Understanding Pharmacologic Properties of Analgesics in the Treatment of Acute Pain

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Objectives

- Discuss ways knowledge of pharmacology can enhance analgesia
- Describe relationship between pharmacokinetics and pharmacodynamics and its importance
- List strategies to maximize analgesia

Nociceptive/Acute/Physiologic Pain

- Usually a known stimulus—examples…
  - Surgical incision
  - Crush injury
  - Fractures
  - Ischemia
  - Snake bite
- Temporary in nature
- Normal pain processing

Pharmacology

- Mechanism of action
- Onset of action
- Peak effect
- Duration of action

Pharmacokinetics

- The action of drugs in the body, including
  - Absorption
  - Distribution
  - Elimination
  - Half-life
  - Steady state

Pharmacodynamics

- Opioid responsiveness depends on:
  - Liver function
    - Drug metabolizing enzyme activity
  - Renal function
  - Medication history
- Pharmacogenetic differences
- Sex differences
Analgesics

• Nonopioids
  – NSAIDS
  – Aspirin
  – Acetaminophen
• WHO Ladder for analgesia

NSAIDS

• Antiinflammatory, antipyretic, analgesic
• Mechanism of action—prostaglandin inhibition by way of COX-1
  – Important in maintaining integrity of GI and duodenal mucosa
  – Important in modulating renal plasma flow
• NSAIDs inhibit formation of thromboxane—effecting platelet aggregation
• Use with caution in pts. with history of asthma
  – Inhibits prostaglandin E—responsible for bronchodilation

Transduction: Nociceptive Chemical Stimuli

Risk Factors for NSAID-induced GI effects

• Increasing age—>60 (due to possibility of other disease processes)
• Past history of peptic ulcer, bleeding or perforation for any cause
• Extent of frailty
• Dose of NSAID (higher doses more likely)
• Combinations of NSAIDs
• Concomitant use of glucocorticoids
• History of GI toxicity with NSAIDs

Prevent GI effects with misoprostol—400µg/d

• Prevents gastric and duodenal ulcers
• Decreases incidence of ulcer complications
• Heals gastric and duodenal ulcers
• Does not improve symptoms
• May lead to improved gut motility; increase in diarrhea at full dose
• May need to decrease dose due to side effects

Risk factors for NSAID-induced renal effects

• Caused by inhibition of renal prostaglandin synthesis
• High risk
  – Volume depletion states
  – Severe CHF
  – Hepatic cirrhosis with or without ascites
  – Clinically significant dehydration
  – Creatinine clearance <30 ml/min
• Low to moderate risk
  – Intrinsic renal disease—Diabetic neuropathy, nephrotic syndrome, hypertensive nephropathy
  – Induction of anesthesia
• Questionable risk
  – Older age
**Acetaminophen**

- Mechanism of action is not certain
- Probably centrally acting—?cox-3 inhibitor
- Acetaminophen toxicity
  - Hepatotoxicity
    - Toxic metabolite (NAPQI)
    - Several other mechanisms lead to hepatotoxicity
    - Mechanism not completely understood
  - Nephrotoxicity >4g/day for long periods
    - Uncertain cause
    - May be caused by activity of NAPQI in renal microsomes
    - Increase frequency to 6-8 hrs in renal failure

**COX-2 Inhibitors**

- May have fewer GI effects than COX-1 inhibitors
- Should be avoided in patients with creatinine clearance <30ml/min
  - Carry same risk as traditional NSAIDs
- Celecoxib—Celebrex
  - UAD=100-200 mg q12h max=400 mg/d

**“Opioids” vs “Narcotics”**

- Characteristics of Opioids
  - No ceiling effect
  - Usually no end organ damage with chronic use
  - Metabolized by the liver
  - Excreted by the kidney
  - Cause tolerance and physical dependence
  - Reversible with an antagonist
  - Bind to opiate receptors—µ, κ, δ
**PRN**
- What does “PRN” mean?
- If pain is ongoing give opioids ATC
- Half-life
- Steady state

**Opioids**
**Mu-agonists**
- Bind to mu opiate receptors blocking transmission of pain
  - Morphine
  - Fentanyl
  - hydromorphone
  - oxycodone
  - hydrocodone
  - Codeine
  - *Methadone
  - *meperidine
  - *propoxyphene
  - *tramadol

**Morphine**
- Hydrophilic—delayed onset and longer duration
- One active metabolite—morphine-6-glucuronide (M6G)
  - Accumulation results in neurologic side effects as well as potentially life-threatening overdose
  - Removed with dialysis
- Patients with renal impairment should start at ¼ dose and titrate as needed

**Hydromorphone**
- Hydrophilic—similar to morphine
  - Metabolized in the liver
  - Several metabolites
- Use decreased amounts in renal impairment due to possible sensitivity to hydromorphone-3-glucuronide
  - there is no 6-glucuronide so may have fewer SEs
- May be safer than morphine in renal insufficiency

**Fentanyl**
- No active metabolites
- Safer in renal failure
- Lipophillic→Short half-life, short duration of action
- Half-life extends with continuous use

**oxycodone**
- Metabolized in the liver by cytochrome CYP2D6
- Binds at μ and κ receptors
  - Half-life and bioavailability slightly longer than MS
  - One active metabolite—oxymorphone
  - Women eliminate it 25% more slowly than men
  - Excretion impaired in uremic patients and
    - Elimination half-life is severely impaired in these patients
  - May cause CNS toxicity and sedation in renal failure
Hydrocodone

- Combination with acetaminophen
- Metabolized in the liver
  - Several metabolites
- Significant renal excretion of active forms
- Should be avoided in patients with renal failure

Demerol (meperidine)

- Half-life is 2-3 hrs (parenterally)
- Bioavailability from p.o. is ¼ that of parenteral
- More likely than other opioid drugs to cause delirium in postop pts of all ages
- Limit use to 600mg/d and no more than 48 hours due to metabolite—normeperedine

Normeperidine

- Normeperedine—only active metabolite of meperidine
  - Toxic metabolite
  - Half-life 15-20 hrs
  - Causes neuroexcitation—hyperreflexia, myoclonus, agitation and grand mal seizures
- Half analgesic potency but twice the toxicity
- Use extreme caution in patients with seizure disorder
- Use caution in patients with renal insufficiency
- Contraindicated with MAOI (monoamine oxidase inhibitors)—can cause serotonin syndrome or death

Codeine

- 60mg = 600 mg of aspirin
- Not appropriate for moderate to severe pain
- Usually more constipating
- Has more psychotomimetic effects
- Metabolized in the liver to morphine
  - Several metabolites
  - Metabolism is necessary for analgesia
  - Poor metabolizers may show absence of analgesia
- Reduced renal clearance in advanced renal failure
  - Reports of serious adverse effects in renal failure

Methadone—good news

- Inexpensive
- Adverse effects similar to other opioids
- Rapid onset
- ~ 80% bioavailability
- No active metabolites
- Long duration
- No ceiling dose other than side effects
- Has some SSRI and NMDA antagonist activity
- For opioid naïve patients start at 2.5mg Q8H
- Excreted in feces—considered safe in renal insufficiency

Methadone—?? good news

- Long half-life—15-60 hours
  - Unpredictable
  - Difficult to titrate
  - Difficult to convert from other opioids to methadone
- Duration initially is 3-6 hrs→8-12 hr with repeated dosing
- Efficacy is greater with repeated dosing
Propoxyphene (Darvocet)

- ½ to 1/3 as potent as codeine
  - 100 mg = 60 mg codeine = 600 mg aspirin
- Half-life 6-12 hrs
- Metabolized to norpropoxyphene (nonopioid)—
  - Half-life 30-36 hrs—half as effective as propoxyphene—has proarrhythmic lidocaine-like effects and cardiac anesthetic effects
  - Accumulation results in arrhythmias and pulmonary edema—reports also of apnea, cardiac arrest, and death
  - Not reversible by naloxone
- Inappropriate for elderly

Tramadol

- Weak mu-agonist
- norepinephrine and serotonin reuptake inhibitory activity similar to TCAs
- Peak effect in ~ 2 hrs of 100mg dose
- Ceiling effect
- Max dose is 400mg/24h in healthy adults due to risk of seizures
- >age of 75—300mg/24h (150mg Q12H)
- Renal insufficiency (CC<30ml/min) 200mg/24h
  - CC<10ml/min 100mg/24h (50mg Q12H)
- Hepatic insufficiency—100mg/24h

Titration of Opioids

- Based on effect
  - Increase dose 25%-100%
    * Ask patient how much pain was relieved by last dose
  - Estimate 24 hr total and change to long-acting formula…for example
    - 2 tabs 5/325 Percocet Q4H→30 mg OxyContin Q12H

Equianalgesic Dosing Guidelines

- Equianalgesic means approximately the same pain relief
- The chart is a guideline. Titrate meds according to pt’s response
- Chart is helpful when switching from one drug to another or when switching to another route
- Dosages are not necessarily starting doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral Dose</th>
<th>IV Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>30 mg</td>
<td>10 mg</td>
<td>3-5 hours</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>breakthrough only (OTFC)</td>
<td>100mcg</td>
<td>0.5-1 hour</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5 mg</td>
<td>1.5 mg</td>
<td>2-4 hours</td>
</tr>
<tr>
<td>Meperidine</td>
<td>300 mg NR</td>
<td>75-100 mg</td>
<td>2-4 hours</td>
</tr>
<tr>
<td>Codeine</td>
<td>200 mg</td>
<td>120-130 mg</td>
<td>3-4 hours</td>
</tr>
<tr>
<td>Methadone</td>
<td>20 mg</td>
<td>10 mg</td>
<td>4-8 hours</td>
</tr>
<tr>
<td>Oxycodeone</td>
<td>20-30 mg</td>
<td>————</td>
<td>3-4 hours</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30 mg</td>
<td>————</td>
<td>3-4 hours</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>————</td>
<td>10 mg</td>
<td>3-6 hours</td>
</tr>
</tbody>
</table>

Treatment of Side Effects

- Anticipate and prevent—esp. constipation
- Most side effects are dose dependent
  * Lower opioid dose
  * Add nonopioid
- Nausea—usually subsides
  * Chemoreceptor trigger zone activation
    * Treat with Zofran, Compazine, Torcan, Haldol
  * Decreased gastric motility
    * Treat with metoclopramide
  * Nausea associated with motion—treat with Dramamine
- Antiemetics are usually sedating—avoid if possible
Side effects—continued

- Pruritis
  - Benadryl—sedating
  - Narcan
  - Nubain
- Sedation—usually subsides
  - Treat with methylphenidate (Ritalin) or pemoline (Cylert)
  - Monitor sedation to avoid respiratory depression
- Respiratory depression—avoid with proper titration
  - If unresponsive consider naloxone

In Summary

- Titrate to effect
- Expect and treat side effects—use medications are they were intended
- Combine opioids and nonopioids whenever possible
- Applying knowledge of pharmacology, pharmacokinetic and pharmacodynamics provides safety and leads to adequate analgesia
REFERENCES
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