Salicylate Toxicity

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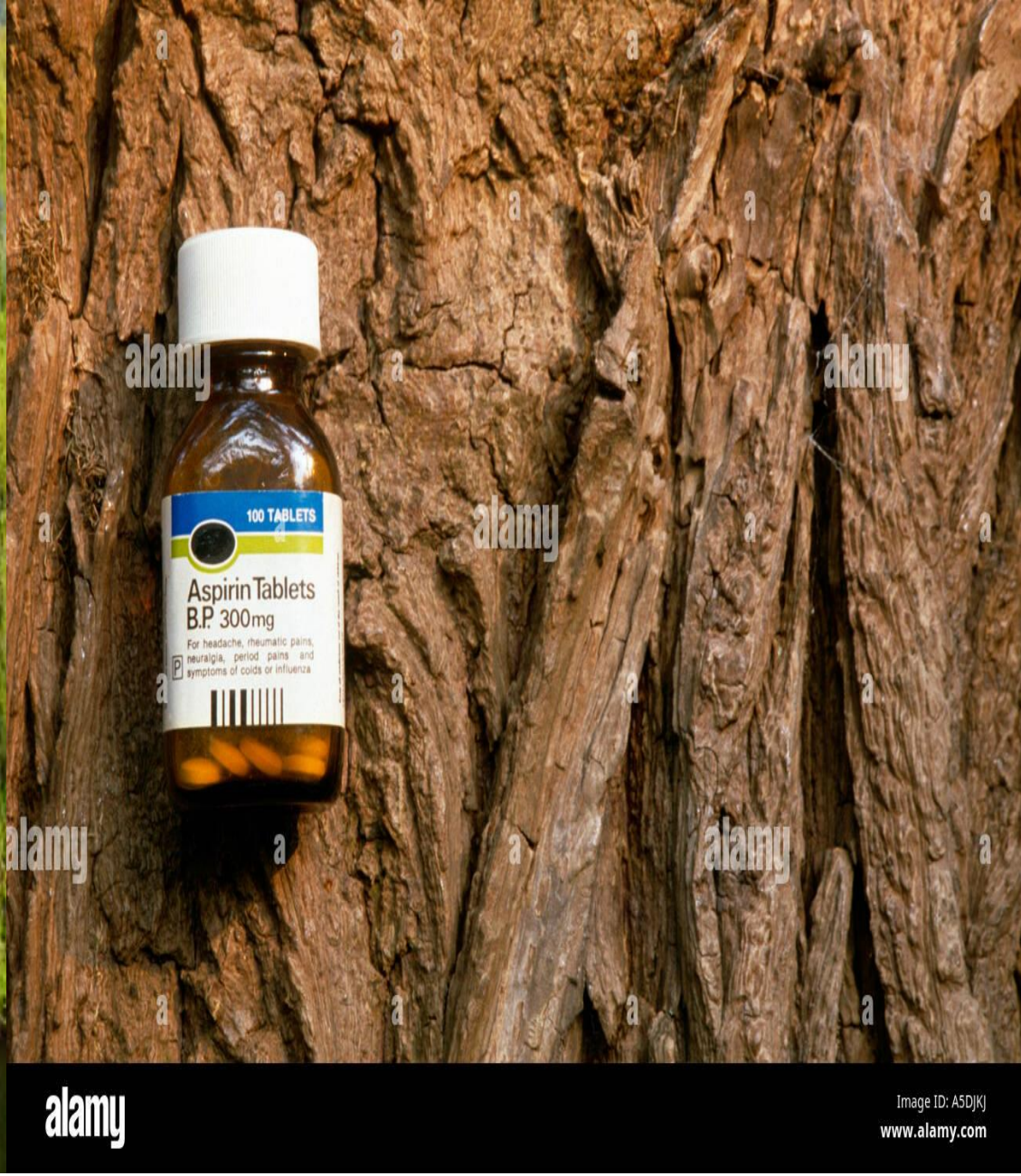
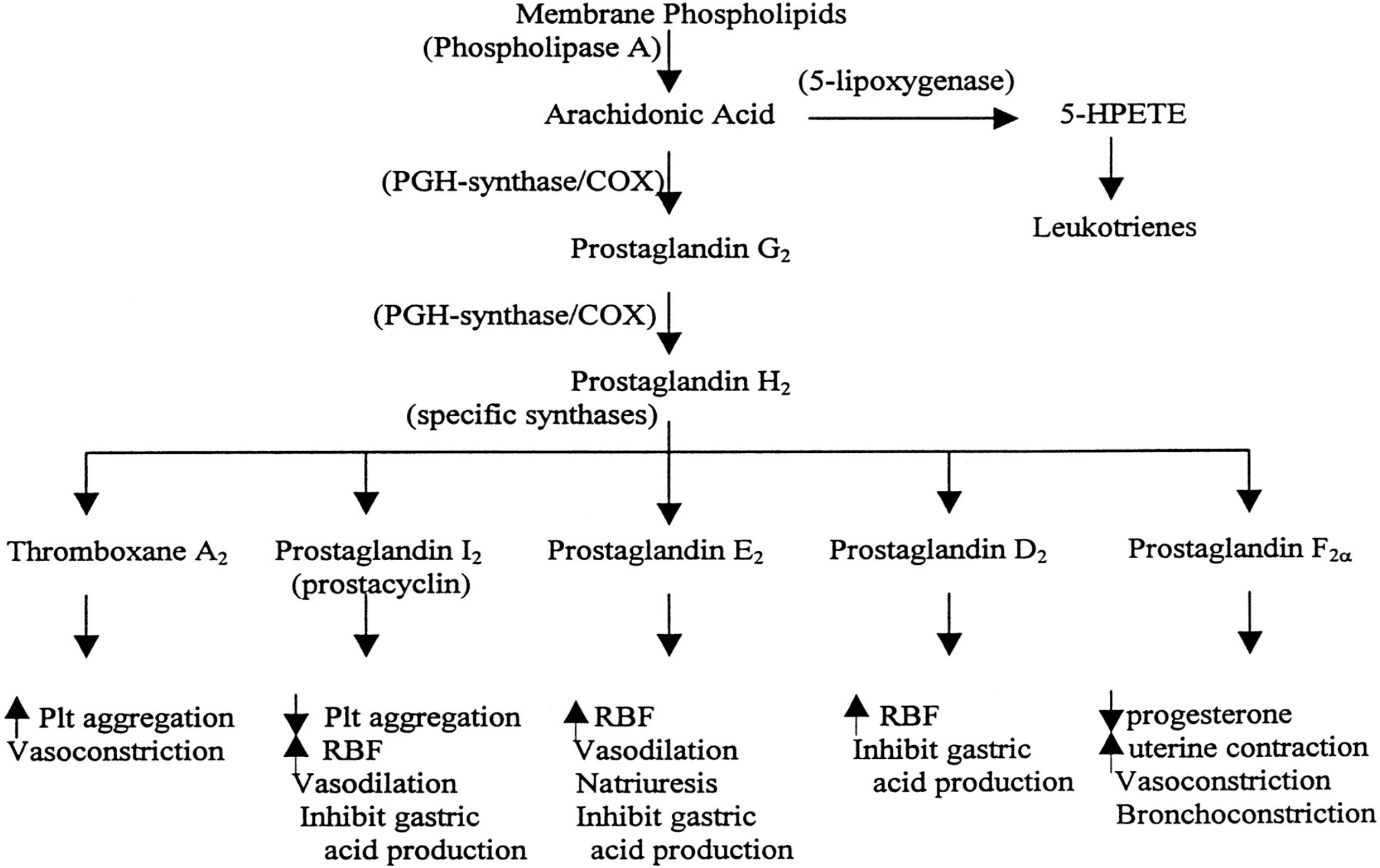
Salicylates

- 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 decrease 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

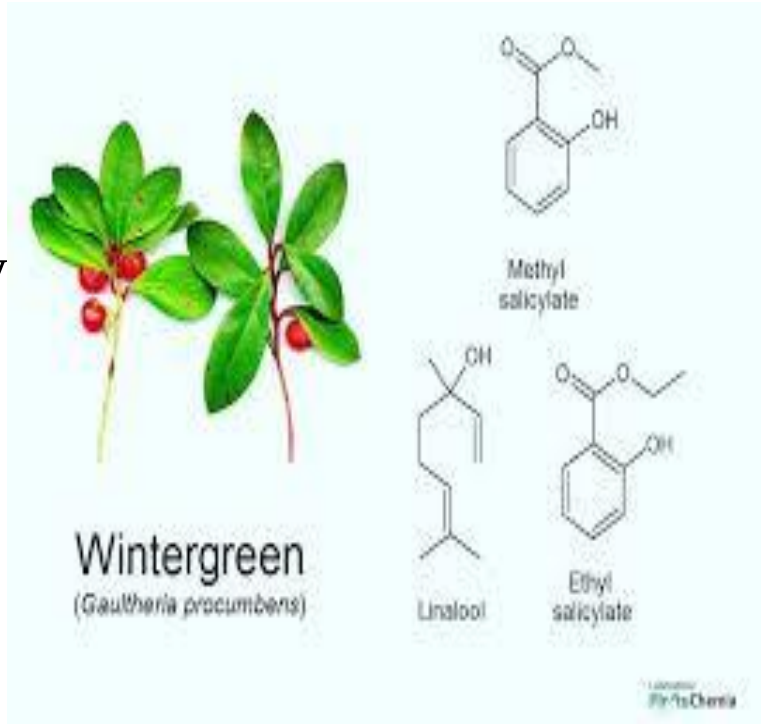
- Salicylates are rapidly absorbed from the stomach.
- Delayed absorption is seen in the following situations: enteric coated preparations.
- Salicylic acid and methyl salicylate are readily absorbed through intact skin.
- Metabolism occurs chiefly in the liver.
- Excretion is mainly through urine.
- 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

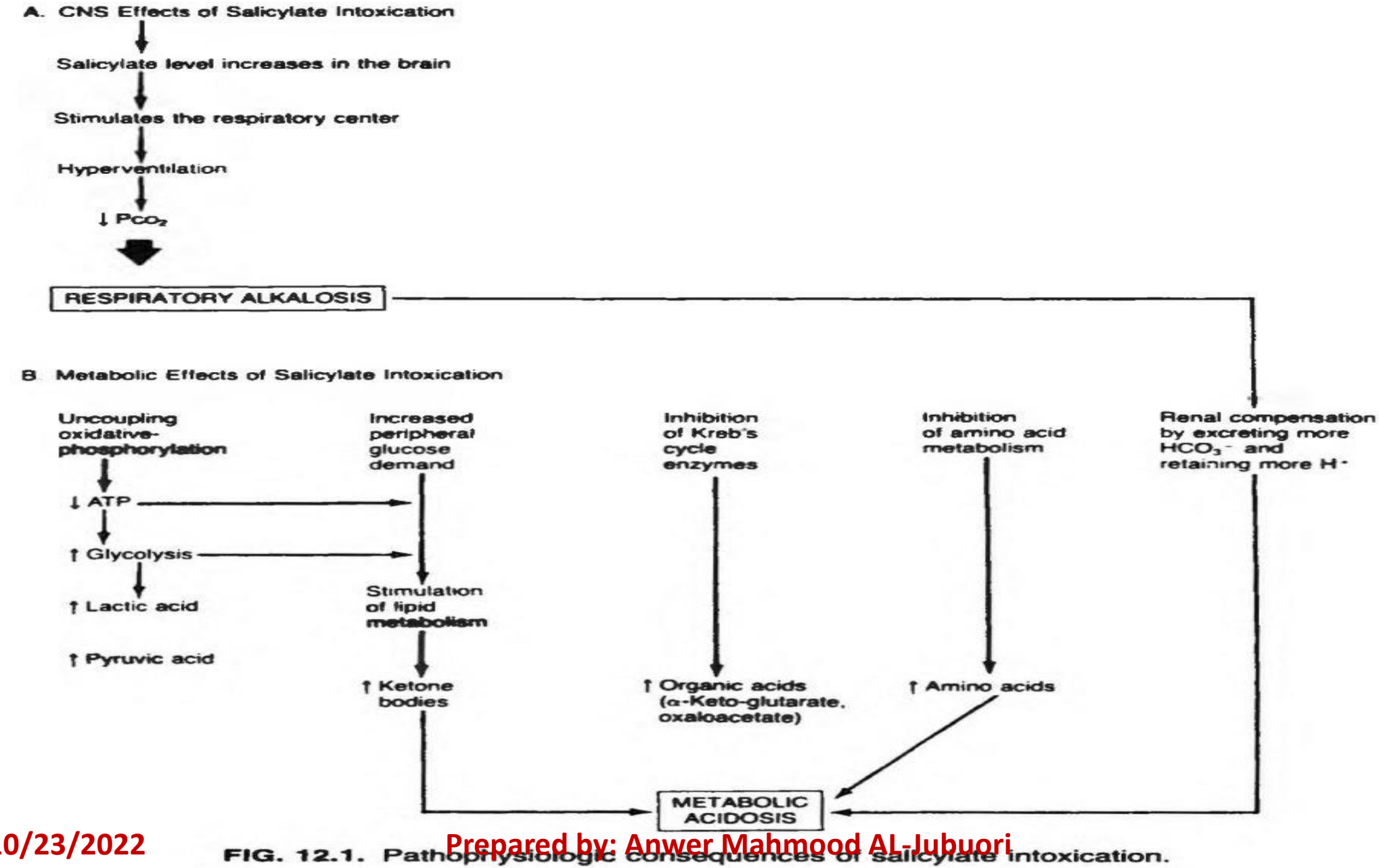


FIG. 12.1. Pathophysiologic consequences of salicylate intoxication.

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 (PG2 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.

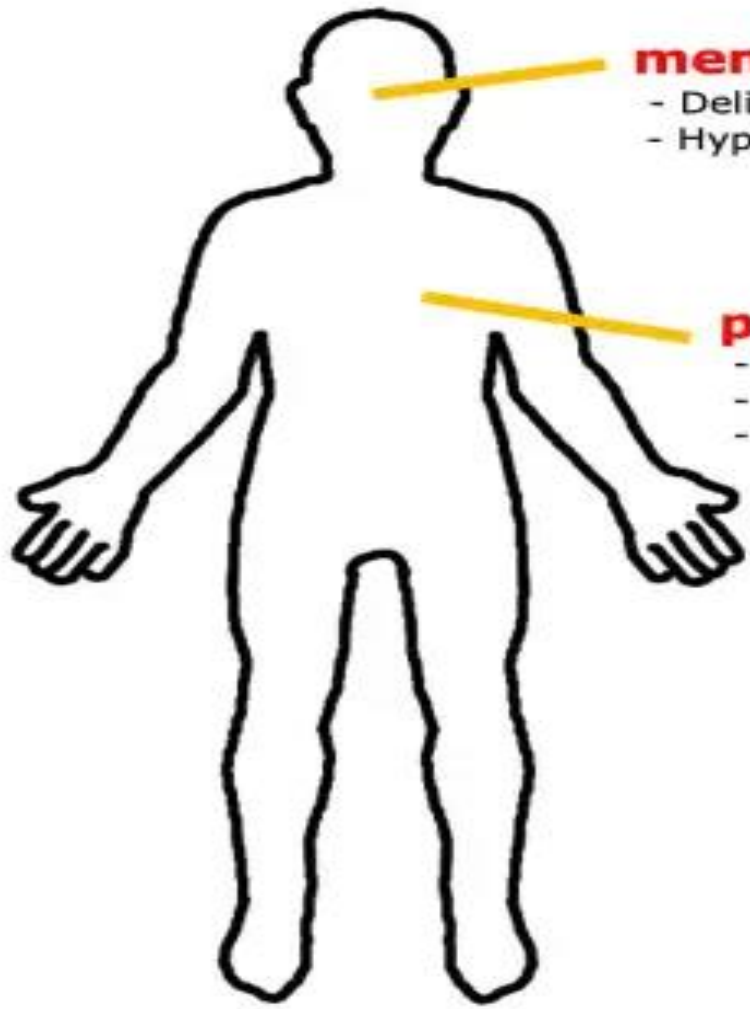
Mechanism of toxicity

- 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

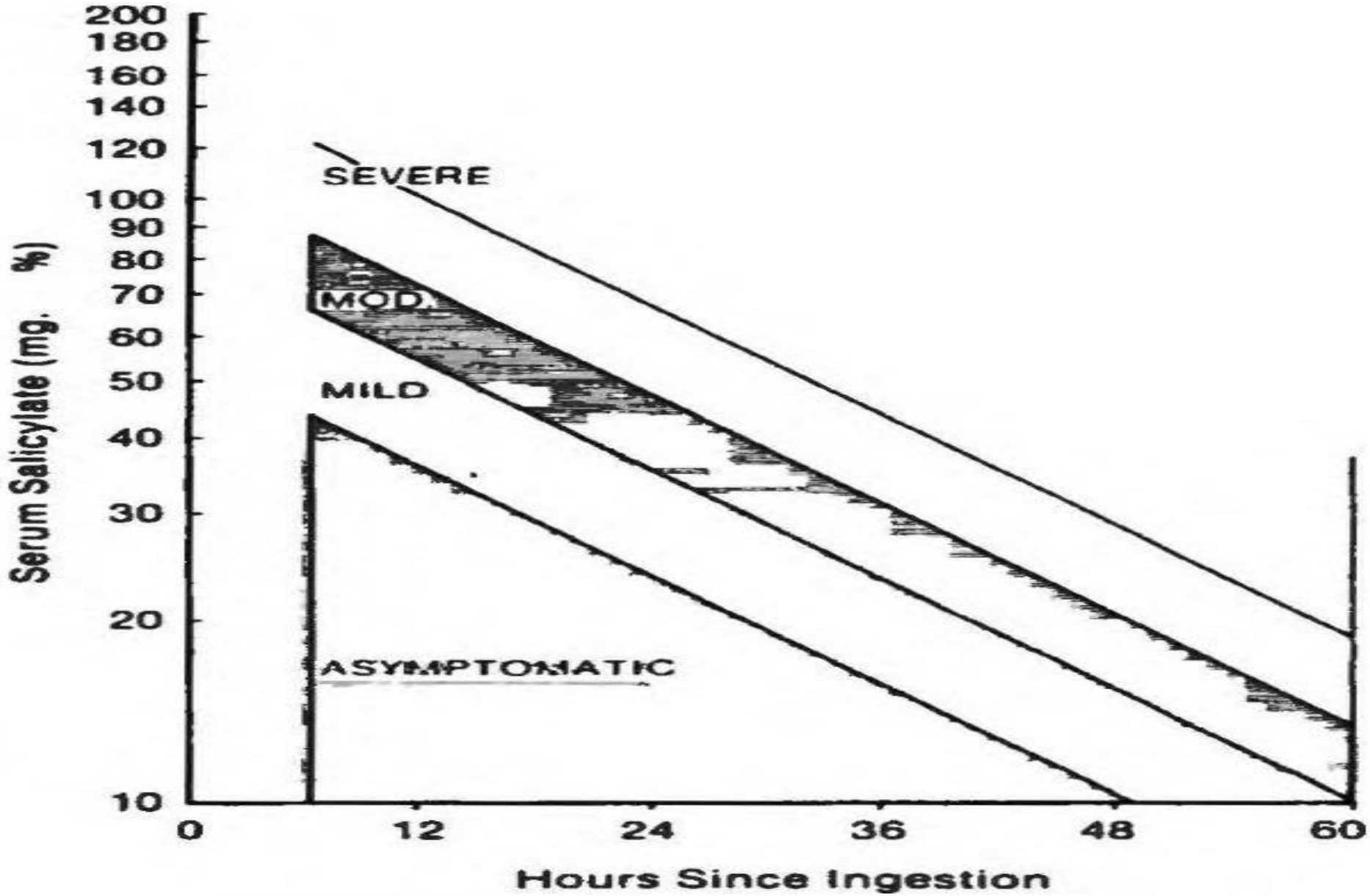
- Electrolytes,
- BUN, creatinine,
- Glucose,
- Serum osmolarity
- Calcium
- arterial blood gases
- PT and partial thromboplastin (PTT) time
- An ECG should be obtained for all patients as a screening test for potentially life-threating electrolyte abnormalities secondary to dehydration, hypokalemia, 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


Serum Salicylate (mg. %)
200
180
160
140
120
100
90
80
70
60
50
40
30
20
10
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

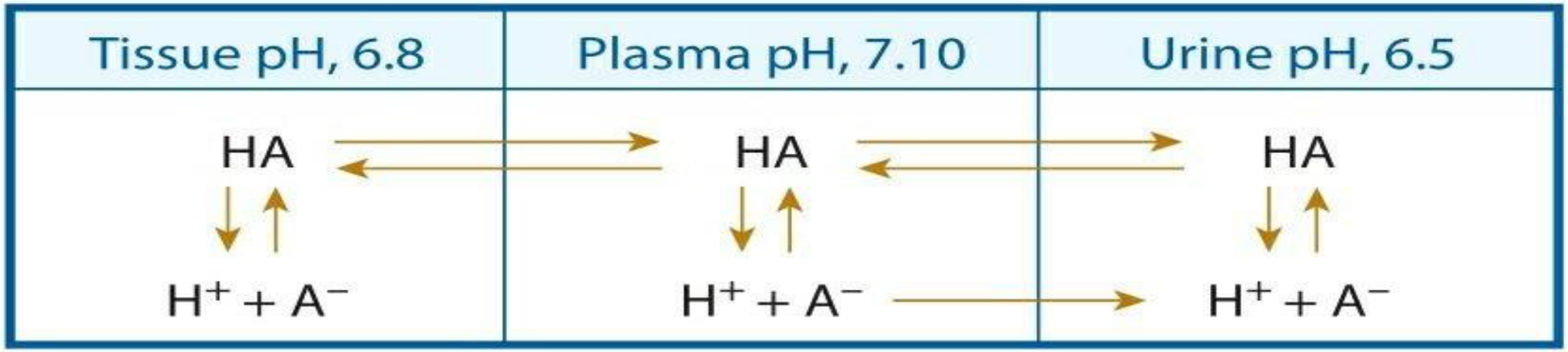
Management

- 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.

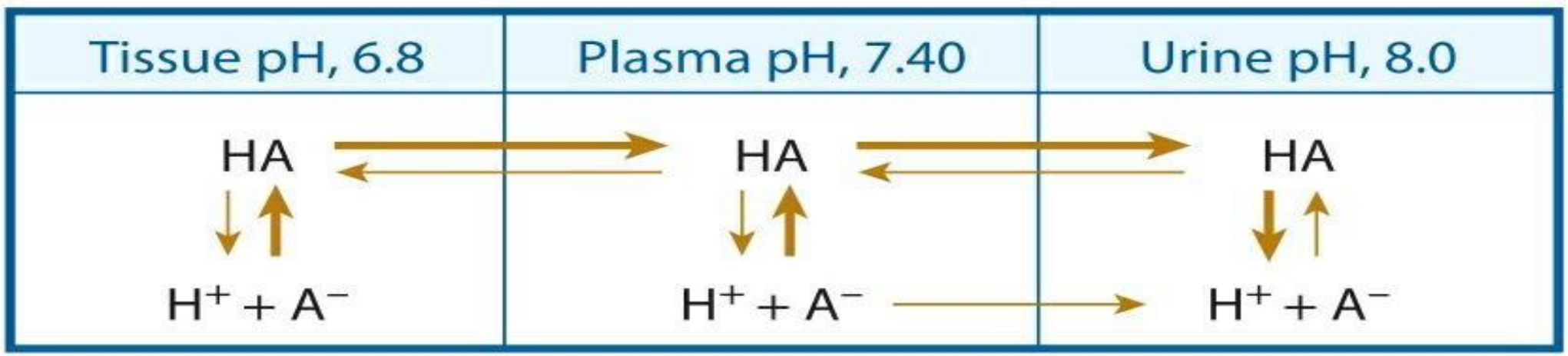
Management

- ❖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