Opioid Analgesics: Pharmacology and Methods of Administration

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**Yale-New Haven Hospital**
Opioids: The Foundation of Surgical & Chronic Pain Management

- Large number of compounds with variable pharmacokinetics & pharmacology
- Multiple delivery systems (oral, parenteral, transdermal, neuraxial)
- High safety profile
- No ceiling effect for achievable pain relief (full agonists)
**Endogenous Opioids** (Natural peptides)

**Cannabinoids**

**Opioids**

**Cocaine**

**Barbituates**

**Opioids**: Agents that bind to opioid receptors

- **Opiates** (Derivatives of Opium)
  - Morphine
  - Codeine
  - Thebaine

- **Semi-synthetics** (Substituted derivatives of morphine or codeine)
  - Hydromorphone
  - Oxymorphone
  - Oxycodone
  - Hydrocodone

- **Agonist/Antagonists**
  - Nalbuphine, Butorphanol, Naloxone, Naltrexone

- **Antagonists**
  - Naloxone, Naltrexone

- **Synthetics** (Non morphinians)
  - Phenylpiperidines
  - Meperidine
  - Fentanyl
  - Sufentanil
  - Alfentanil, Remifentanil

- **Endogenous Opioids**
  - Enkephalin
  - Endorphin
  - Dynorphin

**Narcotics**: Drugs that lead to habituation, physical and psychological dependence

- **Dual Acting**
  - Tramadol
  - Tapentadol
Opioid Analgesics: Categories of Drug

**Agonists**: bind and activate opioid receptors providing dose dependent analgesia (morphine, fentanyl, methadone, oxycodone, hydromorphone, etc)

**Partial agonists**: bell-shaped analgesic curve effect (buprenorphine)

**Agonist-antagonists**: bind multiple receptors; ceiling analgesic curve (pentazocine, butorphanol, dezocine, nalbuphine)

**Antagonists**: block action of agonists by binding to opioid receptors/no analgesia (naloxone, naltrexone)

The Opioid Receptor

Morphine

Anionic Binding Site

Tertiary Nitrogen Binding Site

Flat Phenolic Binding Site

R Sinatra 2003
Opioid Binding: Increased Na+ Conduction and Neuronal Hyperpolarization

Ion Channel

K+

Axonal Membrane
Lipid Bilayer

Opioid Receptor

G-protein
$G_1/G_0$

N-CH3

Adenylate
Cyclase

cAMP

Decreased Electrical
Excitability

Na+

R Sinatra 2004
Opioid Receptors on Spinal Cord

- Inhibitory Interneuron
- Spinal Sensory Neuron
- Pain Fiber
- Descending Inhibitory Fiber

- Postsynaptic Opioid Receptors
- Presynaptic Opioid Receptors

ENK

(+)

(-)

(-)

(-)
Opioid Pharmacology

Potency: High Lipid Solubility

Onset: High lipid solubility, Low degree of ionization, High receptor affinity

Duration: Low lipid solubility (CSF trapping), High receptor affinity, Large volume of distribution, Low hepatic/renal clearance, active metabolites

Safety: Mu receptor specificity

Efficacy: Multiple receptor specificity, high receptor affinity, high intrinsic efficacy
Opioid Dose Response Curves

In the context of opioid analgesia, the graph illustrates the increasing effect with respect to the increasing dose (mg) for different opioids. The x-axis represents the increasing dose (mg), and the y-axis shows the level of analgesia, ranging from Perceptable Analgesia to Profound Analgesia, and finally to Anesthesia.

- **Perceptable Analgesia**
- **Profound Analgesia**
- **Anesthesia**

The graph includes curves for:
- Sufentanil
- Fentanyl
- Hydromorphone
- Morphine
- Butorphanol
- Naloxone

The y-axis is labeled as ‘Increasing Effect’ and the x-axis is labeled as ‘Increasing Dose (mg)’. The curves show how different opioids reach various levels of analgesia at different doses.
Substitutions at the Tertiary Amine and Phenolic Ring Influence Receptor Binding and Efficacy

Pure Agonist (Morphine)

Partial Agonist (Buprenorphine)

Mixed Agonist (Butorphanol)

Antagonist (Naloxone)
Opioid Pharmacokinetics (IV administration)

Effective Analgesia

Perceptible Analgesia

Profound Analgesia, Respiratory Depression

Time (Minutes)

Cp

T1/2 𝜋 (Redistribution in Plasma)

T1/2α (Redistribution in VRG)

T1/2β (Elimination)

Morphine 0.15mg/kg
Fentanyl 4mcg/kg

T1/2

(Effective Analgesia)

(Perceptible Analgesia)

(Redistribution in Plasma)

(Redistribution in VRG)

(Elimination)

2                  20                                                           200
Opioid Pharmacokinetic Modeling

Morphine

IV Dose

BBB

CNS

VRC (Vc)

VPC (V₂)

Elimination

Fentanyl

IV Dose

CNS

VRC (Vc)

VPC (V₂)

Elimination
Opioid Side Effects

Incidence and severity of side effects are generally dose dependent

Common (annoying)
- Constipation
- Nausea
- Somnolence
- Dizziness
- Vomiting
- Pruritus
- Headache

Serious (Life threatening)
- Respiratory depression
- Apnea
- Respiratory arrest
- Circulatory depression
- Hypotension
- Shock

- May improve over time, except constipation

Cherny NI. Drugs. 1996;51:714-37.
Opioid Toxicity

• Potentially toxic metabolites
  – Normeperididine from meperidine
    • Anxiety, tremors, myoclonus, and seizure
  – Norpropoxyphene from propoxyphene
    • Accumulation with repetitive dosing
  – Morphine-6-glucuronide (M-6-G) from morphine
    • Accumulation and toxicity may occur in severe renal impairment

• Can be lethal in overdose
  – Overdose varies by dose, patient, and circumstance

Opioid Dependence

• Psychological dependence: need for a specific drug, either for its pleasurable effect, or to avoid negative effects associated with its withdrawal.

• Physical dependence: a physiological state of adaptation to a specific drug, characterized by a withdrawal syndrome during abstinence, which is relieved by the drug.
Patient Variability in Opioid Response

Significant inter-individual variability in sensitivity to opioids (efficacy, side-effect, & tolerance profiles) are well described

- Mu receptor (OPRM1) polymorphisms
- Genetic differences in opioid metabolism (CYP450)
- Non Mu receptor genetic differences
  - Transporter P-glycoprotein COMT, β-arrestin (signaling)
- Incomplete cross-tolerance

Incomplete Cross Tolerance

- Observed when analgesic efficacy is maintained with one agonist despite decreasing efficacy with other agonist(s)

- Proposed mechanisms include
  - Differing agonist selectivities for receptor subtypes
  - Pharmacogenetics, eg:
    - OPRM1 receptor polymorphisms
    - CYP2D6 polymorphisms
    - Downstream events

Opioid Tolerance: Increased K+ Conduction and Neuronal Depolarization

Increased Electrical Excitability

- K+
- Na+
- G-protein $G_1/G_0$
- Opioid Receptor
- PO$_4$
- N-CH$_3$
- cAMP
- PKC
- NMDA Receptor Activation

Receptor Down-regulation
Altered RNA and Protein Synthesis

Axon Membrane Lipid Bilayer

Adenylate Cyclase
Opioid Rotation

“Failure to respond to one opioid does not mean the patient will not respond to others. Rotating from one opioid to another may result in or recapture effective analgesia while improving tolerability”

- Use incomplete cross-tolerance to clinical advantage by employing opioid rotation
Quest for “Holy Grail” of Opioid Analgesia

- “Analgesia with limited-to-no risk of respiratory depression, abuse/diversion, & tolerance development”
- After 100 yrs of semisynthetic and synthetic development, opioids can provide effective analgesia for short to prolonged periods of time with minimal side effects1,2
- Highly unlikely that a single molecule will be safe and effective in all patients

Mu-Opioid Receptor Pharmacology

- Primary site of analgesic activity for most commonly used opioids
- Multiple subtypes (e.g., μ₁, μ₂, μ₃ etc)
- Structural differences at C-terminus affect signal transduction and G-protein activation
- Opioid agonists differ in their ability to activate various mu subtypes
- Pharmacologic effects of a given agonist reflect the sum of all receptors activated (μ subtypes as well as κappa and delta).

More than a dozen splice variants of the mu-opioid receptor have been detected;
Genetic Polymorphisms & Response to

- Single nucleotide polymorphisms of the mu opioid receptor gene OPRM1:
  - Alter receptor structure & influence agonist binding affinities
  - Alter receptor densities & distribution
  - Influence receptor activation and G-protein transduction
- SNPs at position 118 (A118G) OPRM1 influence morphine sensitivity in animal and human studies

118A-G Polymorphism of OPRM1 Influences Post-op Morphine Use

- First “bench-to-bedside” evaluation of opioid receptor polymorphism
- OPRM1 genotypes of patients undergoing TKA
  - A118 homozygous (AA): 74 patients (62%)
  - A118 Heterozygous (AG): 33 (27%)
  - G118 homozygous (GG): 13 (11%)
- Group GG self-administered significantly more PCA morphine in first 48 h post-op

<table>
<thead>
<tr>
<th>Genotype</th>
<th>24-h Dose</th>
<th>48-h Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>16.0 mg (±8.0)</td>
<td>25.3 mg (±15.5)</td>
</tr>
<tr>
<td>AG</td>
<td>14.8 (±7.1)</td>
<td>25.6 (±11.7)</td>
</tr>
<tr>
<td>GG</td>
<td>22.3 (±10.0)*</td>
<td>40.4 (±22.0)*</td>
</tr>
</tbody>
</table>

TKA=total knee arthroplasty; *Significant difference vs AA & AG
Opioid Metabolism:
CYP2D6

Codeine \[\text{CYP450-2D6} \rightarrow \text{Morphine}\]
3-O-demethylation

Oxycodone \[\text{CYP450-2D6} \rightarrow \text{Oxymorphone}\]

Opioid Selection

- Short-acting
  - Incident pain
  - To permit activity
    - eg, physical therapy
  - Exacerbations of pain
- Long-acting
  - Persistent moderate to severe pain
  - Baseline analgesia

Cherny NI. *Drugs.* 1996;51:714-37.
Opioid Selection

- Pharmacologically long-acting
  - Methadone
  - Elimination $t_{1/2} \gg$ analgesic duration
  - Levorphanol

- Pharmaceutically long-acting
  - Controlled-release preparations of short-acting opioids

<table>
<thead>
<tr>
<th>Prolonged Duration Opioids: Therapy of Choice For Chronic Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sustained release oral morphine: (MS-Contin, Kadian, Opana), Duration 8 to 24 hours</td>
</tr>
<tr>
<td>• Sustained release oral oxycodone: (Oxycontin), Duration 8 to 24 hours</td>
</tr>
<tr>
<td>• Sustained release oral oxymorphone: (Opana), Duration 12hrs</td>
</tr>
<tr>
<td>• Sustained release oral tapentadol: (Nucynta CR)</td>
</tr>
<tr>
<td>• Transdermal fentanyl delivery system: (Duragesic), Duration 72hrs.</td>
</tr>
</tbody>
</table>

(Jaffe, 1990)
Opioid Tolerance: Analgesia Response Curves

- Profound Analgesia
- Perceptable Analgesia
- Pain

Increasing Effect

Increasing Dose

Naïve Response
Low Grade Tolerance
High Grade Tolerance
Hyperalgesia
Opioid Induced Hyperalgesia

Dextromethorphan

Ca++

N-Type Calcium Channel

NMDA Receptor

Pain Fiber Terminal

Ketamine

PKC

CCG

Dorsal Horn Neuron
THANKS- ANY QUESTIONS?
Relationship Between Opioid Plasma


IM=intramuscular; PCA=patient controlled analgesia
Site of Opioid Analgesia
(Opioid Receptors in Dorsal Horn)

Site of Local Anesthetic Analgesia
(Spinal Nerves)
Mixed agonist-antagonists
- Conventionally defined as mu receptor antagonists and kappa agonists; Include butorphanol, nalbuphine, pentazocine

Advantages
- Ceiling effect to respiratory depression
- Milder withdrawal

Disadvantages
- Precipitate withdrawal if physically dependent on full agonist opioids
- Reverse analgesia of full agonist opioids
- Ceiling effect to analgesia
- Possible psychotomimetic, dysphorogenic effects

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Opioid Rotation in Outpatients With Chronic Non-Cancer Pain

Percentage of patients for whom opioid prescription was effective or stopped because ineffective or intolerable side effects

Opioid

• Partial agonists
  – Advantages
    • Longer duration of analgesia vs morphine
    • Ceiling effect to respiratory depression
    • Includes Buprenorphine
  – Disadvantages
    • May have ceiling effect to analgesia
    • If respiratory depression should occur, large doses of naloxone may be necessary for reversal

Hoskin PJ, Hanks GW. *Drugs*. 1991;41:326-44.
Opioid Analgesics

Agonists
- Bind to one or more opioid receptor subtypes (mu, kappa, sigma, delta)
- eg, morphine, hydromorphone, oxycodone, fentanyl
- No apparent ceiling to analgesic effect, except as imposed by side effects (respiratory depression, excessive sedation, intractable nausea/vomiting)

Cherny NI. Drugs. 1996;51:714-37.
Opioid Metabolism & Response

- Many opioids metabolized by CYP-450 system
  - Eg: CYP2D6 codeine, hydrocodone, oxycodone, tramadol

- Patients may lack normal enzymatic activity
  - Genetics (enzyme deficiency)
  - Interaction with drugs affecting CYP-450
    - Alters analgesic/side-effect profile

- Hydromorphone, morphine, oxymorphone metabolized chiefly by conjugation (UGT enzymes)
  - Not affected by CYP-450 drug-drug interactions

CYP = cytochrome; UGT = uridine diphospho-glucuronosyl transferase

References:
Opioid Rotation

- **Indications**
  - Poorly controlled pain with inability to increase dose because of side effects
  - Adverse event/toxicity of current opioid
  - Rapid tolerance development
  - Development of opioid hyperalgesia

- **Availability of multiple opioids may help improve clinical outcomes**

- **Key to safe rotation includes familiarity with range of opioids & use of equianalgesic dosing tables**

### Time course of opioid withdrawal.

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Onset</th>
<th>Peak Intensity</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meperidine</td>
<td>2-6 hours</td>
<td>6-12 hours</td>
<td>4-5 days</td>
</tr>
<tr>
<td>Fentanyl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>6-18 hours</td>
<td>36-72 hours</td>
<td>7-10 days</td>
</tr>
<tr>
<td>Heroin</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Methadone</td>
<td>24-48 hours</td>
<td>3-21 days</td>
<td>6-7 weeks</td>
</tr>
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Opioid

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Opioid Rotation in Outpatients With Chronic Non-Cancer Pain

Percentage of patients for whom opioid prescription was effective or stopped because ineffective or intolerable side effects

Pseudo-addiction

- Increased drug seeking/drug use in a setting of chronic pain
- May be related to progression of disease, tolerance development, and a need to up-titrate opioid dose to compensate for an increase in functional activity
- May be distinguished from “true addiction” in that the behavior resolves when the patients pain is more effectively treated

Weissman & Haddox, 1989
Opioid Addiction

• “A primary chronic neurobiological disease, with genetic, psychosocial, and environmental factors”
• Increased drug seeking and drug administration for purposes other than pain control.
• Characterized by behavior that includes the following: impaired control, compulsive use, continued use despite harm, and craving
• Rarely observed in patients suffering moderate to severe chronic pain.

AAPM Joint Consensus Statement, 2000
Fentanyl Iontophoretic Transdermal System

Opioid withdrawal syndrome

• A normal physiological response to a sudden discontinuation of opioids

• Characterized by:
  ▪ Increased autonomic activity
  ▪ Physiological and behavioral responses (‘wet dog shakes’, yawning, leg jerks)

• Rarely life-threatening
Opioid Induced Hyperalgesia: Do Opioid Dependent Patients Feel More Pain?

- Opioid addicts are relatively pain-intolerant, and demonstrate significantly decreased pain tolerance
- Continued opioid receptor occupation produces hyperalgesia in pain free states, thus they are less able to cope with sudden acute pain

Opioid Dependence and Pain Relief

• Opioid dependent patients pose special challenges for perioperative pain control.

• Patients on chronic opioid drugs –
  1. Legitimate users
  2. Patients with substance use disorders
Agonist-Receptor Binding Affinities: Why “Dirty” Drugs Work Best for Chronic pain

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<thead>
<tr>
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<th>Mu</th>
<th>Kappa</th>
<th>Sigma</th>
<th>Delta</th>
<th>NMDA Potentiation of Opioid Analgesia</th>
<th>Alpha Potentiation of Opioid Analgesia</th>
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<tbody>
<tr>
<td>Morphine</td>
<td>++</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Hydromorphone</td>
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<tr>
<td>Oxycodone</td>
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<td>Fentanyl</td>
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<td>Sufentanil</td>
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<td>Butorphanol</td>
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<td>Buprenorphine</td>
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<td>Methadone</td>
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R Sinatra 2003
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<td>Buprenorphine</td>
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R Sinatra 2003
NMDA Receptor

- NMDA receptors increase the excitability of spinal neurons (windup) and potentiate pain.
- NMDA antagonists block the Ca++ channel and prevent intracellular Ca++ flux.
- Non specific NMDA antagonists (Ketamine)
- Specific antagonists (Dextromethorphan, Ziconitide, Memantine) reduce pain intensity and analgesic requirements in settings of acute and chronic pain.
Perioperative Opioid Anesthetic/Analgesic Guidelines

- Maintain baseline opioid administration
- Increase perioperative opioid dose 20% or more to compensate for opioid tolerance
- Use adjunctive analgesics, regional blockade, NSAIDS, clonidine
- Postoperatively increase baseline opioids, or start IV-PCA opioids at 20% or more of usual dose

CYP2D6 Variants: Allele Frequencies & Phenotypic

- CYP2D6 activity depends on allele polymorphisms
  - Poor metabolizer
  - Intermediate metabolizer
  - Extensive metabolizer
  - Ultrarapid metabolizer

- Poor CYP2D6 function alleles in 6%-10% Caucasians
  - Poor-absent codeine metabolism to active metabolite
  - Tramadol O-demethylated metabolite has 200 X mu-receptor-affinity, 2-4 X potency, & longer half-life
    - Tramadol analgesia may be reduced in population with

Treatment Algorithm for Acute

Maintain Baseline Opioids!

- Clonidine
- Gabapentin
- Cox-2 Inhibitors
- Acetaminophen

Anxiolytics as required

Ketamine as required

IV-PCA, Epidural PCA, Neural Blockade

Maintain Baseline Opioids!
Recently Available Opioid Formulations

- Q24h tramadol ER oral tablet for chronic pain
- Q12h oxymorphone IR & ER oral tablet for chronic pain
- Effervescent fentanyl buccal tablet for breakthrough pain
- Fentanyl iontophoretic transdermal system
  - Patient activated (PCA) dosing for acute pain

Durfee S. Am J Drug Deliv. 2006;4:1-5.1
Fentanyl Iontophoretic Transdermal System

- First needle-free patient-controlled analgesic system
- Indicated for acute pain management
- Utilizes iontophoresis to deliver subdermal doses of fentanyl (40 µg every 10 min)
- Efficacy & side effects similar to standard IV-PCA
- Preprogrammed
  - May avoid programming & medications errors
- Small credit card sized, self-contained
  - No interference with patient mobility

Summary

- Opioid analgesics remain the foundation of acute & chronic pain management
- Inter-patient differences in opioid response may be related to receptor polymorphism, metabolic variability, & incomplete cross tolerance
- Transdermal & buccal delivery of opioids offer simplicity, convenience, & rapid analgesic effect
- Sustained-release opioids offer advantages effective prolonged & uniform pain relief
Opioid

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  - Conventionally defined as mu receptor antagonists and kappa agonists; Include butorphanol, nalbuphine, pentazocine
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