Pharmacology of Selected Opioid Analgesics

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Note:

I plan to discuss only some of the slides, the others remaining available for your reading pleasure ( ? ). But, consonant with requirements for a professional program, I expect that you will read them.
Case 1

As a consequence of an ether explosion while working in his organic chemistry lab, a 25-year-old graduate student suffers extensive 3rd degree burns over his right arm, face and neck. He rates his pain as excruciating, 10 out of 10. The opioid that is least advisable for controlling the student’s pain over the course of several weeks is which one of the following?

A. Fentanyl
B. Morphine
C. Meperidine
D. Buprenorphine
An 82 year-old woman with end-stage hepatic cancer is provided with morphine to reduce her pain and suffering. While she has been on morphine over the past month, she has experienced breakthrough pain requiring increased doses of morphine. Although her pain relief improves with the higher drug dose, over a period of several days the patient’s pain returns. This outcome:

A. is a consequence of acute dysphoria precipitated by chronic morphine treatment
B. is to be expected because she is experiencing tolerance to the analgesic effects of morphine
C. is to be expected because she has become dependent on morphine and is experiencing an abstinence syndrome
D. is to be expected because her pain is neuropathic in origin, and opioid analgesics control such pain less effectively than they control nociceptive pain
E. is related to morphine-induced contraction of the sphincter of Oddi
Case 3

A woman is admitted to Kenmore Mercy hospital with a repeat episode of viral meningitis / aseptic encephalitis. After a suitable workup, the ER nurse administers an IV dose of morphine to treat the woman’s pain. Within 30 seconds the patient feels heavy, unable to move her arms and legs, experiences difficulty breathing, intense fear, and anxiety.

How do you explain these reactions?
A former heroin addict is maintained on methadone, but succumbs to temptation and buys an opioid on the street. He takes it and rapidly experiences signs of withdrawal. Which opioid did he buy?

A. Meperidine
B. Heroin
C. Pentazocine
D. Codeine
E. Propoxyphene
Opioid classification

- **Agonist**
  - Strong
  - Mild-to-moderate

- **Opioids with mixed actions**
  - Agonist-antagonist (Ag-Antag)
  - Partial agonist

- **Antagonist**
Strong agonists

- Morphine*  
- Heroin*  
- Hydromorphone (Dilaudid)  
- Oxymorphone (Numorphan)  
- Methadone (Dolophine)*  
- Meperidine (Demerol)*  
- Fentanyl (Sublimaze)*  
- Levorphanol (Levo-Dromoran)
Metabolism of Heroin

- Heroin is biologically inactive
- In the body it is converted to MAM and then into morphine
- MAM and morphine are responsible for the effects elicited upon injection of heroin
Methadone (Dolophine)

- μ-Agonist
- Similar to morphine
- Prolonged use give rise to tolerance
- Uses:
  - Relief of pain
  - Treatment of opioid abstinence
  - Treatment of opioid dependence
- Oral efficacy!
Opioid Withdrawal Syndrome

• **Within hours** of missing first dose of morphine
  – sense of intense fear (this can be alleviated by a placebo)

• **8-16 hrs**: lacrimation, rhinorrhea (as in a severe head cold), yawning, sweating, mydriasis, anorexia, nervousness, irritability, tremors, increased anxiety and fear, restless sleep
• **W/i 36 hrs:**
  – skeletal muscle fasciculation and twitch
  – severe/painful cramps develop in legs and stomach
  – intense/uncontrolled vomiting, salivation, diarrhea, and urination
  – weakness, depression, chilliness/sweating, gooseflesh ("cold turkey"), muscle spasms, kicking movements ("kicking the habit").
    – patient is unable to sleep; ↑ respiratory rate, ↑ blood pressure, ↑ temperature, ↑ blood sugar, ↑ basal metabolic rate

• Withdrawal syndrome reaches its peak within 48-72 hours, and subsides over the next 10 days.

• **Withdrawal reaction is evidence for physical dependence.**
• Intensity of withdrawal reaction depends
  – **Half-life of drug being used**

  - For morphine, with a short half-life, symptoms of abstinence are intense but brief.
  - For methadone, with a long-half-life, symptoms are less intense but more prolonged.

  – **Degree of physical dependence**

• Withdrawal syndrome of **methadone** and **codeine** qualitatively the same but less intense than for morphine.
It is to be emphasized that ..... 

• Although withdrawal from opioids is unpleasant, the opioid withdrawal syndrome is rarely dangerous to the patient.

• In contrast, withdrawal from CNS depressants (barbiturates; alcohol) can be lethal.
Methadone

• Why is it used in treatment of opioid dependence?
  - Methadone withdrawal is
    • Slower in onset
    • Longer in duration
    • Much less intense

• Why don’t opioid addicts like it?
Meperidine (Demerol)

• μ-Agonist.
• Actions are similar to morphine.
• In equianalgesic doses produces as much sedation, respiratory depression, and euphoria as does morphine.
  – The rise in bile duct pressure is *thought to be* less than that caused by morphine.
• Constipation, urinary retention less common than with morphine.

\[
\text{Meperidine (Demerol)}
\]

\[
\text{NCH}_3\text{C}_2\text{H}_4\text{O}\text{C}_2\text{H}_3
\]
Meperidine toxicity

- Large, repeated doses can lead to an *excitatory syndrome*
  - Hallucinations; tremors; muscle twitches; dilated pupils; hyper-reflexia; convulsions
  - Due to the accumulation of normeperidine
    - $t_{1/2} \approx 15-20$ hours (*meperidine*=3 hours)
  - Not drug of choice for treatment of severe, prolonged pain
Fentanyl

• A μ-agonist.
• 80-times more potent than morphine as an analgesic.
• USES:
  – For anesthesia and post-op analgesia.
  – Duragesic (transdermal patch) releases fentanyl over a period of 72 hours (for treatment of chronic pain; cancer pain)
    – Patient controlled anesthesia (Actiq)
Mild-to-Moderate Agonists

- Codeine
- Oxycodone (OXYCONTIN)
- Hydrocodone (VICODIN)
- Propoxyphene (DARVON)
Codeine

• High oral/parental ratio
  - Partially protected from conjugation by the methyl group at C3

• Has very low affinity for opioid receptors

• Analgesic efficacy is due to its conversion to morphine
  - Polymorphisms in cytochrome P450 isoform CYP2D6

• Dispensed alone or in combination with aspirin or acetaminophen
Codeine and gene polymorphisms

- Neonate without pain relief
- 57-year-old Ethiopian man who derives no pain relief from codeine
- 37-year-old Caucasian woman who post-dental procedure derives no pain relief from codeine

**Question:**
Is it safe to prescribe codeine for nursing mothers?
Codeine and gene polymorphisms

**Poor metabolizers**

**Caucasians (7%)**

**Ultra-rapid metabolizers**

Saudi Arabia, 20%
Ethiopia, 29%

A newborn died from morphine poisoning when his mother used **codeine** while breastfeeding.

Independent mechanisms of analgesia

- **Hydrocodone**
  - Dispensed only in combination with other drugs
    - Acetaminophen (NORCET, VICODIN, LORTAB)
    - Ibuprofen (VICOPROFEN)

- **Oxycodone (OXYCONTIN)**
  - Dispensed alone or in combination with
    - Aspirin (PERCODAN)
    - Acetaminophen (PERCOCET)
    - Ibuprofen (COMBUNOX)
Ototoxicity

• Rapid, progressive, and profound (> 83%) sensorineural hearing loss in patients taking Vicodin
  – Successful rehabilitation with cochlear implants
• Hearing loss reported with propoxyphene
• Other ototoxic agents?

Antineoplastic agents, such as cisplatin
Loop diuretics: Furosemide, ethacrynic acid
Analgesics: Aspirin
Macrolide antibiotics: erythromycin
Aminoglycoside antibiotics: gentamycin
Opioids with mixed actions
Agonist-Antagonist Opioids

• Substances that appear to be agonists at some receptors but antagonists at others.
  • Pentazocine (Talwin; Talwin-NX)
  • Butorphanol (Stadol)

• Partial agonists:
  • Buprenorphine (Buprenex; Suboxone)*
### Drug Action at μ and κ Receptors

<table>
<thead>
<tr>
<th>Receptor Subtype</th>
<th>μ</th>
<th>κ</th>
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<tbody>
<tr>
<td><strong>Pure Opioid Agonists</strong></td>
<td></td>
<td></td>
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<tr>
<td>Morphine, codeine, meperidine, and other morphine-like agents</td>
<td>Agonist</td>
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<td><strong>Agonist-Antagonist Opioids</strong></td>
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<td>Naloxone, naltrexone</td>
<td>Antagonist</td>
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Agonist-Antagonist Opioids

• Will discuss
  • Buprenorphine
  • Pentazocine

• Will not discuss
  • Levorphanol
  • Levallophan
  • Butorphanol
Pentazocine

- The intrinsic $\mu$ antagonistic activity is sufficient to afford advantages over morphine as analgesic
- $20 \text{ mg } \Rightarrow \downarrow \text{ respiration } = 10 \text{ mg morphine}$
  - $\uparrow$ Doses do not cause proportionate depression of respiration
- But, high doses $\Rightarrow \uparrow \text{ BP; } \uparrow \text{ HR}$

- $\uparrow$ Cardiac work in patients with coronary artery disease
- May precipitate withdrawal when given to $\mu$-opioid dependent individual
Pentazocine

- Talwin-NX (50mg Talwin + 0.5mg naloxone)
  - Oral pill laced with naloxone, to prevent abuse potential through injection.

- The added naloxone is degraded in liver.
- If oral pill is powdered for injection naloxone produces aversive effects in individuals dependent on opioids.
Levorphanol
[LEVO-DROMORAN]

Pharmacological effects parallel those of morphine
Clinical reports suggest that levorphanol may produce less vomiting and nausea
Metabolized less rapidly than morphine
Elimination half-life = 12-16 hrs
Repeated administration can lead to accumulation of the drug in the plasma

Strong agonist

Levallorphan

Ag-antag
Ag-Antag Opioids

Butorphanol (Stadol)

- More potent than morphine (on a per weight basis)
  - 2-3 mg $\Rightarrow$ 10 mg morphine
  - Onset, peak activity, duration $\approx$ morphine
  - Lowest abuse potential
- Actions similar to pentazocine.
  - $\uparrow$ Pulmonary arterial BP $\Rightarrow$ $\uparrow$ work of heart
  - Thus, less useful in patients with CHF or MI
AG-ANTAG SUMMARY

Why developed?
Same intensity of side effects as morphine
Psychotomimetic effects
Precipitate withdrawal effects in addicts
Analgesia has “ceiling” effect

* ↑ Pulmonary arterial tension
  → ↑ HR
  → ↑ Cardiac work
Buprenorphine (Buprenex)

- Highly lipophilic opioid derivative of thebaine
- Partial μ-agonist; 25-50-fold more potent than morphine.

\[\text{0.4 mg } \approx \text{10 mg morphine (im)}\]

- Produces analgesia and other CNS effects \(\approx\) to those of morphine.

- Duration of analgesia is longer than that of morphine.

On a per weight basis, more potent and longer lasting than morphine.
Ag-Antag Opioids

Buprenorphpine (Buprenex)

- Used as analgesic
- Absorbed well by most routes, including sub-lingual
- Approved for use as maintenance drug for opioid-dependent subjects

Suboxone
(Buprenorphpine + naloxone)
Opioid Antagonists

- Opioid antagonists produce few effects unless opioid agonists have been administered previously.
  - Naloxone
  - Naltrexone*

Devoid of agonist activities
Probably interact with all opioid receptors (albeit with different affinities)
Naloxone: Clinical use

1. In treatment of opioid toxicity, especially respiratory depression.
   - In patients with respiratory depression small doses IM or IV promptly reverse effects of μ-opioid agonists
     - Respiratory rates, within 1-2 minutes
     - Sedation is reversed
     - BP, if reduced, returns to normal
   - In dependent subjects ⇒ PPTs withdrawal syndrome.
Naloxone (Narcan)

2. In diagnosis of physical dependence on opioids.
   - In opioid-dependent subjects:
     - IM small doses of naloxone precipitate moderate-to-severe withdrawal syndrome.
     - **Symptoms appear within minutes and subside in about 2 hours.**
     - Severity and duration?
       - Are related to dose and degree of dependence
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<td><strong>Oral efficacy</strong></td>
<td>100-1000 times less potent orally than parenterally</td>
<td>Efficacious by the oral route</td>
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<tr>
<td><strong>Elimination $t_{1/2}$</strong></td>
<td>$\approx 1$ hour</td>
<td>Duration of action $\Rightarrow 24$ hours</td>
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Extended-release naltrexone
Naltrexone (Trexan)

• Used in long-term management of opioid addiction
  – The long duration of action serves as a safety valve after detoxification for patients with high motivation to remain opioid-free
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Case 3

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The End ...