Salicylate Toxicity

PREPARED BY:

ANWER MAHMOOD AL-JUBUORI

MSC. PHARMACOLOGY AND TOXICOLOGY

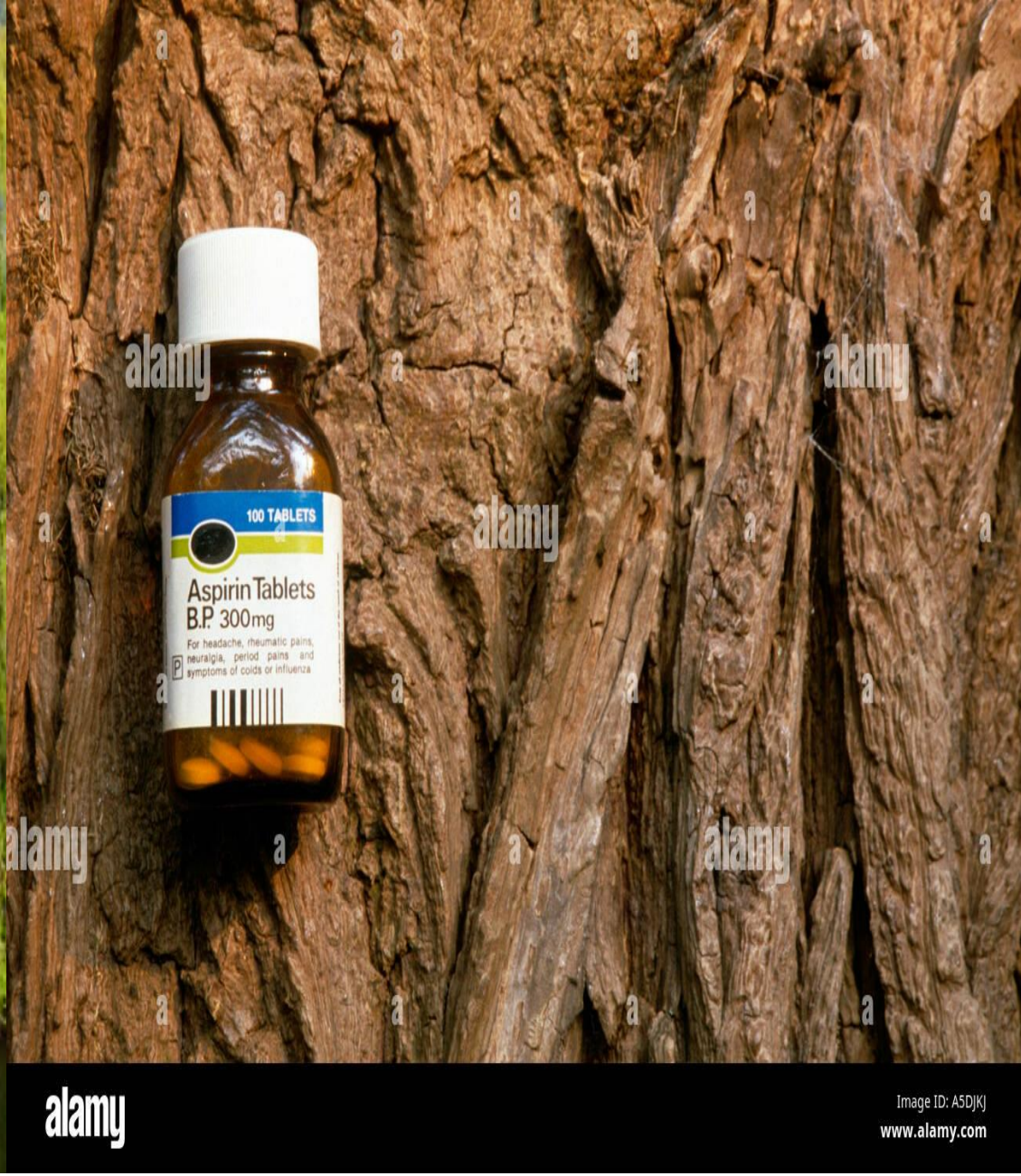
DEPT. OF PHARMACOLOGY

TIKRIT UNIVERSITY- COLLEGE OF PHARMACY

2023-2022

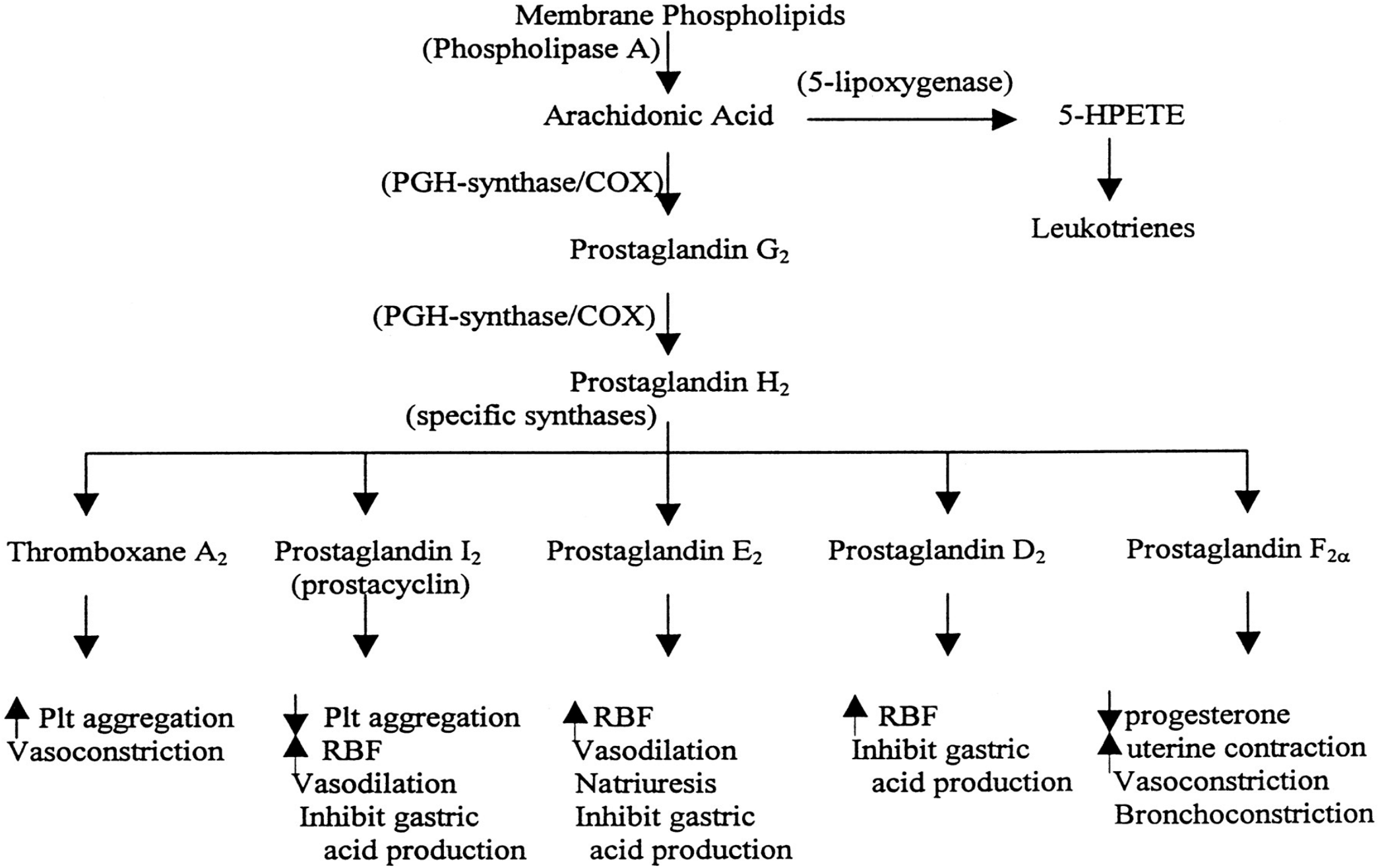
Salicylates

- **Salicylates** e.g., Acetyl salicylic acid (aspirin/**ASA**)
- Others: **Sodium** salicylate, **methyl** salicylate
- They common in many **OTC** oral preparation include cold preparation and others.
- **Naturally**, active agent in the **willow** tree is **salicin**, a bitter glycoside, which is converted upon hydrolysis to glucose and salicylic alcohol
- Aspirin is a **prototypical**/classical NSAID
- Aspirin (acetyl salicylic acid) is rapidly converted in body to salicylic acid, which is responsible for the action
- One of the **oldest** analgesic anti-inflammatory drugs


100 TABLETS
Aspirin Tablets
B.P. 300mg
For headache, rheumatic pains, neuralgia, period pains and symptoms of colds or influenza
alamy
Image ID: A5DJKJ
www.alamy.com

MECHANISM OF ACTION

- Aspirin and most of the NSAIDs **inhibit** both COX-1 and COX-2 isoforms
- Thereby ↓ PGs and thromboxane synthesis.
- The **anti-inflammatory** effect of NSAIDs is mainly due to inhibition of **COX-2**.
- Aspirin causes **irreversible** inhibition of COX activity.
- **Rest** of the NSAIDs causes **reversible** inhibition of the enzyme


Membrane Phospholipids
(Phospholipase A)
Arachidonic Acid
(5-lipoxygenase)
5-HPETE
Leukotrienes
(PGH-synthase/COX)
Prostaglandin G2
(PGH-synthase/COX)
Prostaglandin H2
(specific synthases)
Thromboxane A2
Prostaglandin I2
(prostacyclin)
Prostaglandin E2
Prostaglandin D2
Prostaglandin F2α
↑ Plt aggregation
Vasoconstriction
↓ Plt aggregation
↑ RBF
Vasodilation
Inhibit gastric
acid production
↑ RBF
Vasodilation
Natriuresis
Inhibit gastric
acid production
↑ RBF
Inhibit gastric
acid production
↓ progesterone
↑ uterine contraction
Vasoconstriction
Bronchoconstriction

Toxicokinetics

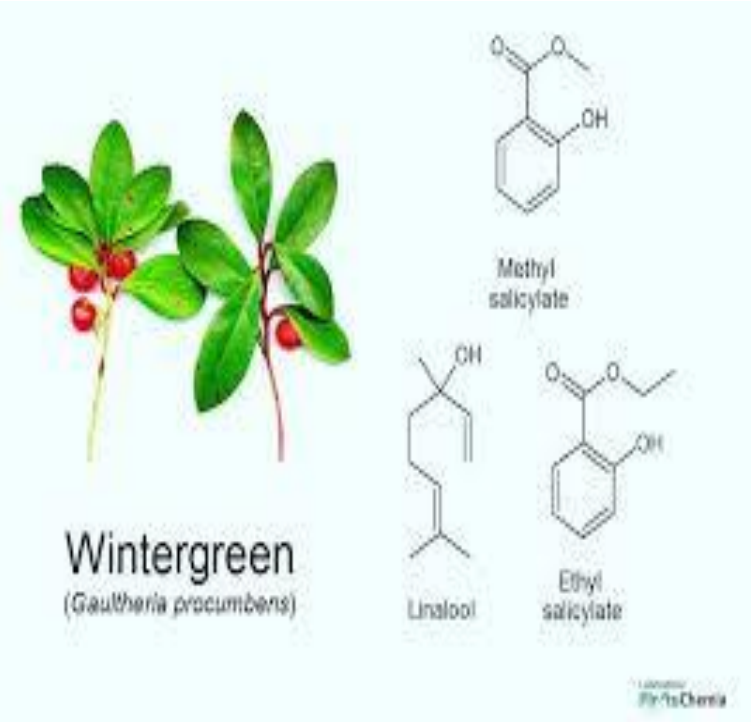
- Salicylates are **rapidly** absorbed from the stomach.
- **Delayed** absorption is seen in the following situations: **enteric** coated preparations.
- **Salicylic acid** and **methyl** salicylate are **readily** absorbed through intact skin.
- Metabolism occurs chiefly in the **liver**.
- Excretion is mainly through **urine**.
- The half-life of salicylates is 2 to 4 hours

Salicylate poisoning

- **Accidental** acute pediatric ingestion.
- A **child over** treated with salicylate by parents during the first few days of an illness, resulting chronic toxicity.
- Acute toxicity may result from a single large ingestion as attempted **suicide**.
- **Elderly** patients may stiffer chronic toxicity following a **gradual alteration** in the patient metabolic processes or due to **simultaneous** ingestion of medications such as **acetazolamide** that enhance the toxicity of salicylate.

Toxic dose

- for **children** the dose **150** mg/kg.
- **Methyl** salicylate liquid **one** teaspoonful which **contain7g** of salicylate
- Doses: Less than **150mg**/kg generally result in **no** clinical toxicity
- More than 150 (**l50-300mg**/kg) → **mild** to **moderate** toxicity.
- An ingestion **more** than **300mg**/kg → **sever** toxicity.
- Ingestion of **more** than **500mg**/kg → **lethal**.
- Toxicity also developed in those with **chronic** administration of more than **100** mg/kg/24hr. for 2 days or more.



Mechanism of toxicitv

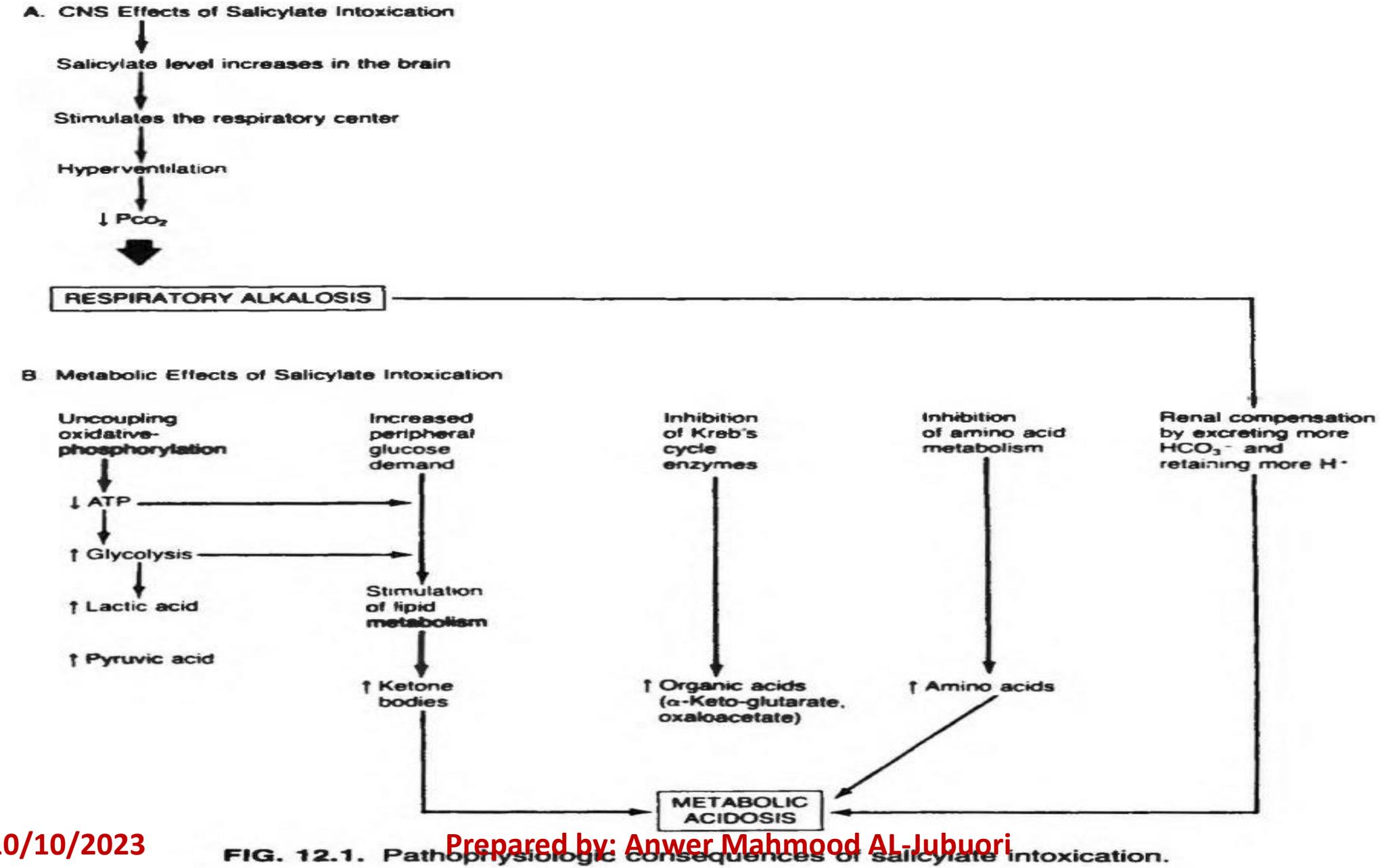


FIG. 12.1. Pathophysiologic consequences of salicylate intoxication.

Mechanism of toxicity

❖. **CNS**→ stimulate respiratory center → Hyperventilation occurs → tachypnea → lead to respiratory alkalosis →lead to compensatory increase in bicarbonate excretion by the kidney.

❖**GIT**: salicylate affect by **two** mechanism:

1. a. **inhibit PG** synthesis (PG decrease gastric acid secretion and PGE2 stimulate synthesis of protective mucus in both the stomach and small intestine) resulting increase gastric acid secretion and diminish mucus protection.
2. It **readily** crosses into mucosal cell and potentially cause **direct** damage to the cells/ both cause microscopic GI bleeding (**melena**).

Mechanism of toxicity

- **Renal**: cyclooxygenase inhibitor prevent synthesis of PG (that are responsible for maintaining renal blood flow) resulting in retention of sodium and water lead to cause **edema**.
- **Platelet function**: the **irreversible** acetylation of platelet cyclooxygenase decrease the level of platelet **TXA2** resulting in inhibition of platelet aggregation and prolonged bleeding (PT prolong).
- Salicylate **directly** inhibit certain enzymes in kerbs cycle. This inhibition result **increase** amounts of pyruvate and lactate with **lower** the plasma **pH**.

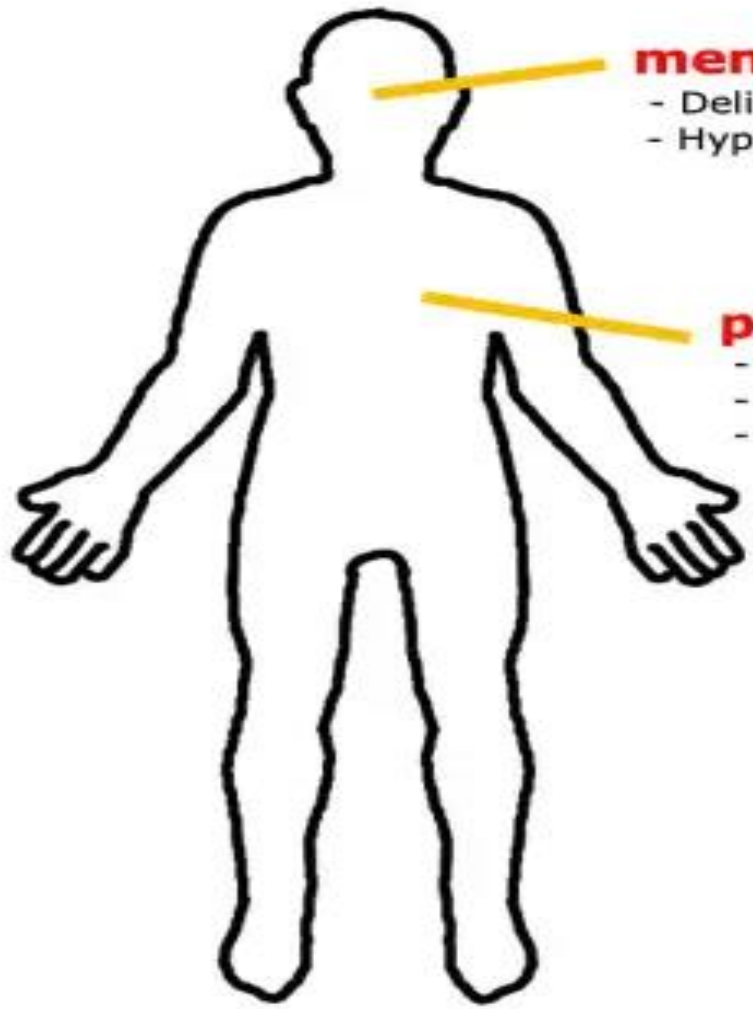
Mechanism of toxicity

- Salicylate induced increase in tissue **glycolysis** and peripheral demand for glucose.
- **Serum** hypoglycemia as well as **CNS** hypoglycemia is common during **chronic** intoxication or **late** course of acute ingestion
- **Metabolic process**:- uncoupling of oxidative phosphorylation may result in hyperthermia and increase metabolic rate.
- A **decrease** in ionized **calcium** due to the respiratory alkalosis lead to **CNS** abnormalities may include **lethargy** or **coma** with cerebral **edema**, **seizure** and syndrome of inappropriate antidiuretic hormone secretion.
- **Hepatic** toxicity: Reye syndrome in children during viral infections

Clinical presentation

- Asymptomatic:blood conc. <**45** mg/dl
- **Mild** toxicity: Nausea, Gastritis, Mild hyperpnea, Tinnitus. Occur at dose < **150** mg/kg
- **Moderate** toxicity: Hyperpnea, Hyperthermia, Sweating, Dehydration, Marked lethargy, Possible excitement. Occur at dose 150-300 mg/kg
- **Severe** toxicity: Severe hyperpnea, Coma, Convulsions, Cyanosis, Pulmonary edema, Respiratory failure, Cardiovascular collapse. Occur at dose 300 - 500 mg/kg.
- **Lethal**: coma, death. Occur at dose >500 mg/kg.

salicylism will usually present as a mimic



meningitis mimic
- Delirium, agitation
- Hyperthermia, diaphoresis

pneumonia mimic
- Pulmonary edema
- Tachypnea
- Diaphoresis, hyperthermia

sepsis mimic
- Acidosis, elevated lactate
- Tachypnea
- Diaphoresis, hyperthermia
- Tachycardia, hypotension
- Leukocytosis/leukopenia

The Internet Book of Critical Care

Laboratory analysis

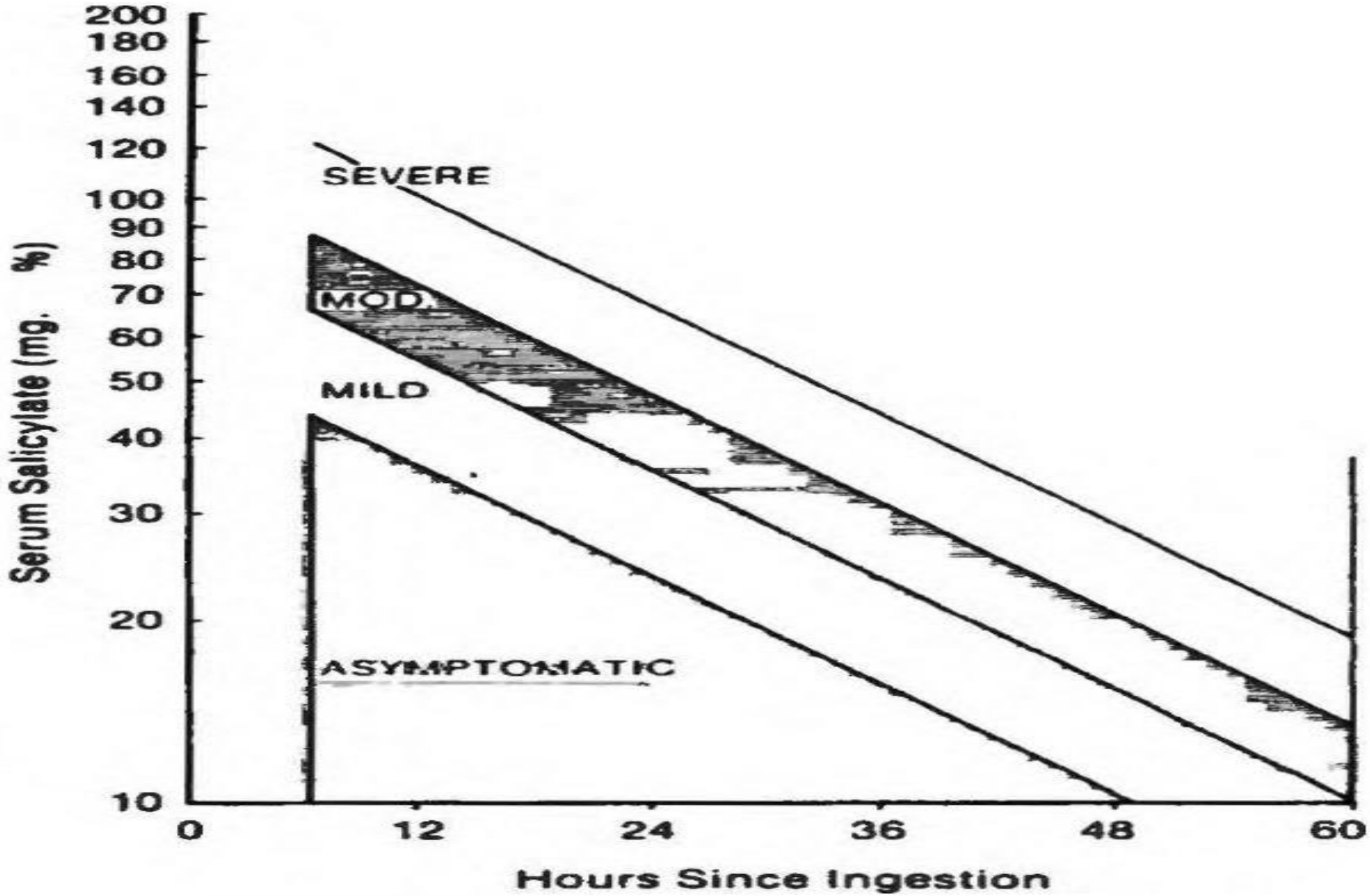
- Electrolytes,
- BUN, creatinine,
- Glucose,
- Serum osmolarity
- Calcium
- arterial blood gases
- PT and partial thromboplastin (PTT) time
- An ECG should be obtained for all patients as a screening test for potentially life-threating electrolyte abnormalities secondary to dehydration, hypokalemia, hyperkalemia or hypercalcemia.
- Chest X-ray is necessary to exclude pulmonary edema or respiratory distress syndrome.
- Rectal examination should be done to exclude GI hemorrhage.

Laboratory analysis

❖Salicylate Levels :

❖A- A rapid **qualitative** test for presence of salicylates may be done by adding several drops of l0% **ferric chloride** to l ml of boiled urine. A **purple** color change indicate the presence of **salicylates**.

❖B- Serum measurement of salicylates are important after acute single ingestion. Initial levels on presentation and at 6 hr. after ingestion may be obtain and plotted on the done nomogram


200
180
160
140
120
100
90
80
70
60
50
40
30
20
10
Serum Salicylate (mg. %)
SEVERE
MOD.
MILD
ASYMPTOMATIC
0
12
24
36
48
60
Hours Since Ingestion

Management

- **Removal** of aspirin from GIT.
- **Correction** of metabolic acidosis, dehydration, hyperthermia, hypoglycemia and hypokalemia.
- l- For a **symptomatic** or **mild** intoxication, activated charcoal **lg/kg** should be administrated with **cathartic** (to prevent intestinal obstruction and enhance the transit time of charcoal) such as **sorbitol** (30 ml by mouth or nasogastric tube).
- **Gastric** lavage shortly after ingestion

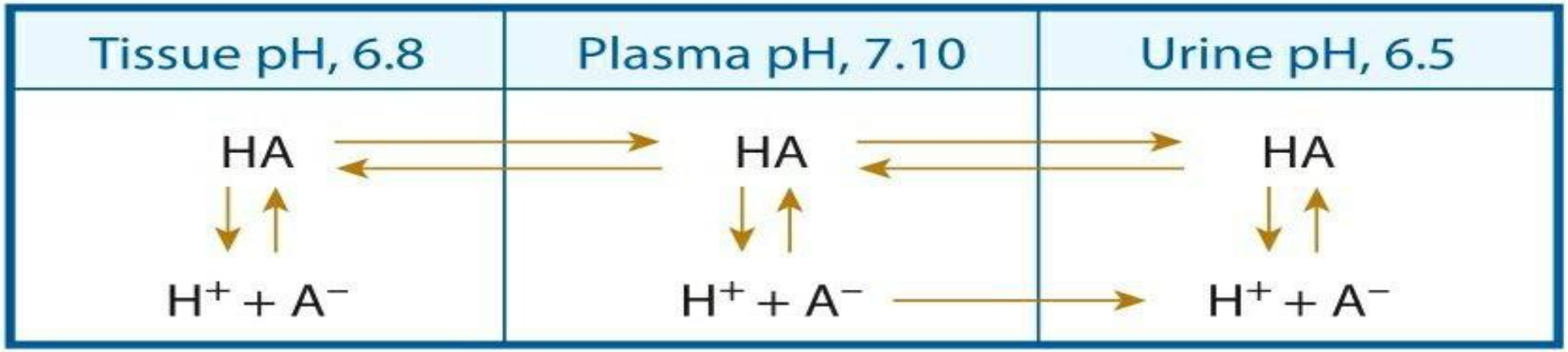
Management

- For more **severely** intoxication patient standard advanced cardiac life support measures must be instituted including **intubation**, **ventilation**, and **treatment** of shock as indicate.
- **Sever hyperpyrexia** must be treated by covering the patient with **wet** sheets and **cooling** with ice and water.

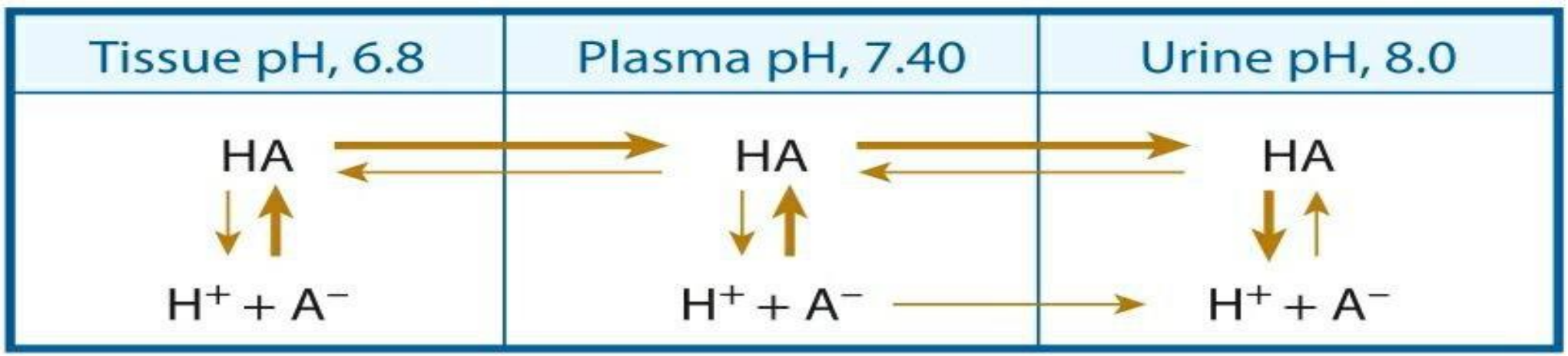
Management

- **Glucose** for treatment CNS hypoglycemia and ketosis.
- **Respiratory** and **metabolic** acidosis must be corrected by:
  - **Alkalinization** of urine with sodium bicarbonate to promote movement of salicylate from intracellular sites to plasma.
  - **Abolus** of sodium bicarbonate **l-2** mEq/kg is given slowly, followed by **5%** DW solution with **l-2** mEq of sodium bicarbonate infused at dose of **100-200 ml/hr**. over 6-9 hrs.
- Urine pH should be maintained at **7.5-8**. The **arterial** pH must not be allowed to rise above **7.5**, therefore with severe poisoning large amount of bicarbonate are required and used as long as the PH is followed closely.

Before plasma and urine alkalinization



After plasma and urine alkalinization



Management

- **Hypokalemia** need k replacement prior to the administered of bicarbonate, hypokalemia **prevent** excretion of bicarbonate into urine.
- **Hemodialysis** or **hemoperfusion** is recommended for any patient with initial blood salicylate level for **more than l60** mg/dl or a 6hr level of more than **l30** mg/dl, acidosis **unresponsive** to bicarbonate, **renal** failure.
- Coagulation defects may treated with **vitamin K** S.C every day.
- I.V and oral fluid to correct dehydration.
- Seizure treated with **diazepam**.


Thank
You