

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

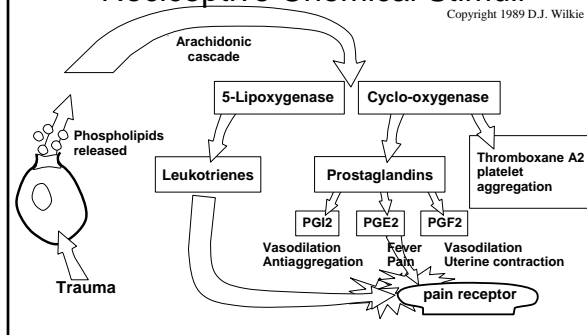
- Nonopioids
 - NSAIDs
 - Aspirin
 - Acetaminophen
- WHO Ladder for analgesia

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

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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

Class	Generic name	UAD	Brand name
Propionic acids	Naproxen	500 mg initially- followed by 250mg q6-8h	Naprosyn, Anaprox, Alleve
	Flurbiprofen		Ansaid
	Oxaprozin		Daypro
	Ibuprofen	400-800mg Q6-8h 25-75 mg Q6-8h Max 120mg/d (parenteral)	Motrin
	Ketoprofen		Orudis, Oruvail
	Ketorolac		Toradol
Indoleacetic acids	Sulindac	200mg Q12h	Clinoril
	Indomethacin	25-50mg q8h	Indocin
	Etodolac	200-40mg q6-8h	Lodine

Class	Generic name	UAD	Brand name
Phenylacetic acids	Diclofenac	50 mg/q8h	Cataflam, Voltaren
Salicylic acids (nanacetylated)	Salsalate	1000-1500 mg/q12h	Disalcid
	Choline magnesium trisalicylate	1000-1500 mg/q12h	Trilisate
Naphthylalkanone	Nabumetone	1000-2000 mg/day	Relafen
oxicam	Piroxicam		Feldene

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

Acetaminophen

- Acute pain (short term): MDD=4 g/d
- Chronic pain (long term): MDD = 3 g/d
- Preexisting organ damage: MDD = 2 g/d

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 | • Codeine |
| • Fentanyl | • *Methadone |
| • hydromorphone | • *meperidine |
| • oxycodone | • *propoxyphene |
| • hydrocodone | • *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→possible neuroexcitation
 - 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
- Lipophilic→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 $\frac{1}{4}$ 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—normeperidine

Normeperidine

- Normeperidine—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

Drug	Oral Dose	IV Dose	Duration
Morphine	30 mg	10 mg	3-5 hours
Fentanyl	Breakthrough only (OTFC)	100mcg	0.5-1 hour
Hydromorphone	7.5 mg	1.5 mg	2-4 hours
Meperidine	300 mg NR	75-100 mg	2-4 hours
Codeine	200 mg	120-130 mg	3-4 hours
Methadone	20 mg	10 mg	4-8 hours
Oxycodone	20-30 mg	-----	3-4 hours
Hydrocodone	30 mg	-----	3-4 hours
Nalbuphine	-----	10 mg	3-6 hours

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, Torecan, 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 as they were intended
- Combine opioids and nonopioids whenever possible
- Applying knowledge of pharmacology, pharmacokinetic and pharmacodynamics provides safety and leads to adequate analgesia

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