TOXICOLOGY TEAM · C.S.I KSU · 436

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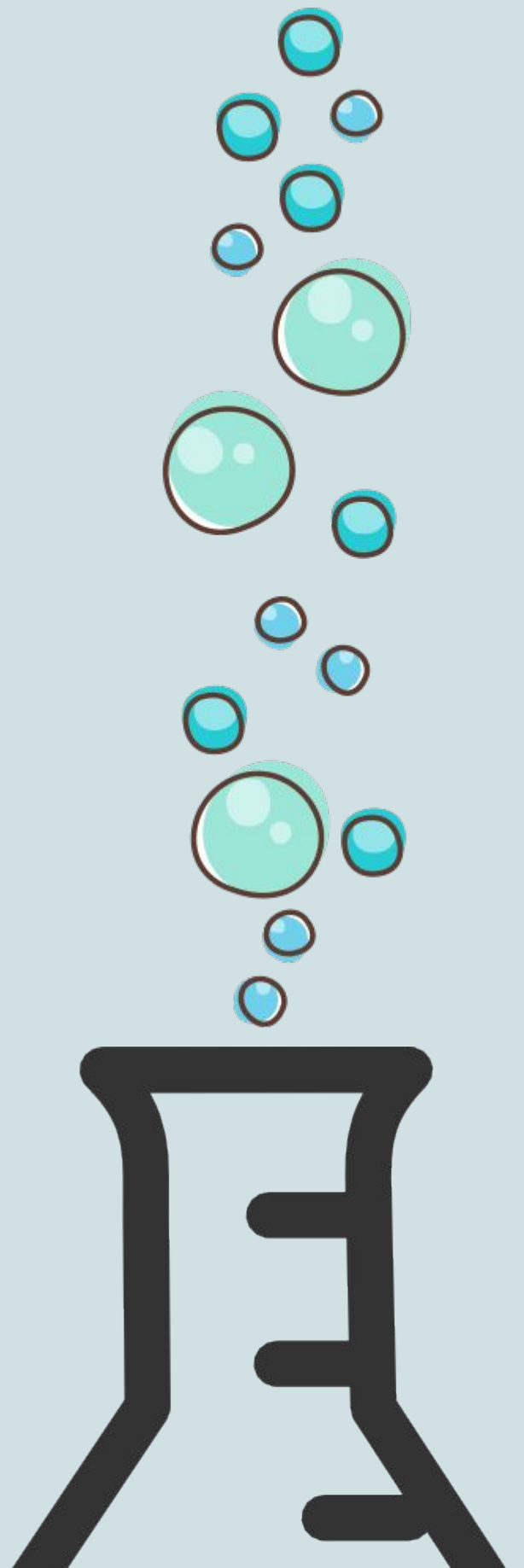

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THINGS TO REMEMBER

"This file is **not** intended for studying, it is only for revision and if you really don't have time to check the lecture"

This file includes:

-All important points
-Golden notes
-Doctor notes

GOOD LUCK! May Allah grant you success

A+

Introduction To Toxicology

Toxidrome	Clinical features	Potential interventions
1- Anticholinergic (Antimuscarinic)	- Hyperthermia - Altered mental status - Mydriasis - Dry flushed skin - Urinary retention	- Cooling - Physostigmine - Benzodiazepine for sedation - Supportive
2- Cholinergic (Muscarinic) (e.g. Organophosphate)	- Salivation - Lacrimation - Nausea -Vomiting - Miosis - Muscle fasciculations	- Airway protection + ventilation - Atropine - Pralidoxime
3- Sympathomimetics (e.g. Amphetamine)	- Psychomotor agitation - Mydriasis - Diaphoresis -Tachycardia - Death ←seizures and hyperthermia	- Cooling - Sedation with benzodiazepine - Hydration
4- Opioids	- CNS depression - Respiratory depression - Miosis	- Naloxone - airway support and ventilation
5- Sedative-Hypnotic (e.g. Benzodiazepines ,Barbiturate)	- Depressed LOC - Ataxia - Bradycardia - Slurred speech - Respiratory depression	- Ventilatory support
6- Hallucinogenic	Hallucinations- Dysphoria- Anxiety- Hyperthermia- Mydriasis	Supportive

Diagnostic tests:

Bedside	-Blood Glucose level : hypoglycemia -ECG: Arrhythmias -VBG: i.e. metabolic acidosis —> paracetamol
Laboratory	-Blood / urine drug level
Electrolytes:	-K level : i.e. hyperkalemia in digoxin overdose
Liver Function Tests:	-Elevated liver enzymes in Paracetamol Toxicity

Introduction To Toxicology

Management

"You should check the whole list in the lecture"

1 Resuscitation: the first thing you do is ABC

"These are some presentations if you saw them, start resuscitation immediately"

Presentation	Management
Hypoglycemia	If BGL < 4 mmo→ give IV dextrose (Glucose)
Cardiac Arrhythmias	- O2 sat - Antidote (i.e. digoxin Fab in digoxin overdose)
Seizure	-1st : IV benzodiazepine (except in Isoniazid toxicity —> Pyridoxine) -2nd: Barbiturates -Treat hypoglycemia and hyponatremia
Agitation	-1st : Benzodiazepine -2nd: Antipsychotic agents
Hyperthermia and hypothermia	> 39* —> aggressive cooling <32* —> aggressive rewarming

Poison	Antidote
Beta blockers	Glucagon
Cholinergics	Atropine
Cyanide	Hydroxycobalamin
Digoxin	Digoxin FAB
Iron	Deferoxamine
Methanol	Ethanol
Opioids	Naloxone
Serotonin repute inhibitors	Cyproheptadine
-Arsenic -lead	Penicillamine Succimer (DMSA

2 Decontamination:

1- GIT Decontamination

- Activated Charcoal: -Charcoal sensitive substances →Paracetamol.
-Charcoal resistance substances →Iron.
- Whole Bowel irrigation
- Gastric lavage
- Induced Emesis (Syrup or Ipecac)

2-Enhanced Elimination

- Multiple dose activated charcoal
- Urine alkalinisation
- Extracorporeal technique of elimination

3 Disposition :

"If asymptomatic for 6 hours in ED—> discharge, otherwise admission to hospital is required"

DON'T GIVE UP! WE KNOW YOU CAN DO IT!

Acetaminophen

Therapeutic Dose	Toxic Dose	Metabolic Pathways
In children: 10-15 mg/kg/dose **Adults:** 325-1000 mg/dose every 4-6 hours	**Children:** < 12 months: 150 mg/kg 1 – 6 y (no risk factors) : 200 mg/kg 1 – 6 y with risk factors : 150 mg/kg 7 – 12 y : 150 mg/kg **Youth & Adult:** 7.5 - 10 g	1- **Hepatic Conjugation (90%)** 2-Excretion of unchanged APAP in the urine (5%). 3- Oxidation by P450 →NAPQI → GSH combines with NAPQI → cysteine → Excreted in urine

Metabolic changes in overdose	Saturation of Glucuronidation → Amount of APAP metabolized by p450 cytochromes to NAPQI increases.			
Clinical manifestation of APAP OD	**Stage1:** N/v, anorexia, asymptomatic **(0.5-24h)**	**Stage2:** RUQ pain, elevation of PTT, INR, bilirubin + enzymes **(24-48h)**	**Stage3:** Coagulopathy, peaking of enzymes, acidosis, hypoglycemia, bleeding diathesis, jaundice, anuria, cerebral edema, coma. ARF in 25% of pts with hepatotoxicity **(48-96h)**	**Stage4:** Resolution **(4-14d)** If there is no improvement within <2 wks then liver transplant is needed
Diagnosis	•By serum APAP level which should be measured between 4 and 24 hours after ingestion. To know if the pt is at high risk to develop hepatotoxicity and if you should give NAC or not, Rumack-Matthew nomogram must be used. •**"AST"** is the most sensitive lab test for early detection of hepatotoxicity			
Antidote	**N-Acetylcysteine (NAC)** •Early effect <8h: Prevents binding of NAPQI to hepatocytes,increases GSH stores (either by being a precursor or sulfur group of NAC binds and detoxifies NAPQI into mercaptate/cysteine conjugate) Late effect 12-24h: Modulates the inflammatory Response,Antioxidant •NAC should optimally be given within 8 to 10 hours after ingestion •More delayed therapy is associated with a progressive increase in hepatic toxicity •some benefit may still be seen 24 hours or later after ingestion.			
Indication for N-Acetylcysteine (NAC)	•APAP level above the treatment line (In Rumack-Matthew nomogram) •Hx of significant APAP ingestion presenting close to 8h (give while waiting for level) •Hx of exposure and FHF •All APAP ingestions who present late>24h with either detectable APAP or elevated transaminases •Chronic ingestions (>4g/day in adult, >120mg/d in child) with elevated transaminases			
Poor prognostic indicators	•pH <7.3 (2 days after OD, after fluids) •Hepatic encephalopathy •PT >1.8 times normal •Serum creatinine >300 mmol/L •Coagulation factor VIII / V ratio of >30			

Psychiatric Drugs

Monoamine Oxidase Inhibitors

-Bind irreversibly to monoamine oxidase ➔thereby preventing inactivation of biogenic amines such as norepinephrine, dopamine and serotonin leading to ➔increased synaptic levels

-Aged cheese and pickles have double effect with Monoamine oxidase inhibitors because they both contain: Tyramine precursor➔Hypertensive emergency (fatal).

-Patient can present with seizures and rigidity (more excitation)

Selective Serotonin Re-uptake Inhibitor (SSRIs)

-Has a wide therapeutic index that's why overdose is rarely fatal (but got a lot of toxic syndromes) and it is safer than the other classes.
-Delayed clinical effect
-Commonly prescribed for DEPRESSION.

Effects:

-On ECG (QT prolongation)
-Seizures due to severe hyponatremia
(Hyponatremia in old patients, think about diuretics especially hydrochlorothiazide. Young patients, think about SSRIs)
-SIADH at therapeutic dose. (SIADH= Syndrome of inappropriate ADH secretion)

Nonspecific management:

History and examination (:

Serotonin Syndrome

-Potentially **lethal** condition
-**Caused by:** Excess serotonin accumulation in the synaptic cleft.
- Likely to develop when drugs from different classes are **combined**, e.g. increased release and impaired uptake
-**Clinical features of serotonin syndrome**: Cognitive, Autonomic & Neuromuscular. (Each will show a spectrum; major or minor)
-**Clonus** associated ➔ think of serotonin Syndrome Immediately. Clonus sometimes can be masked by increased muscle tone

Management:

1- should be taking the meds for **AT LEAST 5 WEEKS**
2- should present with typical symptoms of serotonin syndrome: **Hunter's criteria**
3- After that, start treating the patient:

- Stop all serotonergic therapy
- Supportive treatment
- Consider **cyproheptadine** (when to consider it? When moderate to severe symptoms are refractory to supportive treatment!)

QRS vs QT prolongation:
-QRS is due to purely Na channel blockade. (Monomorphic)
-QT is due to muscarinic receptor blockade, histamine receptor blockade and Potassium efflux blockade. (Polymorphic)

Important to know

Tricyclic Antidepressants (TCA)

It has 7 MOAs:
1-Na channel blockade (quinidine like membrane stabilizing effect) (Monomorphic Ventricular Tachycardia)
2-Alpha adrenoceptor blockade
3-Inhibition of reuptake of biogenic amines
4-Muscarinic receptor blockade (Anticholinergic)
5-K efflux blockade (Torsades de pointes)
6-Histamine receptor blockade(Antihistamine)(Torsades de pointes)
7-Indirect GABA antagonist (picrotoxin receptor)

Tricyclic Antidepressants (TCA)

Peripheral and Central effects:

-Anticholinergic: Mydriasis

-Alpha 1 adrenoceptor blockade: Miosis

-Excitation:Agitation

-Inhibition: Sedation

Effects on ECG "Remember, TCA is a cardiotoxin (;" :

-Sinus Tachycardia

-Prolonged QT Interval (Due to antihistaminic and K efflux blockade effect)

-Widening of the QRS interval (Due to Na channel blockade)

-RAD (Right axis deviation).

-Prominent R in aVR (also called positive aVR) → Due to Sodium channel blockade

Specific management:

-Plasma Alkalinisation (Promotes TCA protein binding)
-Na load (Overriding Na channel blockade)

Serotonin Syndrome

Hunter's Criteria (This is a red flag, ok? احفظوها زي اسمكم) :

In the setting of exposure to a known serotonergic agent, serotonin syndrome can be diagnosed by the presence of any of the following:
-Spontaneous clonus.
- Inducible clonus and agitation or diaphoresis.
- Ocular clonus and agitation or diaphoresis.
- Tremor and hyperreflexia.
- Hypertonic with temperature >38C + ocular or inducible clonus.

Differential Considerations for Serotonin Syndrome:

1-Serotonin Syndrome (Clonus)
2-Anticholinergic Toxidrome (Dry)
3-Neuroleptic Malignant Syndrome (it always reminds me of Parkinson's Disease) (Lead-pipe rigidity)
4-Malignant Hyperthermia (It always reminds me of a dying person) (46 C° hyperthermia)(Rigor-mortis like rigidity)

Differential diagnosis = differential considerations

{ Organophosphate }

Lipid Solubility

- Organophosphorus insecticides are highly lipid soluble and are readily absorbed via dermal, GI, and respiratory routes AND cross BBB.
- This lipid solubility results in the storage of organophosphorus compounds in body fat, making toxic systemic levels possible from gradual or rapid accumulation from repeated low-level exposures .

Inhibition

- The parent compound and its metabolites are acetylcholinesterase inhibitor
- Inhibition of cholinesterase results in the accumulation and subsequent prolonged effect of Acetylcholine at neurotransmitter receptors. **the level of toxicity relates to amount of inhibition of Ach**

Acetylcholine Receptors

Sympathetic & parasympathetic Ganglion (Nicotinic sites)	Postganglionic Cholinergic sympathetic and parasympathetic (Muscarinic sites)
Skeletal muscle (Nicotinic sites) (motor nerves)	Central nervous system sites Mainly NMDA receptors, can cause seizures and coma

Enzyme Complex Aging

- Unique effect of organophosphorus insecticides results from "aging," the irreversible structural change that occurs in cholinesterase enzyme when the organophosphorus agent is bound to it for a prolonged time. **On average, for commercial organophosphorus agents aging will occur by 48 hours the antidote can not regenerate the cholinesterase.**

Signs and Symptoms

SLUDGE

Salivation
Lacrimation
Urinary incontinence
Defecation
Gastrointestinal cramps
Emesis

DUMBELS

Diarrhea/Diaphoresis
Urination
Miosis
Bradycardia/Bronchorrhea /Bronchospasm
Emesis
Lacrimation
Salivation

SLUDGE/DUMBELS are due to muscarinic effect (most of Organophosphate toxicity is due the activation of this receptor)

The Intermediate Syndrome (IMS)

-Happens within 24-96 hrs after exposure
-Abnormality at NMJ
-Proximal muscles are commonly involved (respiratory failure)
-Ventilatory support

Organophosphorus-delayed neuropathy

-Happens within 7-21 days after exposure
-Affects axonal enzyme known as Neurotoxic esterase
-Peripheral sensorimotor neuropathy
-Self limiting

How to diagnose

Known or suspected, all must be confirmed by:
-Plasma (4-6 wks to recover)
-RBC Cholinesterase levels (6-12 wks to normalize)
In acute exposures: the plasma cholinesterase levels decrease first, followed by decreases in RBC cholinesterase levels
In chronic exposure: only reduced RBC cholinesterase activity, with a normal plasma cholinesterase level.
RBC cholinesterase is **more indicative** of tissue level

Management

Fours aims:
1-Decontamination "THIS IS THE FIRST THING YOU DO"
2-Supportive care "ABC" : suctioning of secretions and vomitus, oxygenation, and when necessary, intubation and ventilatory support
3-Reversal of muscarinic activation (Atropine); when to stop? When your pt is dry (;
4-Reversal of the toxin-enzyme binding (Oxime); it is important to know when enzyme complex aging happens with the agent, once it occurs, you cannot use oxime!!

In brief, both toxicities -Organophosphate and carbamate- are similar but with less severity of signs and symptoms and shorter duration seen in carbamate and no role of oxime in the latter. Both respond to Atropine. Binding in carbamate is reversible while in Organophosphate is irreversible leading with time to ENZYME COMPLEX AGING!!!

CVS Drugs Overdose

	Beta Blockers	Ca Channel Blockers	Nitrates and Nitrites	Digitalis
Mechanism of Action	-Inhibits endogenous catecholamines -Peak occurs in 1 to 4 hrs	-Block the slow calcium channels leading to vasodilation. -Reduce cardiac contractility, Depress SA nodal activity, Slow AV conduction. -Inhibits insulin release, resulting in hyperglycemia. -Onset of action and toxicity ranges from less than 30 minutes to 60 minutes	-Vasodilator and reduces afterload -At lower doses, they dilate VEINS while higher dose, they dilate ARTERIES -Oxidizing agents; converts Hemoglobin into Methemoglobin (Impairs Oxygen carrying)	**At toxic doses:** -paralyzes the Na-K pump, K can't be transported into cells -Directly halts the generation of impulses in SA node, depresses conduction through AV node, and increases the sensitivity of the SA & AV nodes to catecholamines.
Manifestations & complications	-**Bradycardia** & **Hypotension** (VERY common) -**Hypoglycemia** (uncommon in adults, common in children) -Seizures (common with Propranolol)	Lactic acidosis and hyperglycemia = you should think of CCB. CCB and beta-blockers have very similar symptoms so these two symptoms will help you differentiate between them.	-Hypotension usually transient and responds to supine positioning -Reflex tachycardia unless taking drugs that slows HR (e.g, BBs) -Methemoglobinemia (can cause seizures and death)	-cardiac:can give any type of arrhythmia -non cardiac symptoms : 1-**neurologic** (eg. Dizziness,Headache,acute psychosis, Somnolence) 2-**Ophthalmologic** (eg., Photophobia, Yellow-green chromatopsia) 3-**General** (Fatigue) 4-**Gastrointestinal** (eg.Nausea and vomiting)
Diagnostic strategies	Depends on clinical picture (No serum levels are available)	-Glucose and Electrolytes (Ca & Mg) -Hyperglycemia. -Lactic Acidosis with hypotension and hypoperfusion -ECG: a prolonged QRS or QT interval suggest bedpril or a co-ingested cardiac toxin such as TCA	-	Serum digoxin levels (peak in 1.5 to 2 hours) with a range of 0.5 to 6 hours (The only drug among the four that has serum level)!!!
Management	CCBs intoxication management is the same as beta blockers management, except in CCBs we give calcium salts that are in the form of Ca Chloride and Ca Gluconate. Ca is the antidote for CCBs while Glucagon is the antidote for BBs. First thing to do is to give IV Fluids. If bradycardia and hypotension are there then Atropine must be used. Catecholamines can be used if the latter failed.		-IV methylene blue, but this antidote is usually not needed unless methemoglobinemia approaches 30%. (Oxygen doesn't improve the condition) (Management of Methemoglobinemia) -Supine positioning, IV fluids and reducing the dose to manage Hypotension.	1-Atropine 2-Pacing 3-Electrolytes correction 4-Fab Fragments(Digifab or Digibind)(digitalis antibodies) (Antidote) **(First thing to do is to give fluids and check K level)**

Opioids and Sedatives

Opioids

Examples:
-Morphine (Histaminic effects so NOT used in hemodynamically unstable patients) (Natural)
-Fentanyl (No histaminic effects) (Synthetic)
-Meperidine (More euphoria, less analgesia and more side effects)
-Heroin (most commonly used)

Opioids receptors:
1-**Mu**:Analgesia and respiratory depression, Miosis, euphoria, reduced GI motility
2-**Kappa**: Analgesia, miosis and sedation
3-**Delta**: Delusions, Hallucinations, Dysphoria and analgesia

Toxidrome and management:
-The well known triad of Opioids toxicity (CNS depression, Respiratory depression "AKA hypoventilation" and miosis "Pinpoint pupils")
-Management includes (ABCDE, Supportive and Antidote "Naloxone")
-Naloxone half-life is SHORTER than Opioids' (Patients must be observed for recurrence) (It is a pure opioid antagonist)

Opioids withdrawal and management:
-It is **NOT** life threatening, are in hyperadrenergic state.
-Symptoms include (Goosebumps "classic sign", CNS excitation"Dysphoria", Mydriasis, yawning)
-**Clonidine** is the first line of treatment.
-**Methadone** to maintain therapy (chronic abusers) and could be given to pregnant women. Single dose every 24 hr

Benzodiazepines

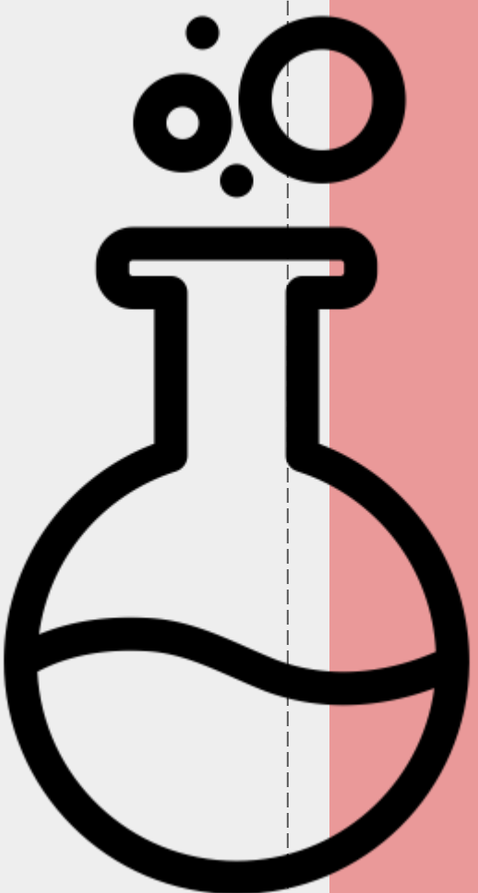
Mechanism of Action and more...:
-Benzodiazepines bind to benzodiazepine receptor & potentiates GABA effects on the chloride channel —> increasing intracellular flux of Cl ions & hyperpolarizing the cell
-Common examples [Alprazolam (Xanax), Diazepam (Valium), Lorazepam (Ativan), Midazolam (Versed)]
-The strongest indication is Anticonvulsant

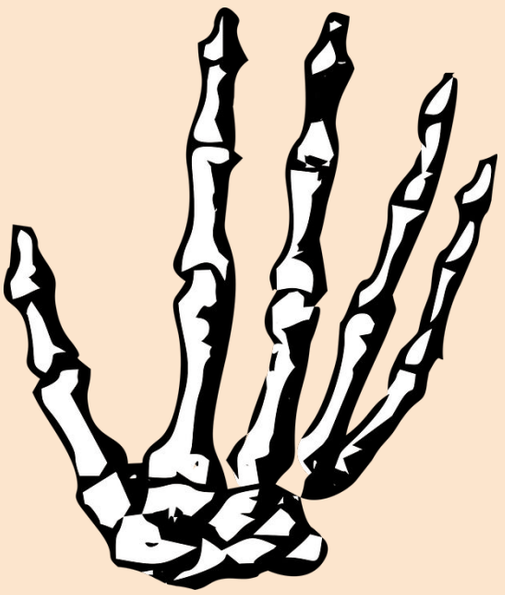
Toxicity and management:
-CNS depression (spectrum), Respiratory depression (NON central)
-Management includes (Supportive and antidote "Flumazenil")
-DDX: Stroke, hypoglycemia
-Diagnosis: No labs; clinical and Hx

Flumazenil:Nonspecific competitive antagonist of the benzo receptor.

Indications	-Isolated benzodiazepine overdose in non habituated user -Reversal of conscious sedation. - we give it just once	
Contraindications	A-absolute contraindication: -suspected co-ingestant that lowers seizure threshold. -Patient taking benzodiazepine for control of a potentially life-threatening condition. -Concurrent sedative-hypnotic withdrawal. -Seizure activity or myoclonus -Hypersensitivity to flumazenil or benzodiazepines -Patient with neuromuscular blockade	B-relative contraindication: -Chronic benzodiazepine use, -Known seizure not treated with benzo -Head injury -Panic attacks -Chronic Alcoholism
Complications	Seizures, Dysrhythmia, Reported mortalities, Precipitate withdrawal	
Withdrawal	-non specific Anxiety, Depression, Insomnia, Tremor, Tachycardia, sweating. -sever :Visual, hallucinations, Delirium, Seizures.	

Thank you and good luck!





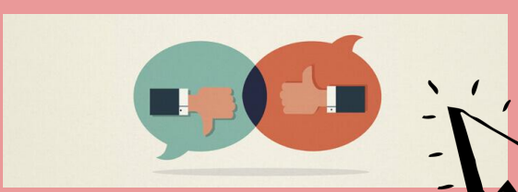
Very Toxic but you are gonna do it!

A+ is yours (:

- Email us at:

436toxicology@gmail.com

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



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