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Clinical toxicology

Laboratory handbook

Fifth STAGE

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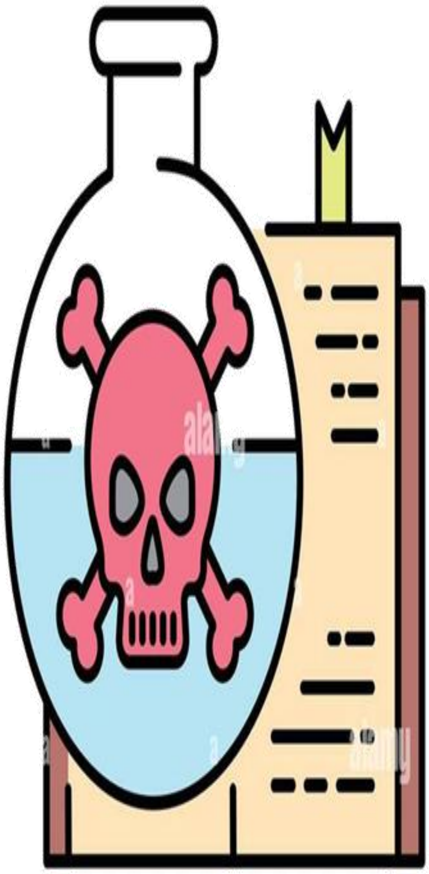
The initial assessment and management of a poisoned patient



Objectives

To learn the principles of the drugs and chemicals-induced toxicity in humans, and gain experience in evaluation steps and treatment measures based on sample analyses and interpretation of toxicity signs and symptoms

Introduction to Clinical Toxicology

Clinical toxicologists are Individuals who specialize in clinical toxicology. Their work focuses around the identification, diagnosis, and treatment of conditions resulting from exposure to harmful agents. They usually study the toxic effects of various drugs in the body, and are also concerned with the treatment and prevention of drug toxicity in the population.

The basic guide to the management of poisoned patients

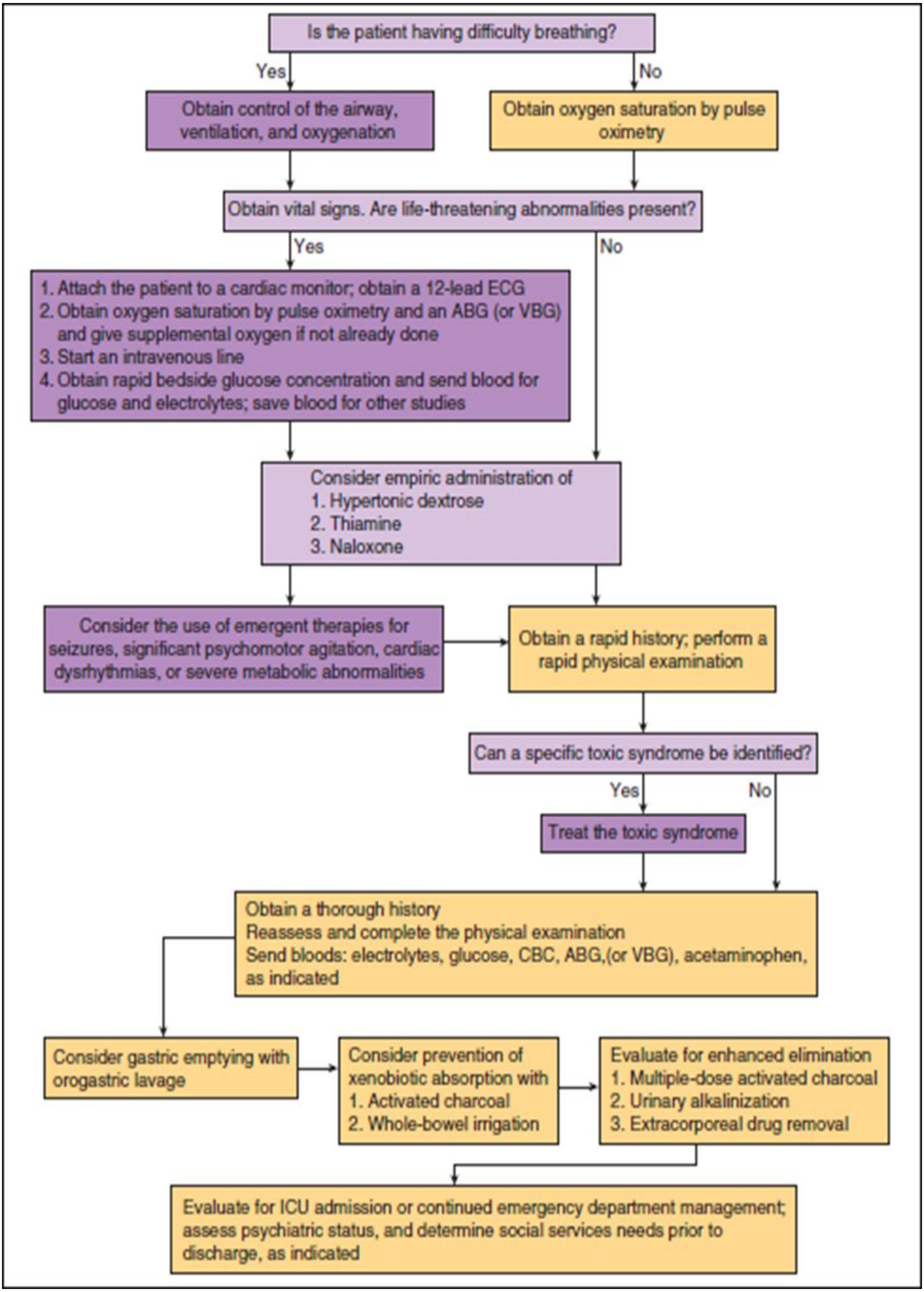
A health care facilities have a systematic approach for the assessment of the poisoned or overdosed patient (fig.1)that involves:

A) Providing supportive care (ABC)

B) History

C) Management if required (reduce abs & increase elimination) .

D) Observation.



(Figure1)Algorithm for basic guide to the management of poisoned patients

History

Taking a good history is possibly more important for drug overdose than for other medical problems, it includes:

- Determine the mode of exposure (inhalation, ingestion, etc.)
- State of the toxin (solid, liquid, gas)
- Quantity
- Time of exposure, and other circumstances
- Age/weight, symptoms, reason for exposure, previous therapy

General Treatments

Treatment begins with first aid at the scene and continues in the emergency department and often the intensive care unit (ICU)

1. Terminate exposure **2. Prevent absorption**

3. Enhance elimination **4. Medications, antidotes**

1- Terminate exposure

Depends on route of exposure:

- Eye exposures – immediately flush eyes with water/saline for 15-20 minutes
- Dermal – Remove jewelry, clothing. Brush off powders. Immediately flush with water for 15 minutes (longer for caustics)
- Inhalation – Move to fresh air
- Injection/Bites and Stings – Remove clothing, jewelry that might constrict the extremity. Do not excise and apply suction to bites/stings
- Ingestion – Give a glass of water to dilute chemicals such as caustics

2- Prevent absorption:

Indicated for recent ingestion, toxic substance, toxic amount.

a) Syrup of Ipecac

- Ipecac may be used to induce emesis to treat unintentional ingestions
- Can be used at home if there are no contraindications

- Should be administered within 30-60 minutes of ingestion

- Vomiting should be induced only if there is sufficient bulk (fluid) in the stomach to serve as a carrier for the ingested poison. Adequate dilution with water increases the efficacy of emetics.

- Contraindications: Unconscious patient, recently undergone surgery, Ingestion of liquid HCs, sharp objects, Children under 6 months, CVD patients or emphysema.

- Side effects include drowsiness , diarrhea, and aspiration pneumonitis

- Ipecac causes emesis through both early and late phases of vomiting:

Early vomiting occurs within 30 min and is due to direct stimulant action on the GIT, while the second phase occurs after 30 min resulting from stimulant action on the chemoreceptor trigger zone (CTZ).

The recommended dose of syrup of ipecac (PO)

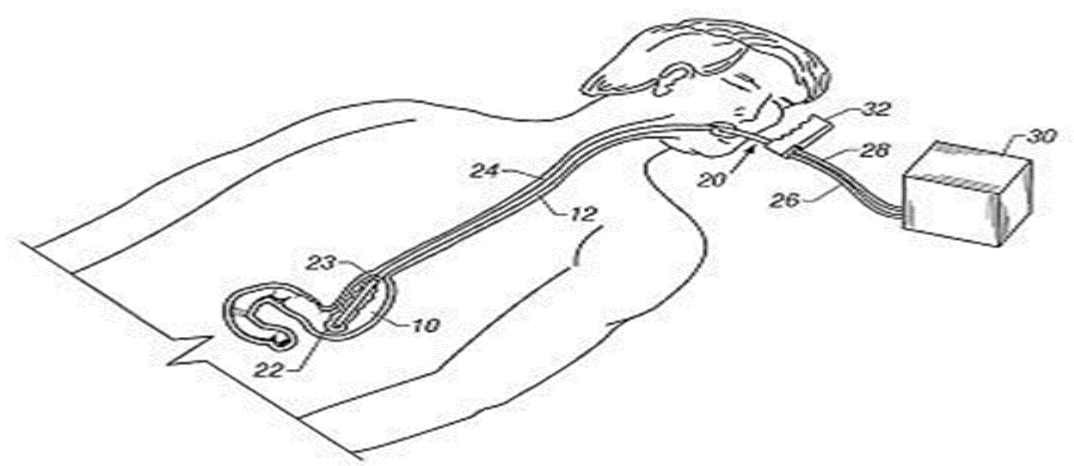
Children (1-12 years) 15 ml Adults 30 ml

A second dose may be given if the patient fails to vomit within 20-30 min (80% will vomit).

b) Orogastric Lavage:

Process of washing out the stomach with solution including water or saline (fig.2).

- A minimum of 2 L are required to wash out most of the stomach contents through a large bore tube until the return is clear



(Figure 2) orogastric lavage

- Little or no benefit over activated charcoal; consider for substances not adsorbed by activated charcoal

- Lumen size is a limitation, especially in children.

- **Adverse effects:** aspiration, cyanosis, epistaxis, oesophageal perforation, hypothermia, fluid and electrolyte imbalances.

- Activated charcoal is usually instilled following gastric lavage.

C) Activated Charcoal

- First line of therapy in the emergency department, the most commonly used method of gastric decontamination.

- Adsorbs substances to prevent systemic absorption

- More effective than ipecac

- Contraindicated if foreign bodies are ingested

- Does not adsorb: Iron, lithium, sodium, lead, cyanide, Hydrocarbons, Caustics, and alcohols.

- Dosage: 1 gram/kg administered orally or by nasogastric tube

- For maximum effectiveness, AC should be administered within 30 min of poison ingestion. However, when used to adsorb drugs that slow gastric emptying (e.g. anticholinergic and sedatives), beneficial effects have been obtained when activated charcoal was given 6-8 hours after poison ingestion.

- Activated charcoal may be given with a cathartic (usually sorbitol or magnesium citrate) to hasten the elimination of the charcoal/toxin complex

- Second dose may be administered for single acute overdoses of drugs for which delayed or continued absorption occurs (e.g., carbamazepine, salicylates, valproic acid, sustained release or enteric coated preparations)

d) Demulcent

Substances that relieve irritation of the mucus membrane in the mouth by forming a protective film.

Ice cream, milk or another soothing demulcent are used to reduce irritation caused by ingestion of irritant plant or chemical of non serious toxicity.

Egg white serves as a source of readily available proteins (90% water & 10% albumins, globulins, mucoproteins) have been given for corrosive intoxication.

3- Enhancing elimination

a) Forced diuresis and PH alteration:

- Manitol, furosemide are useful when compounds /active metabolites are in the blood & eliminated by the kidney and diuresis enhances their excretion.
- Urinary PH manipulation can enhance renal excretion of a compound by increasing the amount of ionized

(polar) form so decrease its tubular reabsorption.

- Ideally, increased elimination of weak acid will occur when urinary PH is more alkaline, while enhanced elimination of weak base will occur when urinary PH is more acidic.

PH alteration to enhance the diuresis

Acid diuresis is possible by using ammonium chloride, 75 mg/kg/24 hrs until a urinary PH of 5.5 – 6 is achieved.

ex: amphetamine, phencyclidine and quinidine (WBs).

Alkaline diuresis is achieved by sodium bicarbonate 1-2 mEq/kg every 3-4 hours to increase urinary PH to 7 -8.

ex: Salicylates, and Phenobarbital, Phenoxy acetate herbicides

b) Hemodialysis/Hemoperfusion

- Indication: progressive deterioration despite intensive supportive care
- Dialysis depends on the principle of diffusion from an area of high concentration to one of lower concentration
- Hemodialysis: phenobarbital, salicylates, alcohols, lithium.
- Hemoperfusion: meprobamate, theophylline, phenobarbital.

c) Chelation

- Involves the use of binding agents to remove toxic levels of metals from the body, such as mercury, lead, iron, and arsenic
- Examples: dimercaprol (BAL in oil), calcium disodium edetate (EDTA), succimer (DMSA), and deferoxamine

- Concerns about the toxicity of the chelators; their tissue distribution characteristics; and the stability, distribution, and elimination of the chelator–metal complex make chelation a complicated procedure

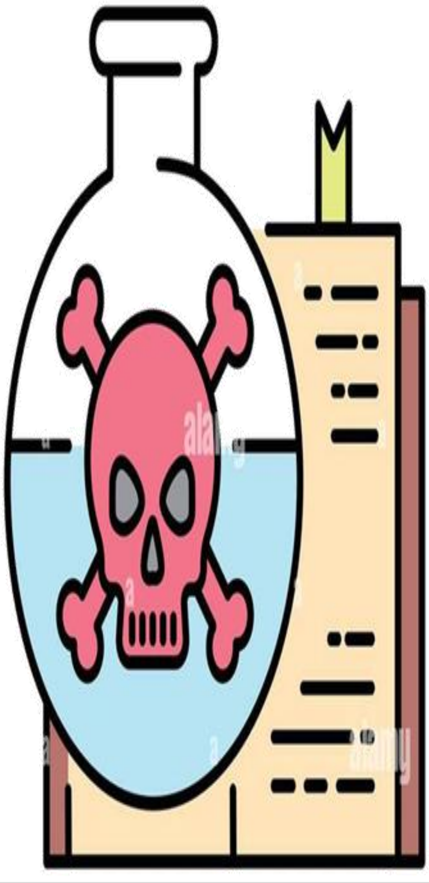
4- Medication and antidotes

- Chemical agents, which attack or combine with the poison in such a way as to render it insoluble, and so inert.
- No one antidote is suited to all emergencies (fig.3).

POISON	ANTIDOTES
acetaminophen	N-acetylcysteine
anticholinergics	physostigmine
benzodiazepines	flumazenil
beta blockers	glucagon
calcium channel blockers	calcium, glucagon
carbamates	atropine
carbon monoxide	oxygen
cyanide	sodium nitrite/sodium thiosulfate
digoxin	digoxin immune Fab
ethylene glycol	ethanol, fomepizole
heavy metals	DMSA, BAL, CaEDTA, penicillamine
iron	deferoxamine
isoniazid	pyridoxine
lead	DMSA, BAL, CaEDTA, penicillamine
methanol	ethanol, fomepizole
nitrates/nitrites	methylene blue
opiates	naloxone
organophosphates	atropine, pralidoxime
snakes(pit viper)	Crotalidae antivenin, CroFab

(Figure 3) list of drugs and their antidots.

Acetaminophen toxicity



Pharmacology

Acetaminophen [N-acetyl-para-aminophenol (APAP)], also known as paracetamol, is one of the most common used drugs worldwide. Since its clinical introduction in 1955, it has become the most widely utilized analgesic/anti-pyretic in many countries around the world.

Therapeutic peak concentrations of APAP (10–20 µg/mL) are detected as quickly as 90 min after its oral ingestion due to its fast absorption in the duodenum.

Serum half-life for a healthy individual taking a therapeutic dose ranges from 1.5 to 3 h. However, a prolonged half-life of more than 4 h can occur in individuals that either consume an overdose of APAP or that exhibit a clinical history of hepatic injury or chronic liver disease.

Acetaminophen metabolic pathway:

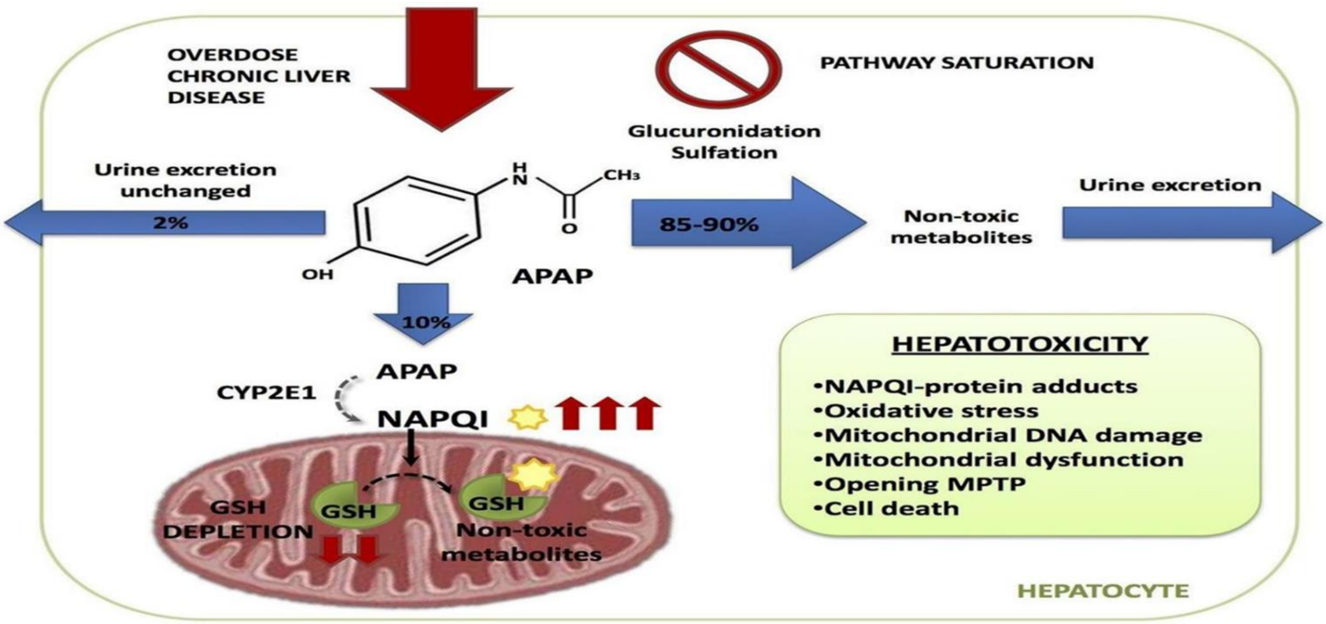
APAP is metabolized in the hepatocyte through three different pathways (Figure 1).

- 2% is excreted through the **urine unchanged**
- 85–90% is converted into glucuronidated & sulfated **non- toxic metabolites**
- 10% is metabolized via CYP2E1 generating the **highly toxic metabolite** N-acetyl-p-benzoquinone imine (NAPQI).

NAPQI is then conjugated with gluthatione (GSH) resulting in non- toxic metabolites.

During APAP overdose or in susceptible patients, as the ones with chronic liver disease, glucuronidation & sulfation pathways become saturated & more APAP is metabolized through CYP2E1 which increases NAPQI generation **depleting GSH liver stores.**

Free unconjugated NAPQI reacts with proteins generating NAPQI- protein adducts in hepatocytes leading to mitochondrial dysfunction & cell death (fig.2).



(Figure1) Acetaminophen (APAP) metabolic pathway

Stage	Time Post-Ingestion	Characteristics
I	0 – 24 h	Anorexia, nausea, vomiting. Hepatic transaminases may start to rise.
II	24 – 72 h	May see improvement in clinical findings, some patients may report right upper quadrant abdominal pain. Elevated AST, ALT, bilirubin, INR.
III	72 – 96 h	Hepatic failure, acidosis, sometimes renal failure and pancreatitis. Peak AST, ALT, bilirubin, and INR levels.
IV	> 5 days	Progression to multiple organ failure (sometimes fatal) Resolution of hepatotoxicity in survivors

(figure 2) Stages of acute acetaminophen poisoning

Factors that increase the risk of acetaminophen toxicity:

Decreased hepatic capacity for glucoronidation

- Gilbert's disease
- zidovudine, trimethoprim/sulfamethoxazole

Inducers of CYP2E1 (increase metabolism of acetaminophen into toxic NAPQI)

- isoniazid, rifampicin, phenobarbital, phenytoin, carbamazepine

Hepatic depletion of glutathione

- chronic alcohol ingestion
- chronic acetaminophen use
- chronic liver disease
- malnutrition

Risk determination after acute overdose:

With acute ingestions of APAP, the **Rumack-Mathews nomogram** (fig.3) is a valuable tool to assess the risk of hepatotoxicity. After an acute overdose, a 4-hour APAP level, or as soon thereafter as feasible, should be obtained & plotted on the Rumack-Matthew nomogram to assess risk.

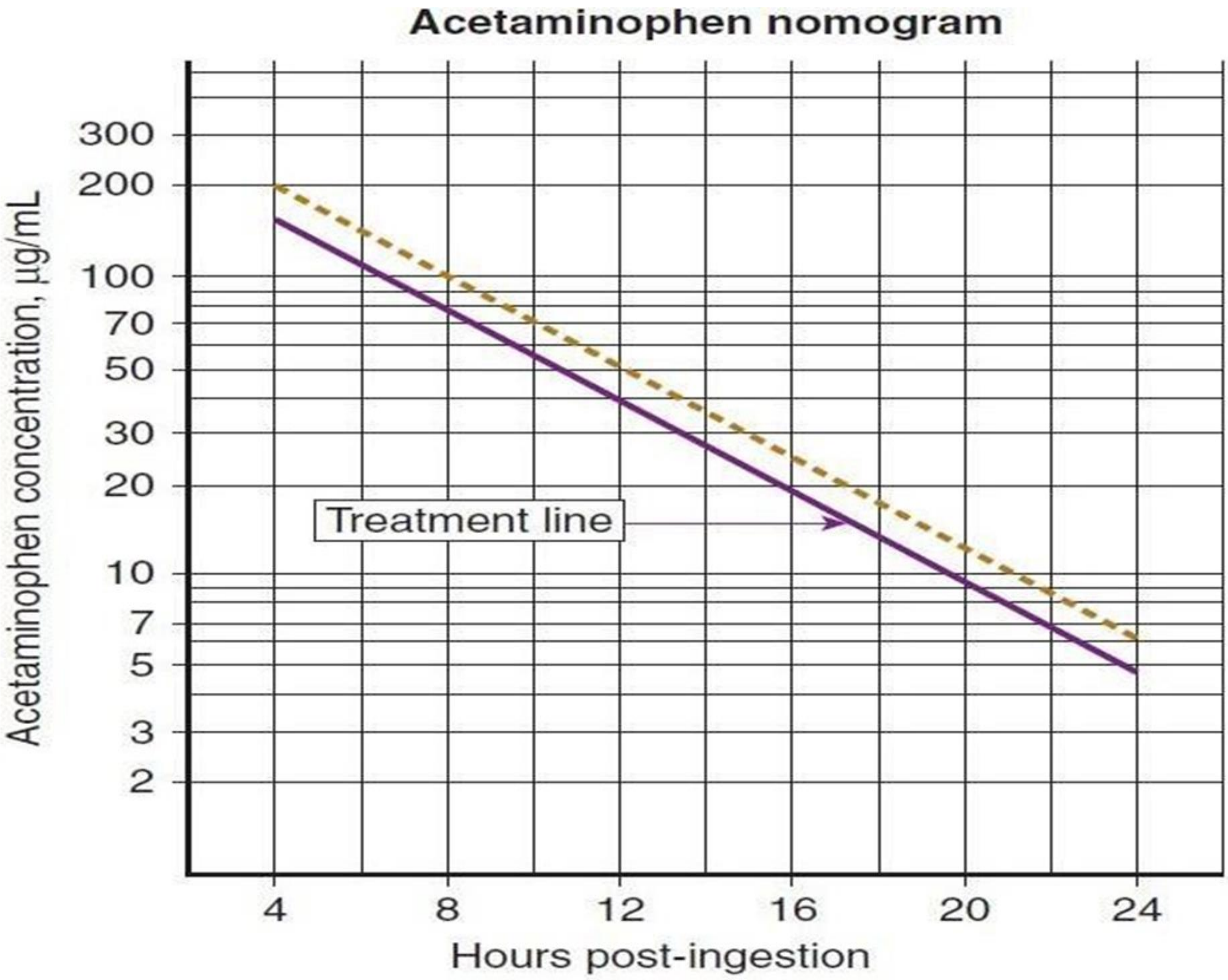


Figure 3. The Rumack-Matthew nomogram (reconstructed) for determining the risk of acetaminophen-induced hepatoxicity after a single acute ingestion. Serum concentrations **above the treatment line** on the nomogram indicate the **need for N -acetylcysteine therapy**.

Risk determination when the time of ingestion is unknown:

If the time window during which the APAP ingestion has occurred **cannot be established** or is so broad that it encompasses a span of more than 24 hours, the following approach is suggested.

Determine both [APAP] & aspartate aminotransferase (AST) concentrations.

- If the AST concentration is **elevated,** regardless of [APAP], **treat the patient with N -acetylcysteine (NAC).**
- If [APAP] is **below the lower level** of detection & the AST concentration is **normal**, there is little evidence that subsequent consequential hepatic injury is possible; **NAC is unnecessary**

Assessing actual toxicity:

Critical components of the diagnostic approach:

I. Initial testing:

- APAP concentration — AST concentration
- Prothrombin time (PT) — International normalized ratio (INR)

II. Ongoing monitoring & testing:

- If elevated AST concentration is noted, then PT & INR & creatinine concentration should be measured & repeated every 24 hours or more frequently if clinically indicated.
- If evidence of actual liver failure is noted, then careful monitoring of blood glucose, pH, PT & INR, creatinine, lactate, & phosphate concentrations are important in assessing extrahepatic organ toxicity & are vital in assessing hepatic function & the patient's potential need for transplant.

Management:

I. Gastrointestinal decontamination:

- Administration of activated charcoal (AC) shortly after APAP ingestion may decrease the number of patients who have an [APAP] above the treatment line.
- If delayed or repeated AC dosing is indicated because of suspected delayed absorption or coingestants, then a strategy using an IV NAC protocol should be considered.

II. Supportive care:

- Controlling nausea &vomiting & managing the hepatic injury, renal dysfunction, & other manifestations.
- Monitoring for & treatment of **hypoglycemia** as a result of liver failure are critical.
- If adequate viable hepatocytes are present, **vitamin K** may produce some improvement in coagulopathy.
- One of the most important advances is use of prolonged **NAC** for treatment of fulminant hepatic failure.

Antidotal therapy with N-acetylcysteine (NAC):

Mechanism of action:

NAC prevents toxicity by serving as a glutathione precursor as a glutathione substitute, combining with NAPQI, & being converted to cysteine & mercaptate conjugates.

NAC may also lead to increased substrate for nontoxic sulfation, allowing less metabolism by oxidation to NAPQI.

Administration of NAC:

NAC is available both orally & intravenously. A 20-hour IV infusion of NAC has been widely used worldwide. This regimen includes a loading dose of 150 mg/kg IV over 15 minutes followed by 50 mg/kg over the next 4 hours (rate of 12.5 mg/kg/h) & then 100 mg/kg over the next 16 hours (rate of 6.25 mg/kg/h).

The standard oral course of NAC is a 140 mg/kg loading dose followed by 70 mg/kg orally every 4 hours for a total of 18 doses over 72 hours.

Hepatic transplantation:

Liver transplantation may increase survival for a select group of severely ill patients who have acetaminophen induced fulminant hepatic failure.

Case 1

24- year-old non-pregnant female presents 40 minutes after ingestion of 18 g of standard release acetaminophen. She has no complaints and decided to seek care after telling her boyfriend about the ingestion. She has no significant medical history, is on oral contraceptives and denies drug use. Her vital signs are within normal limits and her exam is unremarkable other than she is tearful.

Case 2

A 16-month-old presents to the emergency department (ED) after being found drinking from an open bottle of acetaminophen liquid. The bottle was new and is now empty. The child is healthy, weighs 14 kg and appears well. The bottle contained 120 mL of 160 mg/5 mL acetaminophen suspension.

Aspirin toxicity

Pharmacology

Salicylates are a types of drug found in many over-the-counter and prescription medicines. Aspirin is the most common type of salicylate. Aspirin and other salicylates has a mild analgesic, antipyretic, and anti-inflammatory effects at moderate doses. Aspirin poisoning has significantly decreased in the past few decades because of its association with Reye Syndrome, limitation of tablets per bottle, and child resistant packaging. Symptoms of toxicity in children are likely to occur with a dose of 150 mg/Kg.

After ingestion, acetylsalicylic acid is rapidly converted to salicylic acid, its active moiety. Salicylic acid is readily absorbed in the stomach and small bowel. At therapeutic doses, salicylic acid is metabolized by the liver and eliminated in 2-3 hours.

Salicylate poisoning is manifested clinically by disturbances of several organ systems, including the central nervous system **(CNS)** and the **cardiovascular, pulmonary, hepatic, renal, and metabolic** systems. Salicylates directly or indirectly affect most organ systems in the body by uncoupling oxidative phosphorylation, inhibiting Krebs cycle enzymes, and inhibiting amino acid synthesis.

The toxic effects of salicylates are complex. **Respiratory centers are directly stimulated**, causing a primary **respiratory alkalosis**. These processes all contribute to the development of an elevated anion-gap metabolic acidosis in patients with salicylate poisoning.

This **combination of a primary respiratory alkalosis and a primary metabolic acidosis is characteristic** of salicylate poisoning, especially in adults, and should make the clinician suspect the diagnosis when it is present.

Mechanism of Toxicity

CNS effect of salicylate Intoxication

↓

Salicylate level increase in the brain

↓

Stimulate the respiratory center

↓

Hyperventilation

↓

↓ Pco2

↓

Respiratory alkalosis

↓

Renal compensation by excreting more HCO3 and retaining more H ion

↓

Metabolic acidosis

Characteristics of poisoning

The symptoms are varied as shown in (fig.1).

■Vital signs: tachypnea, hyperthermia, tachycardia, hypotension

■Nausea and vomiting: GI irritation or stimulation of chemoreceptor trigger zone in medulla

■Ototoxicity: tinnitus or deafness

■Hypoglycemia

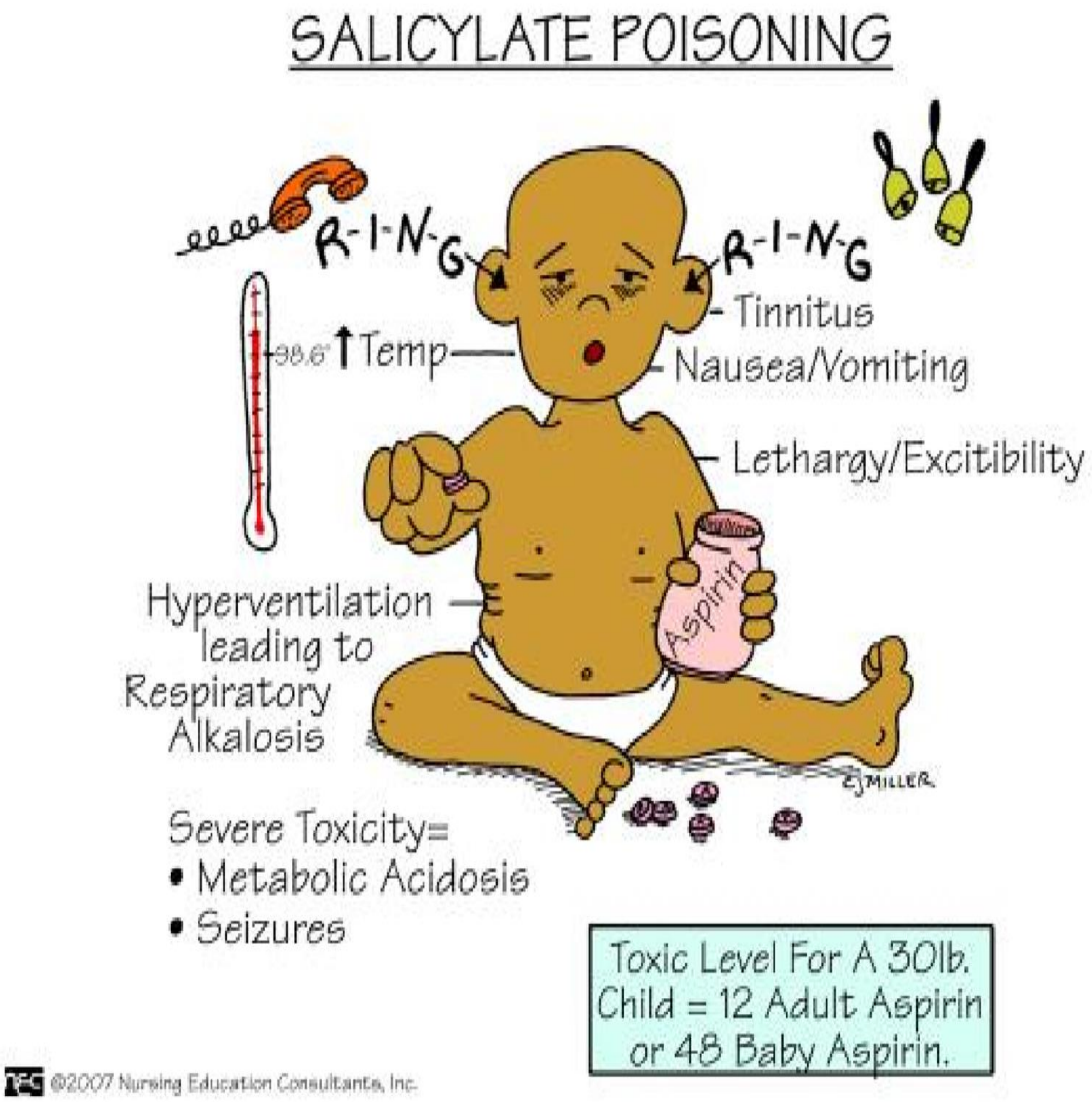
■Hypokalemia

■Metabolic acidosis

■CNS toxicity: confusion, dizziness, seizures are more common in children.

■Pulmonary or cerebral edema: result of severe acidosis, more common in adults but can occur in children.

■Acute renal failure, and respiratory failure, cardiovascular collapse.



Management of poisoning

Management strategies involve removal of Aspirin from GIT, correction of metabolic acidosis & dehydration, hyperthermia, hypoglycemia, & hypokalemia.

After ingestion, Aspirin may take 8-12 hours of continuous absorption and delay in reaching peak concentration.

Gastrointestinal Decontamination:

 Gastric lavage can be considered up to 4 hours after ingestion if substantial poisoning is suspected (>500mg/kg) and there is no airway compromise.

 Activated charcoal has been shown to decrease absorption and peak salicylate plasma concentrations. The recommended dose is 1g/kg (maximum 50g) with sorbitol. 0.5g/kg of activated charcoal without sorbitol can be given until asymptomatic or plasma salicylate level is less than 40mg/dL.

Elimination enhancement:

 alkalinizing the urine will trap salicylate in the renal tubules and increase excretion. This is done with $NaHCO_3$. The goal is to maintain urine pH >7.5 until asymptomatic or until plasma salicylate is less than 30 mg/dL.

Hemodialysis is only indicated in the case of coma, seizures, focal neurologic signs, pulmonary or cerebral edema, renal insufficiency, plasma salicylate level >100mg/dL.

Supportive care

There is no specific antidote.

Glucose to correct hypoglycemia and ketosis.

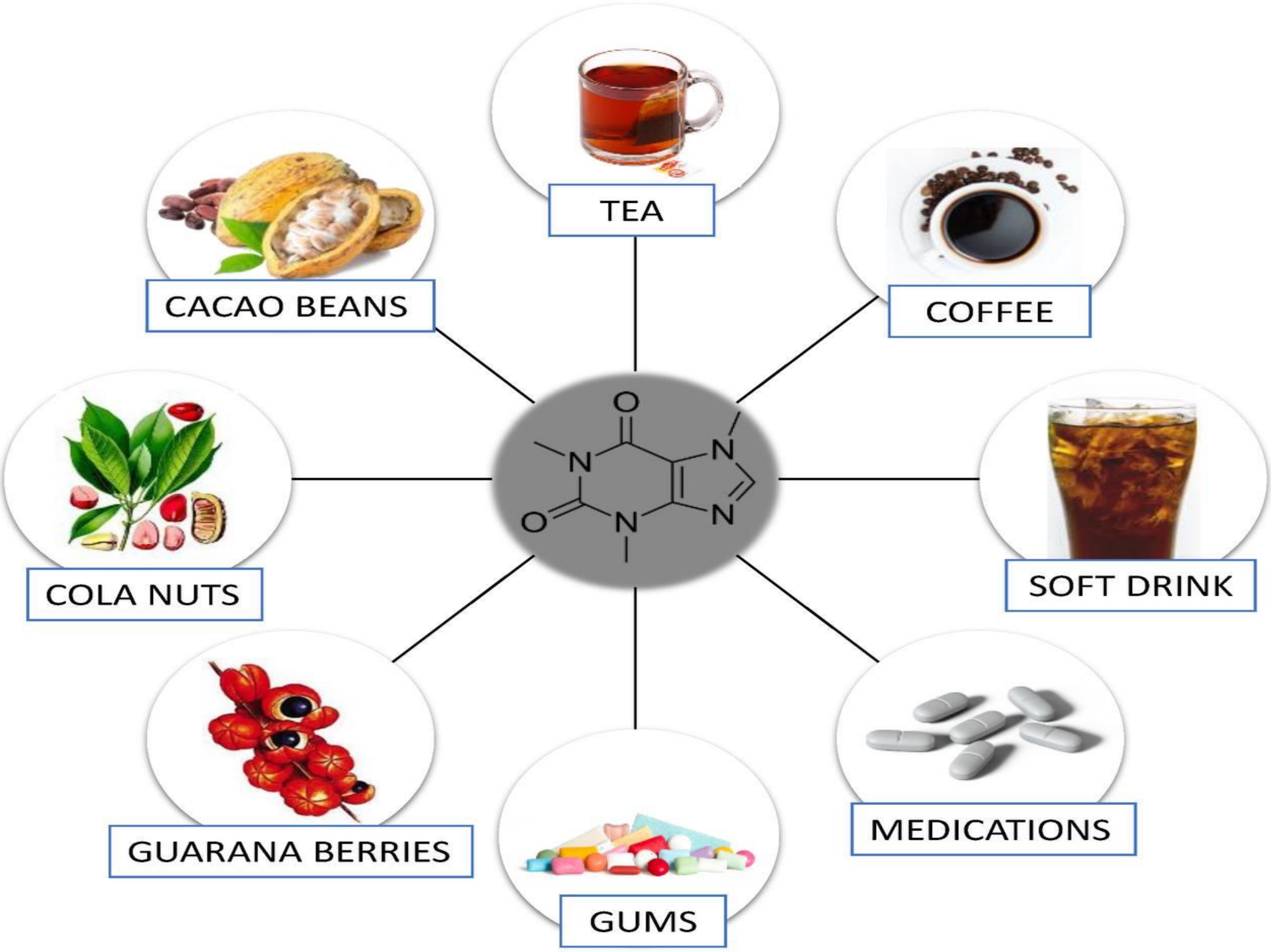
Potassium chloride is given to correct hypokalemia and to prevent alkalosis from sod. bicarb.

Diazepam for seizure.

Case 1

A 61-year-old woman presented to the Emergency Department after awakening with **left-sided weakness**. She had a history of ischemic stroke with an associated seizure disorder. The patient denied recent seizure, and brain magnetic resonance imaging (MRI) showed no evidence of an acute stroke. Following her arrival, she became acutely confused and complained of **tinnitus, shortness of breath, and blurred vision**. On direct questioning, she gave **a history of excessive use of salicylate** for the previous two to three weeks. Her initial **serum salicylate level** was significantly increased at 78.1 mg/dl (upper therapeutic limit, 19.9 mg/dl). She recovered completely following treatment with **oral activated charcoal, intravenous sodium bicarbonate, and potassium replacement.**

Theophylline and caffeine toxicity



Pharmacology

□Caffeine is a widely recognized psychostimulant.

□desirable effects at lower doses (i.e., ≤ 400 mg) and undesirable effects generally above this level of intake

□a dose of 500 mg -------to increase tension, nervousness, anxiety, excitement, irritability, nausea, paresthesia, tremor, perspiration, palpitations, restlessness and possibly dizziness.

□lethal dose 10 gm. or greater.

□After oral absorption caffeine is metabolised to theophylline (fig.1).

□Theophylline is a bronchodilator and respiratory stimulant

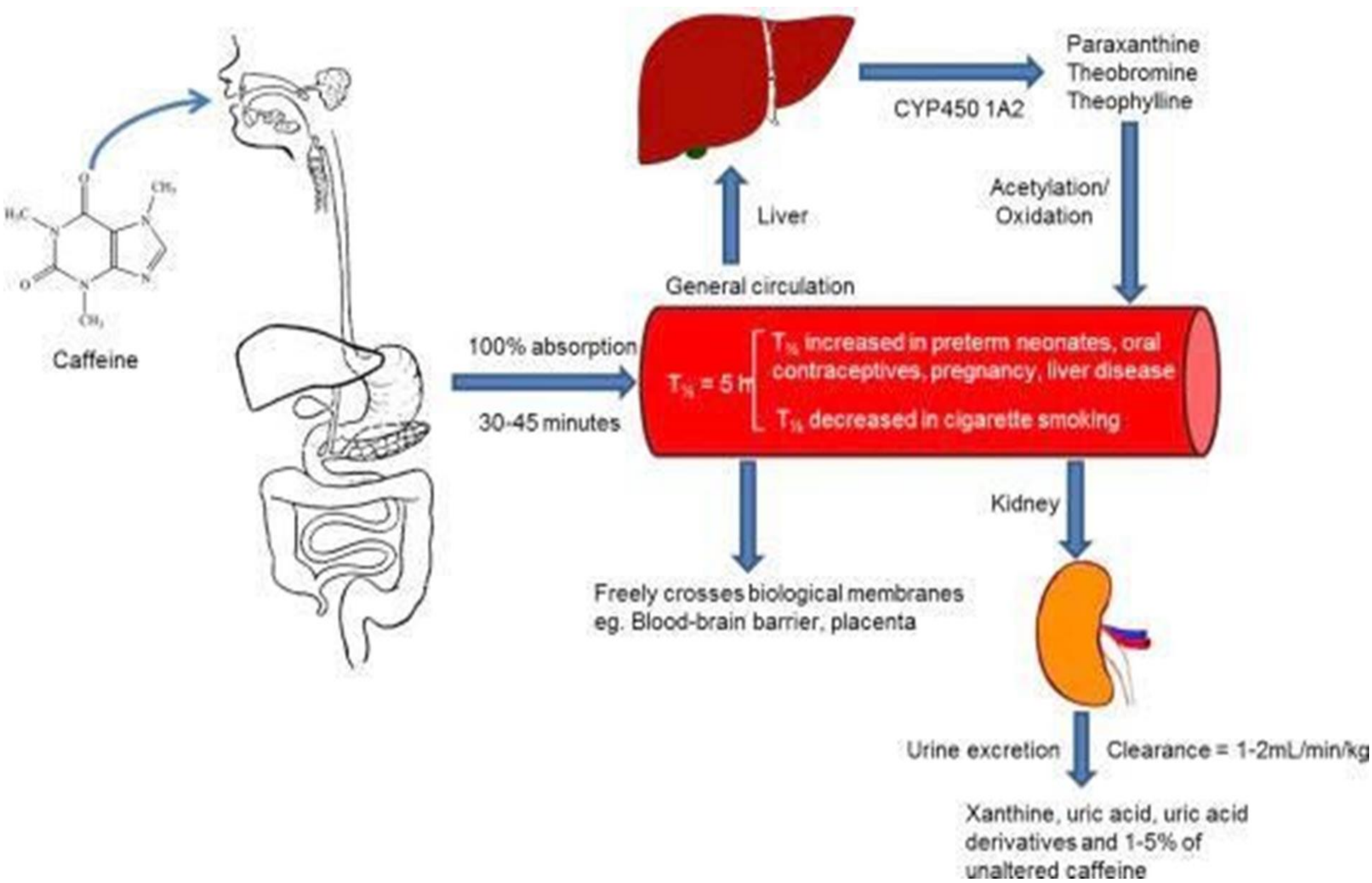
□Used to treat asthma, COPD, neonatal apnea syndrome and weight loss agent

□Theophylline has narrow TI.

□Some preparations may form concretions in the stomach especially with the sustained release preparations.

□Toxicity can occur in low doses in patients taking theophylline chronically.

Pharmacokinetics



(figure1) caffein pharmacokinetics.

Theophylline is 100% bioavailable by oral route.

Theophylline is rapidly absorbed but may be delayed in sustained- release preparation

The VD is 0.6 L/kg, and 36% is protein bound.

It is metabolized hepatically, undergoes entero- hepatic circulation after 6-8 hrs. & up to 18 hrs. in SR forms.

Rapidly diffuses into the total body water and all tissues, readily crosses the BBB .

Clinical presentation

Any patient with severe intractable vomiting + Tachycardia in the PCC ER unit = Theophylline toxicity till proved otherwise.

GIT: nausea, severe up to intractable vomiting +/- upper GI bleeding, diarrhea and abdominal pain.

CVS: palpitation and hypotension

CNS: Tremors, agitation, restlessness, seizures and coma in late severe stages.

Respiratory: Tachypnea

Mechanism of Toxicity

1- **Adenosine antagonist:**

– Adenosine modulates histamine release and cause bronchoconstriction

– Adenosine antag. Results in nor- epinephrine release.

IN therapeutic dose ----------------Bronchodilator

IN overdose -------------------------CNS manifestations

2- +++ **release of endog. Catecholamines:** CARDIAC & CNS symptoms.

3-**Inhibit phosphodiesterase:**

- Elevate cAMP.
- B, adrenergic stimulation.

4-**Stomach:**

- ↑↑ gastric acid secretion
- Smooth muscle relaxation
- Stimulation of CTZ.

5-Increase striated muscle contractility:

- ↑↑ intracellular calcium content.
- ↑↑ muscle O2 consumption

- ↑↑ the BMR.
- These effects are sought by users of methylxanthines to enhance or improve athletic performance or lose weight.
- Acute intoxication ↑↑↑ Epi. & NE. levels fourfold to tenfold normal.
- In chronic overdose ↑↑↑ NE & dopamine levels were elevated

Characteristics of poisoning

GIT: Nausea and vomiting are the predominant.

CVS: ↑↑ cardiac conduction, favoring reentrant arrhythmias even at therapeutic serum concentrations.

Coronary ischemia due to A2 receptor antagonism increases in circulating catecholamine,

hypokalemia, and acidosis all causes arrhythmias.

The hypotension is due to Vasodilatation due to theophylline beta2- adrenoceptor stimulation.

Tachyarrhythmias result in ↓↓ filling time & ↓↓ COP; hypovolemia 2ry to gastrointestinal

losses & theophylline induced dieresis.

CNS: agitation, tremor, & seizures either focal or generalized also, NCSE which are difficult to control.

Metabolic: hypokalemia, hyperglycemia, mild hypomagnesaemia & metabolic acidosis. • Hypokalemia and hyperglycemia are more common in acute than in chronic. • Hypokalemia is from intracellular shifting of potassium, Severe lactic acidosis has been reported with pH as low as 6

•Hyperlactemia has been reported with therapeutic use of theophylline

•Rhabdomyolysis & compartment syndrome have been reported after acute theophylline & caffeine intoxication. •

Management of poisoning

REDUCE ABSORPTION

- GI elimination is of utmost importance.
- Ipecac is not preferred as the patient may already have intractable vomiting.
- We can just give plenty amount of water to induce vomiting unless it is contraindicated e.g. comatose patient, severely shocked patient, history of upper GI bleeding
- GI Elimination should never be skipped even if the presentation is delayed esp. with SR tablets.
- Gastric lavage can be done in uncooperative patients.
- Activated charcoal is a cornerstone in our management plan and should be given in multiple doses as a GI dialysis.

ELIMINATION ENHANCEMENT:

Multiple doses of AC

reduce theophylline half-life from 25 h to (6.5 - 12.6 h)

The recommended regimen is 25 g of AC every 2 h until the serum theophylline concentration declined to a level associated with clinical improvement.

haemodialysis

hemoperfusion is more efficient than haemodialysis at removing theophylline, it has not been shown to be better at improving clinical outcome.

MANAGING TOXICITY SYMPTOMS:

Severe vomiting: Metoclopramide up to Ondansetron. (Never to use phenothiazines as antiemetics as they decrease threshold of seizures.)

Hypotension: Crystalloids, colloids or even vasopressors e.g. NEp.

Seizure: benzodiazepam cardiac arrhythmia:

For atrial Tachyarrhythmias: we can use propranolol (unless there is bronchospasm), esmolol or verapamil.

For Ventricular arrhythmias: use lidocaine.

Metabolic acidosis: $NaHCO_3$ + serial ABG monitoring.

Hyperthermia: Cold fomentations +/- BZP to calm the patient down

Case 1

SP, a 33-year-old male, is admitted to the hospital on Friday evening with asthmatic bronchospasm. He has uncontrolled asthma. The on-call medical resident initiates SP on an aminophylline infusion. The infusion is started at a rate of 20 mg/hr. The theophylline level is drawn at 6 AM, less than 12 hours after the aminophylline infusion was started. When the resident returns to check on SP, he calls the laboratory to obtain the results of the theophylline level. He is informed that the level is only 6 mg/L. The resident would like the level to be 12 mg/L (twice the current level), so he doubles the rate of the aminophylline infusion.

Monday morning, the clinical pharmacist receives a phone call from the nurse taking care of SP. The nurse explains that SP is complaining of nausea, a racing heart, and nervousness. She is concerned that one of his medications may be causing these symptoms and would like the pharmacist to review his medication profile. When the clinical pharmacist notices that SP's aminophylline infusion has been running at 40 mg/hr since Saturday morning, she contacts the resident. She recommends obtaining another aminophylline level because SP's symptoms are consistent with theophylline toxicity The initial level was drawn before the aminophylline reached steady state (I day). By increasing the infusion rate, rather than waiting for steady state, the theophylline level exceeded the therapeutic range.

Supplement toxicity

Pharmacology

- toxicity in children under 5------Accidental poisoning
- toxicity in adults -------mega dose.
- MEGA DOSING --------10 or more (RDA).
- most therapeutic formulas-----2 to 5 times the RDA.
- Toxicity more commonly seen with fat-soluble vitamins A and D.
- vitamin K toxicity less common probably because it is not available for self-administration in OTC products.
- Vitamin E is practically nontoxic, at least according to current knowledge.
- For the most part, excessive intake of the water- soluble B complex group and vitamin C is eliminated by the kidney. These are not generally life- threatening.
- An exception is vitamin C, which can induce serious renal toxicity in a small number of susceptible individuals.
- Therefore, the potential seriousness of vitamins are mainly related to overdosing of vitamin A, D, and C

Vitamin A

- prophylactic self-therapy.
- large doses of vitamin A or other vitamin A analogues to treat skin diseases such as acne
- Chronic renal disease, patients on haemodialysis because of the failure of this procedure to remove it from the blood.

Mechanisms of Poisoning

1- On the CNS

Vit A overdose

↓

retinol-binding protein becomes saturated

↓

Cellular membranes are then exposed to unbound vitamin

↓

degradation of the membrane structure

↓

increased cerebral spinal fluid pressure and other CNS manifestations

2- On the liver:

- fibrosis, portal hypertension and ascites .
- Overdose is stored in the Ito cells (lipocytes)
- this transforms the Ito cells into fibroblasts that can produce collagen, which in turn causes subsequent hepatic pathology.

3- On the PTH,& bone:

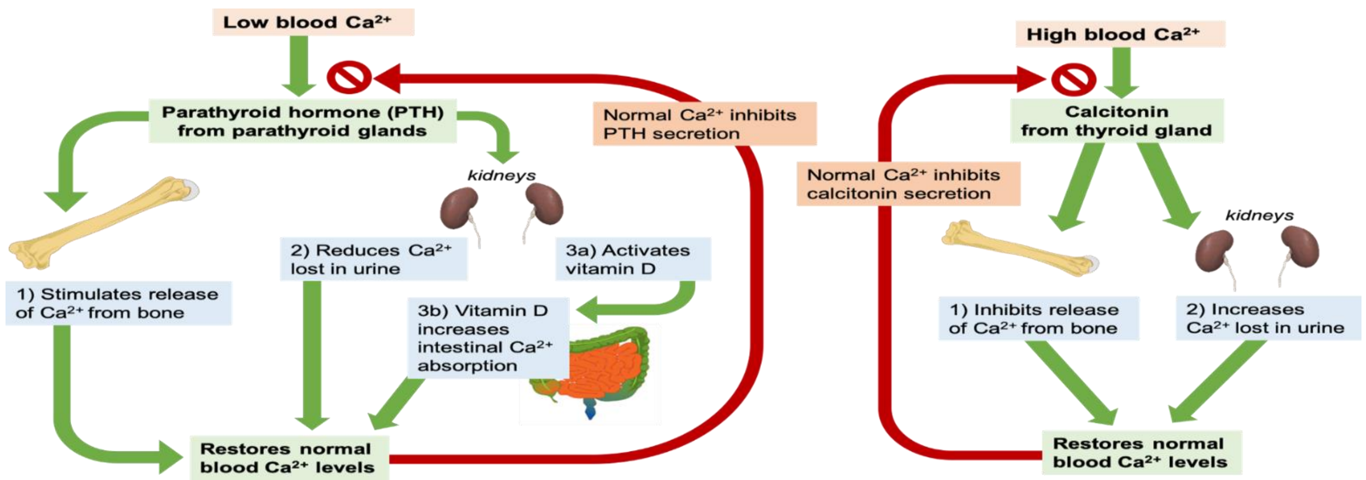
- doses as low as 25,000 U ↑↑↑ PTH.
- hypercalcemia, bony changes, and premature epiphyseal closure are felt to be due to this action

Management Of Vitamin A Poisoning:

- immediate discontinuation of the substance if not irreversible hepatic damage occurs.
- Most signs and symptoms will disappear within a week or two.
- Vitamin E is reported occasionally to protect against hypervitaminosis A .
- Although some papers state that vitamin E offers a degree of protection against toxicity, others have shown that vitamin E may actually enhance tissue uptake of vitamin A.

Vitamin D toxicity

- Vitamin D is the most toxic of all vitamins.
- All signs of vitamin D toxicity are caused by its action to ↑↑↑calcium.
- Vitamin D is converted to 1,25. dihydroxycholecalciferol.
- Once formed, 1,25-dihydroxycholecalciferol exerts activity at several sites, including intestinal epithelium, to promote calcium absorption .
- Vitamin D toxicity is more severe in an individual whose thyroid has been removed since the counter hormone, calcitonin, is synthesized within this gland (fig.1).



(Figure 1) regulation of calcium levels

Management of vitamin D toxicity

- immediate discontinuation.
- reducing calcium intake.

Normally this will lead to rapid disappearance of symptoms.

When they persist:

- administering glucocorticoids such as prednisone (20 to 40 mg or more orally per day) can be given to reduce intestinal absorption, control hypercalcemia, and prevent irreversible renal damage and ectopic calcification.
- assuring a generous fluid intake.

This will lower of calcium to normal concentrations within days

Vitamin K toxicity

- The major toxicity is associated with water soluble synthetic analogue such as menadione.
- These derivatives are oxidants and cause haemolysis, jaundice, and kernicterus.
- Erythrocyte damage occurs more prevalently in persons with glucose-6- phosphate dehydrogenase deficiency and at doses exceeding 10 mg.
- Vitamin K1 (phytonadione) generally does not lead to hyperbilirubinemia and for this reason, it is the preferred form.

Vitamin E Toxicity

- At present, vitamin E is believed to have a low toxicity profile.
- S.E. include headaches, nausea, fatigue, dizziness, blurred vision (perhaps related to the fact that large doses may antagonize the action of vitamin A)
- inflammation of the mouth, chafing of the lips, gastrointestinal disturbance, muscle weakness, hypoglycaemia, degenerative changes, and emotional disorders.
- Also reported are disturbances in growth, thyroid function, mitochondrial respiration rate and bone calcification, and decreased haematocrit
- vitamin E may interfere with vitamin K metabolism, resulting in a prolonged prothrombin time.

Vitamin C Toxicity

Vitamin C toxicity is not a cause of death .

megaloblastic anemia: large doses of vitamin C over a period of several years destroy substantial amounts of vitamin B12, to produce symptoms of megaloblastic anemia.

Scurvy (fig.1): Large doses of vitamin C taken during pregnancy may cause scurvy in some newborns its also reported with doses as little as 400 mg ascorbic acid daily throughout pregnancy.

rebound scurvy: is reported occasionally in adults who suddenly withdraw from large doses. For these reasons, it is considered wise to taper mega-doses of vitamin C by about 10% to 20% daily.

Kidney Stone Formation: Ascorbic acid increases renal excretion of oxalate, uric acid, and calcium. This increase the potential for stone formation in the kidney and bladder. This potential seems to be governed by genetic factors, and only occurs in a small segment of the population. When it does occur, however, susceptible individuals may experience the problem at doses of 1 g or more daily.

(Figure2) gum bleeding in patients suffering from scurvy

B- Complex group (B1, B6, B12, niacin) Toxicity:

Vitamin B12 (cyanocobalamin):

- is associated with rare occasion of allergic reactions to the injectable products.

Vitamin B1 (Thiamine):

- Numerous toxicities were reported to parenterally administered vitamin B1
- Symptoms ranged from nervousness, convulsions, weakness, trembling, headache, and neuromuscular paralysis to cardiovascular disorders including rapid pulse, peripheral vasodilation, arrhythmia, edema, and anaphylactic shock.
- With the subsequent decline in use of thiamine in its parenteral form, there have been fewer toxicities reported and it is no longer considered to possess a major toxicologic threat.

Niacin (Nicotinic Acid) Toxicity:

Abnormal liver function and jaundice: The body uses niacin for NAD and NADH formation, which serve as coenzymes for various dehydrogenase enzymes in oxidation-reduction reactions.

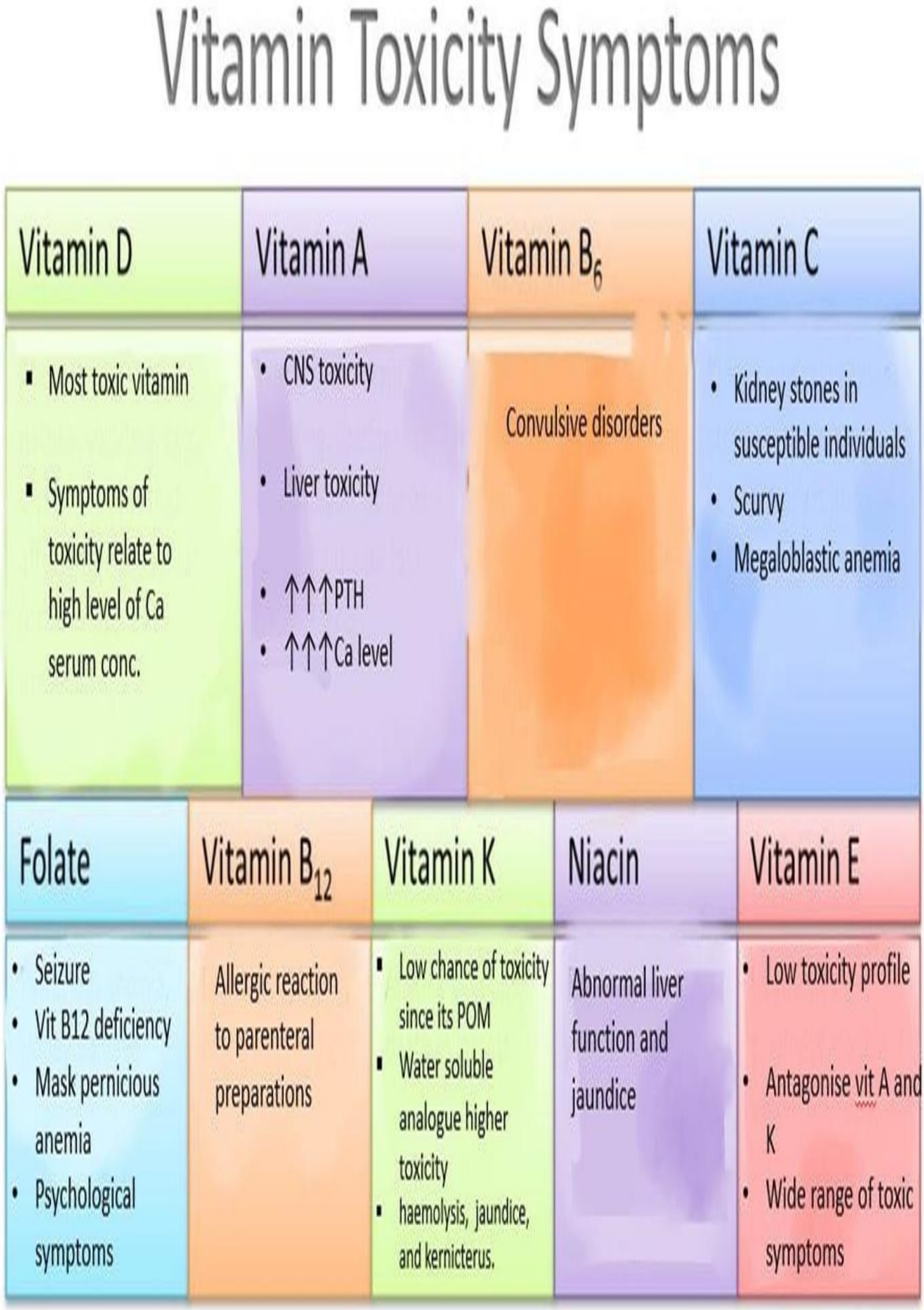
Many of these enzymes are found in the liver, and modulation of their activity with megadoses of niacin may explain the abnormal hepatic functions.

Vitamin B6 (Pyridoxine) Toxicity:

- Rare
- Convulsive disorders have occurred due to both vitamin excess as well as a deficiency state.
- Oral doses of up to 1 g daily have not shown adverse reactions, although doses of 200 mg daily followed by abrupt withdrawal have caused symptoms of dependency.

Folic Acid Toxicity:

- long-term folic acid therapy increased seizure frequency in some epileptic patients
- and may precipitate vitamin B12 deficiency neuropathy in some cases of megaloblastic anemia.
- It is also suspected of inducing mild psychologic disorders in normal subjects
- Although not a direct toxicity, folic acid can mask symptoms of pernicious anemia.



(Figure3) summery of vitamin toxicity

Household Poisoning

Pharmacology

- Among the thousands of harmless products available for household, very few are hazardous (fig.1).

- Even then, poisoning with these substances is one of the common modes of poisoning all around.

(Figure1) household toxins

Classification

Household agents can be also classified according to their chemical natures (fig.2).

Acid	Alkaline	Volatile substances	Others
Toilet cleaner Hair colour Phenol Antiseptic solution Sterilizing tablet Vinegar Food colours	Sodium hypochlorite Hydrogen peroxide Shaving gel/foam After shave lotion Hair remover Shampoo Mouthwash Shower gel Washing-up liquid Fabric conditioner Soap Automatic washing/dish washing machine liquid Lyme	Perfume Kerosene Petrol Paint thinner Paintbrush cleaner Turpentine substitute Furniture and floor polish Mothballs	Nail polish Nail polish remover Talcum powder Button battery Glue

(Fig.2) classification of household toxins

Pathophysiology

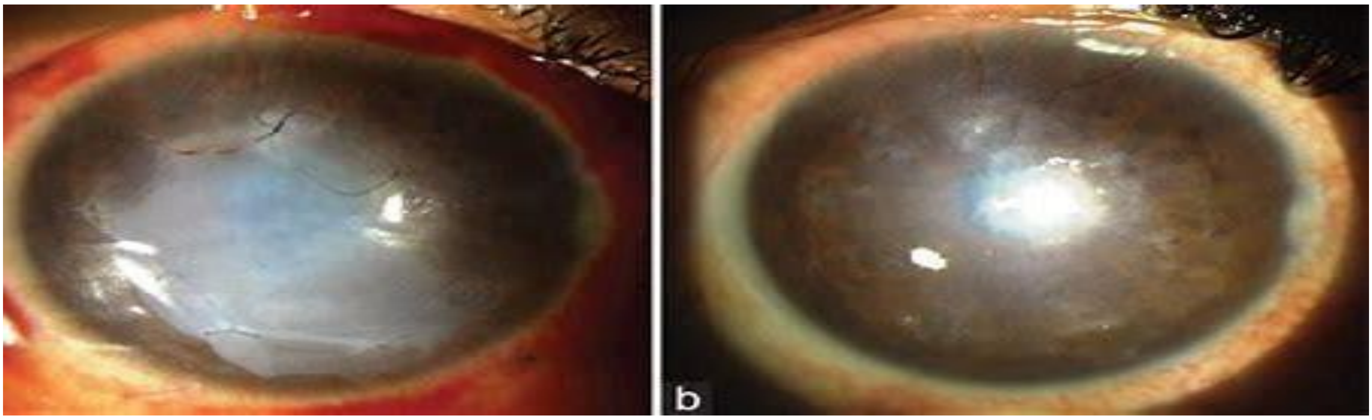
A wide range of lesions may occur after exposure to corrosive substances including mild epithelial injury to necrosis. The pathology depends on the route of exposure.

Most cases occur via oral ingestion leading to corrosive effects in the alimentary system along with systemic toxicity.

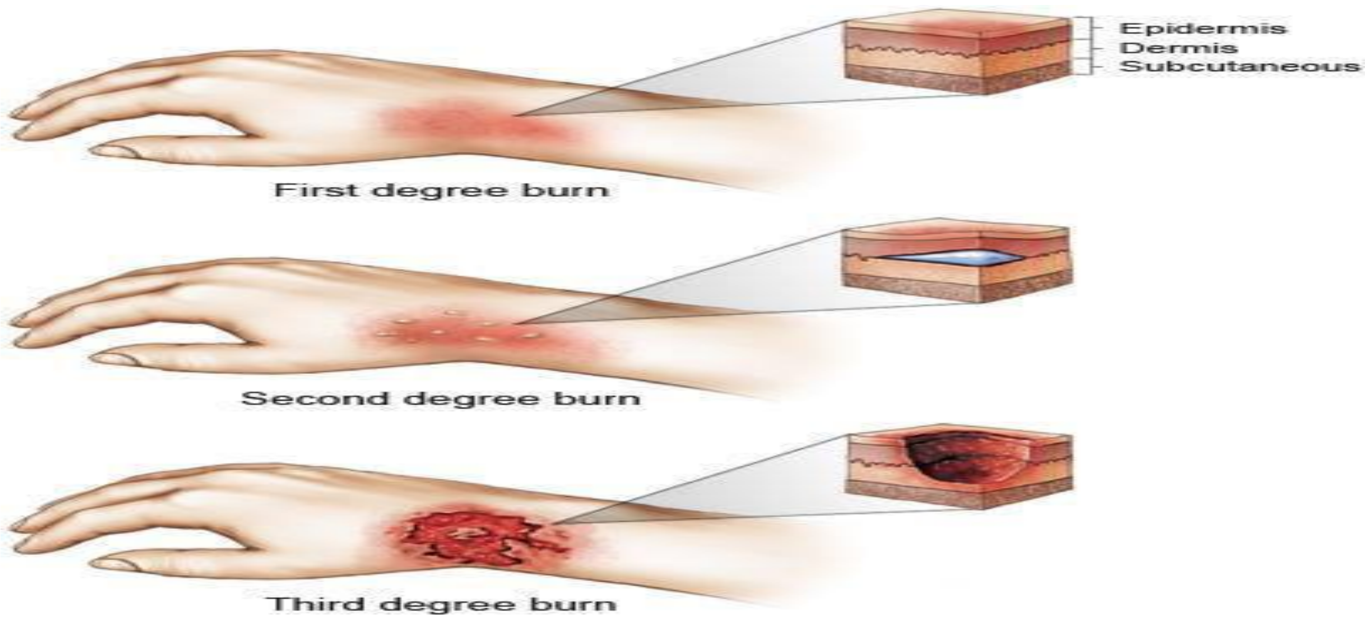
Long-term complications include the formation of the oesophageal stricture, antral stenosis and even the development of the oesophageal carcinoma

Pathophysiology and clinical presentation

- Skin may result in sloughing out of the affected tissue, ulceration and necrosis. Inflammatory changes in the skin occur if contact is prolonged.
- Ocular contamination can cause various degrees of damages to the eyes (figure 1,2).



(Figure 1) effect of corrosive substance on the ocular structures.



(Figure 2) classifications of skin burn

Management of poisoning

1. Acid exposure:

Dilution or neutralization, induce emesis, gastric aspiration and lavage are contraindicated.

Have early endoscopy as soon as possible.

Give analgesic for pain.

Give soluble calcium tablet for hydrofluoric acid ingestion if patient is able to swallow followed by intravenous infusion of 10 % calcium gluconate 10 ml in saline.

For external burn and eye injury, wash immediately with water or saline for 10–30 minutes then use silver sulphadiazine ointment for the skin and chloramphenicol ointment for the eye.

Manage symptoms.

2.Alkali exposure:

Dilution or neutralization, induce emesis, gastric aspiration and lavage are contraindicated.

Irrigate exposed eyes with sterile cold water or saline at least for 20 min and continue until the P H returns to normal.

Demulcents – egg white, olive oil, butter and cold milk – should be avoided.

Analgesic, including narcotics, may be given to relieve pain.

Diagnostic endoscopy shouldbe performed within 12–24 h of alkali ingestion.

As there is no specific antidote for alkaline corrosives, symptomatic treatments are to be done.

3. Volatile agents:

(A)Asymptomatic cases: Admit for observation and discharge after 24 h if no symptom develops.

(B)Symptomatic cases:

•Evaluate and maintain the ventilation and administer O 2 to all patients with respiratory symptoms.

•If the skin has been exposed to volatile agents, remove all contaminated clothing and wash the skin with copious amounts of water.

•Provide other supportive treatments.

•Corticosteroid, activated charcoal, cathartics, mineral oil and olive oil have no beneficial effect.

Case

A male, 24 years old, was brought to the emergency department, with history of accidental ingestion of about 10-15ml of acid (toilet cleaner) followed by severe burning sensation in throat, retrosternum and epigastrium. This was followed by multiple episodes of vomiting, few episodes of haematemesis and severe retching.

He was admitted in the (ICU), given intravenous fluids, proton pump inhibitors (PPI), anti- emetics, analgesia with intravenous fentanyl and empirical antibiotic.

On examination his blood pressure was 120/70 mmHg, heart rate 95/minute, respiratory rate 20/minute with an oxygen saturation of 98% on room air, normal systemic examination except for epigastric tenderness.

Gastroenterolgy team planned for an upper gastrointestinal (UGI) endoscopy within 24 hours of ingestion which revealed grade 2a injury to the gastric mucosa.

A diagnosis of corrosive gastritis was made. His vitals and blood haemoglobin remained stable with no further haematemesis and he discharged after 4 days, on oral liquid diet with advice for a regular follow-up.

Clinical toxicology lab 7

Digoxin toxicity

Introduction:

•Digitalis glycosides are life-saving drugs when used in therapeutic doses in the treatment of congestive heart failure (CHF) & for management of certain supraventricular arrhythmia.

•Digitalis protects ventricles during certain atrial arrhythmias.

•Digoxin is the one of the **most widely prescribed** drugs.

•It is estimated that **20-30%** of patients taking a digitalis preparation will experience toxicity because the drugs have an extremely narrow therapeutic index.

•The serum concentration of digoxin for therapeutic activity is in the normal range of 1.2-1.7 ng/mL & clinically significant toxicity usually occurs with concentrations **2-3 times higher**.

•The mortality rate with toxic dose is reported to be as great as **25%.**

Factors that increase the risk of toxicity to digitalis glycosides:

❖Concurrent administration of a **diuretic that induces potassium loss** is reported to be the most frequent cause of toxicity.

❖Individuals with **Eubacterium lentum** in their colon may require larger doses of digitalis to achieve the desired therapeutic serum concentrations. This microorganism reduces the lactone ring of digitalis. Digitalis blood concentrations may become toxic when these patients receive antibiotics, such as tetracycline or erythromycin, which eradicate the organism.

❖Many factors can increase the risk of toxicity to digitalis glycosides such as:

•renal diseases

•stress

•interactions with other drugs such as verapamil & quinidine (they cause increase in plasma concentration of digoxin probably by digoxin displacement from tissue-binding sites)

•hypokalemia

•hypothyroidism

Characteristics of poisoning:

•Early manifestations of intoxication that occur in approximately 50% of all cases generally involve the gastrointestinal tract.

•Anorexia, nausea, vomiting, & abdominal pain are common.

•Nausea & vomiting occur from direct drug action on the chemoreceptor trigger zone (CTZ).

•Blurred vision, loss of visual acuity, & green yellow halos have been described as early-appearing symptoms.

•CNS effects include a variety of neuropsychiatric disturbances.

•Digitalis intoxication can provoke a large number of arrhythmias. These include bradyarrhythmias or tachyarrhythmias, or a combination of both (figure1).

(Figure1) symptoms of digoxin toxicity

Management of poisoning:

•Management of acute digitalis toxicity involves **removal of ingested drug**, maintenance of a normal **potassium concentration**, reversal of **arrhythmias**, & the use of a specific **antidote** (digoxin immune Fab).

Reduce absorption

•**Gastric lavage** should be performed to remove the unabsorbed drug, although **vomiting** may already have accomplished this.

•Repeated administration of one the adsorbents (activated charcoal, cholestyramine, or colestipol) is recommended to enhance elimination of the glycoside by interrupting to entero-hepatic cycling exhibited by digitoxin, & possibly digoxin.

K level normalisation

•Hyperkalemia (5.5-13.5 mEq/L) is caused by acute digitalis toxicity, while hypokalemia is more common after chronic digitalis toxicity.

•Hyperkalemia may require treatment with insulin, dextrose, bicarbonate, & sodium polystyrene sulfonate, with frequent monitoring of ECG & electrolyte determination.

•If hypokalemia is encountered with tachy- or bradyarrhyhthmias, continuous potassium replacement alone may be sufficient.

•For atrial & ventricular arrhythmias that do not respond to potassium therapy, the treatment of choice includes phenytoin & lidocaine.

•Potassium administration in a person with digitalisinduced hyperkalemia can result in heart block.

Supportive care

•If digitalis has produced atrioventricular (AV) block, **atropine** is given to produce vagolytic effect to increase the heart rate & AV conduction.

•**β-blockers**, such as propranolol, are useful to suppress supraventricular & ventricular arrhythmias but may depress the sinoatrial (SA) node & AV conduction especially in a patient with an already failing heart, that limiting their usefulness.

Enhance elimination

• Because digoxin has a large volume of distribution, hemodialysis is not a successful method to enhance elimination of digoxin. However, hemodialysis is still sometimes required to control hyperkalemia.

Antidote Digoxin Immune Fab (Digibind):

Digoxin immune Fab is used as an antidote reserved for life-threatening overdoses.

Indications of such toxicity include:

•ingestion of more than 10 mg of digoxin by healthy adults or 4 mg by children,

•Steady-state serum concentrations greater than 10 ng/mL;

•or if blood potassium concentration exceeds 5 mEq/L.

•**Adverse effects** to digibind have been minimal including sensitivity, erythema at the site of injection, & rash & urticaria have been reported.

Case1

The 32 - year old doctor , failing to cope up with day to day pressures of life , thought of ending his life and chose an unusual method ,The doctor chose two cardiac drugs for definite cardiac arrest and one drug for certain brain damage .Firstly , he ingested 100 tablets of digoxin , Simultaneously , he injected himself with 1600 units of regular insulin , He also consumed large quantities of a drug propranolol ,As the effects of drugs started , the doctor had a sudden change of mind -- he wanted to live . He informed his relatives and was immediately rushed to the casualty of SGRH within two hours of his ingesting the drugs ,The first challenge was to find an antidote for drug Digoxin which was digoxin specific antibody fragments (Fab) . ' But this is not readily available in India and moreover the cost of one vial is about USD 1600, he was needed 15-20 vials , Time was running out and patient's condition deteriorated, A team of cardiologists , nephrologists and critical care specialists after a thoughtful deliberation decided to attempt charcoal – based hemoperfusion . The second challenge was to reduce propanol toxicity which was done by injecting glucagon. .The third challenge of low blood sugar levels the patient was tackled by giving Glucagon, He was also given large doses of glucose intravenously. Finally the patient was discharged after 6 days following consultations with psychiatrist.

Case 2

A 69 year old woman was admitted with general malaise, anorexia, vomiting, and confusion. She had a history of congestive cardiac failure and had been taking a thiazide diuretic and digoxin 250 pg daily. Her general practitioner had measured her plasma digoxin concentration two days before at 16 nm old. On admission her serum potassium concentration was 29 mmol/l. Correction of the hypokalaemia produced a considerable improvement in all of her original symptoms. She was discharged taking the same dose of digoxin and a combination formulation containing a thiazide diuretic and a potassium sparing diuretic.

Conclusion

This case illustrates two problems: firstly, the difficulty in interpreting a plasma digoxin concentration without the serum potassium concentration, and, secondly, the patient's increased sensitivity to digoxin in the presence of hypokalaemia, which resulted in digoxin toxicity despite a plasma digoxin concentration within the therapeutic range

Toxicity of β–adrenergic Blockers

Pharmacology:

▪β-adrenergic blockers are widely used for treatment of many disease states, including hypertension, arrhythmia, angina, glaucoma & migraine prophylaxis.

▪They have significant pharmacologic & pharmacokinetic differences (Table 1).

▪These differences influence their therapeutic applications, incidence of side effects, & type & severity of toxic reactions when taken in overdose.

Toxicity of β-adrenergic blockers:

▪Most of the toxicity of β-adrenergic antagonists is because of their ability to competitively antagonize the action of catecholamines at cardiac β-adrenergic receptors.

▪A membrane depressant effect likely contributes to the cardiac depressant effects of propranolol.

▪Most poisonings involve propranolol.

▪ The high lipid solubility of certain β–adrenergic blockers, especially propranolol accounts for the CNS effects.

▪ In overdose, pharmacokinetic parameters may change drastically due to decreased cardiac output with subsequently reduced hepatic & renal blood flow.

▪ Blood drug level determination alone is unreliable for assessing possible overdose because clinical symptoms might persist beyond the drug's half-life.

Characteristics of poisoning:

▪Electrographic changes consist of first-degree AV block (prolonged PR interval), widening of the QRS complex, absence of P waves, & prolongation of the QT interval.

▪Sotalol & acebutolol prolong the QT interval. The prolonged QT interval by sotalol predisposes to torsades de pointes, & ventricular dysrhythmias may complicate the therapeutic use of sotalol.

▪ Cardiac changes do occur most frequently with drugs that have membrane-stabilizing action.

▪ Propranolol possesses the most membrane stabilizing activity of this class, propranolol poisoning is characterized by coma, seizures hypotension, and bradycardia impaired AV conduction, prolonged QRS interval (fig.1).

Cardiac	CNS	Other
Arrhythmias	Sleepiness	Bronchospasm
Bradycardia	Dizziness	Pulmonary edema
Atrioventricular block	Unconsciousness	Hypoglycemia
Hypotension	Coma	Hyperkalemia
Tachycardia	Seizures	
Shock	Respiratory depression	

(figure1) Clinical manifestations of β- adrenergic blocker toxicity.

Management of poisoning:

Reduce absorption:

▪**Orogastric lavage** is recommended for patients with significant symptoms such as seizures, hypotension, or bradycardia if the drug is still expected to be in the stomach.

▪ **Activated charcoal** can be given repeatedly during the first 24 hours

▪ **Whole bowel irrigation with polyethylene glycol** should be considered in patients who have ingested sustained release preparations

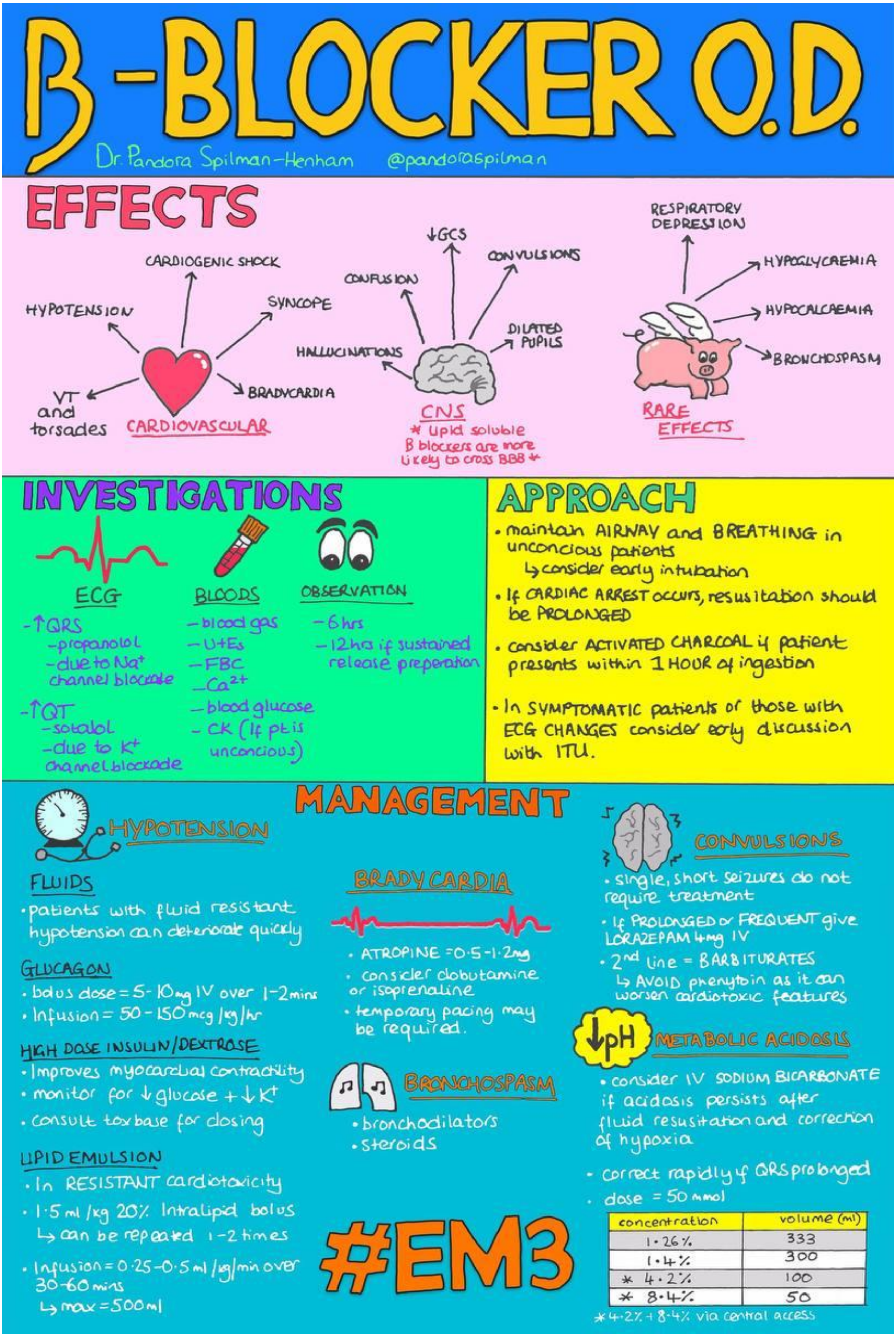
Supportive care:

As shown in the figure

If all fails, then give:

•**phosphodiesterase inhibitors**

▪ **Hemoperfusion hemodialysis** may be considered in cases involving nadolol & atenolol.



(Figure2) summery of B blockers toxicity

Case 1

A case of self-poisoning death due to ingestion of propranolol by a young male physician. A 31-year-old man with major depressive disorder was found dead in his room. Fifteen empty packages, each having contained ten 40-mg propranolol tablets, were found without any tablets leftover in his room. A suicide note was also found in his room. He was thus alleged to have ingested 6 g of propranolol for self-poisoning. Autopsy findings revealed approximately 150 mL of pink fluid with some partially dissolved pink tablets in the stomach. No anatomic cause of death was found, except for mild dilatation of cerebral ventricles. Toxicologic analysis revealed propranolol in his blood and gastric contents. The cause of death was attributed to acute cardiac arrest due to severe acute propranolol intoxication from self-poisoning caused by major depressive disorder.

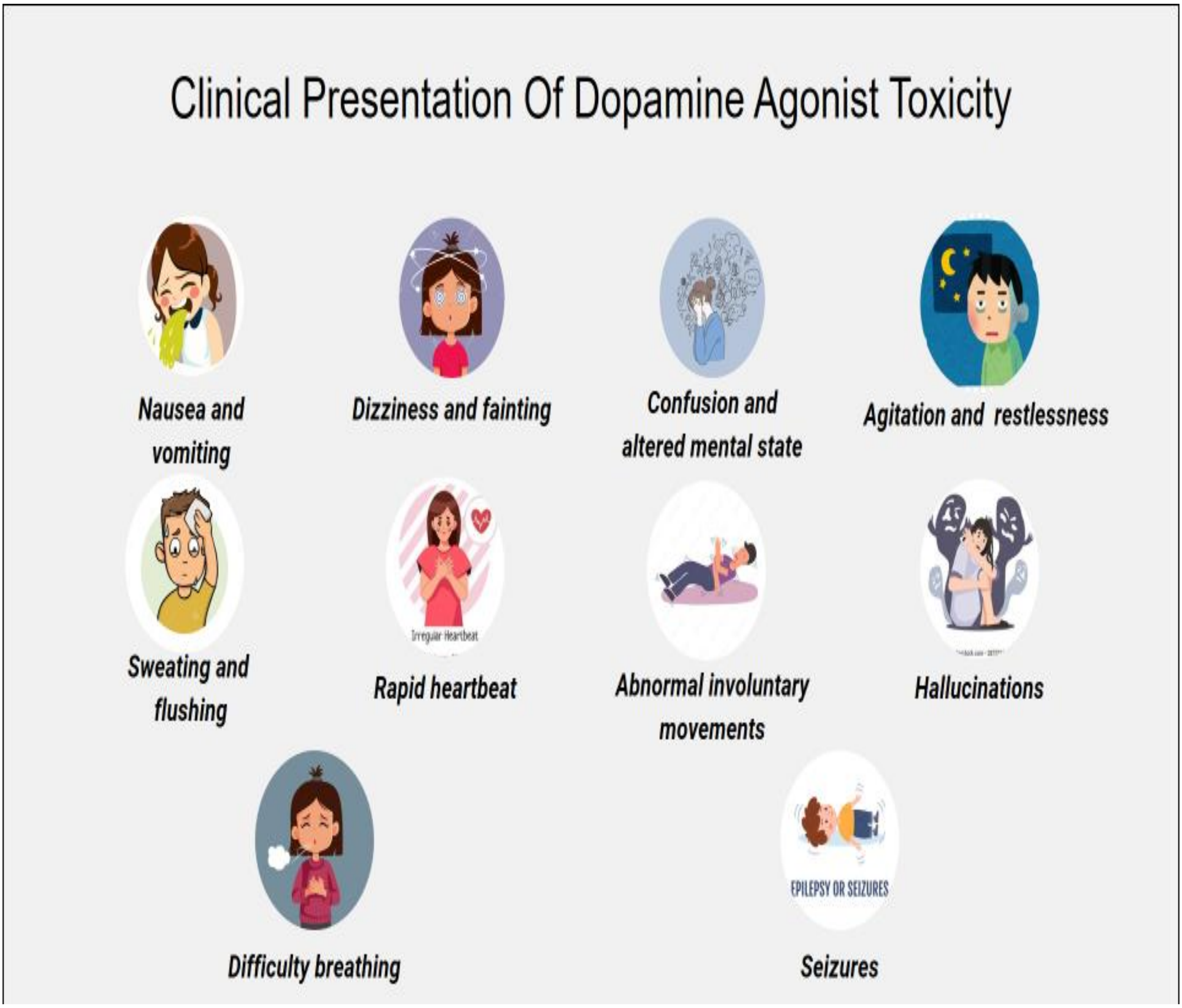
Case2

An 18-year-old man was brought to the emergency department after ingesting an estimated 2.4 grams of propranolol. On admission (30 minutes after eating) he was breathing laboriously. It was not possible to obtain blood pressure. He had a brief seizure before admission. The patient was not taking any other treatment. Treatment with isoproterenol and glucagon was initiated. Gastric lavage restored a few portions of the tablet. Treatment was started with activated charcoal at a rate of 100 grams every 4 hours. Shortly after stabilization, the patient developed bronchospasm. Blood pressure became gradually lower. Although treatment with isoproterenol and glucagon was continued. Despite all attempts, the patient developed bradycardia that rapidly progressed to asystole 9 hours after eating. He died after that. At autopsy, no other substance was found in urine and serum drug testing.

Toxicity of Anti-Parkinson medication (levodopa)

Introduction:

- Parkinson's disease is a progressive disorder that affects the nervous system and the parts of the body controlled by the nerves.
- Symptoms include tremor, Speech changes, bradykinesia, impaired posture and balance (figure1).
- Treatment include levodopa and carbidopa , dopamine agonists, MAO inhibitors, COMT inhibitors, anticholinergic medication, amantadine.
- Levodopa is often viewed as the first-line drug for the management of Parkinson's motor symptoms.
- Levodopa crosses the blood brain barrier where it is converted to dopamine by decarboxylation in the presynaptic terminals of dopaminergic neurons.



(figure1) Clinical Presentation of Dopamine Agonist Toxicity

Management of dopamine toxicity

The treatment for levodopa toxicity depends on the severity of the symptoms and the overall condition of the patient.

If the symptoms are **mild to moderate**

1. Discontinuation of levodopa

2. Fluid and electrolyte replacement

3. Monitoring of symptoms

In cases of **severe** levodopa toxicity:

1- Gastric lavage

2- Supportive care

3- Medication

1. Supportive care

Monitoring and managing the patient's vital signs, such as blood pressure, heart rate, and oxygen saturation.

Intravenous fluids may be administered to maintain hydration and electrolyte balance. Oxygen therapy may be provided if the patient is experiencing respiratory distress.

2. Symptoms management

Benzodiazepines may be administered to control agitation and seizures. Antipsychotic medications, such as haloperidol or chlorpromazine, may be used to manage hallucinations and psychosis.

3. Dopamine elimination

Haemodialysis, a process that filters the blood to remove toxins, may be utilized.

Forced diuresis or urine alkalization, may be employed to enhance the excretion of dopamine through the kidneys.

4. Monitoring and observation

Close monitoring in an intensive care unit (ICU) or a specialized toxicology unit.

Continuous monitoring of vital signs, cardiac function, and neurological status is essential to assess the patient's response to treatment and detect any complications.

5. Antidote

Phentolamine is an antidote that will counteract the effect of vasoactive agents.

Case

Patient Information:

Name: John Smith Age: 68 Gender: Male

Medical history:

John has been diagnosed with Parkinson's disease for the past five years. He has been taking levodopa-carbidopa (Sinemet), an antiparkinson medication, to manage his symptoms. He has been compliant with his medication regimen and has not experienced any significant adverse effects until recently.

Presenting Complaint:

John's wife brings him to the emergency department with complaints of altered mental status, confusion, and significant motor impairment. She noticed that his symptoms worsened over the past three days. John appears drowsy and disoriented during the assessment.

Assessment Findings:

1. Neurological examination reveals bradykinesia, rigidity, and resting tremors, which are consistent with his Parkinson's disease.

2. John's blood pressure is slightly elevated, and his heart rate is within the normal range.

3. He has a dry mouth, dilated pupils, and decreased bowel sounds.

4. John's wife mentions that he has been experiencing persistent nausea and vomiting for the past two days.

5. No signs of trauma or other acute medical conditions are noted.

Working Diagnosis:

Based on the patient's medical history, clinical presentation, and medication use, the working diagnosis is anti-Parkinson medication toxicity, specifically levodopa-carbidopa (Sinemet) toxicity.

Plan:

The medical team initiates the following management plan:

1. Supportive care: John's vital signs are continuously monitored, and intravenous fluids are administered to maintain hydration.

2. Discontinuation of medication: Sinemet is immediately stopped to prevent further toxicity.

3. Symptomatic treatment: Medications such as benzodiazepines may be administered to manage the patient's agitation and motor symptoms.

4. Gastric decontamination: If ingestion of the medication was recent and an overdose is suspected, activated charcoal may be considered to reduce further absorption of the drug.

5. Close monitoring: John is admitted to the hospital for close observation and monitoring of his neurological status, cardiovascular function, and fluid balance.

6. Consultation: A neurologist or a movement disorder specialist is consulted to provide further guidance in managing the patient's Parkinson's disease and adjusting his anti Parkinson medication regimen.

Follow-Up:

John's condition gradually improves over the next few days with supportive care and discontinuation of Sinemet. The neurologist adjusts his medication regimen, titrating the doses to find a balance between symptom control and minimizing the risk of toxicity. John is discharged with appropriate follow-up instructions and referrals for ongoing management of his Parkinson's disease.

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