Management of Acute Pain

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Pain Control: How Well Am I Doing?

- Pain is whatever the patient says it is
- Pain scores are inherently variable and subjective
  - Single measures are almost useless
  - Repeated measures are used to assess response to therapy
- Use functional outcomes to assess efficacy of therapy
  - Pain score with movement, not rest pain
  - Even better ... pain score after maximal movement or stress
  - Even better ... degree of movement
- Other functional outcomes
  - Time to ambulation, length of ambulation
  - Time to return of bowel function, incidence side effects
  - Mortality benefit

Different "Pain" Diseases

- Acute Pain (broken bone, surgical incision)
  - Highly variable intensity, short duration
  - Great fear of respiratory depression
- Cancer Pain
  - Relatively steady intensity
  - Less fear of respiratory depression
- Chronic Non-Malignant Pain (headache, backache)
  - Substantial component of anxiety and depression
  - Opioid tolerance common, especially in the young
- Neuropathic Pain (Complex Regional Pain Syndromes, Shingles)
  - Burning, lancinating, electric pain
  - Opioids don't work well

"If It Ain't Broke, Don't Fix It"

- Opioids are the mainstay of acute pain management
- Long history of safety
  - Lots of side effects (nausea, constipation/ileus, pruritus, urinary retention, respiratory depression, myoclonus)
  - Essentially no direct organ injury
  - Except Demerol, which has multiple problems with seizures, tachycardia, and severe drug interactions
- If your acute pain patients have:
  - Adequate pain control (reaching functional goals)
  - No significant opioid toxicity
  - ... then you shouldn't feel pressed to use new or novel analgesics
Opioid Side Effects Are A Spectrum

- By varying the opioid dose you can move between:
  - Screaming in pain
  - Awake and comfortable
  - Nauseous, itching, “woozy”
  - Somnolent
  - Dead (from respiratory depression)
- I can get you to any point on the spectrum with any opioid
  - Except Demerol, which may kill you first
- Changing the pain intensity has the same effect as changing the opioid dose
  - Epidural infusion clogs --> Pain --> IV morphine --> Comfort
    --> Epidural unlogged --> Respiratory Arrest

General Principles of Acute Pain Management

- Pain and no side effects ---------> increase opioid dose
- Side effects and little pain -------> decrease opioid dose
- Both side effects AND pain:
  - Change opioids (usually doesn't work)
  - Add non-opioid adjuncts
  - Prevent and prophylactically treat opioid toxicity
- By definition an acute pain problem includes opioid toxicity

Opioid Respiratory Depression

- The lungs do two things
  - Absorb oxygen (“oxygenation”)
  - Excrete carbon dioxide (“ventilation”)
- We have a good non-invasive test for oxygenation
  - Pulse oximetry
- There is no good test for ventilation
  - ABG is invasive and not continuous
  - Respiratory rate does NOT reliably predict hypercarbia
  - Arousability is the best test

Opioid Respiratory Depression

- Hypoxia rapidly causes injury
- Acidosis in the absence of hypoxia is very well tolerated
- Prophylactic oxygen "buys you time" to diagnose and treat opioid induced respiratory depression before permanent injury occurs
- Prophylactic oxygen should be routinely considered for all acute pain patients at high risk for opioid toxicity
"Prophylactic" Oxygen is Not a Generally Accepted Standard of Care

- "Currently, there is no consensus in the literature regarding recommendations on the prophylactic administration of supplemental oxygen to all postoperative patients ... We suggest that the decision to administer supplemental oxygen not be based on routine ..."
  – Fu ES et al. Chest 2004;126:1552

Fu ES et al. Chest 2004

- 288 patients admitted to the PACU after general anesthesia
- Randomized to room air or 30% face mask
- Supplemental oxygen significantly reduced episodes of hypoxia
  - 2.3% vs. 9.0% (p = 0.02)
- Why wouldn't you routinely give prophylactic oxygen?

Pulse Oximetry Can (sort of) Monitor Both Oxygenation and Ventilation

- A normal oxygen saturation on room air effectively rules out both hypoxia and hypercarbia
- How? It conclusively proves that the patient hasn’t crossed the "red line" (pCO2 > 80)
- Alveolar Gas Equation: PaO2 = FiO2(713) - PaCO2(1.2)
  - As the pCO2 rises above 80, the pO2 falls below 50
- The Henderson-Hasselbach Equation (pH, pCO2, and HCO3)
  - As the PaCO2 rises above 80 mmHg, the pH will fall below 7.1
- A normal SpO2 on room air means you alveolar pCO2 can not possibly be > 80

Is Pulse Oximetry The Only Thing That I Need to Monitor?

- A normal oxygen saturation on room air rules out both hypoxia and severe hypercarbia
- The problem is we can’t continuously monitor SpO2 on a regular ward
  - The rate of false alarms is too high
Opioid Respiratory Depression: Prevention

- Frequently assess SpO2, ideally on room air
  - Consider "bedside pulse oximetry" on the regular wards to facilitate frequent assessments every time the nurse is in the room
- Regularly assess arousability using a sedation scale
- Give prophylactic oxygen to all "at risk" patients who are not on highly reliable continuous pulse oximetry

Who is At Risk for Opioid Respiratory Depression?

- Morbid obesity/history of sleep apnea
- Concomitant use of other sedatives
  - Benzodiazepines are synergistic with opioids
- Rapidly changing "acute" pain stimulus, especially when being treated with long acting opioids
  - PCA basal rates
  - Fentanyl Patch, OxyContin, MS Contin, Methadone

Opioid Toxicity: Treatment

- Treatment is easy: low dose naloxone
  - 40 mcg iv q1-2 min (one tenth of a 0.4 mg ampule)
- Naloxone is shorter acting than any opioid that you are going to see outside of the operating room.
  - If you give naloxone, and the patient wakes up, then you will probably need to start a naloxone infusion to prevent recurrence of somnolence

Post-op Patients Requiring Naloxone

Gordon DB et al. Pain Manag Nursing 2005

- All adult inpatient post-op patients at one academic center for one year
- 56 out of 10,511 (0.53%) needed naloxone
  - 65% of episodes occurred within 24 hours after surgery
  - 48% had no sedation scores recorded
  - 63% had RR > 12
  - Patients were older and received more concomitant sedatives than matched controls
  - No significant difference in opioid quantity or route
Recipe for Acute Pain

• Non-opioid adjuncts ATC
• One short acting opioid, always PRN
  – With a dose large enough to work
• One long acting opioid, always ATC
  – Order only if they are using the short acting opioid regularly
• Oral opioids are superior to IV in every way except a 10-30 minute advantage in speed of onset
  – Cheaper, more gentle offset, not dependent on IV access, easier to convert to a home regimen upon discharge

IV Opioid Patient Controlled Analgesia (PCA) for Acute Pain

• Better patient satisfaction
• More convenient for staff
• Patient self-administration allows for faster dose titration
  – Useful when you don’t know what the patient’s requirements will be
• Notice that I am NOT saying less opioid consumption

IV Opioid PCA/PRN for Acute Pain

• Dose Per Injection
  – “When I hit the button it doesn’t do anything”
  – Make the dose large enough to work
  – If they are using frequent demand injections, you can safely increase the demand dose (assuming the pain doesn’t suddenly go away)
• Lockout interval
  – “When I get behind it takes me a long time to catch up”
  – Keep the lockout interval short enough to break a “pain crisis” quickly
  – Almost no use for a lockout interval > 6-10 minutes

IV Opioid PCA/PRN for Acute Pain

• Basal Rate
  – “The button works, I’m just sick of hitting it all the time”
  – Don’t treat acute pain with a basal rate
  • Increase in the dose per injection instead
  • Add a basal rate for maintenance of analgesia
  • Acute pain patients often only need only 0-25% of their total opioid consumption as a basal rate
  • Chronic pain patients may need 70-80% of their total opioid consumption as a basal rate (their pain won’t go away anytime soon)
**IV Opioid Choices**

- **Morphine**
  - Familiar (so therefore less administration error)
  - Multiple problems
    - Histamine release
    - Active metabolite accumulates in renal failure
    - More confusion in elderly
- **Hydromorphone (Dilaudid)**
  - Roughly the same onset and duration as morphine
- **Fentanyl**
  - Faster onset and offset (inconvenient for IV prn, but works fine in a PCA or IV prn in an ICU setting)
  - Not always appropriate for IV bolus use on regular floors

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**Meperidine (Demerol)**

- Often preferred by patients (the best “buzz”)
- Not useful as a primary analgesic:
  - Long acting metabolite normeperidine can accumulate and cause seizures, even with normal renal function
  - Interacts with MAO inhibitors, and possibly SSRIs, precipitating a serotonin crisis
  - Atropine like action causes tachycardia
- Low doses (12.5-25 mg IV) good for rigors
- Has been “banned” at UCSF as an analgesic except for procedural sedation
  - SFGH has been this way for years

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**"Weak" Oral Opioids**

- **Codeine**
  - With acetaminophen (Tylenol #3)
  - Weak, frequent side effects
- **Propoxyphene**
  - With acetaminophen (Darvocet)
  - Cardiotoxicity (rare)
  - Long acting metabolite accumulates in elderly
- **Hydrocodone**
  - With acetaminophen (Vicodin, Lortab, Norco 10/325)
  - With ibuprofen (Vicoprofen 7.5/200)

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**"Strong" Oral Opioids - Short Acting**

- **Oxycodone**
  - Schedule II even with acetaminophen (Percocet)
- **Hydromorphone (Dilaudid)**
- **Morphine**
- **Fentanyl**
  - Oral only as a lollipop or a new "lozenge"
  - Not recommended for chronic use except in palliative care (patients rapidly develop opioid tolerance)
- Numerous other infrequently used agents
  - Opana (oxymorphone) is new
Long Acting Opioids

- Extended release oxycodone (OxyContin)
  - Easy math, fewest side effects so therefore the most desired by abusers
  - Can’t crush to give down a feeding tube
- Extended release morphine (MS Contin, Avinza)
  - Same issues as OxyContin
- Fentanyl Patch
  - Not dependent on PO intake
  - 12+ hr onset and offset, absorption increases with fever
  - New PCA Patch: 40 mcg/inj, 10 min lockout, no basal rate
- Methadone
  - Available as an elixir (for feeding tube) and in an IV form
  - May have advantages with long term therapy (NMDA antagonist)
  - A dose change takes 2+ days to take effect

Opioid Tips: Beware Dose Conversion Tables

- You need to conversion tables for standing regimens, not single bolus doses
  - “1 mg of X = 2 mg of Y” is completely useless
  - You need “1 mg of X q4hr = 2 mg of Y q8hr”
- The standard deviation of the population is high
  - For each individual, you probably need to adjust down by 50% to be safe

Preprinted Oral Opioid Order Set: An Example for Acute Pain

- Oxycodone 5 - 15 mg PO Q2hr PRN Pain
  - Dosing interval is based on time to peak effect, not duration
  - The dose range should be sufficiently wide to deal with the different levels of pain that might be encountered
  - May need to write, in the order itself, a recipe for choosing between 5 and 15 mg for regulatory compliance.
- Non-opioid adjuncts ordered ATC
  - You want them to take them even if they aren’t having pain
- Check boxes for:
  - Anti-emetics and laxatives (ondansetron is now cheap!)
  - Prophylactic oxygen
  - Regular assessment of arousability

Why Opioids Fail

- Aggressive opioid therapy is not always the solution
- Opioids can induce hyperalgia and actually make the pain worse
- Opioid tolerance and hyperalgia may be much more common and rapid in the young
Preemptive Analgesia: Meta-analysis
Ong CKS Anes Analg 2005

- Randomized trials of "pre vs. post" incision treatment
- 66 studies with 3261 patients
- Combined outcomes for pain score, supplemental analgesic consumption, and time to first analgesic consumption in the first 24-48 hours.
- Epidurals, NSAIDs, and local anesthetic wound infiltration showed significant benefit
- Systemic NMDA antagonists had a trend toward a benefit
- Systemic opioids showed no benefit

Meta-analysis of Combined Outcomes
(Pain, Analgesic Use, Time to Rescue Dose)
Ong CKS Anes Analg 2005

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
<th>95% CI</th>
<th>p value</th>
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<tbody>
<tr>
<td>Epidural</td>
<td>0.38</td>
<td>0.28-0.47</td>
<td>0.00</td>
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<tr>
<td>Local Anesthetics</td>
<td>0.29</td>
<td>0.17-0.40</td>
<td>0.00</td>
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<tr>
<td>NSAIDs</td>
<td>0.38</td>
<td>0.27-0.48</td>
<td>0.00</td>
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<tr>
<td>NMDA Antagonists</td>
<td>0.10</td>
<td>-0.03-0.22</td>
<td>0.12</td>
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<tr>
<td>Systemic Opioids</td>
<td>-0.10</td>
<td>-0.26-0.07</td>
<td>0.25</td>
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Acetaminophen Tips
- Give separately ATC
  - They really only need to be combined with opioids in outpatients
- Make the pure opioid PRN
- Max 4 gm/d in healthy people
  - Keep it to 2 gm / day in the malnourished
- 2 gm / day is relatively safe
  - Used frequently in liver transplant or hepatectomy

Non-Opioid Adjuncts: "Pile On"

- Acetaminophen
- NSAIDs: either non-selective or COX-2 specific
- "SAIDs": Dexamethasone
- Local anesthetic
  - Regional block (Epidural, etc.)
  - Local wound infiltration
  - IV infusion
- NMDA Antagonists: Ketamine, Dextromethorphan
- Alpha-2 Agonists: Clonidine, Dexametomidine
- Anticonvulsants: Gabapentin
- Antidepressants: Amitriptyline
NSAIDs: Multiple Toxicities

- Renal injury
  - Even with a mildly abnormal creatinine
- GI bleeding
  - Cox-2 selective agents aren't any better
- Platelet inhibition
  - Absent with Cox-2 selective agents
- Inhibition of bone growth
  - Probably absent with Cox-2 selective agents
- Thrombotic complications (MI, Stroke)
  - The FDA warning is present for all NSAIDs, not just Cox-2 selective agents


NSAIDs and MI Systemic Review: 2006
Hernandez-Diaz S et al. Basic Clin Pharm Tox

<table>
<thead>
<tr>
<th>Pooled RR of MI</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Naproxen</td>
<td>0.98</td>
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<td>Naproxen in non-users of ASA</td>
<td>0.83</td>
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<tr>
<td>Ibuprofen</td>
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<tr>
<td>Celecoxib</td>
<td>0.96</td>
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<td>Rofecoxib</td>
<td>1.26</td>
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<td>Rofecoxib &lt; 25 mg/d</td>
<td>1.18</td>
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<tr>
<td>Rofecoxib in patients without a history of MI</td>
<td>1.39</td>
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“Steroidal” Anti-inflammatories: Dexamethasone for Lap Chole

- RCT dexamethasone 8 mg IV 90 min preop
- Excellent multimodal anesthesia
  - Propofol, fentanyl, cis-astra, incisional LA, ketorolac IV, acetaminophen PR, ibuprofen PO, ondansetron IV PRN
- Improved pain control at 24 hrs and cumulative at 7 days
- Less IV/PO morphine consumption (110 vs. 225 mg, p<0.05)
- Less nausea in first 24 hours (p<0.05)
- Faster return to activity (1 vs. 2 days, p<0.01)

Epidural Analgesia: The “King” of Non-opioid Analgesics

- Gives you a “band” of analgesia in a dermatomal distribution centered roughly around the insertion level
  - C8 = fingers (too high, since C3-5 is the diaphragm)
  - T4 = nipples
  - T10 = navel
- Thoracic epidurals with local anesthetic for large thoracic dermatomal incisions (laparotomy, thoracotomy, etc.) clearly improve pain control and probably reduce perioperative mortality by 20-30%
  - The same may also be true for labor epidurals and spinals for C-section
- Overall rate of serious morbidity from the catheter is probably about 0.03%, less in young healthy patients
Metaanalysis: Outcome Benefit of Neuraxial Blockade
Rodgers A. Anes Analg 2003;97:915-28

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P-value</th>
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<tr>
<td>Mortality</td>
<td>0.78</td>
<td>0.63-0.97</td>
<td>0.03</td>
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<tr>
<td>Myocardial Infarction</td>
<td>0.71</td>
<td>0.51-0.98</td>
<td>0.04</td>
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<tr>
<td>Pneumonia</td>
<td>0.62</td>
<td>0.52-0.75</td>
<td>&lt;0.0001</td>
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<tr>
<td>Renal Failure</td>
<td>0.78</td>
<td>0.55-1.09</td>
<td>0.15</td>
</tr>
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Local Anesthetic: Metaanalysis of Continuous Wound Infiltration

- Continuous infusion of local anesthetic via a catheter placed directly into the wound by the surgeon
  - Systemic review of 44 RCT enrolling 2,141 patients
  - Usually ropivacaine or ropivacaine 0.25 - 0.5%
  - Median infusion 2 days
- Statistically significant reduction in pain and opioid consumption
  - Mean VAS at rest -10 mm WMD, -22 mm with activity
  - Opioid consumption: 11 mg/d WMD
- Trend toward shorter hospital length of stay
  - Significant reduction (7 vs. 8 days, p<0.05) in cardiothoracic and ortho
- No difference in wound infection rates
  - 0.7% in treatment group vs. 1.2% in placebo or no-catheter controls

Local Anesthetic Wound Infusion

- Easy to insert at the end of surgery
- Disposable catheter and elastomeric pumps available
  - With and without a patient demand injection feature
- Patients can be discharged home with them still in place
- Pain Service consultation likely not necessary

Local Anesthetics: IV Lidocaine
Kaba A et al. Anes 2007;106:11-8

- RDBPCT of IV lidocaine infusion for laparoscopic colectomy
  - 1.5 mg/kg bolus then 2 mg/kg/hr intraop
  - 1.33 mg/kg/hr for 24 hr postop
  - Everyone got acetaminophen and ketorolac
- Faster return of bowel function (first flatus 17 vs. 28 hr, first defecation 28 vs. 50 hr, all p = 0.001 or better)
- Less opioid consumption (8 vs. 22 mg piritramide, p = 0.005)
- Faster discharge home (2 vs. 3 days p = 0.001)
**Alpha agonists: Clonidine for C-section**  
Yanagidata F et al. *RAPM* 2001

- n = 46 Elective caesarean section  
  - Combined spinal and epidural anesthesia  
  - PCA morphine post-op (1/10/0)  
- RCT clonidine 4 mcg/kg PO preop  
- Significantly less morphine consumption at 24 and 48 hours (22 vs. 42 mg, p<0.01)  
- No difference in pain  
- Non-significant trend towards less nausea (4.4% vs. 8.8%)

**"Low Dose" Ketamine**

- NMDA antagonist, dissociative anesthetic  
  - Relatively little respiratory depression  
- Hallucinations possible at high “anesthetic” doses  
  - 2-3 mg/kg IVB  
  - 6-10 mg/kg PO  
- New low dose “analgesic” regimens likely work by blocking opioid hyperalgesia with minimal side effects  
  - 0.15 - 0.5 mg/kg IVB then 1-5 mcg/kg/min IV  
  - 0.2 - 1.0 mg/kg PO q4-8hr

**Ketamine for Acute Post-Op Pain**  
Bell RF et al. *Acta Anaes Scand* 2005

- Metaanalysis of 37 trials  
- Reduced 24 hour opioid consumption  
  - WMD (fixed) = -15.98 (95% CI -19.70, -12.26)  
- Reduced nausea and vomiting  
  - RR (fixed) = 0.77 (95% CI 0.65, 0.90)  
- Adverse effects were "mild or absent"

**Ketamine at UCSF**

- Oral ketamine is available in all inpatient wards  
- Intravenous ketamine infusions outside the ICU have been approved and will start when the new infusion pumps arrive  
- Pain Service consultation is required
Anticonvulsants: Gabapentin

• May also block the development of opioid induced hyperalgesia
  – 12 RCT 896 patients
  – Pain scores lower (Weighted Mean Difference VAS -0.74 CI -1.03 to -0.45 at 24 hours)
  – Opioid usage less (Odds Ratio -17.84, CI -23.50 to -12.18)
  – Associated with sedation and anxiolysis (OR 3.28 CI 1.21 to 8.87)
  – Not associated with a difference in lightheadedness, dizziness, nausea, or vomiting

Gabapentin for Acute Pain

• Typical starting dose for an inpatient is 300 mg PO TID
  – Minimum effective dose is 600-900 mg PO TID
• Major drawback is that it is PO only
  – Can't give to postop patients who are NPO
• Pregabalin (Lyrica) is an alternative oral agent thought to have similar activity
  – Placed on the UCSF Formulary January 2007
  – 50 - 100 mg PO TID

Take Home Messages

• Titrate opioids to match the fluctuating pain intensity
• Regularly assess arousability in addition to pulse oximetry
• Consider prophylactic oxygen in settings where continuous pulse oximetry is not reliably available
• "Pile on" as many non-opioid adjuncts as possible