CLINICAL TOXICOLOGY

OPIOID TOXICITY

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PHARMACOLOGY

- Opioids produce their effects by interacting with specific receptors distributed throughout the central and peripheral nervous systems and in the gastrointestinal tract.

- Their activity resembles that of the endogenous opioid peptides: enkephalins, endorphins, and dynorphins. Which are natural ligands for the opioid receptors.

OPIOID PHARMACOLOGY

- Opioid-receptor activation results in inhibition of adenyl cyclase activity, activation of receptor-operated K^+ currents, and suppression of voltage-gated Ca^{2+} currents. These effects cause hyperpolarization of the cell membrane, which decreases neurotransmitter release, resulting in less pain transmission.

Adverse effects of Morphine

- Severe respiratory depression can occur and result in death from acute opioid poisoning.
- A serious effect of the drug is stoppage of respiratory exchange in patients with emphysema or cor pulmonale.
- Other effects include vomiting, dysphoria, and histamine-enhanced hypotensive effects
- The elevation of intracranial pressure, particularly in head injury, can be serious. Morphine enhances cerebral and spinal ischemia.
- In benign prostatic hyperplasia, morphine may cause acute urinary retention.
- Morphine should be used cautiously in patients with bronchial asthma, liver failure, or impaired renal function.

Tolerance and physical dependence to Morphine

Repeated use produces tolerance to the respiratory depressant, analgesic, euphoric, and sedative effects of morphine.

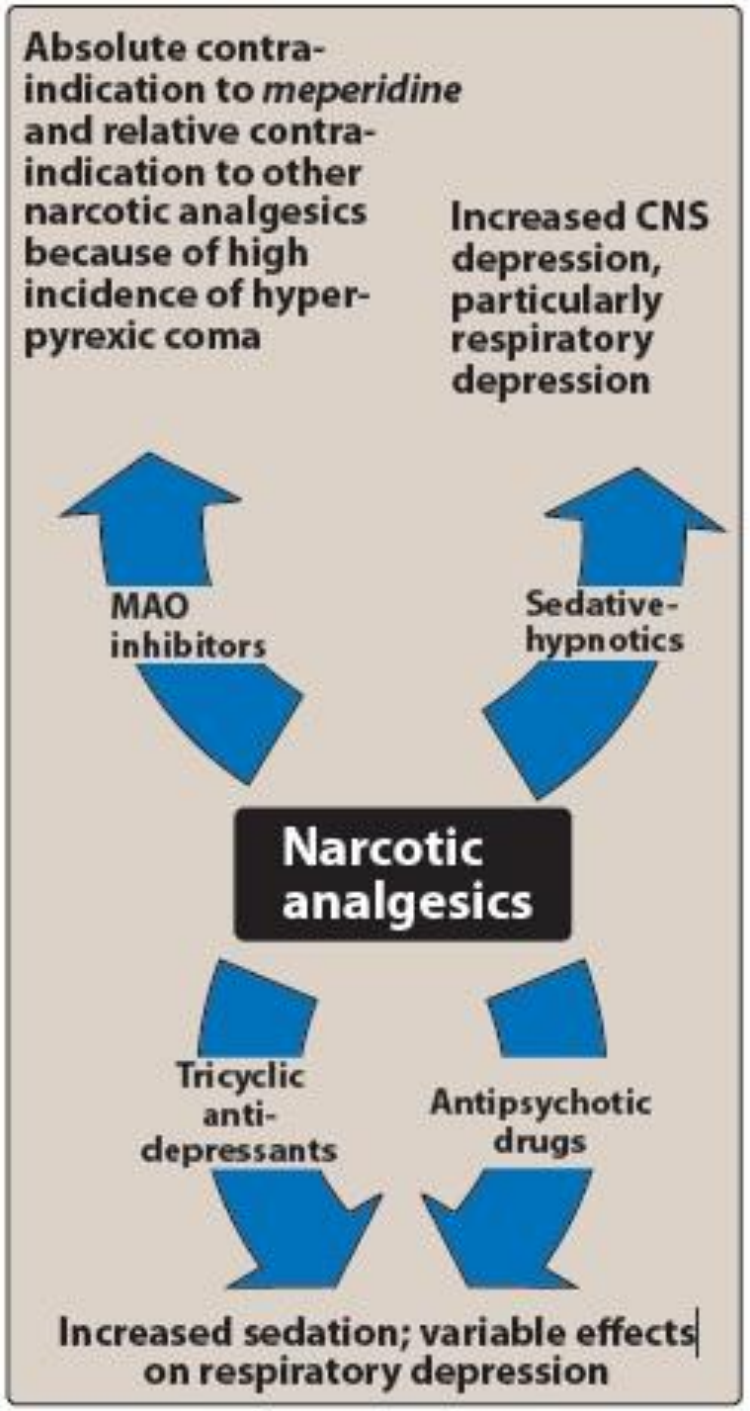
However, tolerance usually does not develop to the pupil-constricting and constipating effects of the drug.

Physical and psychological dependence readily occur with morphine and with some of the other agonists

Drugs interacting with narcotic analgesics.

CNS = central nervous system

MAO = monoamine oxidase.



Drugs interacting with narcotic analgesics.

Drug interactions with morphine appear to be rare, although the depressant actions of morphine are enhanced by phenothiazines, monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants.

SYNTHETIC OPIOIDS

- Diphenoxylate (used as antidiarrheal (lomotil)).
- Fentanyl (sublimaze)
- Meperidine
- Pentazocine (3-4 times less potent than morphine)
- Propoxyphene

Meperidine

- Is a synthetic opioid structurally unrelated to morphine used for acute pain.
- Meperidine binds to opioid receptors, particularly μ receptors. It also binds well to κ receptors.
- Meperidine causes a depression of respiration similar to that of morphine, but it has no significant cardiovascular action when given orally.
- On IV administration, meperidine produces a decrease in peripheral resistance and an increase in peripheral blood flow, and it may cause an increase in cardiac rate.
- As with morphine, meperidine increases CSF pressure.
- Meperidine does not cause pinpoint pupils but, rather, causes the pupils to dilate because of an anticholinergic action.

Therapeutic uses of Meperidine

- Meperidine provides analgesia but is not recommended for long-term use due to its active metabolite, **normeperidine**, which has significant neurotoxic properties.

- Unlike morphine, meperidine is not clinically useful in the treatment of diarrhea or cough.

- Meperidine produces less of an increase in urinary retention than does morphine.

Pharmacokinetics of Meperidine

Meperidine is well absorbed from the GI tract, and is available for oral administration. However, meperidine is most often administered parenterally.

The drug has a duration of action of 2 to 4 hours, which is shorter than that of morphine.

Meperidine is N-demethylated to normeperidine in the liver and is excreted in urine.

Adverse effects of Meperidine

- Large or repetitive doses of *meperidine can cause* anxiety, tremors, muscle twitches, and, rarely, convulsions, due tothe accumulation of normeperidine.

- The drug differs from opioids in that, when given in large doses, it dilates the pupil and causes hyperactive reflexes.

- Severe hypotension can occur when the drug is administered postoperatively.

- Due to its antimuscarinic (anticholinergic) action, patients may experience dry mouth and blurred vision.

Adverse effects of Meperidine

- When used with major antipsychotic drugs, depression is greatly enhanced. Administration to patients taking MAOIs or *dextromethorphan* can provoke severe reactions, such as convulsions and hyperthermia.

- *Meperidine is considered to be inappropriate for* use in geriatric patients and patients with impaired renal function, due to the accumulation of normeperidine.

- Adverse effects associated with normeperidine are not reversible by administration of *naloxone.*

Methadone

Methadone is a synthetic, orally effective opioid which has variable equianalgesic potency compared to that of morphine and the conversion between the two products is not linear. Methadone induces less euphoria and has a somewhat longer duration of action.

Methadone

The actions of methadone are mediated by μ receptors. In addition, methadone is an antagonist of the N-methyl-D aspartate (NMDA) receptor, which is useful in the treatment of neurogenic pain.

Methadone is well absorbed when administered orally, unlike morphine, which is only partially absorbed from the GI tract.

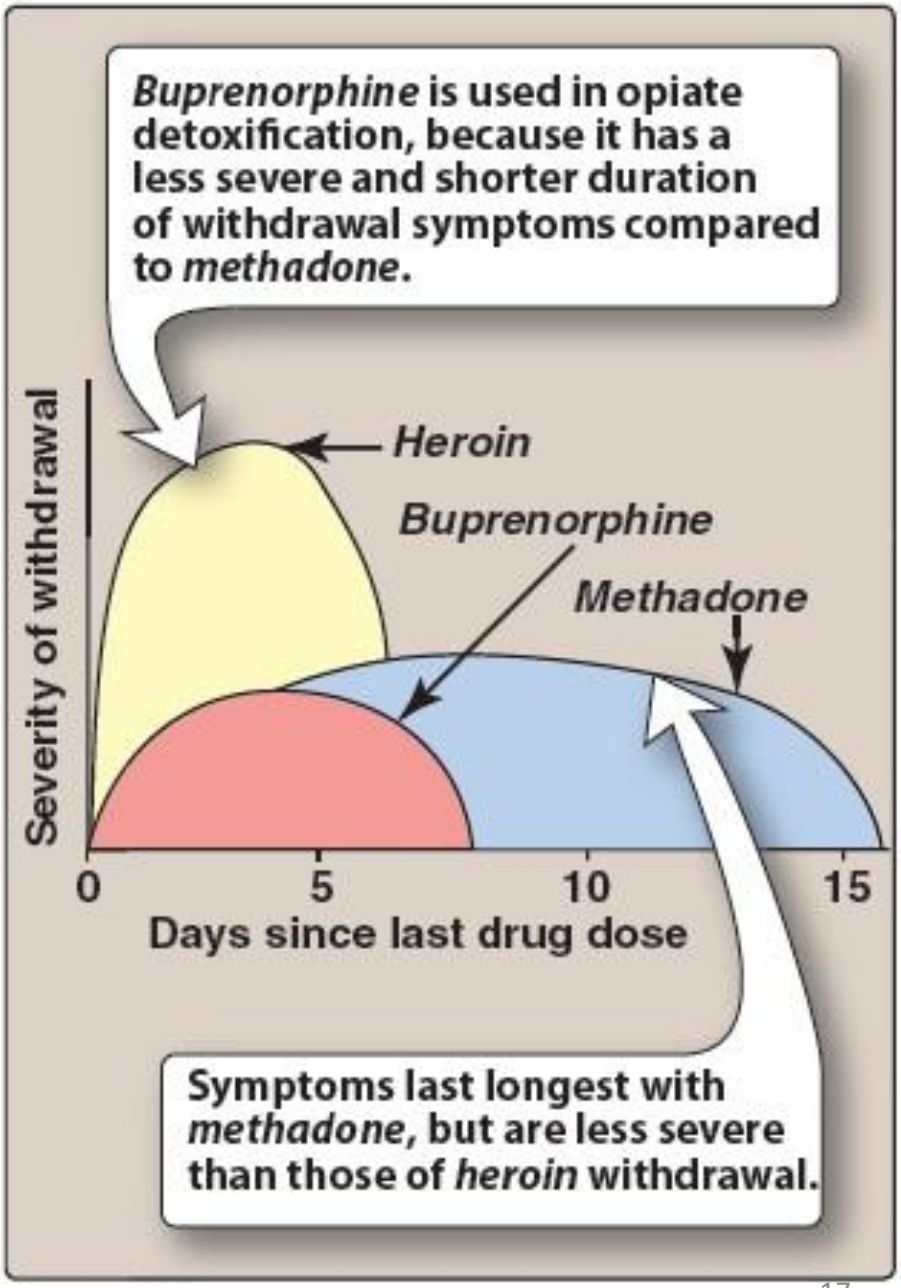
Like morphine, methadone increases biliary pressure and is also constipating (but less so than morphine).

Therapeutic uses of Methadone

Methadone is used as an analgesic in nociceptive and neurogenic pain as well as in the controlled withdrawal of dependent abusers from heroin and morphine.

Orally administered, methadone is substituted for the injected opioid. The patient is then slowly weaned from methadone. Methadone causes a withdrawal syndrome that is milder but more protracted (days to weeks) than that of other opioids

Severity of opioid-withdrawal symptoms after abrupt withdrawal of equivalent doses of heroin, buprenorphine, and Methadone



Pharmacokinetics of Methadone

- Methadone is readily absorbed following oral administration.
- The drug is biotransformed in the liver and is excreted almost exclusively in feces.
- Methadone is very lipophilic, its accumulation in the fat tissues. Its half-life range from 12 to 40 hours and extend up to 150 hours.
- The actual duration of analgesia ranges from 4 to 8 hours.
- Upon repetitive dosing, methadone levels can accumulate due to this long terminal half-life, thereby leading to toxicity.
- The metabolism relies on multiple cytochrome P450 (CYP450) enzymes, some of which are affected by known genetic polymorphisms and are susceptible to many drug drug interactions.

Adverse effects of Methadone

- Methadone can produce physical dependence like that of morphine but has less neurotoxicity than what is seen with morphine due to the lack of active metabolites.

- Methadone can cause torsades de pointes in certain situations.

- Overdosing is possible when prescribers are not aware of the incomplete cross-tolerance between methadone and other opioids, the long half-life associated with methadone and the proper titration guidelines to avoid its accumulation, and the multiple drug-drug interactions that can occur with this agent.

Fentanyl

Fentanyl, which is chemically related to meperidine, has 100-fold the analgesic potency of morphine and is used in anesthesia. The drug is highly lipophilic and has a rapid onset and short duration of action (15–30 minutes). It is usually administered IV, epidurally, or intrathecally. Epidural fentanyl is used to induce anesthesia and for analgesia postoperatively and during labor.

An oral transmucosal preparation and a transdermal patch are also available. The transmucosal preparation is used in the treatment of cancer patients with breakthrough pain who are tolerant to opioids.

The transdermal patch must be used with caution, because death resulting from hypoventilation has been known to occur.

Fentanyl

Fentanyl is often used during cardiac surgery because of its negligible effects on myocardial contractility.

Muscular rigidity, primarily of the abdomen and chest wall, is often observed with fentanyl use in anesthesia.

Fentanyl is metabolized to inactive metabolites by the CYP450 3A4 system, and drugs that inhibit this isozyme can potentiate the effect of fentanyl. Most of the drug and metabolites are eliminated through the urine.

Adverse effects of fentanyl are similar to those of other μ receptor agonists.

Unlike meperidine, it causes pupillary constriction.

Sufentanil, alfentanil, and remifentanil

Three drugs related to fentanyl.

sufentanil, **alfentanil** and **remifentanil** differ in their potency and metabolic disposition.

Sufentanil is even more potent than fentanyl, whereas the other two are less potent and shorter acting.

Heroin

- Heroin does not occur naturally. It is produced by diacetylation of morphine, which leads to a threefold increase in its potency.
- Its greater lipid solubility allows it to cross the blood-brain barrier more rapidly than morphine, causing a more exaggerated euphoria when the drug is injected.
- Heroin is converted to morphine in the body, but its effects last about half as long.
- It has no accepted medical use in USA but is used therapeutically in other countries for the severe pain of cancer.

Oxycodone and oxymorphone

Oxycodone is a semisynthetic derivative of morphine.
It is orally active and is sometimes formulated with aspirin or acetaminophen. Its oral analgesic effect is approximately twice that of morphine. Oxycodone is metabolized via CYP450 enzyme systems. Excretion is via the kidney.

Oxymorphone is a narcotic analgesic with a potency similar to that of hydromorphone. It is available in both immediate-acting and extended-release formulations. There are not any clinically relevant drug-drug interactions associated with the CYP450 enzyme system compared to oxycodone.

Hydromorphone and hydrocodone

Oral **hydromorphone** is a semisynthetic analogue of morphine and about 8-10 times more potent analgesic than oral morphine and preferred over morphine in patients with renal dysfunction due to less active metabolites compared to morphine.

Hydrocodone is a semisynthetic analogue of codeine and is the methyl ether of hydromorphone, but is much weaker an analgesic than hydromorphone. The analgesic potency of oral hydrocodone is equal to morphine. It is also used as an antitussive. Hydrocodone is metabolized in the liver to several metabolites, one of which is hydromorphone via the actions of CYP450 2D6, which can be affected by drug-drug interactions.

MODERATE/LOW AGONIST

Codeine

The analgesic actions of codeine derive from its conversion to morphine by the CYP450 2D6 enzyme system, whereas the drug's antitussive effects are due to codeine itself.
Codeine's analgesic potency is about 30% that of morphine. Codeine shows good antitussive activity at doses that do not cause analgesia.

At commonly used doses, the drug has a lower potential for abuse than morphine. Codeine is often used in combination with aspirin or acetaminophen. codeine has been replaced by drugs such as dextromethorphan, a synthetic cough depressant that has relatively no analgesic action and a relatively low potential for abuse in usual antitussive doses.

MIXED AGONIST-ANTAGONISTS AND PARTIAL AGONISTS

Pentazocine: acts as an agonist on κ receptors and is a weak antagonist at μ and δ receptors. Administered either orally or parenterally. Pentazocine produces less euphoria compared to morphine.

Buprenorphine: is classified as a partial agonist, acting at the μ receptor. A major use is in opiate detoxification, because it has a less severe and shorter duration of withdrawal symptoms compared to methadone. It causes little sedation, respiratory depression, and hypotension, even at high doses. Buprenorphine is administered sublingually, parenterally, or transdermally and has a long duration of action because of its tight binding to the μ receptor.

MIXED AGONIST-ANTAGONISTS AND PARTIAL AGONISTS

Nalbuphine and butorphanol: like pentazocine, play a limited role in the treatment of chronic pain. Neither is available for oral use. Their propensity to cause psychotomimetic effects is less than that of pentazocine. Nalbuphine does not affect the heart or increase blood pressure, in contrast to pentazocine and butorphanol. A benefit of all three medications is that they exhibit a ceiling effect for respiratory depression.

OTHER ANALGESICS

Tramadol: is a centrally acting analgesic binds to μ-opioid receptor. The drug undergoes extensive metabolism via CYP450 2D6, leading to an active metabolite that has a much higher affinity for the μ receptor than the parent compound. Its respiratory-depressant activity is less than that of morphine.

ANTAGONISTS

Naloxone: is used to reverse the coma and respiratory depression of opioid overdose. It rapidly displaces all receptor-bound opioid molecules and, therefore, is able to reverse the effect of a *morphine* overdose.

Naloxone has no effect on pain threshold.

Naloxone has no significant unwanted effects but causes withdrawal symptoms in addicts and can be used to detect opioid addicts.

Nalmefene

Naltrexone

OPIOID PHARMACOKINETICS

- Most oral opioids are completely absorbed from the gastrointestinal tract and peak in 1 to 1½ hours.
- First-pass metabolism is significant, resulting in low bioavailability.
- Protein binding of morphine is only 20 to 40 percent, whereas it is up to 90 percent for methadone.
- Elimination is primarily renal.

OPIOID PHARMACOKINETICS

- Hepatic biotransformation is the primary route of metabolism of all opioids. Patients with severe hepatic disease have impaired metabolism and are theoretically at increased risk of toxicity because of accumulation of active metabolites.

PATHOPHYSIOLOGY OF OPIOIDS

- The adverse clinical effects of opioids are caused by their action at the receptors, especially the μ_2 receptor, which mediates many of the life-threatening effects, including respiratory depression.

PATHOPHYSIOLOGY OF OPIOIDS

- The classic triad of opioid toxicity is CNS depression, respiratory depression, and miosis. However, multiple organ systems can be affected. Patients may be hyporeflexic, hypothermic, or hypotensive or may have decreased bowel sounds. These toxic effects are mediated primarily through stimulation of the μ, κ, and δ receptors.

OPIOID RECEPTORS FOR POSSIBLE TOXIC ACTION

Opioid receptors for possible toxic action

Receptor	Opioid	Clinical effect
mu	Morphine-like analgesics	Analgesia Euphoria Respiratory depression Miosis
kappa	Pentazocine Nalorphine Cyclazocine (morphine-like analgesics may have some kappa activity) Levallorphan	Analgesia Sedation Miosis
sigma	Pentazocine Cyclazocine Nalorphine	Dysphoria Delusions Hallucinations

OPIOIDS TOXICITY

- Acute opioids toxicity may result from intentional, accidental, or therapeutic overdose. Whatever the reason, the toxicological effects are the same.

- There is significant individual variability to these drugs and rapid production of tolerance.

- Signs and symptoms of acute opioid overdose begin within 20 -30 min after oral ingestion and within minutes after parenteral administration.

CHARACTERISTICS OF OPIOID TOXICITY

- CNS depression----Coma
- Respiratory depression
- Pulmonary edema
- Hypothermia
- Miosis
- Bradycardia
- Hypotention
- Decreased urinary output
- Decreased GIT motility

MANAGEMENT OF TOXICITY

- The major treatment objective is to maintain vital functions (respiratory and cardiovascular support).
- Opioid ingestion frequently delay gastric emptying time. Therefore, in acute overdose, as long as the patient is alert, emesis should be performed.
- If the patient is obtunded, gastric lavage is indicated.

OPIOID ANTAGONISTS

- **Naloxone**

  Naloxone is a synthetic *N*-allyl derivative of oxymorphone and is the opioid antagonist of choice. It competitively binds opioid receptors, including κ, δ, and, particularly, μ. It has a greater affinity for receptors than do the agonists.

OPIOID ANTAGONISTS

- Naloxone administration is generally safe in patients with suspected opioid toxicity.

- Complications of naloxone use are reported in 1 percent of heroin users.

OPIOID ANTAGONISTS

- **Nalmefene**

  Nalmefene is a long-acting parenteral antagonist whose use in the acute care setting is controversial.

  Doses of 0.5 to 2.0 mg have been reported to be safe and effective.

  Adverse effects include nausea and vomiting, tachycardia, myoclonus, dizziness, drowsiness, and mental fatigue. Anecdotally, noncardiogenic pulmonary edema has been reported after nalmefene use in a healthy, postoperative patient

OPIOID ANTAGONISTS

- **Naltrexone**
- Naltrexone is an oral opioid antagonist with a longer duration of action than that of naloxone.

- It is used primarily for long-term opioid detoxification therapy.

- Because it is administered orally and because it can induce a very prolonged withdrawal state, naltrexone is not used in the treatment of acute opioid toxicity.

YOU HAVE TO READ

- Case studies and Review questions in the book (Principles of clinical Toxicology, third edition, Gossel and Bricker)

  Page: 302 – 306

- Also, page: 395 – 400 for cardiovascular drugs.