Practical Clinical Toxicology

Toxicity of Salicylates

Lab.4
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Pharmacology & toxicology of salicylates:

- Aspirin & other salicylates are analgesics, anti-inflammatories, & antipyretics, a combination of traits shared by all medications of varying structures known as nonsteroidal anti-inflammatory drugs (NSAIDs).

- Most of the beneficial effects of NSAIDs result from the inhibition of cyclooxygenase (COX). This enzyme enables the synthesis of prostaglandins, which in turn mediate inflammation & fever.

- Adverse effects of aspirin & some NSAIDs related to alteration of COX include gastrointestinal (GI) ulcerations & bleeding, interference with platelet adherence, & a variety of metabolic & organ-specific effects.

- The pK a of aspirin is 3.5, & the majority of salicylate is nonionized in the acidic stomach. Salicylate is rapidly absorbed from aspirin tablets in the stomach.

Toxic doses

In adults 10-30 g aspirin
Children as little as 3 g is potentially lethal.

methyl salicylate (oil of wintergreen): traditional old product used as analgesic for relief of sore muscles contain (530 mg/ml), As little as 4ml of methyl salicylate can be lethal in children.

Table 1. Toxicity profile for salicylate toxicity

Range of toxicity	Signs & symptoms	Blood concentration range (mg/dL)
asymptomatic		>45
Mild toxicity	Nausea Gastritis Mild hyperpnea Tinnitus	45-65
Moderate toxicity	Hyperpnea Hyperthermia Sweating Dehydration Marked lethargy	65-90
Sever toxicity	Sever hyperpnea Coma Convulsions Cyanosis Pulmonary edema Respiratory failure Cardiovascular collapse	90-120
Lethal	Coma Death	120

Acid–base disturbance caused by salicylate poisoning:

- Salicylate stimulates the respiratory center in the brainstem, leading to hyperventilation & respiratory alkalosis.

It also uncouples oxidative phosphorylation, causing accumulation of pyruvic & lactic acids due to increase anaerobic metabolism, causing increase heat production

- Salicylate interferes with the Krebs cycle, which limits production of adenosine triphosphate (ATP), decrease glucose availability and increase organic acid production.

- Salicylate-induced increased fatty acid metabolism and amino acids metabolism.
- Increase electrolyte loss, sodium and potassium depletion.

- The net result of all of these metabolic processes is an anion gap metabolic acidosis.

CNS effect of salicylate intoxication:

↓

Salicylates level increases in the brain

↓

Stimulates the respiratory center

↓

Hyperventilation

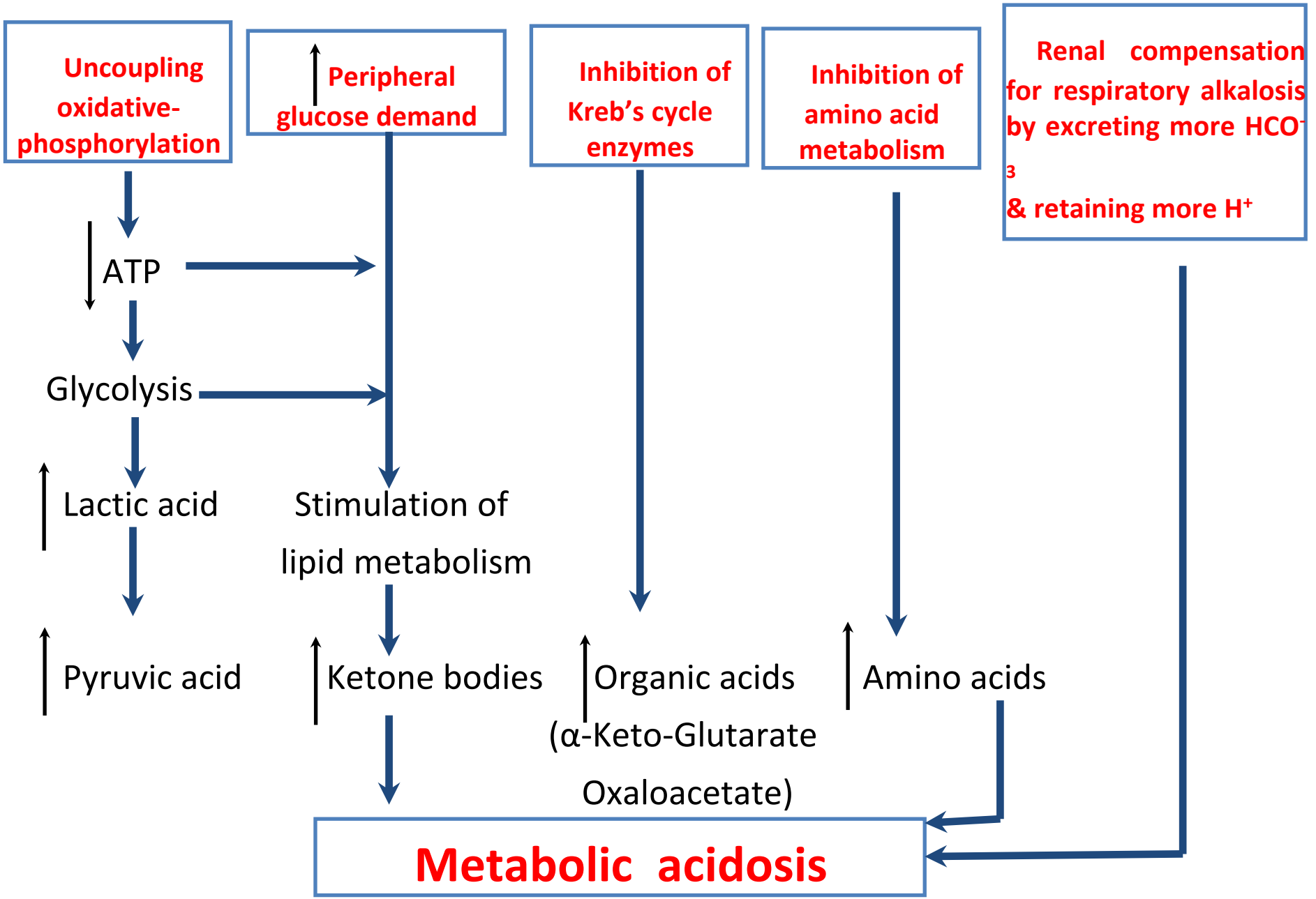
↓

↓ Pco_2

↓

Respiratory alkalosis

Metabolic effects of salicylate intoxication



Clinical manifestations of salicylate poisoning:

Acute salicylate toxicity:

- The earliest signs & symptoms of salicylate toxicity, which include nausea, vomiting, diaphoresis, & tinnitus, typically develop within 1 to 2 hours of acute exposure.

- Other early CNS effects may include vertigo & hyperventilation manifested as hyperpnea or tachypnea, hyperactivity, agitation, delirium, hallucinations, convulsions, lethargy and Coma which is rare & generally it occurs only with severe acute poisoning.

Clinical manifestations of salicylate toxicity:

- Acid–Base disturbances caused by salicylate poisoning
- Central nervous system effects
- Coagulation abnormalities
- Gastrointestinal effects
- Hepatic effects
- Metabolic effects
- Pulmonary effects
- Renal effects

Acid–Base disturbances caused by salicylate poisoning:

- Anion gap increased
- Respiratory alkalosis (predominates early)
- Metabolic acidosis
- Metabolic alkalosis (due to vomiting and loss of stomach acid)
- Hypokalemia

Central nervous system:

- Tinnitus
- Vertigo
- Hallucinations
- Agitation
- Delirium
- Stupor (unconsciousness)
- Coma
- Lethargy
- Convulsions
- Cerebral edema
- Syndrome of inappropriate antidiuretic hormone

Coagulation Abnormalities:

- Hypoprothrombinemia
- Inhibition of factors V, VII, and X
- Platelet dysfunction

Gastrointestinal

- Nausea
- Vomiting
- Hemorrhagic gastritis
- Decreased motility

Hepatic

- Abnormal liver enzymes
- Altered glucose metabolism

Metabolic:

- Diaphoresis
- Hyperthermia
- Hypoglycemia
- Ketonemia
- Ketonuria

Pulmonary:

- Hyperpnea
- Tachypnea
- Respiratory alkalosis
- Acute lung injury

Renal:

- Tubular damage
- Proteinuria
- NaCl & water retention
- Hypouricemia

Chronic salicylate toxicity:

- Chronic salicylate poisoning most typically occurs in elderly individuals as a result of unintentional overdosing on salicylates used to treat chronic conditions such as rheumatoid arthritis & osteoarthritis.

- Presenting signs & symptoms of chronic salicylate poisoning include hearing loss & tinnitus; nausea; vomiting; dyspnea & hyperventilation; tachycardia; hyperthermia; & neurologic manifestations such as confusion, delirium, agitation, hyperactivity, slurred speech, hallucinations, seizures, & coma.

Diagnostic testing:

- Careful observation of the patient,
- Correlation of the serum salicylate concentrations with blood pH, &
- Repeat determinations of serum salicylate concentrations every 2 to 4 hours are essential until the patient is clinically improving & has a low serum salicylate concentration in the presence of a normal or high blood pH.

Management of poisoning:

- Salicylate poisoning from acute oral ingestions of large quantities requires prompt medical attention.

- For a salicylate-poisoned patient who presents severely ill & requires mechanical ventilation for airway stabilization, maintenance of hyperventilation required.

- Gastric decontamination: The general sequence for managing salicylate toxicity should begin with gastric decontamination through gastric lavage & activated charcoal.

- The use of Multiple dose activated charcoal (MDAC) to decrease GI absorption of salicylate overdoses is warranted, particularly if an extended-release preparation is suspected.

- Fluid replacement: the patient's volume status must be adequately assessed & and corrected if necessary, along with any glucose & and electrolyte abnormalities.

- Alkalinization of the serum through intravenously administered sodium bicarbonate reduces the fraction of salicylate in the nonionized form (Figure 1).

- Urine pH should be maintained at 7.5 to 8.0, & hypokalemia must be corrected to achieve maximum urinary alkalinization. Calcium concentrations should be also monitored.

- Enhanced salicylate elimination by urine alkalization: salicylic acid is a weak acid (pK a 3.5),& alkalinization of the urine (defined as pH ≥7.5) with sodium bicarbonate results in enhanced excretion of the ionized salicylate ion.

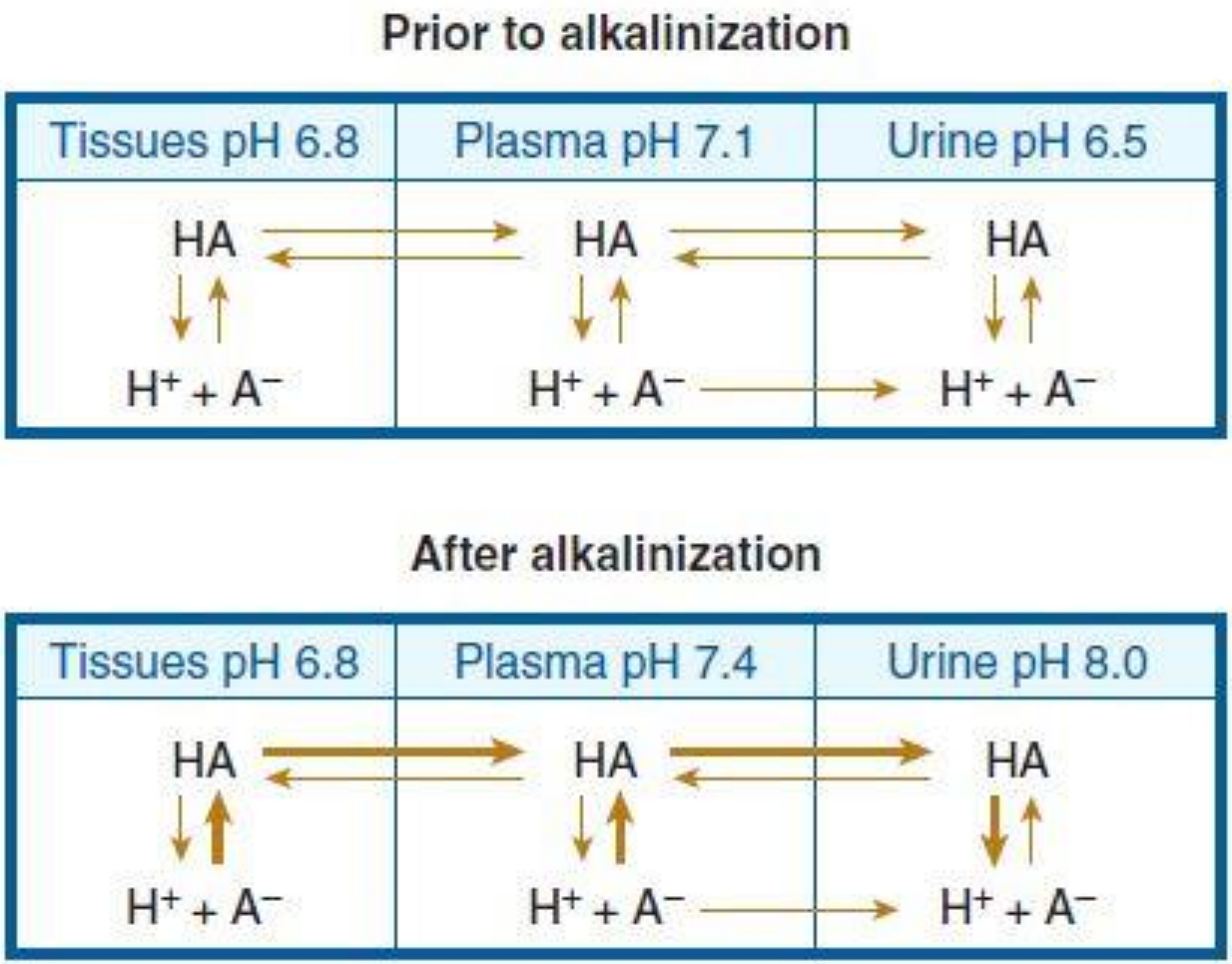


Figure 1. Rationale for alkalinization. Alkalinization of the plasma with respect to the tissues and alkalinization of the urine with respect to plasma shifts the equilibrium to the plasma and urine and away from the tissues, including the brain.

- Extracorporeal removal: Extracorporeal measures are indicated if the patient has severe signs or symptoms, a very high serum salicylate concentration regardless of clinical findings, severe fluid or electrolyte disturbances, hypotension, sever acidosis, or is unable to eliminate the salicylates.

Summery of Treatment

1-Gastric lavage and AC
2-Replace fluids, k, Na, losses from hypermetabolisim and dehydration.
3-Glucose is added to correct hypoglycemia and ketosis.
4-IV $NaHCO_3$ to counteract metabolic acidosis in blood and alkalization of urine for enhancement excretion.
5-Support ventilation.
6-Vitamin K to avoid coagulation defects.
7-diazepam for seizure if present.
8-In sever cases, hemodialysis & hemoperfusion are indicated

Case study:

A 58-year-old man presented to the emergency department after ingesting a large dose of aspirin in a suicidal gesture. On presentation, the patient was diaphoretic & tachypneic, & the initial salicylate level was reported to be 111 mg/dL.

An arterial blood gas measurement revealed pH of 7.5, a PCO2 of 17 mm Hg, & a bicarbonate level of 13 mmol/L. The patient was treated with orally administered activated charcoal, intravenous fluids, & intravenous sodium bicarbonate. The attending physician noted marked tachypnea & thought that the patient might tire. Consequently, the patient was endotracheally intubated. Immediately after intubation, the patient's pH was 7.07, & he died 40 minutes later.

Note:

Normal values:

pH= 7.35-7.45

PCo2= 33-45 mmHg

Bicarbonate level= 22-28 mmolL.


Thank
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