1. The Opioid Class of Analgesics

The Opioid Class of Analgesics

Introduction to Clinical Pain Problems
Tufts University School of Medicine
J. David Haddox, DDS, MD / Purdue Pharma L.P.
2007

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3. Opioid Class of Analgesics: Slide 3

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5. Program Objectives

Program Objectives

1. Compare and contrast opioid agonists, antagonists, partial agonists and agonist/antagonists, and give an example of each.
2. Identify the structural pharmacology of various opioid classes and utilize this information for the purpose of opioid rotation in a patient with true opioid allergy.
3. Differentiate the pharmacology and pharmacokinetics of various opioid analgesics, including their active metabolites, and relate this knowledge to possible adverse events and/or side effects.
4. Select the most appropriate opioid therapy based on individual patient demographics.

6. Definitions

Definitions

- **Opioid** refers broadly to all compounds related to opium
- **Opium** is a drug derived from the juice of the opium poppy, *Papaver somniferum*
- **Opiates** are drugs derived from opium, including the natural products (e.g., morphine) and many semisynthetic congeners derived from them

7. Opioids

Opioids

- Naturally occurring phenanthrene alkaloids
  - morphine - thebaine (precursor)
  - codeine

- Semisynthetic agents
  - hydromorphone - oxymorphone
  - hydrocodone - buprenorphine
  - oxycodone

- Synthetic agents
  - butorphanol - methadone
  - fentanyl - meperidine
  - levorphanol - pentazocine


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8. Opioids & Receptor Activity

Opioids & Receptor Activity

- Agonists - produce a maximal biologic response through binding to the opioid receptor
- Partial agonists - elicit a submaximal response at the receptor even at high doses
- Agonist/antagonists - produce divergent activities at different receptors (mixed)
- Antagonist - reverse or inhibit the effects of agonists by preventing receptor access

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9. **Mu (µ) Receptor Activation**

![Mu (µ) Receptor Activation Diagram]


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10. **Dose-response Curves**

![Dose-response Curves Diagram]

Eum JE, Her A. Br J Pharmacol. 98;74:627-33.

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11. How does this correlate to clinical pain management?

How does this correlate to clinical pain management?

- Different opioids may cause different side effects in an individual patient.

- These differences may actually be due to:
  - individual patient variability
  - differences in receptor subtype binding

12. Opioid Agonists: Structural Pharmacology

Opioid Agonists: Structural Pharmacology

<table>
<thead>
<tr>
<th>PHENANTHRENES</th>
<th>codeine, hydrocodone, morphine, hydromorphone, levorphanol, oxycodone, oxymorphone</th>
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<td>PHENYLPIPERIDINES</td>
<td>meperidine, fentanyl, alfentanil, remifentanil, sufentanil</td>
</tr>
<tr>
<td>DIPHENYLHEPTANES</td>
<td>methadone, propoxyphene</td>
</tr>
</tbody>
</table>

(Phenylheptanone)

13. Opioid Rotation (OR)

Opioid Rotation (OR)

- Switching the opioid a patient is receiving to another opioid to reduce limiting adverse effects and/or increasing analgesia\(^1\)
- OR may eliminate the adverse effects (AEs) produced by accumulation of metabolites\(^2\)
- Interindividual differences in analgesic responsiveness, not sensitivity to AEs, might play a larger role in the advantage that one opioid appears to have over another in a given patient\(^1\)


14. Codeine

Codeine

Antitussive & analgesic (mild – moderate pain)

- Half-life = 2.5–3.5 hours
- Biotransformation in the liver
  - glucuronidation
  - \(O\)-demethylation to morphine via CYP2D6
  - \(N\)-demethylation to norcodeine via CYP3A


15. **Codeine**

**Codeine**

- Analgesic activity
  - requires O-demethylation via CYP2D6 to form morphine
  - CYP2D6 deficiency – poor metabolizers
    - 8% African-Americans
    - 7% Caucasians
    - 1%


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16. **Morphine**

**Morphine**

- IV, SC, IM administration
  - peak in 10-20 minutes; T½ = 1.4 – 3.4 hours
- Oral absorption
  - virtually complete
  - bioavailability 30-40% (range 19-47%)
  - oral:IV conversion ratio = 3:1-6:1
- Distribution
  - rapid, delayed penetration of BBB


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OCW: Introduction to Clinical Pain Problems (J. Haddox)
17. Morphine

Morphine

- Metabolism:
  - biotransformation in the liver to glucuronide conjugates: morphine-3-glucuronide (44-55%) and morphine-6-glucuronide (9-10%)
  - additional metabolites: 3,6-diglucuronide, morphine-3-ethereal sulfate, normorphine and conjugates
- Excretion:
  - in urine unchanged (8-10%) & as conjugated metabolites


18. M-3-G (morphine-3-glucuronide)

M-3-G (morphine-3-glucuronide)

- 44-55% of morphine converted to M3G
- Mean molar plasma M3G: morphine = 22-56:1
- Very low affinity to opioid receptors, thus no analgesic activity
- Controversial role in analgesia
  - very low affinity to opioid receptors of any subtype
  - devoid of analgesic activity
  - may antagonize morphine or M6G
  - newer evidence that M3G doesn’t antagonize morphine or M6G

19. M-6-G (morphine-6-glucuronide)

M-6-G (morphine-6-glucuronide)

- 9-10% of morphine converted to M6G
- Mean molar plasma M6G:morphine = 22-56:1
- More potent analgesic than parent compound in studies in rat or mouse
  - 1-2 x as potent SC, up to 650 x more potent IT
- Accumulation in patients with renal impairment


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20. M-6-G and M-3-G (continued)

M-6-G and M-3-G (continued)

- M6G toxicity profile
  - fewer side effects than after morphine administration\(^1\)
- M3G toxicity profile
  - hyperalgesia, allodynia, myoclonus, seizures (animal)\(^2\)
  - role not clearly established in humans


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21. Renal Dysfunction and Morphine

Renal Dysfunction and Morphine

- Renal dysfunction & morphine metabolites
  - plasma concentrations – several-fold greater than in pts with normal renal function
  - kidney transplantation eliminated metabolite accumulation (Osborne et al)
  - clearance of metabolites directly correlated with creatinine clearance


22. Hepatic Dysfunction and Morphine

Hepatic Dysfunction and Morphine

- Hepatic dysfunction ¹,²
  - severe liver disease – glucuronidation impaired
  - milder disease - glucuronidation preserved
  - extrahepatic metabolism may play a role


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23. Pruritus and Morphine

Pruritus and Morphine

- Pruritus
  - Pruritus may be greater with morphine


24. Oxycodone

Oxycodone

- Oral bioavailability = 60% (50-87%)
- $T_{\text{max}} = 1$ hour; $T_{1/2} = 3.5$-5.65 hours
- Onset of analgesia = $0.52 \pm 0.33$ hours
- Overall profile w/ regard to protein binding & lipophilicity parallels that of morphine

25. Oxycodone

Oxycodone

- Metabolism:
  - $N$-demethylation to noroxycodone (major)
  - $O$-demethylation via CYP2D6 to oxymorphone (10%)
    - oxymorphone possesses analgesic activity, but is present in plasma only in low concentrations
    - blocking CYP2D6 inhibits oxymorphone synthesis (i.e., quinidine), but does not alter oxycodone analgesia


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26. Oxycodone

Oxycodone

- Excretion:
  - oxycodone and its metabolites are excreted primarily via the kidney
    - free oxycodone - up to 19%
    - conjugated oxycodone - up to 50%
    - free oxymorphone - 0%
    - conjugated oxymorphone - ≤14%
    - free and conjugated noroxycodone - not quantified

Data on file: Purdue Pharma L.P.

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27. Hydrocodone

Hydrocodone

- **Metabolism:**
  - a complex pattern including:
    - $O$-demethylation to hydromorphone (via CYP2D6)
    - $N$-demethylation to norhydrocodone (via CYP3A4), and
    - 6-keto reduction to the 6-hydroxymetabolites
  - hydromorphone metabolite contributes to overall analgesic effect
- **Elimination:**
  - parent and metabolites via the kidneys


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28. Hydromorphone (HM)

Hydromorphone (HM)

- Semisynthetic phenanthrene-derived opiate
- Hydrogenated ketone analogue of morphine
- Freely soluble in water, sparingly in alcohol
- Oral bioavailability = 42% ± 23
- Half-life (oral, immediate release) = 2.4 hrs ± 0.6
- Duration of action (oral, immediate release) = 3-4 hours

Dilaudid® (package insert, North Chicago, IL: Abbott Laboratories).

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29. **Biotransformation of HM**

**Biotransformation of HM**

- Large variations in hepatic metabolism of HM have been reported in normal, healthy volunteers\(^1\)
- Major metabolites\(^2\)
  - hydromorphone-3-glucuronide
  - hydromorphone-3-glucoside
  - dihydroisomorphine-6-glucuronide
- Minor metabolites\(^3\)
  - dihydroisomorphine-6-glucoside
  - dihydromorphone
  - dihydroisomorphine


30. **Metabolite Profile of Hydromorphone**

![Metabolite Profile of Hydromorphone](image-url)
31. Potential Role of HM Metabolites

Potential Role of HM Metabolites

- Hydromorphone-3-glucuronide (H3G)\(^1\)
  - Rat: dose-dependent behavioral excitation analogous to that reported for morphine-3-glucuronide (M3G)
  - H3G found to be 2.5x more potent than M3G
  - mean molar ratio H3G:H3M ↑ to 100:1 in renal failure\(^2\)
  - if H3G crosses BBB with equivalent efficiency to M3G, then myoclonus, allodynia and seizures observed in some patients on chronic, large doses of HM could be due to the accumulation of H3G
  - further studies need to be conducted to determine the action of all of hydromorphone’s metabolites in humans


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32. Methadone

Methadone

- Onset within 30-60 minutes via oral route
- Initial duration of action of 4-6 hours
- Incomplete cross-tolerance w/ opioids may be due to non-competitive binding of NMDA receptors
- Bioavailability 41-99%
- Very lipophilic, widely distributed and this may contribute to its long half-life


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Methadone

- Biphasic elimination
  - alpha (2-3 hrs) and beta (8.5-120) half-lives

- Accumulation occurs with repetitive dosing


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Methadone

- Metabolism:
  - extensive biotransformation in liver
  - N-demethylation and cyclization to form pyrrolidines and pyrroline (inactive)
  - minor active metabolites (methadole, normethadole)

- Excretion:
  - in feces and urine as above metabolites and small amounts of unchanged drug


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35. Propoxyphene

Propoxyphene

- Structurally related to methadone
- 1/2 to 2/3 as potent as codeine orally
- N-demethylation via liver to norpropoxyphene which is renally cleared ($T_{1/2} = 30$ hours); accumulation with repetitive dosing
- Evidence does not support use of propoxyphene in osteoarthritis or rheumatoid arthritis pain
- Avoid use due to side effects and limited analgesic effectiveness


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36. Meperidine

Meperidine

- Synthetic opioid agonist
  - less potent, short duration of action (2-3 hrs)
- IM administration still used frequently
  - variably absorbed, painful, local irritation
- Metabolism:
  - hepatica via hydrolysis to meperidinic acid (inactive)
  - hepatically via N-demethylation to normeperidine, which may then be hydrolyzed to normeperidinic acid and subsequently conjugated
- Same effect on smooth muscle as other opioids at equianalgesic doses
- Neurotoxicity due to normeperidine accumulation


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37. Normeperidine

Normeperidine

- Renally excreted metabolite with a $T_{1/2}$ from 14-21 to 24-48 hrs vs. 3.1-4.1 hours for meperidine
- Clinical iatrogenic syndrome of anxiety, hyperreflexia, myoclonus, seizures, and mood changes within 24 hours
- Decreased renal function increases the likelihood of such toxicity


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38. Fentanyl

Fentanyl

- Synthetic opioid related to the phenylpiperidines
- Highly lipid soluble mu-receptor opioid agonist
- Approximately 100 times more potent (IV to IV) than morphine, therefore doses are expressed in micrograms
- Elimination half-life is between 3 and 4 hours
- Undergoes hepatic metabolism and renal excretion


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39. Levorphanol and Congeners

**Levorphanol and Congeners**

- Analgesia via *mu* and *kappa*$_3$-receptor agonism
  - less incidence of psychotomimetic or dysphoric effects
- Well absorbed following oral administration
- Duration of analgesia = 6 to 8 hours
- $t_{1/2} = 12$-16 hrs; accumulation w/ chronic dosing
- Glucuronide conjugation in the liver


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40. Buprenorphine

**Buprenorphine**

Exerts its pharmacologic effects at the *mu* receptor
- high affinity for *mu* receptors leads to preferential agonist effect
- slow dissociation from *mu* receptors may prolong effect
  - plasma levels may not parallel clinical effects
- Also an antagonist at the *kappa* receptor
  - may minimize dysphoric reactions


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41. Agonist-antagonists

**Agonist-antagonists**

- Mixed agonist-antagonists
  
  *e.g.: pentazocine, butorphanol, nalbuphine*

  - mu-receptor antagonists
    
    - may precipitate acute withdrawal in patients physically dependant on pure opioid agonists

  - analgesic actions primarily as kappa agonists
    
    - ceiling effect to analgesia
    
    - may produce kappa-mediated psychotomimetic effects
      
      *e.g.: depression, dysphoria, altered mental status*

42. Opioid Antagonists

**Opioid Antagonists**

- Antagonists
  
  *e.g.: naltrexone, naloxone, naltrenone*

  - bind to opioid receptors, but do not activate them

  - interfere with agonist actions

  - used to reverse opioid side effects
    
    *e.g.: respiratory depression due to overdose*

  - can induce a withdrawal syndrome in patients taking full opioid agonists

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Hoekn F, Hanks GW. Opioid agonist-antagonist drugs in acute and chronic pain states. Drugs. 1991;41:326-44.

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### Summary

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