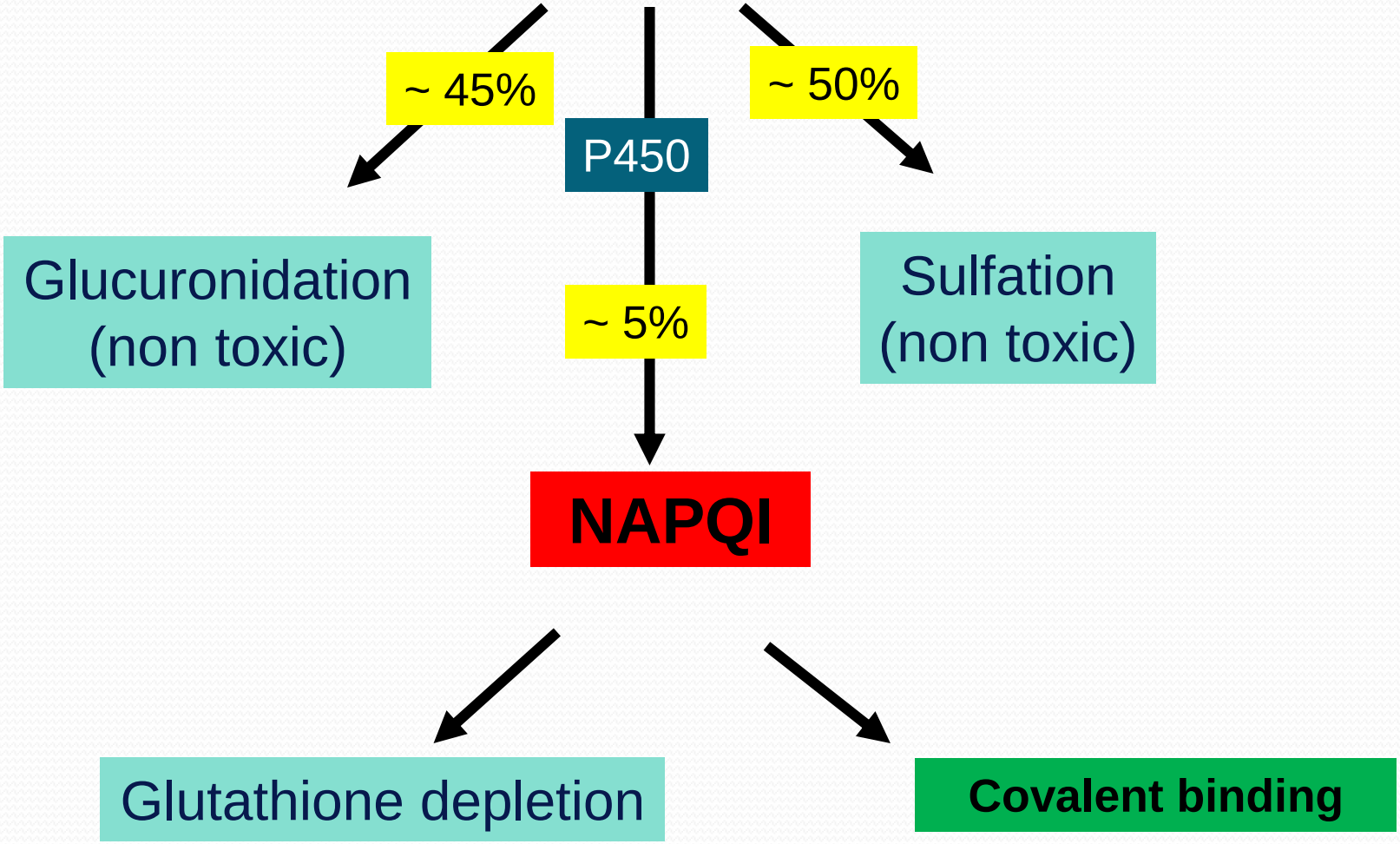
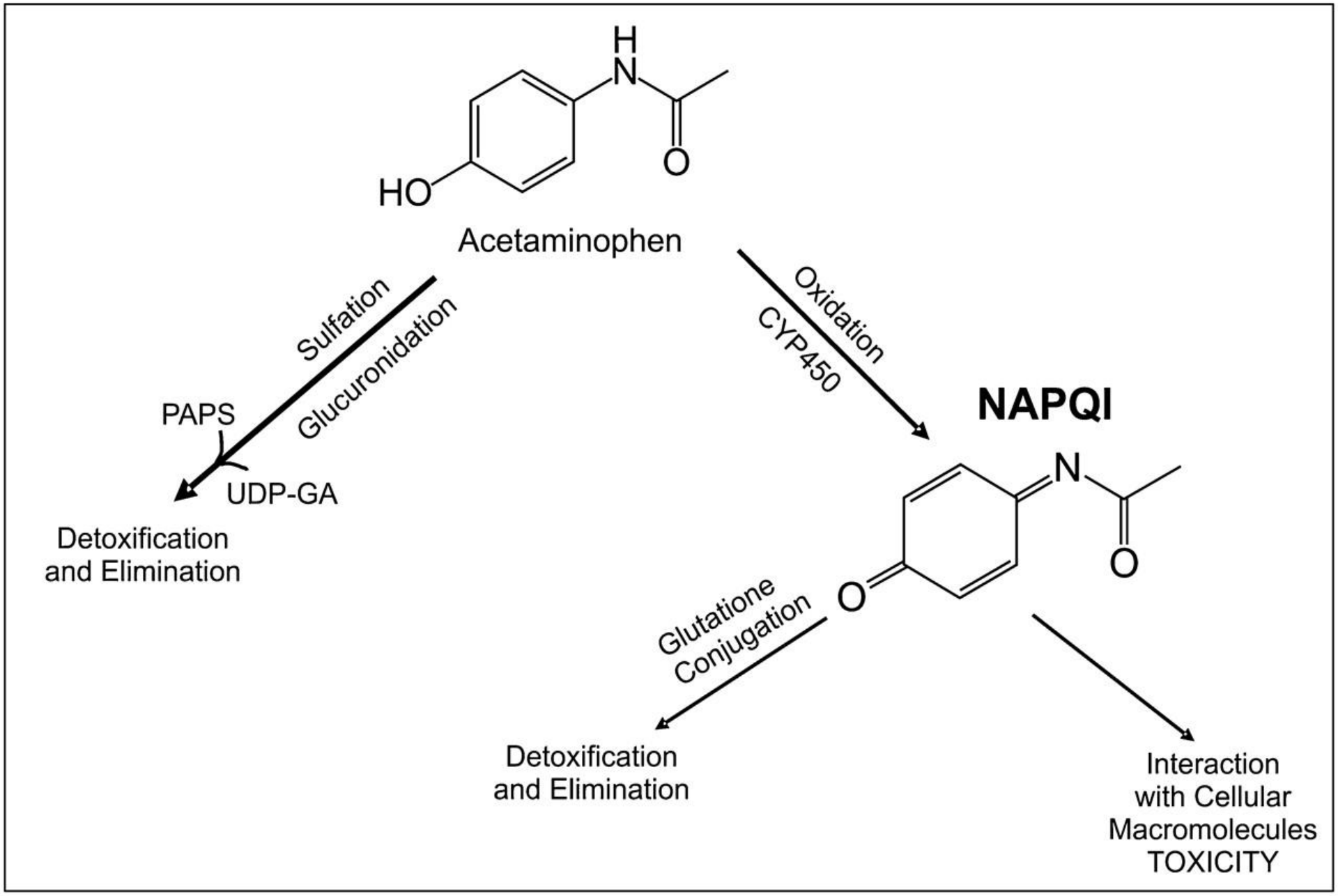
Over the counter drugs Acetaminophen(AC)

- AC now surpasses aspirin as a major cause of poisoning
- The most serious toxic consequence is hepatic necrosis.
- AC absorbed rapidly from stomach and upper GIT, most of the drug metabolized by conjugation with glucuronide and sulfate
- Another pathway of minor importance (4%) involve the CYP-450 to form NAPQI.

Acetaminophen Metabolism



Acetaminophen Metabolism



- NAPQI bind covalently to hepatocyte protein causing necrosis
- glutathione inactivate it by conjugation and subsequent transformation to AC-3-mercapturic acid, which is readily excreted
- threshold dose for producing hepatotoxicity 250mg/kg.
- Adose of 15g in adult and 4g in child sufficient to cause significant hepatotoxicity
- Toxicity of AC more prominent in patients taking alcohol and drugs such as enzyme inducer.

Characteristics of poisoning

- Phase I (up to 1 day):

✓ Gastrointestinal irritability predominates with nausea, vomiting, and sweating.

✓ Large ingestions can result in metabolic acidosis within 4 hours of ingestion.

✓ Cardiac effects (arrhythmias, bradycardia) may develop.

- Phase II (1-3 days):

✓ Hepatic toxicity develops with elevation of hepatic enzymes, prothrombin time, and bilirubin.

✓ Amylase elevation may peak at 2 days.

✓ Oliguric renal failure may develop and may coincide with hepatic encephalopathy.

Characteristics of poisoning

- Phase III (3-5 days):

✓ Hepatic necrosis continues with disseminated intravascular coagulation

✓ hepatic encephalopathy

✓ portal hypertension, and

✓ Icterus.

✓ The patient is at risk for hypoglycemia.

✓ Renal insufficiency may also be present.

- Phase IV (5-14 days):
- Recovery with resolution of elevated hepatic enzymes usually occurs.

Management of poisoning

- Prompt diagnosis and early treatment are essential

- Gastric decontamination should be undertaken and depend on time of ingestion, emesis and lavage are not beneficial after 4hour of ingestion.

- NAC and methionine afford antidotal activity mainly by

1. restoring intracellular glutathione
2. such compounds serve as a source of inorganic sulfur this may promote sulfation.

- Glutathione itself doesn't enter hepatocyte and is therefore useless as an antidote.

- Loading dose of 140mg/kg of NAC orally followed by 70mg/kg every 4hours for 17-18 doses.

Cough and Cold Preparations Toxicity

- different preparations may contain different agents or combinations.
- For example dextromethorphan is often present in combination with pseudoephedrine, antihistamines/anticholinergics, and acetaminophen.

➢ are often abused in combination with other drugs,

Nonprescription sympathomimetics

Ephedrine principal effects are

- CNS stimulation
- Hypertension
- bronchial muscle relaxation and mydriasis.
- arrhythmias, strokes, heart attacks, and deaths, particularly when used by patients with pre-existing cardiac disorders
- abused for their stimulant effects and are commonly found in cold preparations and dieting agents
- Pseudoephedrine shares the same pharmacological properties of ephedrine. It binds to central and peripheral α-1.receptors, resulting in significant CNS stimulation and vasoconstriction, respectively, particularly affecting arterioles of mucous membranes, skin, kidneys, and abdomen

Nonprescription sympathomimetics

ephedrine, phenylpropanolamine, and phenylephrine

- Phenylpropanolamine and ephedrine act primarily via

1. increased β_1- and β_2-adrenergic receptor agonist activity
2. enhanced release of catecholamines.

- Phenylpropanolamine is as potent as ephedrine but causes less central nervous system (CNS) stimulation.
- Recently FDA remove phenylpropanolamine from market because of concern for increased risk of hemorrhagic stroke.
- Phenylephrine is a selective α_1-adrenergic receptor agonist.
- It is a derivative of epinephrine, peripheral vasoconstriction is the most common adverse effects

Substance	Alpha-Adrenergic Response	Beta-Adrenergic Response	CNS Stimulation
Amphetamine	++	++	+++
Caffeine	++	+	+
Ephedrine	++	+++	++
Phenylephrine	++++	0	+
Phenylpropanolamine	+++	+	+++

+, week activity.

++++, strongest activity.

CLINICAL PRESENTATION

- All the nonprescription sympathomimetics share some similar clinical features.

- Common symptoms include nausea, vomiting, diarrhea, abdominal pain, tremors, anxiety, agitation, and headaches.

- more severe symptoms include delirium, seizures, hypertensive crisis, intracerebral hemorrhage, and myocardial infarction.

- Can cause severe hyperthermia that may be lethal if untreated. due to

1. activation of specific dopamine receptors
2. Increased motor activity and stimulant-induced seizures are also possible cause.

- hypertensive crisis is documented in significant acute overdoses.

Chronic Toxicity

- Chronic excessive ingestions of over-the-counter sympatho-mimetic result in tachycardia, hypertension, palpitations, myocardial infarction, vasculitis, cardiomyopathy, and dysrhythmias

- sustained hypertension and subsequent hemorrhage.

- A cerebral vasculitis from chronic use and misuse of ephedrine may cause an acute intracerebral hemorrhage

Methylxanthine derivatives

- Caffeine, theophylline and theobromine present in food, beverage and in drug therapy
- They stimulate CNS, induce dieresis, relax smooth muscle, and stimulate cardiac function
- caffeine also augment the analgesic properties of analgesic drugs
- theophylline causes sever irritation to the GIT where nausea and vomiting are the hallmarks of over dose.
- Are potent stimulant of CNS and CVS most significant toxic sequelae result from over stimulation

Numerous mechanisms explain xanthine toxicity

1. increase calcium release from intracellular site
2. Accumulation of CAMP through inhibition of phosphodiesterase inhibition
3. Adenosine receptor blockade

- Adenosine receptor antagonism leads to vasoconstriction, hypertension, tremor, and agitation.
- Inhibition of phosphodiesterases, causing increased levels of cyclic AMP, which results in increased levels of catecholamines
- Muscle contractility is enhanced through increased intracellular calcium levels and increased permeability of the sarcoplasmic reticulum to calcium.
- Stimulation of gastric acid and intestinal secretions and lowering of lower esophageal sphincter tone by caffeine commonly result in diarrhea and abdominal cramping
- Direct stimulation of CTZ appear to cause nausea and vomiting

Characteristic of poisoning

Caffeine

- Therapeutic blood concentration of caffeine are less than 1mg/dl.
- Adverse effects are observed within dose around 1g, but acute toxic dose appear between 5-10g

- effect on **CNS** including restlessness, excitement, and insomnia that can progress to delirium.
- **Muscle** become tense and spastic
- **CVS effect** include tachycardia, extrasystoles, tachypnea, ventricular fibrillation and cardiopulmonary arrest.
- As **toxicity progress** convulsion, coma and death due to shock are likely.

Category	Product	Amount of Caffeine
Coffee	Brewed coffee	40-180 mg/5 oz(150ml)
Tea	Brewed commercial tea	20-90 mg/5 oz
Soft drinks	Coca Cola	46 mg/12 oz
Food	Milk chocolate	2-7 mg/8 oz
Medications	Cafergot	100 mg/tablet
	Excedrin	65 mg/tablet
	Panadol extra	65 mg/tablet

Characteristic of poisoning

Caffeine

- Physical dependency to caffeine does exist with withdrawal symptoms usually occurring within 12-24 hours following cessation
- A daily dose over 235 mg (about 2.5 cups of coffee/day) can increase the risk for likelihood of withdrawal.
- While lethargy and weakness may occur, facial flushing and severe headaches predominate this syndrome and may last as long as 9 days.
- Symptoms correlate with the amount ingested prior to cessation.

Characteristic of poisoning

Theophylline

- has a narrow therapeutic margin 10-20 ug/ml.
- rapid aminophylline I.V. injection can cause death due to cardiac arrhythmia
- nausea, vomiting, headache, dizziness, palpitations, tachycardia, hypotension, restlessness and seizure.
- Seizure occurs when plasma concentration reach 25-40ug/ml.

- The nausea and vomiting seen after theophylline poisoning may result from

1. direct CNS stimulation of the CTZ
2. relaxation of lower esophageal sphincter tone,
3. phosphodiesterase inhibition, and
4. increases in gastric acid secretion.

- Adenosine receptor antagonism in the brain has been implicated in the seizures and status epilepticus
- Peripheral adenosine receptor antagonism may also be partially responsible for the tachycardia and cardiac dysrhythmias

- Patients develop chronic theophylline toxicity as a result of

1. accumulation secondary to inappropriate dosing
2. liver disease,
3. drug-drug interactions,
4. processes that inhibit the elimination of theophylline
5. renal failure patients, the active metabolite, 1,3-dimethyluric acid, may accumulate causing toxicity.

Treatments

- **Seizures** should be treated aggressively with

1. benzodiazepines
2. if required, barbiturates
3. followed by protocols for status epilepticus including continuous IV infusion of midazolam

- **supraventricular dysrhythmias**

1. correction of hypoxia and any fluid and electrolyte abnormalities
2. cardioversion, and diltiazem if needed.

- **Ventricular dysrhythmias**
- lidocaine, cardioversion, or defibrillation as needed.

- **Hypotension**
- adequate crystalloid fluid followed by peripheral α-adrenergic receptor agonists, such as norepinephrine.

Antihistamines

- Absorption of antihistamines from the gastrointestinal tract is usually rapid.
- After a therapeutic dose, the peak drug effect is usually seen in 1 hour.
- anticholinergic toxicity may be prolonged, possibly due to decreased gut motility.
- Dermal absorption of topical antihistamine preparations has resulted in anticholinergic poisoning in children.
- The duration of action for therapeutic doses ranges from 4 to 6 hours for chlorpheniramine, or tripelennamine to 24 hours for meclizine, terfenadine, or astemizole.

Cardiac Toxicity of the Nonsedating Antihistamines

- Some patients taking terfenadine or astemizole develop very high drug levels that result in spontaneous torsades de pointes tachycardia.

- This has been associated with

1. taking extra doses of the drug and
2. concomitant use of ketoconazole or erythromycin, both of which block the cytochrome P-450 3A4 enzyme

- Other inhibitors of this enzyme include clarithromycin, fluconazole, miconazole, itraconazole, fluoxetine, nefazadone, omeprazole, cimetidine, diltiazem, quinidine, and grapefruit juice (flavonoids).

- Ventricular tachycardia has also been seen after overdose. These dysrhythmias occur secondary to prolongation of the QT_c by potassium channel blockade.

Clinical presentation

Antimuscarinic Effects	CNS Effects	ECG Effects
Dry, flushed skin	Seizures	Sinus tachycardia
Dry mucous membranes	Delirium	
Dilated pupils	Coma	
Decreased bowel sounds or ileus		
Urinary retention		

Treatment

Decontamination:
Activated charcoal
Consider gastric lavage in severe cases
Agitation:
Intravenous benzodiazepines
Consider physostigmine IV over 5 minutes
Adult: 1–2 mg
Pediatric: 0.02 mg/kg (maximum, 2 mg)
Hyperthermia:
Ice water immersion or tepid water/fans
Seizures:
Intravenous benzodiazepines
Consider physostigmine for refractory seizures

NSAIDS

Salicylates

- Many of the pathophysiologic consequence of salicylates toxicity can be explained by

1. CNS stimulation
2. interference with uncoupling oxidative phosphorylation

- The respiratory center is stimulated

1. directly by salicylates and
2. indirectly by increasing PCO_2 production.

Figure 12.1

- Salicylates enhance oxygen consumption by increase cellular metabolic rate result in hyperthermia with accumulation of CO_2 which then cause hyperpnea.

- On the other hand direct effect leads to both hyperpnea and tachypnea. These collectively lead to increase amount of CO_2 expired by the lung.

- As a result there is less plasma CO_2 recall the following reactions of bicarbonate buffer system for maintain blood PH:

$$H2O + CO_2 \longleftrightarrow H2CO3 \longleftrightarrow H^+ + HCO_3^-$$

- Since there is less CO2 so less H2CO3 resulting in a deficit of carbonic acid with a subsequent decrease in H^+ concentration.

- Blood PH dependent on bicarbonate/carbonic acid ratio according to Henderson – Hasselbalch equation:
- PH= 6.1 – log [HCO3] / [H2CO3]
- Normally [HCO3]= 27mEq/L
- [H2CO3]= 1.35 mEq/L

- So the ratio 20/1 and at this ratio the PH 7.4,
- as PCO2 and H2CO3 decrease the ratio will increase result in elevation of blood PH

- The kidney try to compensate by excreting more HCO^-_3 and retaining H^+ and non HCO^-_3 and this lead to latent metabolic acidosis(this is the first effect)

- The second action of salicylate poisoning result from uncoupling of oxidative phosphorylation which also lead to metabolic acidosis by

- decrease ATP lead to increase glycolysis this result in increase production of lactic and pyruvic acids this associated with increase periphral glucose demand leads to excessive free fatty acid in the liver producing increase keon bodies and ketoacidosis.

- The third factor lead to metabolic acidosis inhibition of the dehydrogenase enzyme of the krebs cycle causing an accumulation of alpha ketoglutarate and oxaloacetate.

- Finally 4- Inhibition of amino acid metabolism lead to accumulation amino acid and metabolic acidosis.

- Salicylates also interfere with normal glucose concentration resulting in hypoglycemia this important in chronic salicylism.

- **NSAIDs inhibit the synthesis and release of prostaglandins by reversible, competitive inhibition of cyclooxygenase activity.**

- **Cyclooxygenase-1 is found in blood vessels, stomach, and kidney, hence the occurrence of gastrointestinal or renal adverse effects seen in acute or chronic exposure settings**

- **Gastrointestinal adverse effects result from decreased production of the cytoprotective prostaglandins I_2 and E_2, with subsequent local tissue damage and bleeding**

- **Severe adverse renal effects may partly be due to inhibition of renal prostaglandin-mediated compensatory responses leading to diminished renal blood flow, vasoconstriction, further decreased renal blood flow, and decreased glomerular filtration rate**

Characteristic of poisoning

- The major early toxic manifestation from CNS stimulation. These may include nausea, vomiting, tinnitus headache, hyperpnea, respiratory alkalosis and metabolic acidosis

- the toxicity closely related to brain salicylate concentration.

- Dehydration is another serious consequence occurs by several factors:

1-increase heat production from salicylate induce glucose and lipid metabolism lead to hyperpyrexia and diaphoresis

2- when renal componsate for respiratory alkalosis lead to increase excresion of HCO_3, Na, K and equiosmolar quantity of H_2O

3-Metabolic acidosis increase urinary output and electrolyte loss.

Management of poisoning

- removal of aspirin from the GIT, and correction of metabolic acidosis, dehydration, hyperthermia, hypoglycemia, and hypokalemia.

- Emesis is easer and more effective, because after ingestion of overdose absorption may continue 8-12 hours due to decrease gastric emptying and decrease drug dispersion in the GIT. Add to that enteric coated tablet absortion delayed 24 hours.
- For dehydration approperiate fluid replacement is critical,

- Sodium bicarbonate is given to help correct metabolic acidosis and to produce alkaline urine promote movement of salicylate from intracellular site to plasma to enhance excresion
- glucose added to correct hypoglycemia and ketosis.
- Potasium added to correct hypokalemia and prevent alkalosis from NaHCO3 replacement

- Hyperthermia can be reduced by cold or tapid water sponging.
- Diazepam may be required for seizure.

Ibuprofen

- After absorption it is quikly metabolised with an elimination halflife of 2 hours. After acute overdose acute renal failure result from decreased production of intrarenal prostaglandins

- **Charcteristic of poisoning**
- In most reported cases patients either have no symptoms or mild manifestation of GI irritation such as nausea and vomiting. Mtabolic acidosis, hypotension,
- CNS toxicity and renal dysfunction are reported only rarely.

- **Management of poisoning**
- Symptomatic and supportive care , emesis, lavage, and fluid replacement are important.

Vitamine A

- Vitamin A influences differentiation of epithelial membranes particularly corneal, gastrointestinal , and genitourinary epithelia
- Derivatives of vitamin A include retinol, retinal, retinoic acid, and b-carotene (a precursor).

Hypervitaminosis A has occurred in

1. Usually due to prophylaxis use from extended self therapy
2. Some times resulted from food faddism
3. Patients receiving high dose of vit A. or analoges (Isotretinoin and tretinoin) to treat skin disease like ichthyosis, acne and Darier disease.
4. Chronic renal disease and in patients taking supplement of VitA with hemodialysis

➢ Large doses of VitA in pregnancy are teratogenic

Mechanism of poisoning

- Clinical manifestation occur when protein bound become saturated

- Cellular membrane s are then exposed to unbound vitamin which lead to degradation of the membrane structure and this responsible for cerebral spinal fluid pressure and CNS manifestation

- Excessive hepatic vitamineA lead to fibrosis, sclerosis of hepatic vein, destruction of sinusoidal space with subsequent portal hypertension and ascitis

- VitA stored in hepatocyte and excessive dose lead to conversion of Ito cells to fibroblast that form collagene and subsequent pathology

- VitA elevate serum PTH at dose as low as 25000 U. lead to hyper-calcemia, bony changes and premature epiphysseal closure

Charcteristic of poisoning

- Detection is mixed
- 300000-600000U as daily dose given over months—several years lead to symptoms, 50000 may be toxic
- 25000-50000 for 30 days increase intracranial pressure in infant

- GIT symptoms
- CNS
- Skin----dry, pruritic, rash, brittle nail, allopecia
- Bone------hyperosteosis
- Other-----hepatosplenomegaly, lymph node enlargement, anemia, epistaxis, bleeding,-----

Management of poisoning

- Immediate most signs and symptoms disappeared within 1-2 weeks
- hyperosteosis (increase osteoclast activity) remain evident for several months after recovery
- If vit A not withdrawn -------irreversible hepatic damage
- Vit E enhance tissue uptake of vit A but still contraversy

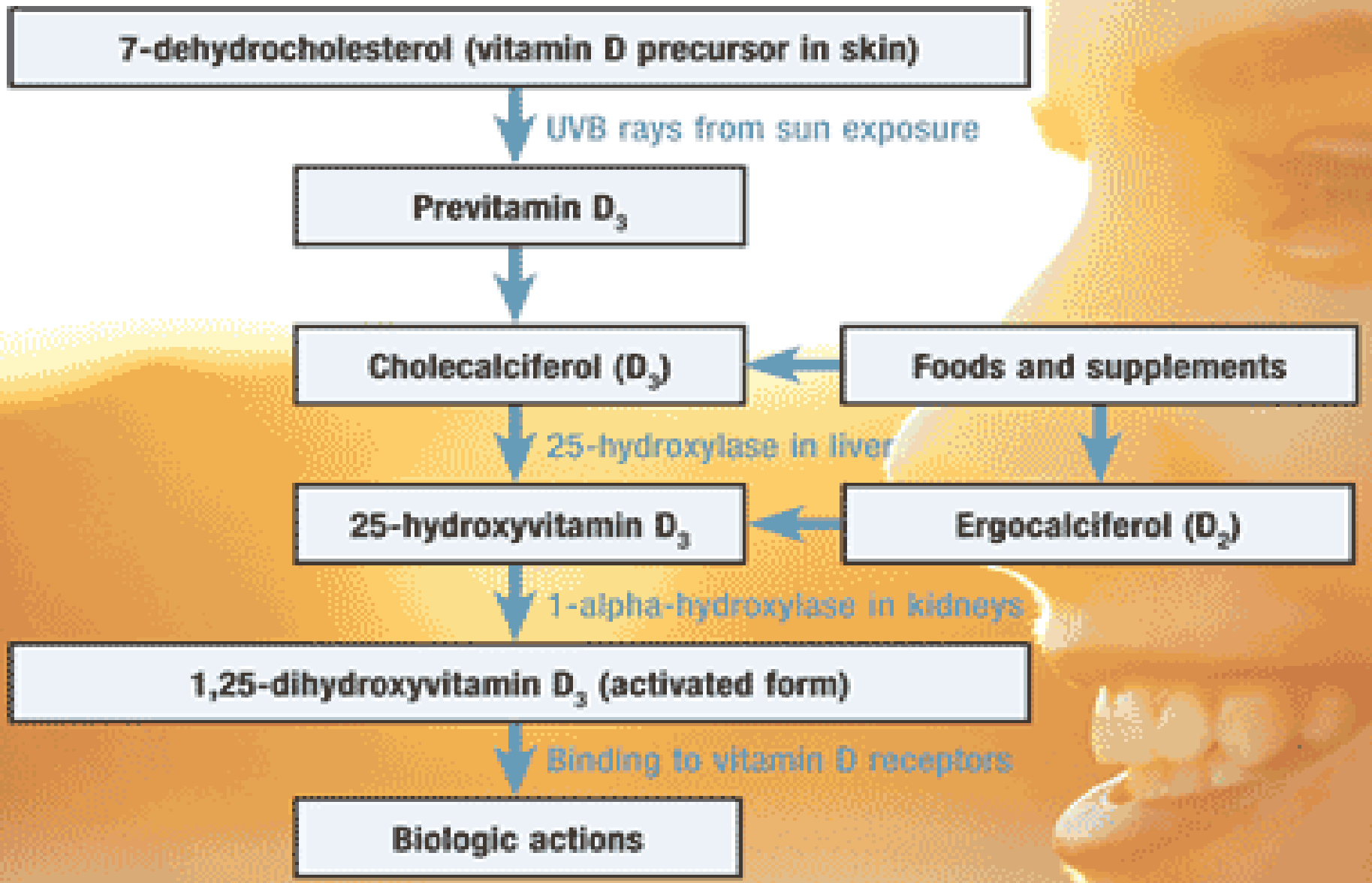
- **Vitamine D**
- Is the most toxic of all vitamins.
- This occurs mainly in patients used VitD to

✓ treat arthritis,
✓ muscle cramps,
✓ cold hand and feet
✓ also this vitamin used in various nutritional disorders

- All the problems associated with VitD toxicity are caused by it is action to elevate the concentration of plasma calcium.
- VitD misuse with intake averaging 300000-400000 U daily responsible for hypercalcemia in infancy

- VitD per se does not elevate Ca rather it is depend on it is conversion to 1,25-dihydrooxycholecalciferol to exert it is activity in several sites
- Calcitonin normally exert anegative effect on plasma calcium concentration. So in deficiency like in patient with removed thyroid gland this lead to rise plasma Ca.

Figure 1. Vitamin D synthesis.

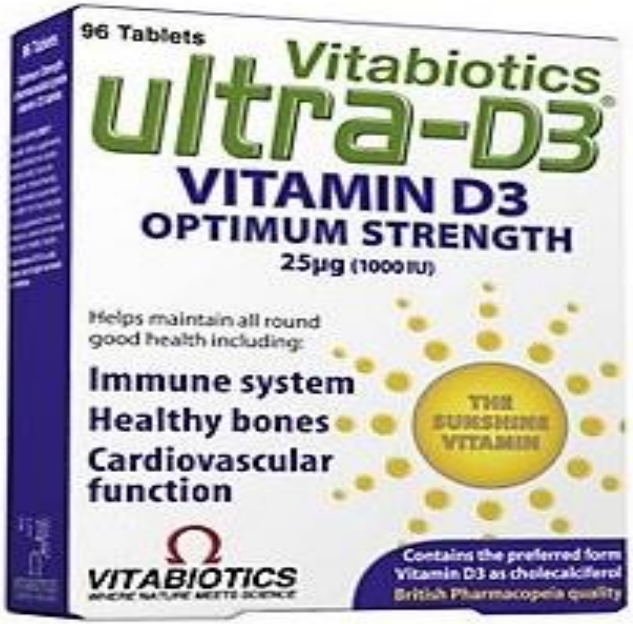


UVB: ultraviolet B.
Source: Reference 32.


Baby
Ddrops
The sunshine vitamin in just one drop
Liquid
vitamin D
Vitamin supplement
90 drops for 90 days
Babies need vitamin D for healthy growth and development. Contains no preservatives, no artificial flavours, no colouring.
400 IU
per drop
2.5 mL / 90 drops
Baby
Ddrops
pour bébé
vitamin
vitamine D
400 IU per drop
UI par goutte


فيت أ+د
فيتامينات أ+د
١٥ ملليلتر
نقط فموية للأطفال


Stérogyl
2000000 UI
100 ml
Stérogyl
2000000 UI
100 ml
Solution buvable en gouttes
Voie orale
1 flacon de 20 ml
1000 gouttes


96 Tablets
Vitabiotics
ultra-D3
VITAMIN D3
OPTIMUM STRENGTH
25µg (1000 IU)
Helps maintain all round good health including:
Immune system
Healthy bones
Cardiovascular function
THE SUNSHINE VITAMIN
VITABIOTICS
Contains the preferred form Vitamin D3 as cholecalciferol
British Pharmacopoeia quality


Stérogyl 15 "H"
Stérogyl 15 "A"

Characteristics of poisoning

- Death after acute toxic dose due to hypercalcemia
- Toxic effect of chronic use are due to deposition of Ca in soft tissues especially kidney and heart.
- Polyuria and polydipsia
- Aortic valvular stenosis, and nephrocalcinosis with calcification of soft tissues are characteristic finding.
- Cardiac rhythm may affected(Ca deposition in cardiac myofibril)
- x-ray examination show metastatic calcification and generalized osteoporosis of bone and arrest growth in children for six months after single episode of sever hypercalcemia.

- However VitD intoxication occur after chronic oral ingestion of large doses of VitD2 or D3(usually 50000 or more unit daily) taken for several months these excessive quantity stored in body fat and then released slowly.

- high doses of vitD(12000 or more per day) was a precipitating cause of myocardial infarction?.

Management of poisoning

- Discontinuing of VitD,
- reduce Ca intake,
- administered glucocorticoids(GC)
- fluid intake.

- GC such as prednisone(20-40)/day to reduce intestinal absorption, control hypercalcemia, prevent irreversible renal damage and ectopic calcification.

- **Vitamin K**
- Few cases reported because it is not OTC drug.

- Major toxicity associated with water soluble synthetic such as menadione.
-
- cause erythrocytic membranes to rupture lead to hemolysis, jaundice and kernicterus(oxidative damage).

- more prevalent in patients with G6PD deficiency and in doses more than 10mg.

- VitK1(phytomenadione) not lead to hyperbilirubinemia and for this it is preferred.

- **Vitamin E**
- It has low toxicity profile,

- mega dose may lead to

✓ headache, nausea, fatigue, dizziness,

✓ blurred vision(large dose antagonized action of VitA),

✓ inflammation of mouth, chafing lips, GI disturbance,

✓ muscle weakness, hypoglycemia,

✓ increase bleeding tendency, decrease in hematocrit

- Adult can tolerate dose up to 1000 U/day without developing toxicity.

- Vit E may interact with VitK metabolism result in prolonged prothrombin time----------increase bleeding time.
- Also decrease wound healing in experimental animals.

VitamineC

- Numerous unwanted effect occur when taken in overdose
- large doses of VitC reduce concentration of VitB12 in the blood?
- Vit C acidify urine in 1-6g.
- In pregnancy large doses of VitC cause scurvy in some newborn when pregnant women ingest 400mg/day this caused by:

1. Vit C enhances development of fetal liver microsomal enzyme which then enhanced destruction of Vit C after birth.
2. fetus recognize the danger of increase vitC concentration and increases it is metabolic rate to destroy excess concentration of the Vitamin.

- After birth such destruction is enhanced and symptoms of scurvy are seen shortly after delivery.
- Also the same finding some time observed in adults who suddenly withdrawn from large doses of VitC.
- tapering megadoses of vitamin by about 10% to 20% daily.
- Vit.C increases renal excretion of oxalate, uric acid, and Ca.? this increase potential of stone formation in the kidney and bladder . this may occur at doses of 1 gram or more daily.
- Interfere with urine and stool testing like false negative reaction with glucose oxidase tests

- **Vitamin B1(thiamine)**
- Numerous cases were reported to parenterally thiamine administration,
- symptoms ranged from nervousness, convulsions, weakness, headache and neuromuscular paralysis to cardiovascular disorders including rapid pulse, peripheral vasodilation, arrhythmia, and anaphylactic shock.

- **Niacin(B3)**
- In single doses of 50 mg niacin(nicotinic acid), intense flushing, and pruritis have been reported .
- increase dose to 30g or more associated with more serious toxicity

- Abnormal liver function and jaundice are the most common toxicities could be explained by that niacin used for formation of NAD and NADH which serve as co-enzyme for various dehydrogenase enzymes in oxidation reduction reaction

- **Vitamin B6**
- Pyridoxine induce reactions are rare.
- Convulsive disorder have occurred due to both deficiency and excess.
- 1g daily may not associated with toxicity.

- **Vitamin B12**
- Cyanocobalamin associated sometimes with allergic reaction to injectable product.

- Symptoms of edema of the face, urticaria, shivering, bronchospasm, rash, dyspnea, and anaphylaxis have appeared but only after years of vitamin administration.

- **Folic acid**

- It is relatively nontoxic with oral doses of 15mg but a few sensitivity reaction had been reported.

- Long term folic acid therapy increase seizures frequency in some epileptic patients

- may precipitate B12 deficiency neuropathy in some cases of megaloblastic anemia.

- A

1. Mechanisms behind Ipecac induce vomiting mention doses used
2. Method of Modification of dialysis fluid
3. Complications of Hemodialysis

- **B**

1. Proposed Mechanisms behind char coal administration mention doses used
2. Efficacy of Hemoperfusion depends on
3. Numerate the antidote for each of the following compound(iron, isoniazid, benzodiazepines and cyanide)