Update on Opioids in Palliative Care

Disclosures
Judith A. Paice has no real or perceived conflicts of interest that relate to this presentation.

Objectives
1) Describe the pharmacology of opioids used in clinical practice
2) Identify strategies for equianalgesic conversions
3) Identify the strengths and weaknesses of current knowledge
Historical Perspectives

- Opium poppy – *Papaver somniferum*
- Cultivated as early as 4000 BC and recorded by Egyptians


- Sertturner described “morpheus” in 1806
- Bayer developed heroin (heroic) in 1898


- Osler called opium “God’s own medicine”
- 1914 – Harrison Narcotic Act
- Today – ?

Classes of Opioids: Natural Opium Alkaloids

- Phenanthrenes
  - Morphine
  - Codeine
  - Hydromorphone (semisynthetic)
  - Oxycodone (semisynthetic)
  - Oxymorphone (semisynthetic)

Classes of Opioids: Synthetic Compounds

- Morphinans
  - Levorphanol

- Phenylethylamines
  - Methadone
  - Propoxyphene*

- Phenylpiperidines
  - Fentanyl
  - Meperidine

* no longer available in US

Schedule of Controlled Substances: "Narcotics"

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Hallucinogenic substances, heroin, marijuana</td>
</tr>
<tr>
<td></td>
<td>Not approved for medical use in the US</td>
</tr>
<tr>
<td>II</td>
<td>Opium, morphine, codeine, hydromorphone, oxycodone, oxymorphone, methadone, fentanyl, dextroamphetamine, methamphetamine, methylphenidate, amobarbital, pentobarbital, secobarbital</td>
</tr>
<tr>
<td>III</td>
<td>Combos of codeine or hydrocodone with acetaminophen or NSAIDs; certain sedative drugs: drowsiness, buprenorphine</td>
</tr>
<tr>
<td>IV</td>
<td>Benzodiazepines, phenobarbital, certain sedative drugs, butorphanol</td>
</tr>
<tr>
<td>V</td>
<td>Antitussive, antidiarrheal preparations containing moderate quantities of opioids</td>
</tr>
</tbody>
</table>
Pharmacokinetics

- Absorption
- Distribution
- Metabolism
- Elimination


Pharmacokinetic curve (linear plot)

Tmax = 60 minutes oral morphine
30 minutes SQ
6-15 minutes after IV

Absorption of Opioids

- Lipophilicity
- Partition coefficient (octanol/water)
  - Morphine - 1
  - Hydromorphone - 1
  - Methadone - 115
  - Fentanyl - 820

Tmax = 60 minutes oral morphine
30 minutes SQ
6-15 minutes after IV
Distribution of Opioids

- Body fat
- Water stores
  - Dehydration/Aging
- Plasma proteins
  - Morphine 30%-35% bound
  - Fentanyl 80%-85% bound


Metabolism of Opioids

- Age, liver disease, genetics
- Hepatic biotransformation
  - Dealkylation
  - Glucuronidation
  - Hydrolysis
  - Oxidation

Metabolism of Opioids

- Morphine metabolites
  - Morphine-3-glucuronide 50%
  - Antinociceptive, hyperalgesia, myoclonus
  - Morphine-6-glucuronide 5%
  - Normorphine – toxicity?
- Hydromorphone
  - H-3-G and H-6-G (H-3-G>M-3-G in rodents)
- Fentanyl
  - Norfentanyl
- Oxycodone
  - Noroxycodone > oxymorphone
Elimination of Opioids

- Renal excretion 90%
- Fecal excretion 10%
  - Methadone fecally excreted

Pharmacodynamics

- Mechanism of drug action
- Opioid pharmacodynamics
  - Receptors: mu, delta, kappa
  - Lamina I & II of DH, brainstem
  - G-protein coupled

Pharmacogenomics of Opioids

- Genetic polymorphisms >1% of normal population
- Sensitivity of mouse strains to morphine
  - Sensitivity ranges from 0% to 90% based upon the strain of mouse
Pharmacogenomics of Opioids

- Codeine
  - Metabolized via CYP 2D6 to morphine
  - Poor metabolizers - 5-10%
  - Intermediate - 2-11%
  - Extensive - 77-92%
  - Ultra-rapid - 1-2%


Opioids

- Codeine
- Fentanyl
- Hydrocodone
- Hydromorphone
- Methadone
- Morphine
- Oxycodone
- Oxymorphone
- Tramadol
- Tapentadol

Adverse Effects of Opioids

- Respiratory depression
- Nausea and vomiting
- Constipation
- Sedation
- Pruritus
- Urinary retention
- Myoclonus
- Rigidity
- Seizures (meperidine)
- Miosis
- Diuresis
- Diaphoresis
- Edema
- Hormonal changes
Novel Routes

- Fentanyl – Requires REMS
  - Transmucosal
  - Buccal
  - Buccal polymer film
  - Sublingual spray
- Buprenorphine
  - Transdermal patch ±

REMS – Risk Evaluation Mitigation Strategy

Abuse Deterrent Opioids

- Prevent chewing, snorting, injecting
  - Agonist-antagonist mix
  - Sequestered naloxone
  - Physical barriers/alternate form of administration
  - Gel forms when tablet dissolved

Methadone Use for Pain Control

- Stigma
- Lack of education regarding safe use
- Increase in deaths
  - Illicit use in excessive doses
  - Use with other sedating drugs (e.g. benzos) either illicit or prescribed
  - Accumulation during first few days of treatment

www.samhsa.gov
www.zerodeaths.org
Methadone: Efficacy in Cancer Pain

- Cochrane review 2007: methadone is effective in relieving cancer pain
- Study investigated methadone vs. morphine as first line agent, morphine still gold standard

Methadone: Pharmacodynamics

- Opioid Agonist: mu receptor, some delta receptor binding
- NMDA (N-methyl-D-asparate) receptor antagonist
- Inhibits reuptake of norepinephrine & serotonin


Issues in Methadone Use

- Case reports of QT prolongation
- P450 interactions
- Long and variable half life

Inducers That May Decrease Methadone Effects

- Abacavir
- Amprenavir
- Barbiturates
- Carbamazepine
- Cocaine
- Dexamethasone
- Efavirenz
- Ethanol (chronic use)
- Fusidic Acid
- Heroin
- Lopinavir+Ritonavir
- Nelfinavir
- Nevirapine
- Phenytoin
- Rifampin
- Spironolactone
- St. John’s wort
- Tobacco
- Urinary acidifiers

Inhibitors That May Increase Methadone Effects

- Cimetidine
- Ciprofloxacin
- Delavirdine
- Diazepam
- Diltiazem
- Disulfiram
- Ethanol (acute use)
- Fluconazole
- Grapefruit
- Haloperidol
- Ketoconazole
- Macrolides (erythromycin, clarithromycin)
- Metronidazole
- Omprazole
- SSRI (fluoxetine, paroxetine, nefazodone, sertraline)
- Urinary alkalinizers
- Verapamil

Methadone

- Opioid naïve patient
  - Start at 5 mg bid
- Opioid tolerant patient
  - Do not do equianalgesic conversions
  - Start at 5-10 mg tid
  - Provide breakthrough medications
  - Titrate every 3-7 days
  - Do not combine with benzodiazepines
- Caution in patients with sleep apnea, respiratory infection
Opioid Rotation

• Calculate 24 hour opioid dose including both ER and IR doses
• Determine approximate equianalgesic dose using standard tables
• Reduce dose by approximately 25%
• One study - 74% had good response to morphine, most obtained good control with switch, few required more than one trial


Equianalgesic Dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral (mg)</th>
<th>IV (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>morphine</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>hydromorphone</td>
<td>7.5</td>
<td>1.5</td>
</tr>
<tr>
<td>oxymorphone</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>codeine</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>oxycodone</td>
<td>20-30</td>
<td>-</td>
</tr>
<tr>
<td>hydrocodone</td>
<td>30</td>
<td>-</td>
</tr>
</tbody>
</table>

Calculation

\[
\text{Equianalgesic dose and route for currently administered opioid} = \frac{\text{Equianalgesic dose and route for desired new opioid}}{\text{Total 24 hr dose and route for currently administered opioid}}
\]

\[
\text{Total 24 hr dose with route for desired new opioid}
\]
Calculation: Case 1

\[
\text{PO oxycodone} \\
20 \text{ mg} \\
\text{__________} = \text{__________}
\]

Calculation: Case 1

\[
\text{PO oxycodone} \\
\text{PO morphine} \\
20 \text{ mg} \\
30 \text{ mg} \\
\text{__________} = \text{__________}
\]
Calculation: Case 1

PO oxycodone       PO morphine
20 mg             30 mg

\[
\frac{60 \text{ mg PO oxycodone current total } \sim 24 \text{ hrs}}{20 \text{ mg}} = \frac{1800 \text{ mg}}{20 \text{ mg}} = 90 \text{ mg PO morphine every 4 hrs}
\]
Calculation: Case 2

\[
\text{IV hydromorphone} \quad 1.5 \text{ mg}
\]

\[=\]

Calculation: Case 2

\[
\text{IV hydromorphone} \quad 1.5 \text{ mg}
\]

\[=\]
Calculation: Case 2

IV hydromorphone       PO oxycodone
1.5 mg                20 mg

\[
\frac{24 \text{ mg hydromorphone current total in 24 hrs}}{24 \text{ mg hydromorphone current total in 24 hrs}} \times \text{(the new total 24 hr dose of PO oxycodone)}
\]

\[
\frac{24 \text{ mg}}{24 \text{ mg}} \times 20 \text{ mg} = 480 \text{ mg}
\]

\[
\frac{480 \text{ mg}}{1.5 \text{ mg}} = 320 \text{ mg oxycodone/24 hrs}
\]

\[
\frac{320 \text{ mg}}{2} = 160 \text{ mg ER oxycodone Q 12 hours}
\]

• Reduce dose by approximately 25%
Equianalgesia: Summary Points

• Equianalgesic doses are approximate
• Observe individual patient response: titrate dose and interval accordingly
• Always consider context of situation:
  • Age, renal and liver status, previous opioid tolerance, past experiences with opioids, nature and duration of pain, other concomitant medications, psychological considerations

Clinical Implications

• Individualize the treatment plan
• Assess, assess, and re-assess
• Prevent and treat adverse effects
• Opioid rotation using equianalgesic tables

Never doubt that a small group of thoughtful, committed citizens can change the world. Indeed, it is the only thing that ever has.

*Margaret Mead*