DRUGS OF ABUSE

OPIOID

INTRODUCTION

- **Opiates**: a group of naturally occurring compounds derived from the opium poppy
- **Opioids**: the class of drugs that includes all synthetic and semisynthetic drugs that mimic the actions of the opiates
- **Narcotics**: group of drugs with actions that mimic those of morphine (can cause the classic triad of respiratory depression, miosis, and decreased mental status)

INTRODUCTION

- They are subdivided into **natural, semisynthetic, synthetic and mixed agonist/antagonist subclasses**
- ***Natural opium agonists*: morphine and codeine**
- ***Semisynthetic***: heroin, hydromorphone, oxymorphone, oxycodone
- ***Synthetic opioids*** produced **completely by lab. synthesis**. Ex: meperidine, **methadone**, diphenoxylate, fentanyl, propoxyphene

Papaver somniferum, Opium poppy, common poppy

- *Opioids with **mixed agonist-antagonist** properties include:*
  - ✓ Nalbuphine,
  - ✓ Pentazocine

…..have agonist activity at some receptors and antagonist activity at other receptors:

- ***Partial agonists*:**
  - ✓ Buprenorphine

INTRODUCTION

- Opioids are commonly used clinically as **analgesics** and **anesthetic agents**……..
- But also available illicitly as **drugs of abuse**
- Absorption may occur via **parenteral**, **oral**, or **inhalational** routes

Toxicodynamic

- The opioids exert their pharmacologic effects by interacting with ***3 specific receptors in the CNS……mu, delta, kappa***
- All three mediate **analgesia**
- The **μ-receptor** activation plays major role in the respiratory depression and slow GI transit
- ***κ-receptor*** activation also slows gastrointestinal transit and seems to be involved **in sedative actions**
- **δ-receptor** activation may play a role in the development of **tolerance**

Receptor Stimulation

Mu (μ)

Physical dependence

Analgesia, sedation, cough suppression

Respiratory depression

Dopamine release…euphoria

Receptor Stimulation

Kappa (κ)

Sedation, decreased respiration

Analgesia, Miosis

Delta (δ)

Analgesia, antidepressant properties

release of growth hormone

Dopamine released

Tolerance

DEFINITIONS

- **Psychological Dependence** (also dependence, abuse)
  - Loss of control over drug use
  - Compulsive drug use
  - Continued use despite harm
- **Physical Dependence**

  Stopping the drug leads to a withdrawal syndrome
- **Tolerance**

  Less effect after prolonged use; dose escalation required to maintain effect

CLINICAL EFFECTS

- **Addicts use** opioids for
  - Excitement,
  - Euphoria.
    - The rapid onset of these effects with an i.v. bolus…. activation of the mesolimbic dopamine system
- …..But dysphoria may occur….(kappa agonist)

TOXICOKINETICS OF OPIOIDS

Elimination

- Most opioids are **metabolized by hepatic conjugation** to inactive compounds that are excreted readily in the urine

- All opioids have a **prolonged duration** of action in patients with **liver disease** (eg, cirrhosis) because of impaired hepatic metabolism….drug accumulation and opioid toxicity

TOXICOKINETICS OF OPIOIDS

- Opiate metabolites are **excreted in the urine**.
- **Renal failure** also leads to toxic effects from accumulated drug or active metabolites (eg, **normeperidine**)
- Certain opiates (eg, propoxyphene, fentanyl, and buprenorphine) are more lipid soluble and can be stored in the fatty tissues of the body

TOXICOKINETICS OF OPIOIDS

- Most of these drugs have **large volumes** of distribution (3–5 L/kg)

- The rate of elimination is highly variable, from 1–2 hours for **fentanyl** derivatives to 15–30 hours for **methadone**

Toxic Doses

- The toxic dose varies widely, depending on the specific **compound**, the **route** and **rate** of **exposure**, and **tolerance** to the effects of the drug as a result of chronic use

- Some newer fentanyl derivatives have **potency up to 2000 times that of morphine**

HISTORY

- In many case of opioid overdose…..**impossible to obtain history** because of CNS depression, coma, lack of cooperation
- History is important to direct the clinician to a better diagnosis…..severity of the exposure, other toxicological syndromes or pathological processes (trauma, infection)
- **If the patient is conscious** it is imp. to determine….the type, amount of opioid, time and route of exposure, other medication, suicidal attempt

PHYSICAL EXAMINATION

- ✓ **Mild to moderate overdose:** **lethargy** is common, "**pinpoint**“ **pupils**. **BP** and **HR** are **decreased**, **bowel sounds** are **diminished**, and the **muscles** are usually **flaccid**

- ✓ N.B: **Miosis** but may not be present if the patient is hypoxic, or took sympathomimetics or anticholinergic

- ✓ **With higher doses:** **coma** accompanied by **respiratory depression**, and **apnea** often results in **sudden death**.
- **Noncardiogenic pulmonary edema** may occur

PHYSICAL EXAMINATION

- Other common feature: **hypothermia & hyporeflexia**
- **Seizures** are **not common** after opioid overdose but occur occasionally with certain compounds (eg, codeine, dextromethorphan, meperidine, methadone, propoxyphene, and tramadol)
- Seizures may occur in patients with **renal compromise** who receive **repeated doses of meperidine** owing to accumulation of the metabolite **normeperidine**

Mortality/Morbidity

- **Cardiotoxicity** similar to that seen with TCA due to severe **propoxyphene** intoxication
- Prolonged QT intervals and torsade de pointes have been reported with **methadone**…sudden death
- The predominant cause of morbidity and mortality from pure opioid overdoses is: **respiratory compromise**

DIAGNOSIS

The triad strongly suggests **opioid poisoning:**

- ✓ Coma (CNS depression),
- ✓ Pinpoint pupils
- ✓ Respiratory depression

DIAGNOSIS

- **Needle tracks marks** is suggestive of addiction
- **Specific levels** not usually performed because of **poor correlation** with clinical effects
- Qualitative screening of the urine is an effective way to confirm recent use (morphine, codeine..)
- But not all…..**tramadol and fentanyl not detected**

PHYSICAL EXAMINATION

- **Opioid withdrawal syndrome:**
- Typical symptoms include: Anxiety and a craving for the drug followed by an increased resting respiratory rate (> 16 breaths/minute).
- mydriasis, and stomach cramps.
- Later… tremors, muscle twitching, tachycardia, hypertension, fever.

CODEINE

- Codeine is 3-methylmorphine
  - De-methylation produces morphine
  - Illicit preparations found
    - combination of codeine and glutethimide (p.o)
      - produce euphoria as heroin
- Possess analgesic and antitussive properties
- Less potent than morphine
- Tolerance doesn’t develop rapidly

MEPERIDINE

- Its structure is similar to Fentanyl
- Is a pure agonist
- Used as analgesic
- Less potent than morphine
- Metabolized in the liver into
  - meperidinic acid &
  - normeperidine(active)

MPTP

- Meperidine analog
  - N-**methyl**-4-**pheny**l-1,2,3,6-**tetrahydropyridine** (MPTP)
  - Associated with severe form of **parkinsonism**
    - reversed by the administration of
      - L-dopa and carbidopa

PENTAZOCINE

- Introduced as an **analgesic in 1967**
- It was frequently encountered in the **illicit trade**
- An attempt at reducing the abuse of this drug was made with the introduction of **Talwin Nx®.**
- This product contains a quantity of antagonist **(naloxone**) sufficient to counteract the morphine-like effects of pentazocine if the tablets are dissolved and injected

THERAPEUTIC APPROACH FOR DRUG ABUSE

1. Treat acute overdose:
   - Symptoms
   - Antagonists
2. Management of withdrawal symptoms:
   - Administration of drugs to suppress acute withdrawal followed by a gradual reduction in dose
3. Long-term rehabilitation

FIRST AID MEASURES AND MANAGEMENT PRINCIPLES

- **ABC:**
  - Profound CNS depression, apnea, impaired gag reflex suggest ***endotracheal intubation*** for airway control and protection against aspiration
  - Patients with altered consciousness should receive intravenous ***thiamine***, and ***glucose***
  - Treat seizures, hypotension, and noncardiogenic pulmonary edema if they occur

FIRST AID MEASURES AND MANAGEMENT PRINCIPLES

- **GI decontamination** may be extremely valuable in massive opioid ingestion within 1hr:
  - Administer activated charcoal orally
  - Gastric lavage with large orogastric tube if needed
  - Consider whole-bowel irrigation after ingestion of sustained-release products
- **Enhanced elimination. Large Vd** of the opioids… no role!

FIRST AID MEASURES AND MANAGEMENT PRINCIPLES

- Administration of antidote (**naloxone**)
  - Is a short-acting competitive opioid antagonist considered in patients with respiratory depression or altered consciousness (no agonist properties)
  - Complete resolution is diagnostic of opioid intoxication
    - The recommended initial dose is
      - 0.2-0.4 mg i.v for adults and
      - 0.01 mg/kg for children,
    - Several doses may be given **2-3** min intervals

FIRST AID MEASURES AND MANAGEMENT PRINCIPLES

- Also i.m, intranasal
- If up to 10-20 mg and still no response…..not opioid intoxication
- ***Caution:*** *The duration of effect of naloxone (1–2 hours) is shorter than that of many opioids…..**do not release a patient** who has awakened after naloxone treatment until at least 3–4 hours has passed since the last dose of naloxone*
- Patients who breath normally does not need naloxone
- Assure a respiratory rate above 14 breaths per minute
- **NALMEFENE**…..longer duration of action (3-5 hours)

FIRST AID MEASURES AND MANAGEMENT PRINCIPLES

- **Over-administration of naloxone** can provoke acute **withdrawal symptoms** in opioid-dependent patients (N, V, agitation, violence), and this can complicate treatment

- If **combined opioid** and **sympathomimetic intoxication** administration of **naloxone** may cause life-threatening condition of sympathomimetic intoxication by removing the "protective" CNS depressant effect of opioid

Treatment of withdrawal syndrome in opioid abuser

- **Pharmacological approach**
  - Two general approaches are commonly adopted
    - A longer-acting opioid, such as **methadone**….followed by a gradual reduction in dosage of the substitute drug
    - Use of various pharmacological agents, such as clonidine and/or a benzodiazapine…….will mitigate symptoms and signs of withdrawal
- **Psychological support**

FDA Approves First Non-Opioid for Withdrawal

- May 17, 2018 -- The FDA approved the first non-opioid drug, lofexidine hydrochloride (Lucemyra), to help treat symptoms of opioid withdrawal in adults.

- The FDA found the drug to be safe and effective in easing symptoms such as diarrhea, nausea, vomiting, anxiety, and an overall feeling of sickness that often keeps patients from withdrawing from opioids.

- Lofexidine may ease withdrawal symptoms but may not completely prevent them. It is approved for treatment for only up to 14 days. It is not a treatment for opioid use disorder but can be used as part of a broader, long-term treatment plan for managing it, the FDA said in a news release.
- https://www.webmd.com/mental-health/addiction/news/20180517/fda-approves-first-non-opioid-for-withdrawal