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Pain Transmission in the Dorsal Horn
Types of Opioid Analgesics

- Mu agonists
- Agonist-antagonist
  - partial agonists (buprenorphine)
  - mixed agonist-antagonist (pentazocine, nalbuphine)
Opioid Genetics: Codeine

- Naturally occurring alkaloid of opium
- Metabolized by the liver primarily by glucuronidation, \(N\)-demethylation and \(O\)-demethylation.
- Codeine has no direct analgesia.
- The \(O\)-demethylation is via cytochrome P450 2D6, and transforms codeine to morphine (2-10% of codeine dose).
- Approximately 9% of white people are deficient of this isoenzyme and have no analgesic benefit from codeine.


Opioid Genetics: Tramadol

Postoperative pain relief with tramadol

<table>
<thead>
<tr>
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<th>Responders</th>
<th>Non-responders</th>
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<tbody>
<tr>
<td>Poor Metabolizer</td>
<td>16 (53%)</td>
<td>14 (47%)</td>
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<tr>
<td>Extensive Metabolizer</td>
<td>189 (78%)</td>
<td>52 (22%)</td>
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*P < 0.05, by $\chi^2$ test.

Opioid Genetics: Kappa Agonists

- Women respond better to butorphanol (Stadol) than morphine.
  - For treatment of acute injury; 45 females, 49 males.

- Women respond better to pentazocine (Talwin) than do males.
  - Post oral surgery; 10 females, 8 males.

- Red-headed women (with two variant MC1 R alleles) have increased response to pentazocine.
  - Experimental electric current pain; 24 women, 23 men.
Effects of Opioids

- Desirable
  - Analgesia
  - Relief from anxiety

- Possibly Desirable
  - Sedation
  - Cough suppression
  - Constipation
  - Euphoria

- Undesirable
  - Respiratory depression
  - Nausea, vomiting
  - Urinary retention
  - Mental clouding
  - Pruritis
  - Tolerance & dependence
  - Ileus
  - Biliary spasm
Side Effects of Pain Medications

Reduce dose to minimize:

- Fatigue: more prevalent complaint than pain in patients with metastatic cancer
- Depressed level of consciousness / sedation: dose-limiting problem, may be treated with stimulants
- Constipation: manage prophylactically with laxatives
- Nausea: change opioid, manage with antiemetics
- Delirium, confusion: change opioid
- Respiratory depression: unusual

1 mg intrathecal morphine = 300 mg oral morphine

Reduction in 15 Toxicities

*Statistically significant (P<0.05)

Opioid-Induced Sleep Apnea

- Observational study of 140 chronic pain patients receiving stable doses of opioids
  - Overnight polysomnography
- Outcomes
  - Obstructive and central sleep apnea occurred in 75% of patients studied
  - Significantly higher rate than the general population
  - Apnea-hypopnea index directly related to daily dosage of methadone and benzodiazepines

Long-Term Opioid Therapy

- Hormonal effects
  - Reduced plasma cortisol levels
  - Increase in prolactin
  - Decrease in LH, FSH, testosterone, and estrogen

- Immunosupression
  - Suppression of NKCA, inflammatory cytokine production, and mitogen-induced lymphocyte proliferation
Morphine Metabolites

- **Morphine-6-glucuronide (M6G)**
  - Active analgesic
  - M6G > M3G with oral dosing

- **Morphine-3-glucuronide (M3G)**
  - Antinociceptive
  - Long half life
  - May lead to myoclonus & hyperalgesia
  - M3G > M6G possible with IV dosing
Caution with Dose Conversions

Change Fentanyl Patch 300 mcg to Morphine sustained release

- Conversion calculator from Purdue Pharma
  - 560 mg/day morphine
- Conversion calculator from Janssen
  - 1035-1124 mg/day morphine

500 mg/day discrepancy!
Methadone

- Naturally long acting
- Bioavailability 80%
- Metabolized by cytochrome P450 system
- No active metabolites
- L-isomer is an opioid agonist
- D-isomer antagonizes the NMDA receptor and inhibits re-uptake of 5HT and norepinephrine
Methadone Dangers

- Non-linear dose equivalence
  - varies with degree of tolerance
- Can prolong Q-T interval -- ? check EKG
  - at doses > 30 mg / day,
  - if patient is on other QT prolonging medications,
  - any patient with cardiac risk factors
- Long half-life
  - Avoid rapid dose adjustments
  - Avoid use in elderly patients
- Interacts with many medications
Methadone Drug Interactions

- Decreases methadone levels
  - Phenytoin
  - Phenobarbital
  - Carbamazepine

- Increases methadone levels
  - Fluvoxamine
  - Fluoxetine
  - Paroxetine
  - Sertraline
  - Tricyclics
    - May increase tricyclic levels

The Addict in Pain

- Weighing two medical disorders with opposing treatments
- Don’t give opioids to the “active” addict
- Get help
- Maintain tight control—e.g. 1 week supplies
- Frequently reassess outcomes
- If on Methadone maintenance:
  - Continue methadone as an unchanged baseline
  - May require higher doses of opioids for acute pain
  - Contact the methadone maintenance team
Chronic Opioids and Hyperalgesia

- Opioid tolerant rats are hyperalgesic
- Lack of analgesia in addicts on methadone
- Neurobiologic changes with opioid tolerance are similar to those in hyperalgesia (NMDA mediated)

Intracellular Mechanisms of Sensitization

Morphine Tolerance Can Be Associated With Environmental Cues

Opioid Agreements/Contracts

- Can help clarify expectations, rules, and consequences
  - Participation in other treatment modalities
  - Compliant use of the medication
  - A single prescribing physician
  - Sporadic drug testing
- May be more binding on the physician than the patient
Treatment Modalities for Chronic Pain

Modulate Ascending Pathways
- Decrease Small Fiber Input
  - antiinflammatory agents
  - opioids
  - nerve blocks or ablation
- Increase Large Fiber Input
  - TENS
  - physical therapy
  - exercise

Modulate Descending Pathways
- Drugs: opiates, NSAIDs, TCAs, anticonvulsants
- Psychotherapy
- Stress management
- ? Acupuncture
Neuropathic Pain Problems

- Postherpetic Neuralgia
- Reflex Sympathetic Dystrophy / Causalgia
- Cancer Pain Components
- Phantom Limb Pain
- Neuroma
- Trigeminal Neuralgia
- Entrapment Neuropathy
- Peripheral Neuropathy
  - diabetic, alcoholic
- Myelopathy -- post-traumatic, HIV
Pharmacology & Neuropathic Pain

- Tricyclic antidepressants
- Anticonvulsants
- Antiarrhythmics
- Sympatholytics
Tricyclic Antidepressants (TCAs)

Provide analgesic treatment for:

- diabetic neuropathy
- postherpetic neuralgia
- post-stroke pain
- migraine & tension headaches--prophylaxis
- rheumatoid arthritis
- fibromyalgia
- reflex sympathetic dystrophy
- low back pain
Cymbalta for the management of pain associated with DPN – pain relief through centrally mediated pain inhibition

- Neuropathic pain is associated with increased excitation and decreased inhibition of ascending pain pathways
  
  - Descending pathways modulate ascending pain signals
    
    - 5-HT and NE are key neurotransmitters in descending inhibitory pain pathways, and are part of the body's endogenous analgesic system
  
- Increasing availability of 5-HT and NE may promote pain inhibition centrally

- Cymbalta is believed to have a clinically relevant effect on both 5-HT and NE
  
  - The mechanism of action of Cymbalta in humans is not fully known


Important Safety Information and Full Prescribing Information, including Boxed Warning, provided at this presentation.
Pregabalin Binds to the $\alpha_2$-$\delta$ Subunit of Voltage-Gated Ca$^{2+}$ Channels in the Central Nervous System

- Pregabalin selectively binds to $\alpha_2$-$\delta$ subunit of calcium channels
  - Modulates calcium influx in hyperexcited neurons
  - Reduces neurotransmitter release
  - Pharmacologic effect requires binding at this site
  - The clinical significance of these observations in humans is currently unknown

Other Neuropathic Medications

- **Anticonvulsants**
  - Gabapentin, pregabalin, dilantin, carbamazepine, valproate, lamotrigine, topiramate, oxcarbazepine

- **Cardiovascular**
  - Alpha-2 agonists & alpha-1 antagonists
    - Clonidine patches applied to affected area
  - Antiarrhythmics: mexiletine

- **NMDA receptor antagonists**
  - Magnesium
  - Amantadine
  - Dextromethorphan
  - Ketamine
  - (Methadone)

- **Corticosteroids**
- **Lidocaine patches & compounded topicals**
Tramadol

- Not chemically related to opioids
- mechanism of action
  - weak mu receptor agonist
  - inhibits reuptake of serotonin and norepinephrine
  - does not inhibit prostaglandin synthesis
- Lowers seizure threshold
  - Avoid combining with antidepressants
Common Neuropathic Medications

- **Gapapentin (Neurontin)**
  - “Sensitive” patients: 100 mg qhs x5 days, increase by 100-200 mg q 5 days.
  - “Non-sensitive” patients: 300 mg qhs x5 days, increase by 300 mg q 5 days.
  - Target: 300 tid – 800 qid.

- **Pregabalin (Lyrica)**
  - 75 mg qhs x 7 days, increase by 75 mg q 7 days.
  - Target: 150 mg bid, may go to 300 bid

- **Duloxetine (Cymbalta)**
  - 20 mg qd x 10-14 days, increase by 20 mg q 10-14 days.
  - Target: 60 mg QD, may go to 60 mg bid.
Phantom Limb Pain

- WW-II veteran with 50 years of pain
- “The docs said I was crazy.”
- Gabapentin (Neurontin) —antiseizeure medication
- “For the first time, I can almost forget about the amputation.”
New Pharmacotherapy

- Ketamine gel
- Topical clonidine
- Lidoderm
- Newer anticonvulsants
- Pregabalin
- Duloxetine
- Bisphosphonates
- Amantadine, Dextromethorphan, Magnesium
General Indications for Blocks

- Diagnostic
- Control of acute pain
- Prolonged steroid effects
  - reduction of inflammation
  - decrease ectopic neuronal firing
- Theoretical “unwinding” and desensitization of sensory pathways
Behavioral Approaches

- Biofeedback
- Hypnosis
- Relaxation Therapy
- Cognitive restructuring

Physical Therapy

- stretching
- **GRADED** exercise program
- to enable exercise: massage, TENS, ultrasound, blocks
- desensitization