Pharmacologic Management of Pain

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Objectives

- **Identify types of pain and options for pharmacologic treatment based on a systematic patient assessment.**
- **Discuss the pharmacology of adjuvant analgesics.**
- **Determine opioid dose on initiation, titration, and conversion.**

Types of Pain

Nociceptive

- **Somatic**
  - **Easy to localize**
  - **Sharp, throbbing**
  - **persistent**
- **Visceral**
  - **Hard to localize**
  - **Difficult to describe**
  - **Comes in waves**

Neuropathic

- **Burning, tingling, shooting**
- **Intermittent**
- **Radiating pain**

Case #1

- **SM is a 23 yo female with relapsed AML diagnosed in Nov 2010. She is s/p 7+3 induction chemotherapy and HiDAC consolodation x2. She has developed severe pain in her bilateral hands and feet.**
- **Describes pain as burning, tingling and numbness**

Pain Assessment

- O – Onset
- P – provoking or palliating features
- Q – quality of pain
- R – radiation (from where to where)
- S – severity (intensity and effect on function)
- T – temporal pattern/course

Patient Assessment

- O – Onset
  - Since chemotherapy
- P – provoking or palliating features
  - Anything that touches feet or hands, even lightly hurts
- Q – quality of pain
  - Burning, tingling, and numbness
- R – radiation (from where to where)
  - Stays in hands and bottoms of feet
- S – severity
  - 8/10, not able to walk
- T – temporal pattern/course
  - Constant

Pain Assessment Expanded

- Severity
  - What is pain now?
  - Worst in last 24 hours?
  - Best in 24 hours?
  - On avg?
  - Pain prior to prn?
  - Pain at peak of prn?
  - How long does prn last?

Neuropathic Pain - Treatment

- Anticonvulsants
- Antidepressants
- Lidocaine
- Ketamine
- Opioids
  - Particularly methadone

Gabapentin (Neurontin®) vs. Pregabalin (Lyrica ®)

Similarities

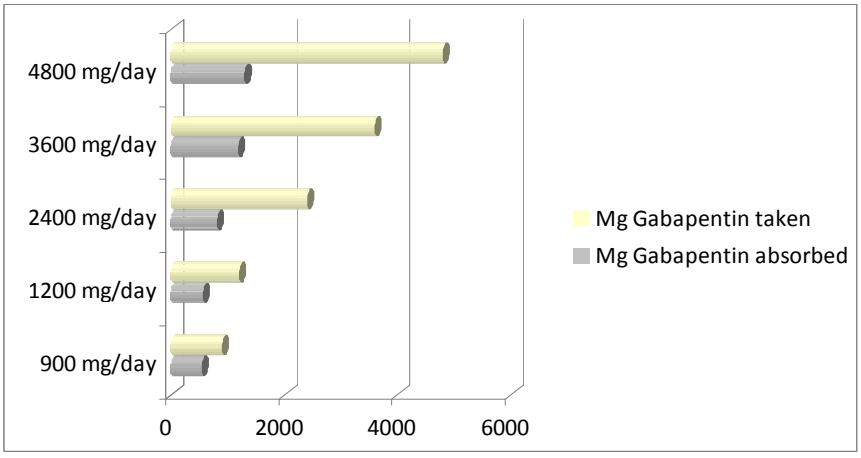
- Mechanism of action
- Pharmacokinetics
  - Renal excretion

Differences

- Pharmacokinetics
  - Absorption
  - Dosing
- Side effects
- Easier to titrate pregabalin
- Gabapentin is generic

Bockbrader HN. Clin Pharmacokinet. 2010;49:661-9.

Gabapentin absorption



Pregabalin [Lyrica] Product Info 2009

Gabapentin [Neurontin] Product Info 2010

Tricyclic Antidepressants

- Mechanism of action:
  - Inhibits reuptake of norepinephrine and serotonin
  - Sodium channel antagonist
- Tertiary amines
  - Amitriptyline, doxepin, imipramine
- Secondary Amines
  - Desipramine, nortriptyline

TCA Comparison: Major differences

- Serotonin (5HT) vs. Norepinephrine
  - Amitriptyline (Elavil®) primarily 5HT
  - Desipramine (Norpramine®) primarily NE
- Na channel effects
  - Desipramine strong antagonist

TCA Comparison: Major differences

- Anticholinergic effects
  - Amitriptyline (Elavil®) most
  - Despiramine (Norpramine®) and Nortriptyline (Pamelor®) least
- Doxepin (Sinequan®) and Imipramine (Tofranil®) strong antihistamines

TCAs Precautions

- Significant cardiac disease
- Anticholinergic
- Suicide risk

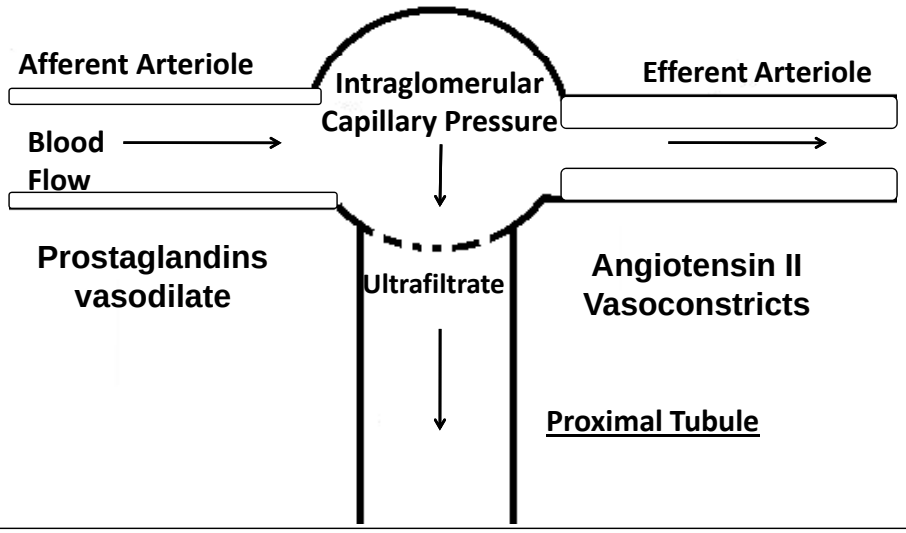
Somatic Pain: Treatment Options

- Non-steroidal Anti-inflammatory Drugs (NSAIDs)
- Acetaminophen (Tylenol®)
- Opioids

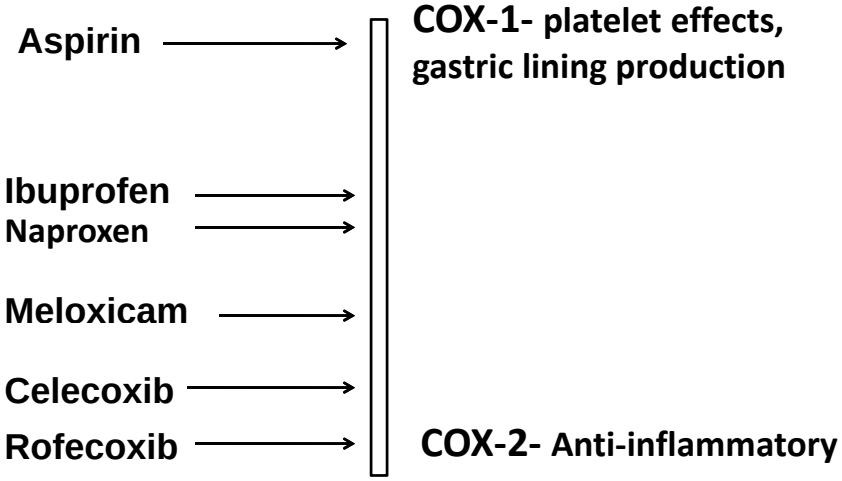
NSAIDs

- MOA: Inhibits cyclooxygenase (COX), leading to decreased prostaglandins and inflammation
- Examples
  - Ibuprofen (Motrin®)
  - Naproxen (Naprosyn®, Aleve®)
  - Meloxicam (Mobic®)
- Caution in patients with renal disease, bleeding disorders, or h/o GI bleed

Autoregulation of Renal Blood Flow



COX-1 vs COX-2



Wong SL. Adv Pharmacol. 2010;60:61-83

COX-2 Inhibitors

- Celecoxib (Celebrex®)
  - Less gastrointestinal irritation
  - Less risk of bleed
  - Use with aspirin negates benefits

Weideman RA. Gastroenterology. 2004 Nov;127(5):1322-8.

WHO Analgesic Ladder

- Step 1:
  - Non-opioid ± Adjuvant
- Step 2:
  - Opioid for mild-moderate pain, ± Non-opioid, ± Adjuvant
- Step 3:
  - Opioid for moderate - severe pain, ± Non-opioid, ± Adjuvant

http://www.who.int/cancer/palliative/painladder/en/

Opioid Analgesic Classes

Phenanthrenes

- **Morphine**
- **Codeine**
- **Hydromorphone**
- **Oxycodone**
- **Hydrocodone**

Phenylpiperidines

- **Meperidine**
- **Fentanyl**

Phenylheptanones

- **Methadone**
- **Propoxyphene**

Opioids: Precautions

- **Constipation**
- **CNS effects**
- **Myoclonic jerking / seizures**
- **Nausea / vomiting**
- **Pruritus**
- **Respiratory depression**
- **Addiction/ Abuse/ Diversion**

Opioids: Major Differences

- Mechanism of action
  - Tramadol (Ultram®)
    - SNRI
  - Tapentadol (Nucynta®)
    - SNRI
  - Methadone
    - NMDA antagonist

Opioids: Major Differences

- Dosage forms
  - Sustained release vs. Immediate release
  - Combined with acetaminophen
  - Transdermal
  - Buccal
  - Sublingual
  - Parenteral

Opioids: Major Differences

- Metabolism
  - Cyp2D6
  - Cyp3A4
  - Glucuronidation
- Active and toxic metabolites
  - Neurotoxicity: Morphine> hydromorphone> oxycodone>> methadone/ fentanyl
- Potency/ Equianalgesic doses

Smith HS. Mayo Clin Proc 2009;84:613-24.

Opioids: Initiation

- Acute and/or breakthrough pain
  - Use IR opioids prn not extended-release formulations
- Interval based on peak effect
  - Point at which patient gets most pain control and highest risk for toxicity (i.e. sedation, respiratory depression)
  - In general, peak effect:
    - PO = 1 hour
    - SC = 30 min
    - IV = 15 min (except Fentanyl = 6 min)

Opioids: Initial doses in opioid-naïve patients	
Morphine (MSIR®, Roxanol®)	PO: 5-15 mg IV/SQ: 2-6 mg
Hydromorphone (Dilaudid®)	PO: 2-4 mg IV/SQ: 0.2-0.6 mg
Oxycodone (Oxy IR®, Roxicodone)	PO: 5-15 mg
Hydrocodone (Vicodin®)	PO: 5-10 mg
Oxymorphone (Opana®)	PO: 2.5 mg

Opioids: Titration

- **Individualize dose by gradual escalation until adequate analgesia**
  - **No therapeutic ceiling unless side effects**
- **If pain is poorly controlled and no side effects, can safely increase using % rule:**
  - **Increase by 25-50% for moderate pain**
  - **Increase by 50-100% for severe pain**

Opioids: dosing for scheduled opioids

- Use scheduled opioids if:
  - adequate relief with prn meds, but pt needs frequent prn meds
  - persistent/chronic pain
- Options for scheduled opioids:
  - Immediate release opioid ATC (around the clock)
  - Sustained release opioid formulations
  - Continuous infusion of IV opioids
- Dosing based on:
  - 50-100% of total 24hr total OME (oral morphine equivalents) in divided doses

Opioids: PRN/Breakthrough for opioid-tolerant patient

- 10-20% of scheduled daily dose
  - Helps overcome tolerance
  - Often need more than anticipated for acute on chronic pain

Chronic Pain Regimen

- **Example**
  - **Morphine ER 60 mg po q8h and Morphine 15-30 mg po q1h prn**
  - **Fentanyl 50 mcg TD q72h and Morphine 15 mg po q1h prn**

Equianalgesic Conversion of Opioids*		
Drug	**SQ/IV Dose**	**Oral Dose**
Morphine	10	30
Hydromorphone	1.5	7.5
Oxycodone	------	20
Oxymorphone	------	10
Hydrocodone^	------	30
Fentanyl	0.1 mg (100 mcg)	Not established

Equianalgesia

- **Home Regimen:**
  - **Morphine SR (MSContin®) 60mg PO q8h**
  - **Oxycodone/APAP (Percocet®) 10/325mg 2 tabs q4prn (uses 4 tablets daily)**
- **NPO for surgery**
- **How would you replace it?**

Equianalgesia

- **How would you replace it?**
  - **Equianalgesic:**
    - **Morphine 30mg PO = Dilaudid 1.5mg IV**
  - **Dilaudid 1.5mg IV = Dilaudid X IV**
    Morphine 30mg PO Morphine 220 mg PO
  - **X = Dilaudid 11 mg IV**
  - **Continuous infusion = Dilaudid 11 mg IV / 24 hours**
    = Dilaudid 0.45 mg / hour

Equianalgiesia

- **Is this patient on a prn medication?**
  - **Percocet 10/325mg q4prn (2 tabs per dose)**
- **How would you replace it?**
  - **Equianalgesic:**
    - **Oxycodone 20 mg PO = Dilaudid 1.5mg IV**
  - **Dose on peak effect:**
    - **Dilaudid 1.5mg IV q15min prn**

Equianalgesic Conversion to Transdermal Fentanyl*	
Oral Morphine Equivalent	Transdermal Fentanyl dose
30 mg/day	12 mcg/hr
60 mg/day	25 mcg/hr
120 mg/day	50 mcg/hr
180 mg/day	75 mcg/hr
240 mg/day	100 mcg/hr

Breitbart W. Oncology 2000; 14:695-702.

Example conversion to Fentanyl

- **Home Regimen:**
  - **Morphine SR (MSContin®) 60mg PO q8**
  - **Oxycodone/APAP (Percocet®) 10/325mg 2 tabs q4prn (uses 4 tabs daily)**
- **Morphine PO 220 mg/day = Fentanyl 50 – 75 mcg/hr patch q72h***

Table 2: Equianalgesic Conversion to Methadone*

Oral Morphine Equivalent	Morphine: Methadone Ratio
< 90 mg/day	4:1
90 - 300 mg/day	8:1
> 300 mg/day**	12:1
Oral methadone: IV methadone ratio= 2:1	

Ripamonti C. J Clin Oncol 1998;16:3216-21

Example Conversion to Methadone

- **Home Regimen:**
  - **Morphine SR (MSContin®) 60mg PO q8**
  - **Oxycodone/APAP (Percocet®) 10/325mg 2 tabs q4prn (uses 4 tablets daily)**
- **Morphine mg/day**
  - **Methadone 8 mg PO = Methadone X mg PO IV**
    Morphine 1mg PO Morphine 220 mg PO
- **Methadone 15 – 27.5 mg PO per day***

Summary

- **Multiple pharmacologic treatment options for pain management.**
- **Systematic assessment important for drug selection.**
- **Many differences within classes of analgesics.**