Clinical Toxicology

Opioid toxicity
Lec.7

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Opioid Toxicity

Worldwide, about 0.5 million deaths are attributable to drug use. More than 70% of these deaths are related to opioids, with more than 30% of those deaths caused by overdose. According to WHO estimates, approximately 115 000 people died of opioid overdose in 2017. Opioid overdoses that do not lead to death are several times more common than fatal overdoses.

Opioid Toxicity

Clinical Uses of Opioid Analgesic

- Analgesia (Relief sever pain, visceral and somatic)
- Acute pulmonary edema
- Cough suppression (Codeine)
- Diarrhea
- Application of anesthesia (premedication for surgery)
- Production of euphoria and relief pain of dying patients

Opioid Toxicity

Epidemiology

Opioids are prescribed widely, often in concert with other analgesics, including NSAIDs, acetaminophen or muscle relaxants. Analysis of data from the Automation of Reports and Consolidated Orders System (ARCOS) from 2004 to 2011 showed that overall, medical use of ***opioids increased 100%;*** use of codeine decreased 20%, but use of other opioids increased as follows:

Buprenorphine: 2318%

Fentanyl: 35%

Hydromorphone: 140%

Oxycodone: 117%

Hydrocodone: 73%

Morphine: 64%

Methadone: 37%

Opioid Toxicity

Epidemiology

Retrospective analysis of data from the Drug Abuse Warning Network (DAWN) for drug misuse data show that abuse of ***buprenorphine*** increased 384% from 2006 to 2011. From 2004 to 2011, increases in abuse of other opioids were as follows:

Hydromorphone: 438%

Oxycodone: 263%

Morphine: 146%

Hydrocodone: 107%

Fentanyl: 104%

Methadone: 82%

Codeine: 39%

Opioid Toxicity

Morbidity and Mortality

- The predominant cause of morbidity and mortality from pure opioid overdoses is respiratory compromise.
- Less commonly, acute lung injury, status epilepticus, and cardiotoxicity occur in the overdose setting.
- Case reports of increased incidence of mortality have been documented in patients with coexistent stenosing lesions of the upper airway.
- Morbidities due to co-ingestants must be considered in polypharmacy overdoses, and they vary depending on the co-ingestant.

Opioid Toxicity

Major effects of opioids – CNS

- Analgesia
- Pain relief occurs both by raising the threshold for pain perception and by increasing pain tolerance
- Respiratory depression
- Sensitivity of the respiratory center to CO2
- Respiratory failure the major toxicity of opioids
- Analgesia and respiratory depression are close and increase with dose in parallel

Opioid Toxicity

Major effects of opioids – CNS

- Euphoria
- Relaxed and dreamy state
- Mental clouding
- Dysphoria may occur in place of euphoria
- Sedation
- More likely to occur in the elderly
- Less likely to occur with synthetic opioids
- Additive with other CNS depressants
- Miosis
- Nausea and Vomiting
- Cough suppression

Opioid Toxicity

Peripheral effects of opioids

Gastrointestinal tract

- Constipation a long recognized effect of opioids
- High density of opioid receptors in GI tract
- Motility decreased in the stomach
- Peristalsis diminished in large intestine

Cardiovascular

- Bradycardia, otherwise no significant effects on the heart, on cardiac rhythm or on blood pressure

Opioid Toxicity

Opioid effects & withdrawal

Opioid effects

- Analgesia
- Sedation
- Euphoria
- Pinpoint pupils
- Low BP, PR
- Dry skin, mouth, ⇩urine
- Constipation, ⇩bowel action
- Nausea, vomiting

Opioid withdrawal

- Increased pain
- Agitation, poor sleep
- Dysphoria
- Dilated pupils
- Increased BP, PR
- Sweating, ⇧urine
- Diarrhoea, abdo. cramps
- Nausea, vomiting

Opioid Toxicity

Opioid Overdose

- Euphoria + + +
- Unconsciousness
- Respiratory depression (slow deep respiration 2-7/min)
- Pinpoint pupils (but may be dilated if brain damage occurred)
- Pulmonary edema
- Seizures
- Hypothermia
- Death

Note: all opioid drugs caused pinpoint pupils except pethidine (meperidine) caused mydriasis because of atropine like effect.

Physical examination

A. **With mild or moderate overdose,** lethargy is common. The pupils are usually small, often of "pinpoint" size. Blood pressure and pulse rate are decreased, bowel sounds are diminished, and the muscles are usually flaccid.

B. **With higher doses,** coma is accompanied by respiratory depression, and apnea often results in sudden death. Noncardiogenic pulmonary edema may occur, often after resuscitation and administration of the opiate antagonist naloxone.

C. **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.

Physical examination

D. **A leukoencephalopathy** with typical magnetic resonance imaging (MRI) changes has been reported in some heroin smokers ("chasing the dragon").

E. **Cardiotoxicity** similar to that seen with tricyclic antidepressants and quinidine (**ventricular arrhythmias**) can occur in patients with severe **propoxyphene** intoxication. Prolonged QT intervals and torsade de pointes have been reported with **methadone** and may account for some of the sudden deaths associated with its use.

F. Some newer synthetic opioids have mixed agonist and antagonist effects, with unpredictable results in overdose. **Buprenorphine** causes less maximal opioid effect than morphine does, and because of strong binding to opioid receptors it can cause acute withdrawal symptoms in persons on high doses of conventional opioids.

G. Opioid **withdrawal syndrome** can cause anxiety, heightened sensation of pain, abdominal cramps and diarrhea, and insomnia.

Opioid Toxicity

Physical examination

- It is important for the clinician to be aware that opioid exposure does not always result in miosis, and respiratory depression is the most specific sign.
- Dependence on miosis to diagnose opioid intoxication can be misleading.
- If sufficiently severe, hypertension and pupillary dilation may be present because of CNS hypoxia.
- Pethidine (meperidine) caused mydriasis.

Opioid Toxicity

Treatment

- Adequate pre-hospital care centers on aggressive airway control.
- Endotracheal intubation is indicated for patients who are unable to protect their airway.
- If advanced life support (ALS) is available, intravenous naloxone may be given to reduce respiratory depression
- In November 2015, the US Food and Drug Administration approved intranasal naloxone for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.

Opioid Toxicity

Naloxone a. As little as 0.2–0.4 mg IV or IM is usually effective for heroin overdose. Repeat doses every 2–3 minutes if there is no response, up to a total dose of 10–20 mg if an opioid overdose is strongly suspected.

b. ***Caution:*** The duration of effect of naloxone (1–2 hours) is shorter than that of many opioids. Therefore, 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. In general, if naloxone was required to reverse opioid induced coma, it is safer to admit the patient for at least 6–12 hours of observation.

2. Nalmefene is an opioid antagonist with a longer duration of effect (3–5 hours).

a. Nalmefene may be given in doses of 0.1–2 mg IV, with repeated doses of up to 10–20 mg if an opioid overdose is strongly suspected.

b. ***Caution:*** If a methadone overdose is suspected, the patient should be observed for at least 8–12 hours after the last dose of nalmefene.

3. Sodium bicarbonate may be effective for QRS-interval prolongation or hypotension associated with propoxyphene poisoning.

C. Decontamination Administer activated charcoal orally if conditions are appropriate .Gastric lavage is not necessary after small to moderate ingestions if activated charcoal can be given promptly. Consider whole-bowel irrigation after ingestion of sustained-release products.

D. Enhanced elimination. Not benefit because of the very large volumes of distribution of the Opioids.

Hallucinogenic Agents

- Hallucinogens are drugs that cause alteration of visual, auditory, or tactile perceptions but are also referred to classes of drugs that cause alteration of thought and emotion.
- The user when ingest these hallucinogenic agents, sees or hears thing that are not in fact true.
- They were first used 3500 B.C, the use of these start with naturally substances inducing alteration in the state of consciousness during religious or cultural ceremonies.
- It started in India with the use of hallucinogenic mushrooms and morning glory and then extend to Mexico.

Hallucinogenic Agents

Classes

These drugs can be divided according to the chemical structure into:

- Ergot alkaloids: indolealkylamines (related to the endogenous serotonin 5-HT)
- Phenylethylamines (similar to NE)
- Anticholinergics
- Miscellaneous psychoactive substances

Hallucinogenic Agents

Indolealkylamines

- LSD (d-lysergic acid diethyl amide, semi-synthetic substance derived from ergot)
- LSA (d-lysergic acid amide, from morning glory seeds)
- psilocybin and psilocin (isolated from hallucinogenic mushroom genus Psilocybe)
- DMT(N,N-dimethyltryptamine), found in trees of genus Virola
- Acts primarily through 5-HT receptor subtypes
- Cannot attribute hallucinogenic effects to one 5-HT receptor subtype

Hallucinogenic Agents

- Well-absorbed from GI tract
- LSD most potent (20-25 mcg. produces marked sympathomimetic effects)
- LSD longer acting (8-12h) and more potent than psilocybin or psilocin (4-12h)
- 1-2 mushrooms hallucinosis for 4-12h
- All compounds mainly cleared by liver; excreted in feces
- LSD no active metabolites
- psilocybin is hydrolyzed to psilocin (active hallucinogen)

Hallucinogenic Agents

Clinical Symptoms of LSD Intoxication

- 20 mcg. clinically detectable symptoms, hallucination dose is about 100-750 mcg.
- Tolerance occurs over time
- Symptoms within 30 min
- Maximum effects at 1-4h, symptoms diminish after 8-16h
- It has both sympathetic & parasympathetic effects, sympathetic stimulation starts first & it is more predominant, it is observed as:
  - Mydriasis & hyperthermia, hyperglycemia, tachycardia, & hypertension followed by:
- Hallucination within 30-90 min. in which the user will feel change in mood & behavior (last feeling lasts for about 6-12 hr.)

Hallucinogenic Agents

- After the average dose the mood changes from euphoria into dysphoria.
- LSD affects sensory perception, the most marked effect is that on the visual perception, color of the objects become more intense, flat surfaces appear depth
- It causes disruption of the ego function & a fair of self-destruction (a person feels that his body part may be foreign) & may lead to self trauma & death.
- LD50 of LSD is about (0.2-1) mg/kg, the minimum dose that lead to toxicity is 14 mg for a 70 kg adult, thus the LSD has a higher therapeutic index, death may be due in general to the complication & not to the pharmacological action, death mainly associated with trauma or suicide.

Hallucinogenic Agents

- The most common adverse reaction is the acute panic reaction (feeling of losing control)
- The most common reaction see with chronic use is the flash back reaction (last for several hrs, it happens just before going to sleep, or when the user is under severe stress)
- It can be divided into the following categories:

1- Perceptual: the user sees variant or different colors, hears sounds from the previous trips

2- Somatic: the user will develop parasthesia, and tachycardia

3- Emotional: the used will develop feeling of loneliness, panic & depression.

- The emotional category of complications is the most dangerous because it may lead to a suicidal attempt.

Hallucinogenic Agents

Management

- Pre-hospital care should focus on preventing harm and transporting patients to an appropriate facility for further evaluation.
- It is important to note that patients under the influence of hallucinogens may exhibit a wide range of behaviors with the potential to rapidly fluctuate from a relaxed, euphoric state to one of extreme agitation and aggression.
- Diazepam is given if necessary to achieve sedation & in case of convulsion
- Chlorpromazine to treat the bad trips

Hallucinogenic Agents

Other Tryptamine related Hallucinogens

- Have the same pharmacological & toxicological features of LSD, major differences are in the potency

  LSD > psilocybin

- Oral dose of about 60-200 mg/kg produces the following symptoms:

- Nausea, weakness, anxiety, dreamy state, delirium, dizziness, blurred vision, dilated pupil (the above symptoms are mediated by both serotogenic & parasympathetic neurons)
- The duration of action is about 3 hrs which is less than that of LSD

Hallucinogenic Agents

Phenylethylamine Hallucinogens

- Close structural similarity to catecholamines, NE and DA
- Mescaline naturally occurring substance found in peyote cactus
- Modification of mescaline molecule led to synthetic amphetamine derivatives with hallucinogenic action
- One dried flower top (mescal button) contains 6-45 mg of active compound
- Ingested fresh or as a powder
- The hallucinated dose is about 5 mg/kg , at larger dose (20-60 mg/kg) produce drop in blood pr., bradycardia, & respiratory depression, death is not reported only in case of suicidal attempts.

Hallucinogenic Agents

Anticholinergic

- Low doses of scopolamine- mild euphoria, sedation, drowsiness
- Clinical findings: muscarinic effects: dry mouth, decreased GI motility, urinary retention, tachycardia, dry mouth, hyperpyrexia with dry, flushed skin
- CNS effects: visual, auditory and tactile hallucinations; disorientation and confusion, memory loss, dilation of pupils, seizures
- Complete episode may last for 24 to 48 hours

Hallucinogenic Agents

Datura stramonium

- Solanaceae family
- All parts of plant are poisonous
- Seeds contain 4% anticholinergic alkaloids (scopolamine, hyoscyamine and atropine)
- Leaves can be eaten raw, prepared as tea or smoked
- As little as 4-5g of crude leaf may be lethal for children
- Adolescents smoke the dried leaves or consume dried seeds to induce toxic delirium
- Effects are dose dependents

Hallucinogenic Agents

- ***Belladonna Alkaloids***
- Atropa belladonna (deadly nightshade)
- Belladonna means beautiful woman – refers to putting a drop of the juice of the plant to dilate pupils
- Also used by witches in middle ages

Hallucinogenic Agents

Miscellaneous Category

- Phencyclidine (PCP) and Ketamine
- Dissociative anesthetics
- Both drugs produce hallucinogenic effects at low levels
- PCP can produce stimulant, depressant, analgesic, anesthetic, and hallucinogenic effects (dose-dependent)
- DXM (dextromethorphan)
- Cough suppressant
- Also used to boost effects of analgesics for sever pain
- Typical dose 15-30 mg. for cough
- High dose (>200-400 mg Dextromethorphan)
- Euphoria
- Auditory Hallucinations and Visual Hallucinations

Hallucinogenic Agents

Management

- There is no specific antidote in such case, the management involves supportive treatment, placing the patient in a quite dark room.
- Diazepam to treat the hyperactivity.
- Diazoxide, nitric oxide or sodium nitroprusside are used if the hypertension was persistent.
- Acidify the urine to about 5-5.5 pH in order to increase the urinary excretion of the drug.

KEEP
CALM
AND
ASK
QUESTIONS