Opioids

Opium is a naturally occurring opiate compound.
- Produced by the opium poppy (*Papaver somiferum*).
- Opium has been used for 1000s of years.
- First federally “controlled substance”.

Effects of Opiates
- Analgesia - More effective for dull, throbbing pain.
- Euphoria - hul gil - “plant of joy”
- Constipation
- Cough Suppression
- Mild Sedation – Origin of “Narcotic”
- Nausea
- Respiratory Depression and Seizures
Types of Opioids.

*2 naturally occurring opiates in opium:*
- Morphine (10% of opium).
- Codeine (0.5% of opium).

Non Natural Opioids

*Semisynthetic* compounds are produced by modifying morphine or codeine.

*Heroin (diacetylmorphine)*
- Morphine + 2 acetyl groups.
- Much more lipid soluble than morphine.

Semisynthetic compounds ctd…
- Oxycodone – similar to codeine, but much more potent.
  - *OxyContin* – Oxycodone in time-release form.
**Fentanyl (Sublimaze)**
- 200X more potent than morphine.
- Short half life (1 hr vs 4 hrs for morphine).
- For preanesthesia (lollipop)
- For intense chronic pain (patch).
- Street drug: “China White”.

**Methadone (Dolophine)**
- Less potent.
  - Produces less euphoria.
  - Longer half life (. 24 hours).
- Treatment for heroin addiction.

**Opioids are often combined with other analgesics or anti-inflammatory drugs.**
- hydrocodone + acetaminophen.
  - Vicodin
- hydrocodone + ibuprofen
  - Vicoprofen

*Synthetic* compounds are produced from non-opioids.
Pharmacokinetics of Opioids

Absorption

- Oral absorption varies:
  - Morphine and heroin poor.
  - Codeine and methadone good.

- Other routes: injection, transdermal, suppository, inhalation.

Pharmacokinetics of Opioids

- Lipid solubility
  - The most potent forms are very lipid soluble (heroin, fentanyl).
  - Less potent forms aren’t very lipid soluble (morphine, methadone).
    - 80% of morphine is metabolized before reaching the brain.

- Opioids are metabolized by the liver.

Pharmacodynamic Effects
of Opioids

- Opioids are naturally found in 2 places:
  - In the opium poppy.
  - In the brain.

- Endorphins - endogenous opioid neurotransmitters.
  - Mediate pain transmission.
3 subtypes of opioid receptors.

- Mu receptor - mediates supraspinal analgesia, euphoria, respiratory depression.
  - Most potent site of action of most narcotic drugs.

- Kappa receptor – spinal analgesia, miosis, sedation, dysphoria.

- Delta receptor – mediates actions of endorphins.

Physiology of pain transmission.

- Sensory neuron detects cellular damage and sends signal to spinal cord.
- Neurons in the spinal cord send the message to brain.

- Normally, the sensory neuron releases NT when a painful stimulus occurs.
• Endorphin release by a third neuron (axo-axonic synapse) inhibits the sensory neuron.

• Opioids therefore inhibit transmission of pain.

What is the purpose of the endogenous opioid system?

• Natural analgesia is likely adaptive.
  • Child birth.
  • Battling saber-toothed tigers?

• Endorphins are released into the bloodstream during periods of stress.
  • Rat model of stress induced analgesia.
  • Runners high?
Acute Toxicity of Opioids
- Death through respiratory depression or seizures.
- Abuse deaths may not be so simple.
  - Purity/potency/drug interaction issues.
  - Release of conditioned tolerance?

Chronic Toxicity of Opioids
- No dramatic life-threatening toxicity.
  - Maybe increases in cancer and liver disease.
  - Suppression of immune system?

Chronic Toxicity of Opioids continued...
- Less serious chronic toxicity.
  - Inhibited sexual response.
  - Constipation.

  - Indirect toxicity:
    - Sores and infections from needles.
    - Malnutrition
    - Risky behavior.

Tolerance
- Most opioids support rapid development of tolerance.

  - Effects show different rates of tolerance.
    - Tolerance to constipation is slow (if at all).
    - Tolerance to analgesia is fast.
    - Tolerance to euphoria is very fast.
Tolerance continued...

Tolerance occurs due to:
• Enzymatic facilitation
• Nervous system changes
• Learning
  • Siegel-conditioned morphine tolerance.

Addiction

• Most opioids are very addictive.
• Opioids increase DA in nucleus accumbens.
• Addictiveness varies:
  • Heroin and fentanyl - very addictive.
  • Codeine and methadone - less addictive.

Addiction continued...

• Physical dependence marked by a withdrawal syndrome.
  • Restlessness
  • Dysphoria
  • Flu-like symptoms
  • Muscle spasms
  • Occurs within 6-12 hours for short duration drugs like heroin.
Treatment for Opioid Dependency

- Traditional approach: weaning.
- Methadone Maintenance
  - Methadone is substituted for heroin.
  - Methadone:
    - blocks the withdrawal symptoms.
    - produces less euphoria.
    - has a longer half life (~24 hrs).
    - tolerizes slower.
    - LESS DISRUPTIVE to normal life.

Treatment for Opioid Dependency continued...

- However, methadone therapy is controversial.
  - Not in my neighborhood!
  - Lessens the impact on society, but what about the addict?

- Buprenorphine (Subutex) now available as an office-based maintenance program.
  - Mu partial agonist.
  - Low overdose potential

Treatment for Opioid Dependency continued...

- Treatment with Opioid Antagonists.
  - Example: Re Via (naltrexone).
  - Antagonists:
    - block the effects of opioids in the brain.
    - displace opioids from the opioid receptor.
      - fast induction of strong withdrawal.
      - Short acting forms can be used for overdose.
      - don’t block craving.
  - Sublingual buprenorphine+naloxone (Suboxone) available for maintenance therapy.
Treatment for Opioid Dependency continued...

- RAAD (Rapid Anesthesia Aided Detoxification)
  - Antagonists are delivered during general anesthesia or sedation.
  - Controversial
    - Dangerous?
    - Doesn’t treat the addiction.

Most Non Narcotic Pain Relievers are Cyclooxygenase (COX) Inhibitors.

- Often called Nonsteroidal Anti-Inflammatory Drugs (NSAIDs).

2 Types of COX:
- COX-1 produces prostaglandins important for normal GI and blood platelet functioning.
- COX-2 produces prostaglandins that activate pain receptors and produce inflammation.
  - COX-2 activated by tissue damage.

Aspirin, Ibuprofen (Advil), and Naproxen (Aleve) are Nonselective COX Inhibitors

- Affect both COX types.
- Produce analgesia.
- Anti-inflammatory effects.
- Reduce fever (antipyretic).
- Cause GI irritation/ulceration.
- Decrease platelet activity (cardioprotective, bruising, bleeding disorders),
Celecoxib (Celebrex) and Rofecoxib (Vioxx) are Selective COX-2 Inhibitors.

- Analgesia.
- Anti-inflammatory effects.
- No GI or platelet side-effects.
- No antipyretic actions.
- Mostly used for arthritis.

- Recent evidence of cardiotoxicity!

Acetaminophen (Tylenol) is in a class by itself.

- Nonselective COX inhibitor but only in CNS.
- Possesses analgesia, antipyretic effects.
- No anti-inflammatory, platelet, or GI effects.
- Especially hepatotoxic.
- Technically not an NSAID.