OPIOIDS AND SEDATIVES

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Objectives

Not given :):

Don’t skip any note in this lecture, please (: You can click here to check the lecture from the textbook.

NOTES Extra BOOK IMPORTANT GOLDEN notes
What are opioids:

- Exudate of the opium poppy (Papaver somniferum). Most common in Afghanistan.
- Addiction to opium became a commonplace e.g. sickle cell patients

Known to:

Relieve pain
Relieve diarrhea
Produce euphoria

Examples:

**Morphine**
- Good for analgesia. But causes nausea and vomiting. (Commonly used analgesic in the hospital)

**Fentanyl**: Synthetic, doesn’t have a histaminic effect.

**Heroin**: Mostly used by lower class people.

**Codeine**: Metabolized into morphine; however, 30% of our population (Arab descents) don’t metabolize it, that's why morphine is preferred. Codeine can be given orally.

**Methadone**

**Tramadol**

**Meperidine (pethidine)**: Synthetic, More euphoria less analgesia and more side effects. Should be given in a controlled setting. It is very addictive.

**Morphine (Natural) vs Fentanyl (Synthetic):**
- Morphine Causes vasodilation due to release of histamines, not used in hemodynamically unstable patients.
- Fentanyl Does NOT cause hypotension.

Opioid vs Opiate vs Narcotic?

- **Opioid:** natural and synthetic
- **Opiate:** natural (e.g. morphine)
- **Narcotic:** any illegal hypnotic drug/drugs that make you sleep. It’s mostly a legal term used by DEA

Opioid receptors:

**MU(μ)**
- Located at supraspinal and spinal sites (Analgesia and respiratory depression, Miosis, euphoria, reduced GI motility)

**Kappa (κ)**
- Dorsal horn of spinal cord and brainstem. (Analgesia, miosis, sedation)

**Delta (δ)**
- Binding sites for endogenous peptides (Analgesia, dysphoria, delusions, hallucinations)

Important!

Opioids do not work on GABA, it has very specific receptors and each one of those receptors has its own specific effect.
- Some are more analgesic and cause less nausea and vomiting, whereas some cause constipation.
- In general the most important features of opioids are:
  - Effect on the CNS.
  - Effect of on the respiratory system (in a very specific way).
  - Effect on the cardiovascular system causing hypotension.
  - GI (patients taking fentanyl must take laxatives).
**Opioids Toxicity**

### Routes of administration of Opioids:

- **Orally**
- **IV**
- **Smoking** (heating up a spoon and inhaling the smoke), "chasing the dragon"
- **Sniffing** (more for cocaine)

### Naloxone:

- **Pure Opioid antagonist (Naloxone)**
  - **Routes:** IV, IM, SC, intra-Nasal
  - **Mechanism:** Competitively binds opioid receptors and reverses all opioid mediated action
  - **Dose:** Injectable solution (0.4-1mg/mL), IM/SC auto-injector (0.4mg/0.4mL, "2 auto-injectors/package")
  - **Half-life is important. Opioids half-life is much longer than Naloxone's half-life.**

- **Naloxone 1/2 life is 1 - 2 hours**
- **Morphine 1/2 life approx. 2 hours**

### Management

- **ABCDE's**
  - **A** - Airway
  - **B** - Breathing
  - **C** - Circulation
  - **D** - Decontamination
  - **E** - Exposure, (Part of the exposure in toxicology is looking in the pockets...)

### Toxidrome and other effects

- CNS depression, Respiratory depression, Miosis "pinpoint Pupils"
- Sensorineural hearing loss
- Mild hypotension (Histamine release)
- Bradycardia
- Nausea & Vomiting (watch out for ileus)
- Urinary Retention
- Pruritus/ Urticaria and Flushing

1-Respiratory depression AKA Hypoventilation. Minute Ventilation is calculated as:

\[ \text{Respiratory rate} \times \text{Tidal volume} \]

In Opioids, the tidal volume is normal. But the respiratory rate is low

2-Other drugs causing hearing loss:
- Aminoglycosides (gentamicin)
- Loop diuretics (furosemide)
- Aspirin (It also causes tinnitus)

**Half-life**

- Naloxone 1/2 life is 1 - 2 hours
- Morphine 1/2 life approx. 2 hours

"The duration of action of many opioids, especially after overdose, is significantly longer than that of naloxone. Patients responsive to naloxone should be observed for recurrence of opioid toxicity after the effect of naloxone has resolved."
Opioid Withdrawal:

In withdrawal patients go into hyperadrenergic state. They are NOT life threatening.

Symptoms:
- Sweating (diaphoresis)
- Hypertension
- Mydriasis
- Yawning
- Diarrhea
- Nausea and vomiting
- Abdominal pain
- Muscle cramps
- Tachypnea
- Tachycardia

CNS excitation (Restlessness, agitation, dysphoria and insomnia)

Management:

Opioid withdrawal patients > Clonidine is the drug of choice

In the ED
- Supportive and Symptoms based:
  - IV fluids
  - Electrolytes replacement
  - Antiemetic
  - Clonidine (Alpha2 agonist) can be used to suppress sympathetic hyperactivity and shorten the duration of withdrawal

Chronic Opioid Abusers: "Long term maintenance therapy provided by addiction clinics"
- Methadone: Given to heroin addict to get them their "fix" and go off of street work. Could be given to pregnant ladies.
  - Long half life and requires a dose every 24 hours

Outpatient Treatment
- Buprenorphine and Buprenorphine-Naloxone combined as single product.
  - Doesn't require inpatient treatment unless severe symptoms.

Doctor insisted to know this part from the textbook so please make sure to study this part very well, we wanted to save your time so we added this point from book here (; Good luck!

Yes, the pharmacist gives Methadone to addicts!
**Benzodiazepines**

**Mechanism of action**

- Benzodiazepines bind to benzodiazepine receptor & potentiates GABA effects on the chloride channel → increasing intracellular flux of Cl ions & hyperpolarizing the cell (lowers the action potential to be more negative, so it will be harder to stimulate the cell).
- The net effect is a diminished ability of the nerve cell to initiate an action potential, which leads to inhibiting neural transmission (like alcohol & barbiturates).

**Clinical effects**

- **Anticonvulsant** (The strongest indication.)
- Sedative
- Hypnotic
- Anxiolytic

**Examples**

- Alprazolam (Xanax)
- Diazepam (Valium)
- Lorazepam (Ativan)
- Midazolam (Versed)

5% of the population have used an illicit drug once in their life. The most common benzodiazepine drug abused is Xanax (alprazolam).

**Benzodiazepines Toxicity**

**Toxicity**

- CNS depression (spectrum)
- Respiratory depression (non-central)
- Potential complications: aspiration, pressure sore
- Hypotension (uncommon) seen only if given intravenously in large doses

1. It’s a spectrum. From slurred speech all the way to coma.
2. Respiratory depression is unlike opioids (Opioids have a central effect. Affecting the medulla hence lowering the respiratory rate), Benzodiazepines non-central, affecting the muscles. The patient feels too weak to breathe.

**Diagnosis**

- Clinical and History. (no labs)

**Differential diagnosis**

- Hypoglycemia
- Stroke

**Management**

- Supportive
- Antidote (Flumazenil)

High Anion Gap metabolic acidosis (HAGMA): Why? Benzodiazepines themselves don’t cause it, it’s usually combined with propylene glycol as a preservative which causes the HAGMA.

Examples causing HAGMA: (MUD PILES)

- Methanol
- Uremia
- Diabetic ketoacidosis
- Paraldehyde
- Iron
- Isoniazid
- Lactic acid
- Ethanol
- Ethylene glycol
- Salicylates

Barbiturates, Benzodiazepines, and alcohol. All are depressants (Downers). Opioids are stimulants (Uppers)
Flumazenil

What is Flumazenil?

Nonspecific competitive antagonist of the benzodiazepine receptor.

- Reverse benzodiazepine-induced sedation after:
  - GA (general anesthesia)
  - PSA (procedural sedation and analgesia)
  - confirmed benzodiazepine overdose

Not recommended for the routine reversal of sedative overdose in the ED.

To give or not to give?

### Indications

- Isolated benzodiazepine overdose in non-habituated user (e.g., accidental pediatric exposure)
- Reversal of conscious sedation

  - Given only in:
    1. overdose
    2. we are sure that the patient only took benzodiazepines (because they usually combine different drugs, if so, we do supportive management only).
    3. we give it just once.

### Contraindications

- Absolute contraindication:
  - Suspected co-ingestant that lowers seizure threshold (e.g., tricyclic antidepressants, cocaine, lithium, methylnaltrexone, isoniazid, propoxyphene, monoamine oxidase inhibitors, bupropion, diphenhydramine, carbamazepine, cyclosporine, chloral hydrate)
  - Patient taking benzodiazepine for control of a potentially life-threatening condition (e.g., seizures)
  - Concurrent sedative-hypnotic withdrawal.
  - Seizure activity or myoclonus
  - Hypersensitivity to flumazenil or benzodiazepines
  - Patient with neuromuscular blockade

- Relative contraindication:
  - Chronic benzodiazepine use, not taken for control of life-threatening condition
  - Known seizure disorder not treated with benzodiazepines
  - Head injury
  - Panic attacks
  - Chronic Alcoholism

### Complications

- Seizures
- Dysrhythmia
- Reported mortalities
- Precipitate withdrawal

### Withdrawal

- Anxiety
- Depression
- Insomnia
- Tremor
- Tachycardia
- Sweating

- Visual hallucinations
- Delirium
- Seizures

- Nonspecific
- Severe (rare)
Opioid:
- Relieve pain.
- Relieve diarrhea.
- Produce euphoria.

**Known to:**

- Morphine, Fentanyl, Heroin, Tramadol, Methadone, Codeine, Meperidine (pethidine).

**Examples:**

- Opioid: natural and synthetic.
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**Routes of administration of Opioids:**
1. Orally
2. IV
3. Sniffing
4. Smoking

**Benzodiazepines**

**Toxicity:**
- CNS depression (spectrum).
- Respiratory depression (*non central*).
- Potential complications: aspiration, pressure sores.
- Hypotension (uncommon).

**Diagnosis**
- Clinical and History. (no labs)

**Differential diagnosis**
- Hypoglycemia.
- Stroke.

**Management**
- Supportive.
- Antidote. (*Flumazenil*)
- Flumazenil Complications: Seizures, Dysrhythmia, Reported mortalities, Precipitate withdrawal.
1- Which one of the following is an appropriate clinical indication of benzodiazepine?
A. It may be used as an induction agent  
B. It may be used as an analgesic  
C. It may be used as an antipsychotic  
D. It may be used as an antidepressant

2- Benzodiazepine potentiate inhibitory GABAergic neurotransmission through which one of the following?
A. Increasing intracellular flux of calcium ions.  
B. Decreasing intracellular flux of calcium ions.  
C. Increasing intracellular flux of chloride ions.  
D. Decreasing intracellular flux of chloride ions.

3- An intravenous heroin user rushed to the ER after he was found unresponsive with shallow breathing and weak pulses, which one of the following is the first in the management?
A. Give him an IV bolus of normal saline.  
B. Start a cardiac massage.  
C. Control his airways and breathing.  
D. Administer activated charcoal.

4- A 23 years old male patient is brought to the emergency department after using some drugs. His initial examination reveals that the patient is drowsy, has bilateral constricted pupils and slow breathing. Which of the following toxidrome is present in this patient?
A- Sympathomimetic  
B- Anticholinergic  
C- Cholinergic  
D- Opioid

5- Which of the following is the drug of choice for opioid withdrawal?
A- Clonidine  
B- Methadone  
C- Naloxone  
D- Ethanol

6- Which one of the following is the antidote for opioid poisoning?
A- Flumazenil  
B- Atropine  
C- Naloxone  
D- Pethidine

7- After injecting intravenous heroin a patient developed severe opioid poisoning and is being treated in the emergency department. Which one of the following is the first step in the management?
A- Give a CNS stimulant drug  
B- Give a respiratory stimulant drug  
C- Airway control and breathing  
D- Give 2L normal saline
Thank you and good luck!

Very Toxic but you are gonna do it!

A+ is yours (:)

Email us at:

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How well do you think we have done? We are waiting for your feedback!