Al-Mustaqbal University
College of Pharmacy
5th stage
Clinical Toxicology
Lab 3

SALICYLATES toxicity (salicylism)

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Salicylate

✓Salicin, a naturally occurring salicylate is a constituent of several plants but is present in highest concentration in the willow tree.

- These compounds are derivatives
- of salicylic acid and include
- **acetyl salicylic acid, sodium salicylate,**
- **Bismuth subsalicylate:Mesalamine**
- **Diflunisal ,methyl salicylate.**

Homomenthyl salicylate (homosalate) is a sunscreen agent

Hoffman, a chemist at Bayer Company first synthesized acetyl salicylic acid in the laboratory in 1897

Toxicokinetics

- Oral **absorption i**s complete; most of absorption occurs from the *stomach* and upper GIT.
- Widely **distributed** to all tissues especialy including In acidaemia, more salicylate is unionised, favouring movement into extravascular spaces, includingCNS.
- **Metabolism** of salicylates occurs by the hepatic microsomal enzymes.
  - At low doses, elimination is done by the *first-order process.*
  - At high doses, elimination is done by the *zero-order process.*
- **Excretion** is increased by *alkalinization of urine* (pH 8) because in alkaline urine, most of aspirin is *ionized and less re-absorbable.*
- The **elimination** half-life of **2–4** hours in normal therapeutic dosing is prolonged up to **24** hours following overdose

Mechanism of toxicity

- Salicylates cause **irreversible inhibition of cyclo-oxygenase enzymes** resulting in decreased prostaglandin synthesis.
- **Stimulation of the respiratory center** causes hyperventilation and respiratory alkalosis.
- **Uncoupling of oxidative phosphorylation** results in accumulation of lactic acid, contributing to metabolic acidosis.
- Promotion of fatty acid metabolism and generation of ketone bodies also contributes to metabolic acidosis.
- **Death** is associated with very high salicylate levels in the CNS.

Toxic mechanism

Respiratory effects:

– **Low toxic doses**: produce **metabolic acidosis** → compensatory **hyperventilation** to wash excess CO2 → prolonged respiratory alkalosis.

– **High toxic doses**: produce metabolic acidosis together with inhibition of RC → death from severe acidosis

Assessing Salicylate Poisoning from Clinical Evaluation

Toxic dose 150 mg /kg

Mild (150mg/kg)	Moderate (150-300 mg/kg)	Severe (300-500 mg/kg)
Nausea	Nausea	Delerium
Vomiting	Vomiting	Hallucinations
Dizziness	Tinnitus	Convulsions
	Headache	Coma
	Confusion	Respiratory arrest
	Hyperventil	
	Tachycardia	
	Fever	

Tachypnea (hyperventilation) is the earliest sign of aspirin toxicity

INVESTIGATIONS

1. Monitor serum salicylate level, glucose and electrolytes every 2 hours

2. Obtain a CBC, renal and hepatic function tests and INR or PT and PTT in patients with clinical evidence of moderate to severe toxicity

a. Anion-gap acidosis.

b. Hypokalaemia (acidosis may mask it).

c. Hypocalcaemia.

d. Hypoglycaemia

Management

1. **Patients with major signs or symptoms** (**metabolic acidosis, dehydration, mental status changes, seizures, pulmonary oedema)** should be admitted to the **Intensive Care Unit** regardless of serum salicylate level.

2. **Gastric lavage (Stomach wash)** may be beneficial **upto 12 hours** after ingestion, since toxic doses of salicylates often cause pylorospasm and delayed gastric emptying.

3- Whole bowel irrigation might be useful in patients with bezoars, or patients who have ingested enteric coated or sustained release products.

Management

4- Decontamination

Activated charcoal (AC): It is said to be **very efficacious** in the treatment of salicylate poisoning .

Administer oral activated charcoal 50 g up to **8 hours** following acute overdose of **>150 mg/kg**.

Following ingestion of **>300 mg/kg**, administer activated charcoal 50 g via a nasogastric tube, after first securing the airway if necessary.

In either case, a second dose of activated charcoal 50 g is indicated after **4 hours** if serum salicylate levels continue to rise.

Management

5- Urinary alkalinisation :.

Alkalinisation of both blood and urine can be achieved with **sodium bicarbonate according to the stage of poisoning**

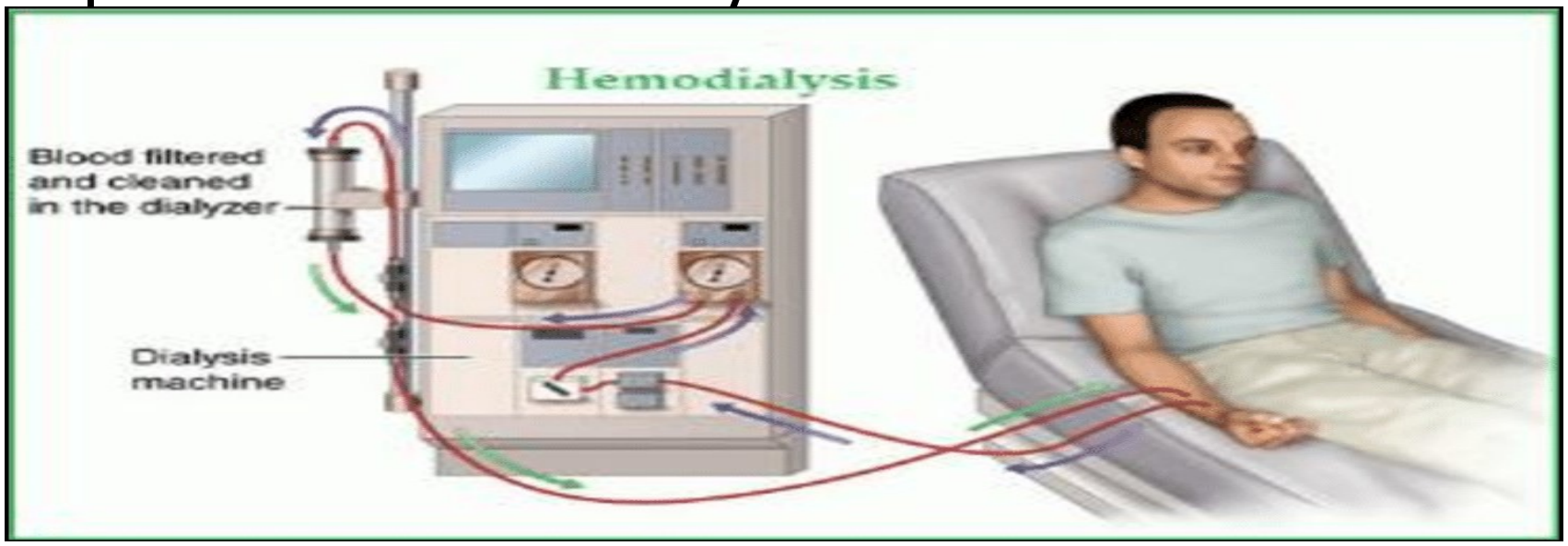
For mild poisoning: 1 mEq/kg of $NaHCO_3$ is added to the first bottle of 5% dextrose. If alkalinisation (i.e. urinary pH between 7.5 and 8.5) is not achieved in a few hours, it can be repeated.

–– ***For severe poisoning***: Additional bolus therapy of 50 to 100 mEq of $NaHCO_3$ over 1 to 2 hours may be necessary

Management

6- Haemodialysis:

It is **very effective** in salicylate poisoning and must always be considered in the presence of cardiac or renal failure, intractable acidosis, convulsions, severe fluid imbalance, Patients with evidence of cerebral oedema require immediate dialysis.



Other supportive Treatment

a. Correction of fluid and electrolyte imbalance

b. Correct dehydration with 0.9% saline 10 to 20 ml/kg/ hr over 1 to 2 hours until a good urine flow is obtained

c. Hypoprothrombinaemia can be corrected by 5 mg of vitamin K IV every day.

d. Hyperpyrexia must be tackled by cooling measures (e.g. ice in the axilla and groin).

Correction of metabolic acidosis with $NaHCO_3$.

f. Correction of hypocalcaemia with calcium gluconate IV (5 to 10 ml in adults).

g. Correct hypokalaemia as needed

h. Correction of hypoglycaemia with glucose IV (50 ml of 5% dextrose or 1 ml/kg).

i. Treatment of convulsions with benzodiazepines.

j. Mild cerebral oedema and elevated intracranial pressure (ICP) can be managed by head elevation and administration of mannitol

Summary of Treatment:

– Repeated gastric lavage with activated charcoal.

– i.v. fluids and sodium bicarbonate to correct dehydration and acidosis.

– Vit K 10 mg i.m. or slowly i.v. to control hemorrhage.

– Alkalinization of urine: to enhance salicylate excretion.

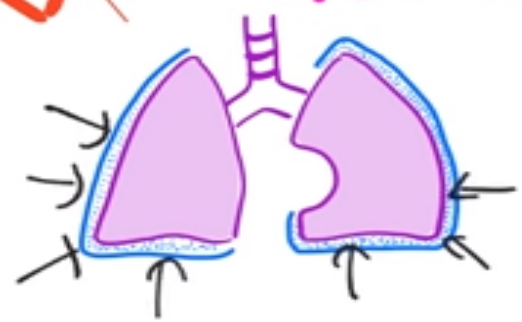
– Hemodialysis in severe cases (when blood levels > 100 mg/dl).

The most common cause of death

in Salicylate poisoning (salicylism)

is

Cardiopulmonary Arrest due to



pulmonary edema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