Objectives

- Describe the pharmacology of opioids used in clinical practice
- Identify strategies for equianalgesic conversions, along with the strengths and weaknesses of current knowledge

Historical Perspectives

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

Historical Perspectives

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


Historical Perspectives

- 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
- Phenylheptlamines
  - Methadone
  - Propoxyphene
- Phenylpiperidines
  - Fentanyl
  - Meperidine

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, methyldopa, amobarbital, pentobarbital, secobarbital</td>
</tr>
<tr>
<td>III</td>
<td>Combinations of codeine with aspirin or acetaminophen; certain sedative drugs; dronabinol; buprenorphine</td>
</tr>
<tr>
<td>IV</td>
<td>Benzodiazepines, phenobarbital, propoxyphene, 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

**Absorption of Opioids**

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

**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

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
    - 2% Asians
    - 2% African Americans
    - 10% Caucasians
    - 20% Middle Eastern

Opioids
- Codeine
- Fentanyl
- Hydrocodone
- Methadone
- Morphine
- Oxycodone
- Oxymorphone
- Tramadol

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
  - Transmucosal
  - Buccal
  - Buccal polymer film
  - Sublingual spray
- Buprenorphine
  - Transdermal patch ±
Abuse Deterrent Opioids

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

Methadone

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 2004: methadone is effective in relieving cancer pain
  - Nicholson AB. Methadone for cancer pain. Cochrane Database of Systematic Reviews 2004
- 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 naive 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

*www.zerodeaths.org*
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

Riley J, et al. Supportive Care Cancer 2006;14:56-64

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>

Equianalgesic Dosing

Equianalgesic dose and route for currently administered opioid
Equianalgesic dose and route for desired new opioid

Total 24 hr dose and route for currently administered opioid
Total 24 hr dose with route for desired new opioid

Calculation

_______ = ________
Calculation: Case 1

PO oxycodone
20 mg

Calculation: Case 1

PO oxycodone
20 mg

Calculation: Case 1

PO oxycodone
20 mg

PO morphine
30 mg

Calculation: Case 1

PO oxycodone
20 mg

PO morphine
30 mg

= 

= 

= 

= 
### Calculation: Case 1

<table>
<thead>
<tr>
<th>PO oxycodone</th>
<th>PO morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg</td>
<td>30 mg</td>
</tr>
</tbody>
</table>

\[
60 \text{ mg PO oxycodone current total } \sim 24 \text{ hrs} \times \text{ the approx equal total 24 hr dose of PO morphine }
\]

\[
60 \text{ mg } \times 30 \text{ mg} = 1800 \text{ mg}
\]

\[
1800 \text{ mg } \div 20 \text{ mg} = 90 \text{ mg}
\]

\[
90 \text{ mg } \div 6 \text{ doses} = 15 \text{ mg PO morphine every 4 hours}
\]
### Calculation: Case 2

<table>
<thead>
<tr>
<th>IV hydromorphone</th>
<th>PO oxycodone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 mg</td>
<td>20 mg</td>
</tr>
</tbody>
</table>

24 mg hydromorphone current total in 24 hrs

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

- 24 mg $\times$ 20 mg = 480 mg
- $480 \text{ mg} \div 1.5 \text{ mg} = 320 \text{ mg oxycodone/24 hrs}$
- $320 \text{ mg} \div 2 = 160 \text{ mg ERT oxycodone Q 12 hours}$
- 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
- Future: microarray techniques to determine an individual’s response – limiting “trial and error”

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