Analgesics and sedative hypnotics
I- Salicylate poisoning

❑ Preparations

1- Acetyls salicylic acid (aspirin)

2- Salicylic acid

3- Methyl salicylate (oil of wintergreen)

A teaspoonful contain 7000 mg

❑ Therapeutic uses

1- Analgesic , antipyretic and anti-inflammatory

2- Salicylic acid use as keratolytic

3- Methyl salicylate (Rheumatism)

❑ Absorption

-Readily absorbed from GIT in an uionized form

- Poorly soluble in the stomach HCl foming concretions with delayed absorption

❑ Metabolism

- 80 % of the therapeutic dose is metabolized in the liver by conjugation (Limited capacity and saturation occurs easily above therapeutic dose)
- Small amount hydroxylated (10%)
- 5% excreted unchanged
- Salicylate crosses the placenta

❑ Excretion

-Toxic dose:50% excreted within first 24 hours
- Increased urine pH increases excretion three folds

❑ Toxic Action

1- Local action: GIT irritation

Gastritis with gastric erosion or even haemorrhage

2- Systemic action:

- CNS :Stimulation of respiratory centre
- Metabolic acidosis

3- Hyperthermia

- Enhancement of o_2 consumption
- Enhancement of cellular metabolic rate
- Dissociation of oxidative-phosphorylation

4- Haematological effects

• Hypoprothrombinaemia

- Transformed in the intestine to dicumarol by the action of the intestinal bacteria which competes with Vit. K
- Interfere with platelets functions
- In toxic dose , destruction of RBCs

5- Other effects

- Stimulation of CTZ inducing vomiting
- Inhibition of VMC
- Cerebral cortex stimulation followed by depression
- Allergic reaction

❑ Mode of poisoning

1- Accidental :

- Children
- Overdose
- application of topical preparation to large skin area

2- Suicidal: In women and young men

❑Fatal dose : 20 gm orally

4 ml of oil of wintergreen

❑Fatal period : 1-3 days

❑Clinical picture:

A- Mild toxicity: 45-65 mg/dl

- Burning pain, mild hyperapnea, nausea, vomiting, lethargy, dizziness , tinnitus

B- Moderate toxicity: 65-90 mg/dl

- Moderate hyperapnea, hyperthermia, sweating, dehydration, marked lethargy, excitation , eccyhmosis.

C- Severe toxicity: 90-120 mg/dl

- Previous symptoms but in severe form
- Convulsion, pulmonary oedema, cyanosis.
- Allergic reaction and skin eruption.

D- Lethal toxicity: more than 120 mg/dl ; coma and death

D.D: Diabetic coma

- **Gerhardt test: (Ferric chloride test)**
- **5ml urine + few drops of ferric chloride ……. Purple colour**
- **Boil urine then cool it ….. Repeat test ….. +Ve result with sailcylate**
- **Treatment**

1-Gastric decontamination

A- Syrup of ipecac

B- Gastric lavage : effective up to 12 hours post-ingestion as tablets stick to gastric mucosa

-Activated charcoal

- **avoid $NaCO_3$ (soluble complex with salicylate)**
- **Saline cathartic**

2- Enhancing elimination

-Forced alkaline diuresis

-Haemodialysis

3- Symptomatic treatment

- **Care of respiration**
- **Fluids for dehydration**
- **Vit. K**
- **Ice bags or cooling blankets for fever**

II- Acetaminophen poisoning

-Synthetic analgesic antipyretic

❑Preparations:

- Paracetamol, abimol, paramol
- In combination with other drugs (analgesics, antihistaminics, opiates, stimulants)

❑ Absorption: Rapid complete absorption after oral administration

❑ Metabolism : In the liver

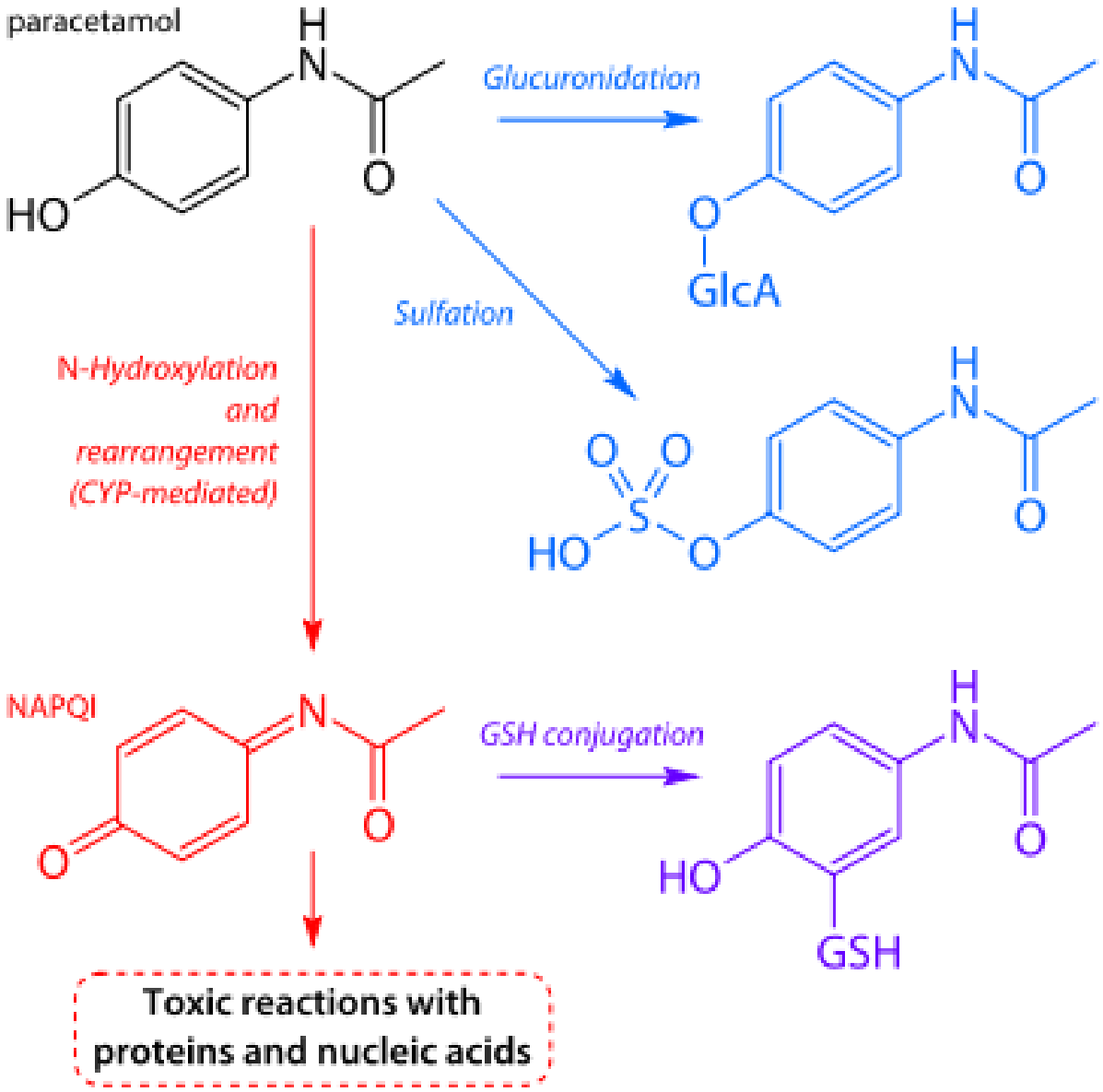
- Sulfation:52 %
- Glucuronid conjugation 42 %

-Unchanged 2 %

-Metabolized by p450 enzyme into toxic metabolite N-acetyl-p- benzoquinonimine (NAPQI) detoxified by glutathione, excreted as mercapturate (Non-toxic)

❑ Mechanism of toxicity:

- Depletion of glutathione
- Production of toxic metabolites
- Toxic metabolites bind with the liver cells components producing necrosis.


paracetamol
Glucuronidation
GlcA
Sulfation
N-Hydroxylation
and
rearrangement
(CYP-mediated)
NAPQI
GSH conjugation
GSH
Toxic reactions with
proteins and nucleic acids

❑Mode of poisoning

1- Accidental : among children
2- Suicidal
❑Fatal dose: 4-5 gm in children ; 12-25 gm for adults
❑Fatal period : 4 days- 2 weeks

❑Clinical Picture:
❖Stage I: 2-24 h
-Anorexia, nausea, vomiting, pallor, malaise , subsidence of symptoms
❖Stage II: 24-48 h
- Symptoms are less severe, patient looks normal, increased liver enzymes and bilirubin, prolonged prothrombin time
❖ Stage III: 3-5 days
- Right hypochondrial pain and tenderness
- Peak abnormalities of liver functions
- Bleeding tendency
- 1-2 % die from liver failure; 1-2 % die from renal failure
❖ Stage IV: 5days- 2 weeks (recovery stage)
- Liver function tests return normal
- Hepatic architecture return normal

❑Treatment:

1- GIT decontamination
Emesis by syrup of ipecac
Gastric lavage with tape water or saline
Activated charcoal ; useful but may interfere with n-acetyl cystein
Sodium sulphate cathartic : rebuild sulphate stores

2- Physiological antidote:
N-acetyl cystein is the first choice (oral /I.V.)
Enhance synthesis of glutathione
Source of inorganic sulphur
Dose: 140 mg /kg followed by maintenance 70 mg/kg

3- Supportive therapy for the liver

III- Barbiturate poisoning

-Sedative hypnotic, derovative of barbituric acid

❑ Classification

A- Long acting (6-8 hours) : phenobarbitol

B- Intermediate acting (4-6 hours) : amobarbital

C- Short acting (3 hours): Secobarbital

D- Ultra-short acting (15 min.): thiopental

❑ Therapeutic uses

Sedative, hypnotics, anti-convulsnat, general anaesthesia, psychoanalysis

❑ Absorption

-Absorbed from GIT when given orally

❑ Distribution

- They are distributed to all tissues

-Cross placental barrier - appear in mother milk

-Should not be given to pregnant or lactating women

❑ Action : CNS depression:

- Depression due to stimulation of GABA release
- Cerebral cortex and reticular formation are more sensitive
- Vital centres are less sensitive
- Depressant to all cellular activities of the body

❑ Mode of poisoning:

-Suicidal : more common because it is easily obtained, widely used , cause deep coma and painless death

- Accidental : common ; drug automatism

- Homicidal : used to facilitate rape, robbery or murder

❑ Fatal dose: minimum lethal dose is commonly 10 times therapeutic

-1 gm ultrashort acting
-1-1.5 gmshort acting
- 1.5-2 gm intermediate acting
- 2-4 gm long acting
- Synergism with alcohol and depressant drugs

❑Fatal period : 1-4 days

❑Clinical picture

1- CNS depression:

-Cortical depression : deep coma may last several days

- Depression of R.C. (Cyanosis, chyne-stokes ; respiratory failure)

- Barbiturate coma : is deep profound coma characterized by:

  - ➢ Intense cyanosis
  - ➢Slightly dilated reactive pupils
  - ➢Skeletal muscles relaxation with loss of reflexes
  - ➢ slow shallow stertorous breathing
  - ➢Manifestation of shock (medullar depression)

2- Renal manifestation

-oliguria, albuminuria, haematuria

3- cutaneous manifestation

-Tens bullae surrounded erythema involving fingers, malleoli, buttocks

- Not diagnostic (prolonged coma, CO, sedative hypnotics)

- **Complications :**
  - ❖ Hypostatic pneumonia, bronchopneumonia, lung abscess
  - ❖ Pulmonary and cerebral oedema
  - ❖ Circulatory collapse
  - ❖ Irreversible renal failure

- **Cause of death**

- Early; asphyxia delayed; complications

- **Treatment:**

1- Care of respiration and adequate ventilation

2- GIT decontamination

3- Respiratory stimulants (Megimide or Bemegride)

-physiological antidote (restricted for short acting) ; avoided in severe cases

-Initial stimulation of R.C. followed by depression ; many complications such as H.F., R.F., arrhythmia.

4- Enhancing elimination

- •Forced alkaline diuresis
- •Peritoneal dialysis
- •Hemodialysis

5- Symptomatic treatment