombogenic response to injury require balance between the activities of thromboxane A2 in platelets and prostacyclin in the endothelium.
- COX 2 inhibitors do not interfere with thromboxane A2 production but inhibit prostacyclin \( (PGI_2) \) in the endothelium.
- Thromboembolic events may occur more frequently in patients treated with COX-2 inhibitors compared with nonspecific NSAIDs
Ketorolac

- Potent analgesic effects
- Moderate antiinflammatory effects
- 30 mg ketorolac IM = 10 mg IV morphine
- Used for moderately severe pain
- Causes ulcers more frequently than any other NSAID (therefore not used more than 5 days)
- Cross tolerance between aspirin and ketorolac
Ketorolac

- $T_{\beta_{1/2}} = 5$ hr
- Onset: 0.5-1 hr
- Duration of action: 4-6 hr
- Dose: 30 mg $\rightarrow$ 15 mg q 6 hr
- Metabolized by glucuronic acid conjugation
Hypertensive effects of NSAIDs

- PG modulates BP by effect on arteriolar vascular smooth muscle (vasodilation-prostacyclin-PGE2) and ECF volume (natriuretic effect by reducing renal vascular resistance).
NSAIDs and asthma

- Incidence
  - 8-20% of adult asthmatics develop bronchospasm with aspirin and NSAIDS.
  - There is marked cross-sensitivity between most NSAIDs, even where they are structurally dissimilar.

- Onset
  - Within 20 min to 3 hr develop respiratory symptoms (bronchospams, rhinorrhea, respiratory arrest)

- Risk factors for asthma
  - Aspirin induced asthma
  - Chronic rhinitis
  - Nasal polyps
Renal effects of NSAIDs

- Usually no adverse renal effect on healthy patients
- Renal medullary ischemia due to NSAID induced inhibition of PG synthesis.
- Risk factors for NSAID induced nephrotoxicity
  - Hypovolemia, preexisting renal disease, CHF, sepsis, DM, cirrhosis, nephrotoxic drug (radiographic contrast)
- Hypertension and edema due to sodium retention
- Hyperchloremic metabolic acidosis often in association with hyperkalemia is due to NSAIDs.
Allergy

- Patient allergy to sulfa $\Rightarrow$ cannot take Celebrex and bextra.
- C/I to pts who has allergic reaction with aspirin- asthma, urticaria, or allergic type reaction.
NSAIDs and bone healing

- Animal experiments suggests that prostaglandins favour bone formation.
- NSAIDs might therefore be expected to inhibit bone formation because they inhibit prostaglandin formation.
- The evidence for this is by no means conclusive,
- Dose and duration of use may also be factors. Experiments on rabbits (over 20 years ago) have shown that NSAIDs can inhibit fracture healing. Ketorolac has been implicated in failed bone fusion in spinal fusion experiments in rabbits.
Patients with concurrent fractures of the acetabulum and long bones who received indomethacin had a significantly greater risk of nonunion of the fractures of the long bones compared with those who received focal radiation or no prophylaxis.
The effect of ketorolac after spinal fusion was studied in a retrospective review of 288 cases between 1991 and 1992.

**Intervention:**
- IM ketorolac 60 mg → 30 mg IM q 6 hr prn with mean 10 doses postop
- Minimum two-year follow up.
- Ketorolac was given to 167 patients, and no NSAID to 121.

**Results**
- Nonunion occurred in
  - 5/121 (4%) of patients having no NSAID and
  - 29/167 (17%) of those receiving ketorolac.
  - The odds ratio was 4.9 (1.8 to 17).
  - There was a dose-dependent relationship between nonunion rates and ketorolac doses
- There was an apparent relationship between postoperative use of ketorolac and cigarette smoking.
  - The nonunion rate was 2% in those who neither smoked nor had ketorolac,
  - 7% for those who smoked but did not have ketorolac,
  - 10% for nonsmokers having ketorolac and
  - 25% for those who both smoked and had ketorolac (Figure 4).
Figure 3: Nonunion rate and postoperative ketorolac doses after spinal fusion surgery

Figure 4: Nonunion rate by smoking and ketorolac status
Figure 5: Nonunion rate with coxibs and ketorolac
Ketorolac and spinal fusion
(Spine 2008:33:19:2079)

- Retrospective study
- 405 pts underwent posterolateral intertransverse process fusion
- Variables:
  - IV Ketorolac 30 mg q 6 hr x 48 hr postop
  - Placebo (177 historical control)
- Duration of F/U: 24 months
- Results:
  - Incidence of nonunion in Ketorolac group: 5.3 % (12/228)
  - Incidence of nonunion in control group: 6.2 % (11/177)
Equianalgesic dose of opioids
Equianalgesic dose ratio (EDR) for opioids

JPSM 2001;22:672

• Equianalgesia refers to different doses of two agents that provide approximate pain relief.
• The EDR exhibit extremely wide ranges
### Equianalgesic dose ratio of opioid

<table>
<thead>
<tr>
<th></th>
<th>Parenteral</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphine</strong></td>
<td>10 mg</td>
<td>60 mg</td>
</tr>
<tr>
<td>(single dose)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Morphine</strong></td>
<td>10 mg</td>
<td>20-30 mg</td>
</tr>
<tr>
<td>(Chronic use)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hydromorphone</strong></td>
<td>1.5-2 mg</td>
<td>6-7.5 mg</td>
</tr>
<tr>
<td><strong>Codeine</strong></td>
<td>120 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td><strong>Oxycodone</strong></td>
<td>5-10 mg</td>
<td>10-15 mg</td>
</tr>
<tr>
<td><strong>Meperidine</strong></td>
<td>75 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td><strong>Pentazocine</strong></td>
<td>60 mg</td>
<td>180 mg</td>
</tr>
</tbody>
</table>
Facts/pitfalls about equianalgesic dose ratio of opioid

- It is mostly derived from single dose cross over study on acute pain patients.
- It is not fixed.
- It is not bidirectional.
Problems of equianalgesic dose ratio of opioid

Most of studies →
single dose crossover designs of opioid naïve patients (acute pain studies)

Extrapolation of the results to opioid tolerant patients?
Example of analgesic equivalences

10 mg IV Morphine → Over 2 months → 30 mg IV Morphine

1.5 mg IV Dilaudid → 4.5 mg IV Dilaudid → 2.5-3 mg IV Dilaudid
Problems of equianalgesic dose ratio of opioid

The ratio may change according to the direction of opioid switch.
Directional difference in conversion

- **Hydromorphone**
  - 10 mg IV morphine $\rightarrow$ 1.5 mg IV hydromorphone
  - 1.5 IV hydromorphone $\rightarrow$ 4.5 mg IV morphine

- **Oxycodone (J of pain and symptom management 2001;21:397)**
  - 20 mg oral morphine $\rightarrow$ 10 mg oral oxycodone
  - 10 mg oral oxycodone $\rightarrow$ 10 mg oral morphine

# Morphine ↔ Hydromorphone

**Comparison of dose ratios for M-HM and HM-M rotations**

<table>
<thead>
<tr>
<th>Unified median dose ratio (n = 91)</th>
<th>M-HM (n = 44)</th>
<th>P-value</th>
<th>HM-M (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median dose ratio</td>
<td>5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.0001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.7&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>(4.2–5.9)*</td>
<td></td>
<td>(2.9–4.5)*</td>
</tr>
</tbody>
</table>

<sup>a</sup>All ratios expressed as M/HM, 4.29 mg of M is equipotent to 1 mg HM.

<sup>b</sup>Using Wilcoxon test.

*(Lower–upper quartiles).*

---

Lawor et al. Dose ratio between morphine and hydromorphone in patients with cancer pain; a retrospective study. Pain; 1997; 72: 79
EDR for morphine ↔ methadone

### Comparison of Dose Ratios for M-ME and ME-M Rotations

<table>
<thead>
<tr>
<th>Unified median dose ratio (n = 20)</th>
<th>M-ME (n = 14)</th>
<th>ME-M (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>dose ratio</td>
<td>P value&lt;sup&gt;a&lt;/sup&gt;</td>
<td>dose ratio</td>
</tr>
<tr>
<td>11.2 (5.06–13.24)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>11.36 (5.98–16.27)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.23 (NS)</td>
</tr>
<tr>
<td>11.2 (5.06–13.24)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>11.36 (5.98–16.27)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.23 (NS)</td>
</tr>
</tbody>
</table>

M: morphine; ME: methadone; NS: not significant.

<sup>a</sup> Using Wilcoxon rank sum test.

<sup>b</sup> All ratios are expressed in the direction of morphine:methadone and as median (lower-upper quartiles).

Problems of equianalgesic dose ratio of opioid

The ratio may be dose dependent.

- Dose dependent
  - Methadone
  - Fentanyl
Fentanyl ↔ Morphine

- IV morphine to IV fentanyl = 100:1
  - 10 mg SQ morphine = 150 µg SQ fentanyl (JPSM 2001;22(2):672)
  - 30-90 mg/day oral morphine = 25 µg fentanyl patch
Fentanyl ↔ Morphine
(JPSM 2001;21(5):403, Pain 1996;64:527)

- The conversion ratio seems to be dose dependent.
- The conversion ratio decreases as the fentanyl dose increases (Potency decreases)
  - 30-90 mg/day oral morphine = 25 µg fentanyl patch

<table>
<thead>
<tr>
<th>Oral morphine (mg/day)</th>
<th>Fentanyl TTS (mg/day)</th>
<th>Fentanyl TTS (µg/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–90</td>
<td>0.6</td>
<td>25</td>
</tr>
<tr>
<td>91–150</td>
<td>1.2</td>
<td>50</td>
</tr>
<tr>
<td>151–210</td>
<td>1.8</td>
<td>75</td>
</tr>
<tr>
<td>211–270</td>
<td>2.4</td>
<td>100</td>
</tr>
<tr>
<td>271–330</td>
<td>3.0</td>
<td>125</td>
</tr>
<tr>
<td>331–390</td>
<td>3.6</td>
<td>150</td>
</tr>
<tr>
<td>391–450</td>
<td>4.2</td>
<td>175</td>
</tr>
<tr>
<td>451–510</td>
<td>4.8</td>
<td>200</td>
</tr>
<tr>
<td>511–570</td>
<td>5.4</td>
<td>225</td>
</tr>
<tr>
<td>571–630</td>
<td>6.0</td>
<td>250</td>
</tr>
<tr>
<td>631–690</td>
<td>6.6</td>
<td>275</td>
</tr>
<tr>
<td>690–750</td>
<td>7.2</td>
<td>300</td>
</tr>
<tr>
<td>Each further 60</td>
<td>+0.6</td>
<td>+25</td>
</tr>
</tbody>
</table>

Pain 1996;64:528
EDR for morphine $\rightarrow$ methadone is dose dependent

<table>
<thead>
<tr>
<th>Morphine dose prerotation</th>
<th>Dose ratio M/ME</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 patients receiving &lt;1165 mg</td>
<td>5.42 (2.95–9.09)</td>
<td>0.007</td>
</tr>
<tr>
<td>(range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 patients receiving &gt;1165 mg</td>
<td>16.84 (12.25–87.95)</td>
<td></td>
</tr>
<tr>
<td>(range)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

M: morphine; ME: methadone.

- Expressed as oral equivalent morphine daily dose for day before rotation (ratio of 2:1 used for oral:subcutaneous routes): median, 1165 (range, 84–24025).
- Expressed as median (lower-upper quartiles).
- Using Wilcoxon rank sum test.

### Selected EDRs (Equianalgesic Dose Ratios): Morphine-to-Methadone Conversion

<table>
<thead>
<tr>
<th>Morphine Dose (mg/d)</th>
<th>30-90</th>
<th>90-300</th>
<th>300+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine:Methadone EDR</td>
<td>4:1</td>
<td>6:1</td>
<td>8:1</td>
</tr>
</tbody>
</table>

**IMPORTANT NOTE:**
These ratios should NOT be used in reverse — that is, for converting from methadone to morphine.

**Ripamonti et al., 1998**

<table>
<thead>
<tr>
<th>Morphine Dose (mg/d)</th>
<th>&lt;100</th>
<th>101-300</th>
<th>301-600</th>
<th>601-800</th>
<th>801-1000</th>
<th>&gt;1001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine:Methadone EDR</td>
<td>3:1</td>
<td>5:1</td>
<td>10:1</td>
<td>12:1</td>
<td>15:1</td>
<td>20:1</td>
</tr>
</tbody>
</table>

**Mercadante et al., 2001**

**Ayonrinde, 2000**
Morphine ↔ Methadone

- From oral morphine to oral methadone
  - Wide EDRs (2.5-14.3:1)
  - Dependent on the previous dose of opioid
    (Clinical J of oncology 1998:16:3216-3221 by C. Ripamonti et al)
    - 30-90 mg oral morphine → 3.7:1 (2.5-8.8:1)
    - 90-300 mg oral morphine → 7.75:1 (4-10:1)
    - > 300 mg oral morphine → 12.25:1 (10-14.3:1)
  - EDR is dose dependent and increases with high dose of morphine.
  - Switched over 3-10 days

- From oral methadone to oral morphine
  - Switched over 1 day
  - The direction of conversion did not significantly influence the dose ratio?
Problems of equianalgesic dose ratio of opioid

The ratio may be time dependent

- EDR may also change over time (duration of exposure)
  - Eg. The EDR of Morphine/Hydromorphone was 7:1 on day 7 but changed to 3:1 on day 13.

Anderson et al. JPSM 2001;21(5):397
Problems of equianalgesic dose ratio of opioid

• Individual variation in oral bioavailability

• Eg.
  • Oral bioavailability of morphine:
    • 15-64% (Clinical Pharmacol Ther 1990;47:639)
  • Oral biloavailability of oxycodone:
    • 50 % (Clinical J Pharm Ther 1978;207:92)
  • Therefore equianalgesic ratio for morphine: oxycodone: 1:1 to 2:1 (depending on individual ability to absorb morphine, oxycodone may range from equipotent to twice as potent)
Problems of equianalgesic dose ratio of opioid

- Individual variation in hepatic metabolism
  - Eg.
    - Genetically determined CYP2D6 isoenzyme of the hepatic P450 is involved in the metabolism of codeine. Codeine is metabolized to morphine. Therefore genetically determined poor metabolizers of codeine will have poor response to codeine.
Possible reasons for inaccurate equianalgesic dose ratio of opioid

- Incomplete cross tolerance occurs during chronic opioid use
- Accumulation of active metabolite
- Individual bioavailability difference between two different opioids
- Individual variation in hepatic metabolism of opioids
Development of tolerance

- Activation of NMDA receptors in dorsal horn neurons by metabolites of morphine may produce a hyperalgesia requiring increased doses of morphine to maintain pain relief.
- The tolerance to opioid has been shown to be attenuated by antagonism of the NMDA receptors (e.g., methadone).
- Therefore conversion to opioid devoid of active metabolites such as methadone could result in decreasing analgesic requirements.
Active metabolites

- Normeperidine
- Morphine 6 glucuronide
  - 5-10% of morphine metabolite
  - 650 times more potent than morphine
  - Longer duration of action than morphine
- Oxymorphone from oxycodone
  - 14 times more potent than oxycodone but very small and often undetectable amount
- Both M6G and M3G from dilaudid and morphine
Other factors influencing relative potency

- Major organ dysfunction
  - Renal failure - morphine
  - Hepatic impairment
  - Adrenal insufficiency and hypothyroidism - prolonged and exaggerated response to opioids

- Demography
  - Race — some Asians are poor metabolizers of codeine
  - Age
  - sex
Approach to conversion

- Go **slow**
- Use conservative ratio: 50 - 75% of calculated dose to minimize overdose and toxicity
- Use breakthrough meds
- **Titrate** to effect
  - Two end points
    - Adequate analgesia
    - Persistent and unmanageable side effects
- Increase vigilance during the conversion
- Caution in the setting of renal impairment
- Be aware of active metabolites
- Elderly patients usually tolerate lower doses than younger patients.
- Neuropathic pain usually require higher opioids than nociceptive pain.
- Methadone:
  - More potent than previously appreciated
  - The ratios related methadone are highly correlated with the dose of the previous opioid
Methadone

- Conversion to methadone
  - Slow process
    - Over 3 days, in hospital setting
    - Reduce opioid by one-third each day
    - Add 10% of the eliminated morphine equivalent dose
How to switch to methadone from other opioids

<table>
<thead>
<tr>
<th>Day</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Decrease the original opioid daily dose by 30% and add oral methadone at a dose of 2.5 to 5 mg every 8 hours (20:1 ratio) and use original opioid for breakthrough. Wait 3 to 7 days to judge initial stabilization.</td>
</tr>
<tr>
<td>Day 4 to 7</td>
<td>Decrease original opioid by a further 30% and increase the methadone dose by 2.5 to 10 mg per dose. Continue to use original opioid for breakthrough.</td>
</tr>
<tr>
<td>Day 7 to 10</td>
<td>Stop the original long acting opioid. Depending on response, increase methadone dose and continue using original opioid for breakthrough or switch to methadone at 25% to 33% total daily dosing q3h</td>
</tr>
</tbody>
</table>
Equianalgesic dose of opioids
Controversial issues
Controversial issues

- Preoperative use of NSAIDs
- Preoperative use of Gabapentin
- Use of NSAIDs for postoperative spinal fusion
References

- Lubenow et al. Chapter 55 pp 1403 of Clinical anesthesia
References

- Sinatra R. Acute pain management and APS. Chapter 26 in 3rd edition of Neural blockade
References

References

References

- Pharmacology and Physiology in anesthetic practice. Third edition. Chapter 3 Pg 77-112.
- British Journal of Anesthesia 2000;84:48
- Pharmacology & Physiology in Anesthetic practice-by R. Stoelting-3rd edition Chapter 11: 247-258
- (Spine 2008:33:19:2079)
References

  - J of pain and symptom management 1999;18:111-119
  - Oral to parenteral ratio for oxycodone ( JPSM 1999;18:53)
  - Clinical Pharmacol Ther 1990;47:639)-Oral bioavailability of morphine:
    - Clinical J Pharm Ther 1978;207:92)- Oral biavailability of oxycordone
  - Oxycodone (Pain 1997;73:37, J of pain and symptom management 2001;21:397)
References for equianalgesic dose

References for equianalgesic dose