"We're out of Dilaudid"… the Pharmacology of the *other* opioids

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Overview

1. Acute vs. Chronic Pain
2. Receptor pharmacology
3. General opioid pharmacology and adverse drug reactions
4. Available products
5. Opioid allergy vs. intolerance

Acute Pain

- Useful physiologic process
  - Warning system
- Noxious stimulus
  - Surgery
  - Trauma
  - Medical procedures
- Resolved once the underlying cause resolves
  - If unresolved may produce deleterious effects
    - Suffering
    - Increased risk for the development of chronic pain syndromes

Chronic Pain

- Pain that persists for months to years
  - Nociceptive, neuropathic/functional, mixed
    - Cancer vs. non-cancer pain
- May result in changes to the receptors and nerve fibers

Characteristic	Acute Pain	Chronic Pain
Relief of Pain	Highly desirable	Highly desirable
Dependence/Tolerance	Unusual	Common
Psychological component	Usually not present	Often a major problem
Treatment goal	Cure	Functionally
Depression	Uncommon	Common

Definitions

- Opioid: broad term related to all compounds related to opium
- Opium: drugs derived from the juice of the opium poppy, *Papaver somniferum*
- Opiates: drugs derived from opium including semisynthetic products
- Narcotic: used to describe opium and its derivatives
  - Narcosis: induces sleep
    - Law enforcement: Narcotic = drug of abuse

Definitions

- Physical Dependence
  - Potential for abstinence on abrupt discontinuation or dose reduction, or administration of an antagonist
- Tolerance
  - Declining effect with drug exposure
- Opioid Induced Hypergesia
  - Paradoxical, abnormal pain secondary to prolonged use of opioids

Pharmacology of Opioids

Opioid Receptors

- Opioid receptors are found throughout the central nervous system and gastrointestinal tract
  - Produce analgesia by binding to and activating opioid receptors
- Opioid receptors
  - mu (μ)
    - Analgesic properties
  - kappa (κ)
    - Modest analgesic properties
  - delta (δ)
    - Spinal analgesia, euphoria
  - sigma (σ)
    - Dysphoria, hallucinogenic and cardiac stimulant

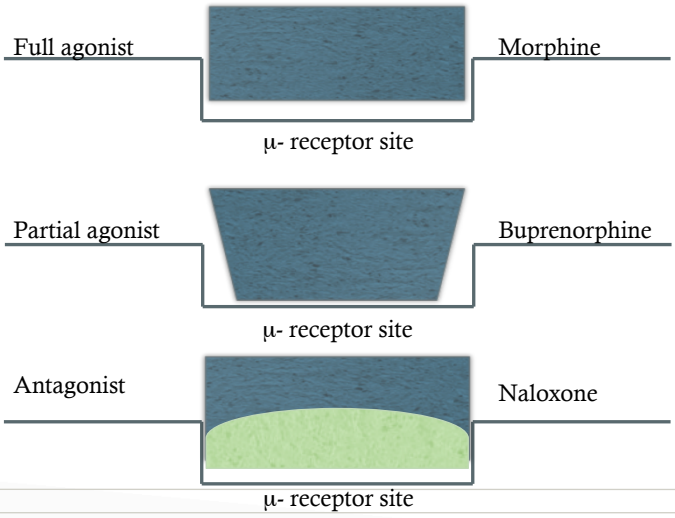
μ Opioid Receptors

- Two type of μ-receptors
  - μ1 (higher affinity)
    - Supraspinal analgesia, inhibit transmission of pain
  - μ2 (lower affinity)
    - Respiratory depression
    - Reduced gastrointestinal motility
    - Physical dependence

Opioid Receptor Activity

- The pharmacologic activity of opioids depends on their affinity for opiate receptors
  - Classified according to their affinity for μ and κ opioid receptors
    - Full agonists
    - Partial agonists
    - Mixed agonist-antagonists
    - Antagonist

μ Receptor Activation



General Pharmacology of Opioids

- Tolerance and cross-tolerance between similar opioid analgesics
- Physical dependence and cross-dependence to other opioid analgesics
  - Most opioids can substitute or maintain the physical dependence of other opioids
- Withdrawal or abstinence syndrome is seen when opioids are withheld from a person physically dependent on the opioids

Pharmacology of Opioids

- Mental clouding
  - Mood changes and other CNS effects
    - Pain: opioids produce **euphoria**
    - "Normal": mental clouding that may be reported as **dysphoric**
  - Drowsy
  - Lethargic
  - Apathetic
  - Difficulty thinking clearly

Pharmacology of Opioids

- Muscle Rigidity (catatonia)
  - High doses are more likely to produce muscle rigidity
    - Compromises respiration
      - Opioid action in the basal ganglia
      - Truncal rigidity reduces the thoracic compliance and interferes with ventilation

Pharmacology of Opioids

- Nausea and vomiting
  - Occurs frequently
    - Stimulation of the chemoreceptor trigger zone
      - Incidence of vomiting is higher in ambulatory patients
        - Vestibular component

Pharmacology of Opioids

- Respiratory depression
  - Decreased response of brain stem respiratory neurons to CO_2
    - Hypoxic drive maintains respirations
      - In opioid over-dose: O_2 could stop breathing
  - Bronchoconstriction
    - Contributor to respiratory difficulties
      - Histamine release
        - Greater amounts of histamine released in IV preparations
  - Cerebrovascular vasodilation
    - Opioid-induced respiratory depression + increased PCO2, may contribute to increased intracranial pressure in patients with head injuries

Pharmacology of Opioids

- Antitussive
  - Suppression of the cough reflex
    - Subanalgesic doses
    - Tolerance develops
- Miosis
  - Opioid excitation of the EdingerWestphal nucleus (n. oculomotor nerve III)
    - No tolerance
    - Miosis can be blocked by atropine

Pharmacology of Opioids

- Urinary Retention
  - Increased ADH by a central mechanism
  - Decreases in blood pressure
  - Increase tone of the bladder sphincter
  - Increase in bladder capacity
  - Inhibited voiding mechanism

Pharmacology of Opioids

- Inhibition of gonadotropin release
  - Decrease LH and FSH release
  - Decreased sexual drive
  - In males, decreased testosterone and sperm count
  - In females, prevents ovulation

Pharmacology of Opioids

- Cardiovascular effects
  - Peripheral arteriolar and venous dilation may produce postural hypotension
    - Histamine release
    - Depressed vasomotor and adrenergic tone
  - Reduce preload
  - Reduced myocardial oxygen consumption

Pharmacology of Opioids

- GI effects
  - Induces gastric hypertonicity
    - Constipation, antidiarrheal
  - Decrease in propulsive contractions
  - Increased sphincter and muscle tone
    - Delay the passage of GI contents and increase fluid absorption
- Pruritis
  - Histamine release
    - Histamine effect reversed by antihistamines but not naloxone

Pharmacokinetic of Opioids

- Absorption
  - Oral
    - Adequate absorption
    - Undergoes first pass metabolism
  - Onset
    - Majority of immediate release opioids onset ~ 20-40 minutes
  - Peak analgesia
    - ~45-60 minutes
- Special considerations
  - Controlled release opioids may have altered absorption with decreased GI transit time

Pharmacokinetic of Opioids

- Distribution
  - Dependent on serum protein binding and lipophilicity
    - Morphine is 30-35% bound to plasma proteins
      - Does not remain in the tissues for an extended period
    - Fentanyl is 80-85% bound to plasma proteins
      - Distributes widely to fat and redistributes slowly into the circulation
- Little drug enters the brain
  - Low lipid solubility
    - Heroin, fentanyl, methadone and codeine are more lipid soluble and cross the blood-brain barrier faster and in greater quantities

Pharmacokinetic of Opioids

- Metabolism and Elimination
  - Primary site of opioid metabolism is the liver
    - Dealkylation, conjugation, hydrolysis and oxidation
  - ~90% of the opioid and metabolite metabolism is renal
    - Risk of metabolite accumulation
  - Metabolites
    - Morphine-3-glucuronide (M3G)
    - Morphone-6-glucuronide (M6G)

Available Opioids

Morphine

- Morphine
  - Dosage forms
    - Immediate-release
      - Tablet
      - Oral suspension (Roxanol)
        - 2 different concentrations
      - Suppository (RMS)
      - Parenteral injection (Duramorph, Infumorph)
    - Extended-release
      - Capsule (Avinza, Kadian)
      - Tablet (MSContin, Oramorph)

Hydromorphone

- Alternative to morphine
  - Safe in renal failure
  - More soluble than morphine
- Dosage forms
  - Immediate release tablets (Dilaudid)
  - Extended release tablets (Exalgo)
  - Oral solution
  - Parenteral
  - Suppository

Oxymorphone

- Highly selective for mu receptor
  - More potent than morphine
- Dosage Forms:
  - Immediate release tablets (Opana)
    - Should not be taken with meals
  - Extended-release tablets (Opana ER)
    - Should not be taken with meals
    - Should not be broken, chewed, etc.
  - Parenteral

Codeine

- Weak opioid activity
- Pharmacogenetic differences
  - Metabolized to morphine by the liver (2D6)
    - Poor metabolizers (lack 2D6)
    - Ultra-rapid metabolizers (2D6 gene duplication)
- Side effects limit use
  - Nausea, vomiting and/or constipation

Hydrocodone/Oxycodone

- Hydrocodone
  - combined with acetaminophen
    - Dosage Forms
      - Lorcet
      - Lortab
      - Norco
      - Vicodin
      - Zydone
  - Acetaminophen concentrations differ
    - Maximum dose of APAP: 4 gm/day)
- Oxycodone
  - Dosage Forms
    - Extended-release tabs (OxyContin)
    - Immediate release caps/tabs (OxyIR, Roxicodone)
    - Oral solution (Oxyfast, Roxicodone)
    - Combination products (Percocet, Percodan, Tylox)

Meperidine (Demerol)

Not a first line agent

- Variable oral bioavailability
  - Short duration of action
- Relatively low potency
- Neurotoxic metabolites
  - Normeperidine has long half-life
- Multiple drug interactions
- Borgess Usage Guidelines
  - Do not use for over 48 hrs
  - Maximum dose: 600 mg/24 hr period
  - Avoid in patients with renal dysfunction or a history of seizures
- Oral use discouraged

Fentanyl

- Highly lipophilic
- Less histamine release than other opioids
- Unique dosage forms/delivery devices
  - Buccal tablet (Fentora)
  - Lollipop (Actiq)
  - Transmucosal film (Onsolis) – restricted use in US
  - Transdermal patch (Duragesic)
    - Not interchangeable
  - Risk and disposal issues with dosage forms

Fentanyl Transdermal Patch

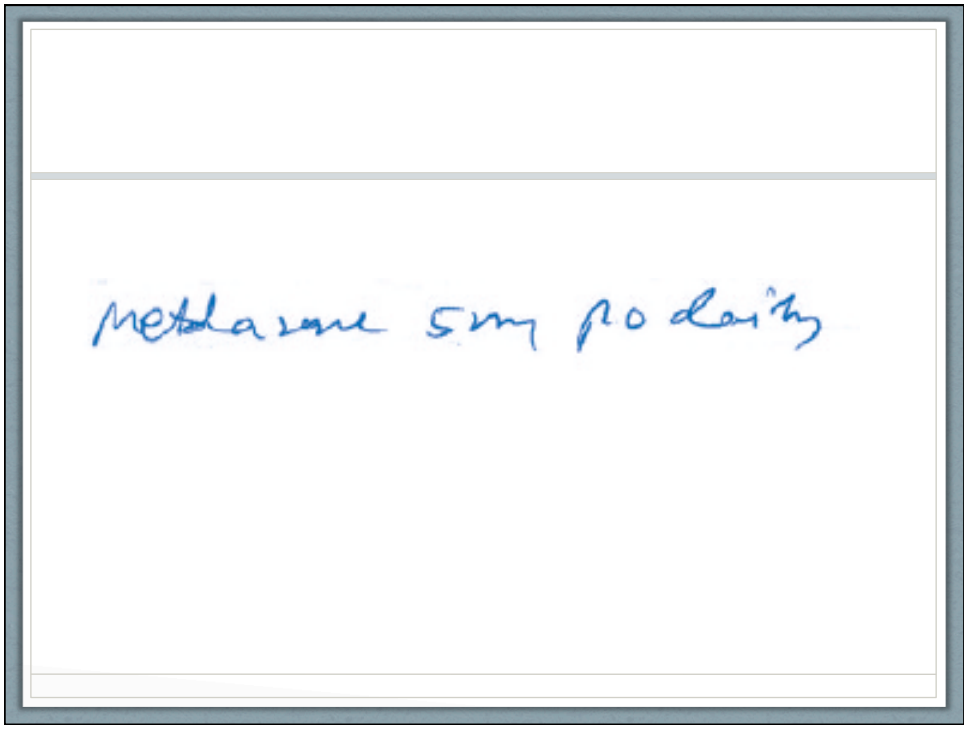
Advantages:

- Sustained-release opioid
- Good in patients with poor compliance
- Good choice if concerned about drug abuse

Disadvantages

- Delay in onset
- Residual activity after patch removed
- Expensive

- Heat increases rate of release from patch
- Special considerations in the elderly
  - Requires subcutaneous fat



Methadone (Dolophine)

- Not a first-line opioid
  - Non-opioid actions provide additional analgesia
- Half-life: 8-59 hours
- Duration: 3-6 hours (initial); 8-12 hours (chronic)
- Benefits:
  - Inexpensive
  - Good for refractory pain
- Cons:
  - Unpredictable
  - Difficult to dose
  - Drug interactions
- Monitoring:
  - Baseline QTc

Tramadol (Ultram)

- Dual mechanism of action
  - μ
  - Norepinephrine
  - Serotonin
- Used for moderate pain
- Less respiratory depression than opioids
- Decreases seizures threshold
  - Maximum dose: 400 mg/24 hrs
    - Decrease dose in elderly & renally impaired
- Drug interaction alerts
  - SSRI/SNRI

Tapentadol (Nucynta)

- New opioid
  - Mechanism of action similar to tramadol
  - Both immediate release and extended release should be swallowed whole
- Available products
  - Nucynta
  - Nucynta ER

Equianalgesic Table

Drug	Oral
Morphine	1 mg
Hydrocodone	1 mg
Codeine	30 mg
Oxycodone	1.5 mg
Oxymorphone	3 mg
Hydromorphone	4-7 mg
Fentanyl	N/A
Methadone	Various

Equianalgesic Dosing Methodology

- Total the 24-hour dose of current opioid usage including prn doses
- Convert for drug & route using table
- Reduce calculated dosage 30-50%
- Calculate breakthrough pain dose, if converting long-acting opioids
  - 5 – 15% of total daily opioid dose

Ref. 15,16

Allergy vs. Intolerance

Opioid Allergy

- True opioid allergy is rare
  - Opioid allergy is often a side effect
    - Stomach upset
    - Pruritus
- Allergic type reaction

Types of Reactions to Opioids

- Pseudoallergy
  - Symptoms resemble a true allergy, but are caused by histamine release from cutaneous mast cells
    - Hives
    - Tachycardia
    - Hypotension
  - Previous exposure is not necessary
    - *In vitro*, risk depends on the concentration of the opioid at the mast cell
  - Dependent on opioid potency, dose and route of administration

Types of Reactions to Opioids

- True allergy
  - IgE-mediated or T-cell mediated
  - Symptoms
    - Allergic skin reactions
      - Hives
      - Maculopapular rash
      - Erythema multiforme
      - Pustular rash
    - Broncospasm
    - Angioedema

Opioid Cross-Reactivity

- 3 main opioid structural classes
  1. Phenanthrenes
     - Morphine, codeine, hydrocodone, oxycodone, oxymorphone, hydromorphone, nalbuphine, butorphanol, levorphanol and pentazocine
  2. Diphenylheptane
     - Methadone
  3. Phenylpiperidines
     - Meperidine and fentanyl

Opioid Cross-Reactivity

- Patients allergic to one opioid less likely to react to an opioid in a different structural class
  - No studies to assess the chance of cross-reactivity
  - Limited evidence suggesting patients can be allergic to one or more opioid class

Questions?

Among the remedies which it has pleased almighty God to give to man to relieve his sufferings, none is so universal and efficacious as opium.

-Sir Thomas Sydenham, 1680