opioids

tolerance & depedence

- Tolerance and dependence are inevitable features of chronic opioid use.
- Tolerance refers to decreasing effectiveness and the need for higher doses with repeated use, whereas dependence refers to the occurrence of withdrawal symptoms on cessation of the drug.
- If tolerance and dependence to opioid analgesics exists, patients may require very large doses to achieve a therapeutic effect. Consultation with a pain management specialist may be warranted for such patients.

withdrawal

- The opioid withdrawal syndrome comprises a unique cluster of symptoms.
- The syndrome includes yawning, lacrimation, piloerection, coryza, and restlessness initially, progressing to abdominal cramps, nausea, vomiting, and diarrhea. Altered mental status is only rarely present.
- The onset and duration of the withdrawal syndrome vary with the duration of effect of the implicated opioid. Although it can be extremely distressing to the patient, opioid withdrawal typically is not life-threatening.
- The exceptions are acute withdrawal precipitated by large doses of antagonist in dependent individuals and opioid withdrawal in the neonate.
- Treatment options for opioid withdrawal include supportive care, treatment with antiemetics and clonidine (a centrally acting a2-agonist that diminishes CNS symptoms), or administration of an opioid agonist, typically methadone.

presentation in overdose

- The classic findings in patients with the opioid toxidromes are miosis, diminished bowel sounds, CNS depression, and respiratory depression, with coma and apnea in extreme cases.
- The major cause of death in opioid overdose is respiratory depression.
- Other complications are usually secondary to hypoxia (e.g., seizures, dysrhythmias, brain injury).
- It is important to note that not all opioid-intoxicated patients present with miosis. Severe systemic hypoxia and presence of co-ingestants can produce normal-sized or dilated pupils.

therapy in overdose

resuscitation

- There is some suggestion that the catecholamine surge associated with rapid reversal with naloxone in tolerant individuals may precipitate acute lung injury (i.e. acute pulmonary edema).
- The appropriate use of naloxone to reverse symptoms of respiratory depression can prevent intubation in most cases.

electrolytes & acid-base

specific therapy

naloxone
- The endpoint for naloxone in chronic opioid dependence should be reversal should be adequate respiration, not complete reversal of sedation.
- High doses of naloxone (e.g., 1 to 2 mg i.v.) may be used safely in children and in nontolerant individuals.
- Continuous infusions may be appropriate for patients who have overdosed with long-acting opioids.
- Symptomatic opioid body packers (i.e., people hired to swallow large amounts of tightly wrapped heroin packets and smuggle them across international borders) are likely to require continuous naloxone infusions until the packets are passed or removed. Tolerance and dependence can occur in these patients if "leaking" is protracted. Body packers usually are not opioid users themselves.

underlying causes

pharmacology

kinetics

Absorption:
- Most opioids are well absorbed via the subcutaneous and intramuscular routes.
- Although gastrointestinal absorption tends to be rapid, the oral bioavailability of many opioids is limited by extensive first-pass hepatic metabolism.
- Codeine and oxycodone are two opioids with very good oral bioavailability.
- The transdermal application of fentanyl is also used in clinical practice.

Distribution:
- Tissue uptake is variable and depends largely on the drug's lipophilicity.
- Highly lipophilic compounds, such as fentanyl, readily penetrate the central nervous system (CNS), the dura of the spinal column, and tissue "reservoirs."
- Opioids exhibit varying degrees of plasma protein binding and typically have large volumes of distribution.
- Redistribution from saturated tissue depots can produce persistent or recurrent sedation after discontinuation of prolonged infusions of certain opioids, such as fentanyl.

Metabolism:
- Hepatic metabolism of opioids, typically by the P450 cytochromes CYP3A4 and CYP2D6, can produce metabolites with either greater or lesser activity than the parent compound.
- Metabolism of certain opioids also occurs by similar mechanisms in extrahepatic sites, especially the kidneys.

Elimination:
- Most opioids and their metabolites are cleared renally and require dosing adjustments in patients with renal failure. Biliary excretion is limited for most opioids.

dynamics

OPIOID RECEPTOR SUBTYPES AND THEIR ASSOCIATED CLINICAL EFFECTS

Traditional notation	mu_1	mu_2	delta	$kappa_{1,2,3}$
IUPHAR notation	OP_{3a}	OP_{3b}	OP_1	$OP_{2a,b,c}$
Endogenous ligand	Endorphins	Endorphins	Enkephalins	Dynorphins
Effect	Analgesia (supraspinal and peripheral), sedation, euphoria, urinary retention, miosis, hypothermia	Analgesia (spinal), respiratory depression, bradycardia, physical dependence, gastrointestinal effects, pruritus, growth hormone release	Analgesia (spinal and supraspinal), antitussive effect, modulation of mu receptor function, inhibition of dopamine release	Analgesia (spinal and supraspinal) antitussive effect, psychotomimesis, dysphoria, miosis, diuresis

SUMMARY OF CLINICAL EFFECTS OF OPIOIDS BY PHYSIOLOGIC SYSTEM

System	Clinical Effect
Cardiovascular	Hypotension (vasomotor centers and histamine), bradycardia (first or second degree), dysrhythmias (overdose, propoxyphene), QRS prolongation (propoxyphene), QT prolongation (methadone)
Dermatologic	Urticaria, flushing, pruritus (centrally mediated)
Endocrinologic	Reduced release of antidiuretic hormone (controversial), reduced release of gonadotropin
Gastrointestinal	Nausea, vomiting (5-HT_2 mediated), delayed gastric emptying, constipation, increased smooth muscle tone (biliary tract, intestinal, pylorus, anal sphincter)
Genitourinary	Urinary retention, ureteral spasm, decreased renal function and renal blood flow, antidiuresis, priapism (neuraxial use)
Immunologic	Mast cell degranulation/histamine release, cytokine stimulation (IL-1), but true allergic reaction is rare
Maternal/Fetal	Placental transmission, neonatal blood-brain barrier immature, neonatal respiratory depression and opioid dependence, neonatal withdrawal (seizures)
Musculoskeletal	Truncal/chest wall rigidity and myoclonus (fentanyl derivatives)
Neurologic	Analgesia, euphoria, sedation, psychotomimesis, seizures (meperidine, propoxyphene, tramadol, rarely fentanyl)
Ophthalmic	Miosis, normal or dilated pupils (meperidine, pentazocine, diphenoxylate, propoxyphene, severe systemic hypoxia)
Pulmonary	Respiratory depression, antitussive effect, bronchospasm, pulmonary edema