Opioids and sedatives

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Objectives:

- Not given...

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[Color index : Important | Notes | Extra | Editing file]

Opioid Toxicity

In general street drugs are divided into two categories ;

1- uppers (stimulators): cocaine, amphetamine 'high class drugs'

* Cocaine is a sympathomimetic (complete opposite of opioids "upper"). Mostly used by upper class (lawyers).

2-downers (depressants): opioids, حشيش. 'Low class drugs' for homeless

What are opioids?

- **Exudate of the opium poppy (Papaver somniferum)** Most commonly from Afghanistan.
- **Known to relieve pain, diarrhea, produce euphoria**
- **Addiction to opium became commonplace e.g. sickle cell patients**
- **Examples:**
  - **Morphine causes histamine release leading to hypotension[1]. Do not use in hemodynamically unstable patient! Good analgesia, but causes nausea and vomiting.**
  - **Heroin Mostly used by homeless (lower class) people**
  - **Codeine is metabolized into morphine however, 10-30% of the population don't metabolize it. That's why morphine is preferred.but Codeine can be given orally.**
  - **Fentanyl. synthetic Doesn't have a histaminic effect**
  - **Meperidine (pethidine) -synthetic-. More euphoria less analgesia and more side effects. Should be given only in a very controlled setting. Shouldn't be used on humans, it is very very addictive.**
  - **Methadone be long half life , needed a dose every 24 hours**
  - **Tramadol less respiratory depression, so we use it for elderly.**

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 (important)		
Mu (μ)	**Kappa (κ)**	**Delta (δ)**
At supraspinal and spinal sites	**Dorsal horn of spinal cord and brainstem**	**Binding sites for endogenous peptides**
Analgesia and respiratory depression Miosis, euphoria, reduced GI motility	**Analgesia, miosis, sedation**	**Analgesia, dysphoria, delusions, hallucinations**

[1] **Why we tap on the hand before taking blood sample ? Tapping will irritate the skin , will lead to histamine release and vasodilation so you can see the vessels**

What is the toxidrome of opioid toxicity? IMPORTANT toxidrome: signs and symptoms

1. **CNS depression**
2. **Respiratory depression** (reduces rate and not tidal volume)unless very large toxic dose it will affect both tidal volume and rate..
3. **Miosis (pinpoint pupil)**

Other opioid effects:

- **Sensorineural hearing loss** (other drugs that causes hearing loss (1-aminoglycosides specifically gentamicin, 2-furosemide, especially in ICU pts when we give them multiple doses. 3-aspirin , and it also causes tinnitus)
- **Mild hypotension (Histamine release) and Bradycardia** Fentanyl doesn't cause hypotension. We give it in very large doses in ICU up to one mg (normal dose is 100 micro gram) and it doesn't cause hypotension . But it causes chest wall syndrome 'rigidity' (the chest wall get rigid the pt can't even talk or breath) but in ICU the patient is already incubated so we don't really care .
- **Nausea & Vomiting (watch out for ileus)**
- **Urinary Retention** not considered toxidrome.Always palatbate Supra public area
- **Pruritus/ Urticaria and Flushing** due to histamine release. After surgery patients usually try to take off their mask to scratch their noses.

Routes of administration:

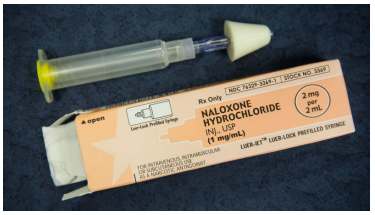
- Orally
- IV
- Smoking (heating up a spoon and inhaling the smoke "chasing the dragon")
- Sniffing (more for cocaine)

Management and Withdrawal

Management:

- **ABCDs and Supportive therapy (D in toxicology stands for decontamination)**
- **Antidote**

Antidote: Naloxone



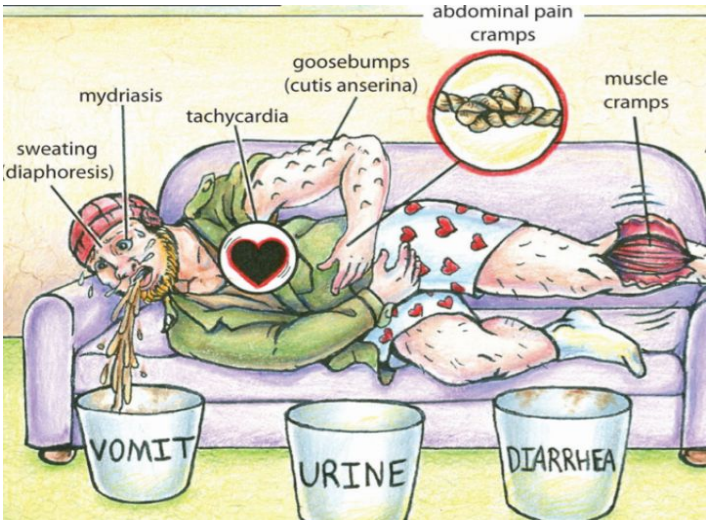
- **Pure Opioid antagonist**
- **Routes: IV, IM, SC, Nasal**
- **Mechanism: Competitively binds opioid receptors and reverses all opioid mediated action**
- **Dose:** you don't need to know this
    - Common dose: 0.4 mg
    - Chronic users: 0.04 mg (to prevent withdrawal)
    - If given intranasal 2 mg (double or triple the normal dose)
    - So normally in the ampule there is 2mg, you don't use it all. it's available in all ambulances.

Half Life? Why is it important?

-Naloxone 1/2 life is 1 -2 hours you will be asked about this

-Morphine 1/2 life approx. 2 hours other opioids have longer half life

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. (So if you treat the patient and he wakes up it's not the end of the story)



Opioid Withdrawal:

It is NOT life threatening

- **Symptoms:**
  - **Sweating (diaphoresis)**
  - **Mydriasis**
  - **Diarrhea**
  - **Goosebumps** classical sign
  - **Abdominal pain**
  - **Muscle cramps** classical sign

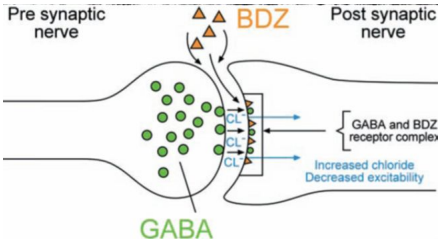
Chronic opioid abusers :

- those abusers who fail to stop taking the drugs, even in the rehabilitation centers, the last choice for them will be giving them methadone under supervision, the patient comes everyday to the hospital or pharmacy to take the dose. And they live their life normally.
- **Methadone :-**
- **Long half life**
- **requires a dose every 24 hours**

Sedatives (benzodiazepine) Toxicity

- 5% of the population have used an illicit drug once in their life
- The commonest abused benzodiazepine is Xanax (alprazolam), which is used for anxiety disorder

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 inhibition of neural transmission** (like alcohol & barbiturates)

Clinical effects:

- **Sedative**
- **Hypnotic**
- **Anxiolytic** e.g. generalized anxiety disorder. It's a magical drug for them, but it's only prescribed as 'used when needed', while SSRI is prescribed for controlling the symptoms every day.
- **Anticonvulsant** The strongest indication. Diazepam and lorazepam (fast onset and long duration of action). Here is when we use benzo as IV.

NAME	USUAL DOSE	ORAL PEAK (hr)	HALF-LIFE (hr)	PARENT METABOLITE ACTIVITY
Alprazolam (Xanax)	0.25-0.5 mg	1-2	6-27	Inactive
Chlordiazepoxide(Librium)	5-25 mg	0.5-4	5-30	Active
Clonazepam (Klonopin)	0.25-0.5 mg	1-2	18-50	Inactive
Clorazepate (Tranxene)	7.5-15 mg	1-2	1-3	Active
Diazepam (Valium)	2-10 mg	0.5-1	20-50	Active
Estazolam (ProSom)	1-2 mg	2	8-28	Inactive
Flurazepam (Dalmane)	15-30 mg	0.5-1	2-3	Active
Halazepam (Paxipam)	20-40 mg	1-3	14	Active
Lorazepam (Ativan)	0.5-2 mg	2-4	10-20	Inactive
Midazolam (Versed)	0.025-0.1 mg/kg	1-2	1.5-3	Active
Oxazepam (Serax)	10-30 mg	2-4	5-20	Inactive
Quazepam (Doral)	7.5-15 mg	2	39-41	Active
Temazepam (Restoril)	7.5-30 mg	1-2	3-19	Inactive
Triazolam (Halcion)	0.125-0.25 mg	1-2	1.5-5.5	Inactive

Poisoning:

- It doesn't have a clear toxidrome (hard to diagnose)
- CNS depression (spectrum)
- Respiratory depression (non central) by affecting muscles, unlike opioids which affect the medulla. We lose the airway.
- Hypotension (uncommon) unless IV with high doses

Potential complications: aspiration, pressure sores

Why do the get HAGMA (high anion gap metabolic acidosis)?

- It's not caused by the drug itself.
- When lorazepam is given as IV drip it is combined with a preservative (propylene glycol) which causes metabolic acidosis.

How to diagnose?

- Difficult to diagnose
- General rule in toxicology, when we want to do blood drug screen we do it for (paracetamol, aspirin and alcohol)
- Urine screening is positive but useless, why? 1-high false positive rate (positive for drugs that are not taken by the patient). 2- the drug remains positive for 2-3 weeks post ingestion

Differential diagnosis?

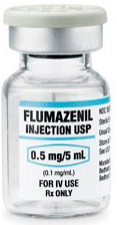
- Acute hypoglycemia
- Alcohol toxicity
- Antidepressant toxicity
- Neuroleptic agent toxicity

Management and Withdrawal

Management:

- Supportive
- Antidote

Antidote: IMPORTANT!!! {Flumazenil}



- Nonspecific competitive antagonist of the benzo receptor
- Reverse benzodiazepine-induced sedation after GA (general anesthesia), PSA (procedural sedation and analgesia "conscious sedation") e.g. A fib, drainage, dislocated shoulder, & confirmed benzodiazepine overdose
- Not recommended for the routine reversal of sedative overdose in the ED.

Indications very important	Absolute Contraindications	Relative Contraindications
Isolated benzodiazepine overdose in non habituated user (e.g., accidental pediatric exposure) Reversal of conscious sedation Given only in: 1- acute overdose . 2-in patient who were accidentally giving high doses of benzodiazepines. (we do it , we reverse it). 3- we are sure that the patient only took benzo (because they usually combine different drugs , if so, we do supportive management only).	Suspected co-ingestant that lowers seizure (because it 'flumazenil' causes seizure) threshold (e.g., tricyclic antidepressants, cocaine, lithium, methylxanthines. 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	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:

- **Nonspecific: Anxiety, depression, insomnia, tremor, tachycardia, sweating**
- **Severe (rare): visual hallucinations, delirium, seizures**

General notes:

- **Alcohol withdrawal is life threatening, why?**
- **Because in normal brain function there is a balance between stimulatory neurotransmitter (epinephrine, norepinephrine, ...) and the inhibitory ones (GABA)**
- **when you are alcoholic, you are taking alcohol for along time you are stimulating the GABA receptors, so normal brain will increase the stimulating neurotransmitters as well to balance the brain activity.**
- **So when you suddenly stop alcohol, GABA levels will drop! The stimulators NT will take the lead and you will be in a mess.**
- **So in acute settings, we usually give them IV benzo (lorazepam or diazepam) to stimulate GABA.**
- **An example of that is when an alcoholic patient is admitted for surgery**

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

Answer: A (induction of anesthesia).

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.

Answer: C

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 .

Answer: C

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

Answer: D

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

Answer: B

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

Answer: C

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

Answer: C