Practical Clinical Toxicology

Toxicity of Salicylates

Lab. 3
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University of Mustansiriyah/College of Pharmacy
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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.

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

- Ingesting high doses of salicylate results in switching salicylate metabolism from first-order to zero-order kinetics (Figure 1).

- After an acute overdose of salicylate, there is an increase in apparent volume of distribution. The toxicity profile for salicylate is shown in (Table 1.)

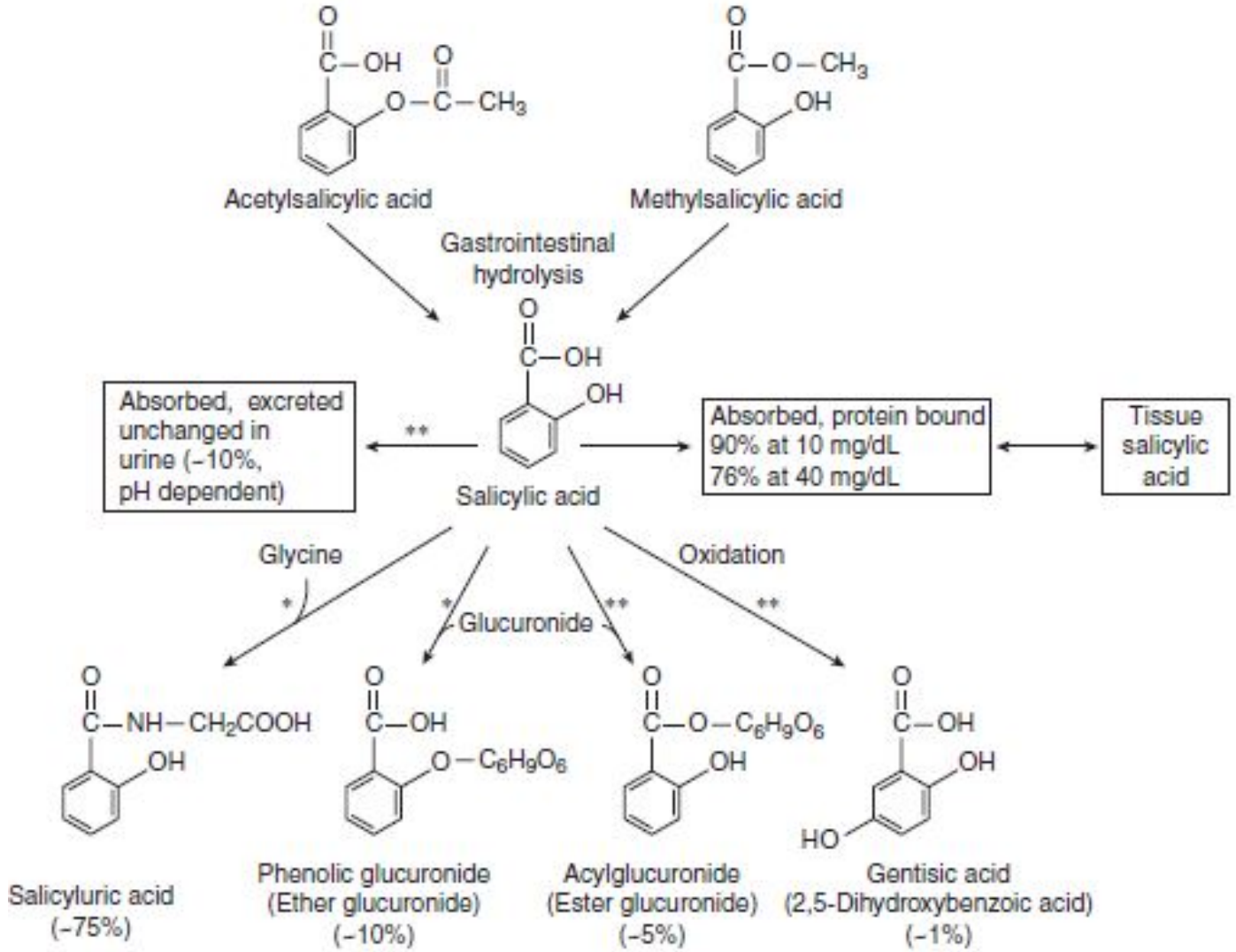


Figure 1. Salicylic acid metabolism. At excessive doses, the 4 mechanisms of salicylic acid metabolism are overloaded, leading to increased tissue binding, decreased protein binding, and increased excretion of unconjugated salicylic acid.* = Michaelis-Menten kinetics; ** = first-order kinetics.

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.

- Salicylates in toxic concentrations titrate approximately 2 to 3 mEq/L of plasma bicarbonate.

- Salicylate interferes with the Krebs cycle, which limits production of adenosine triphosphate (ATP).

- It also uncouples oxidative phosphorylation, causing accumulation of pyruvic & lactic acids.

- Salicylate-induced increased fatty acid metabolism generates ketone bodies, including β-hydroxybutyric acid, aceto acetic acid, & acetone.

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

Clinical manifestations of salicylate poisoning:

Acute salicylate toxicity:

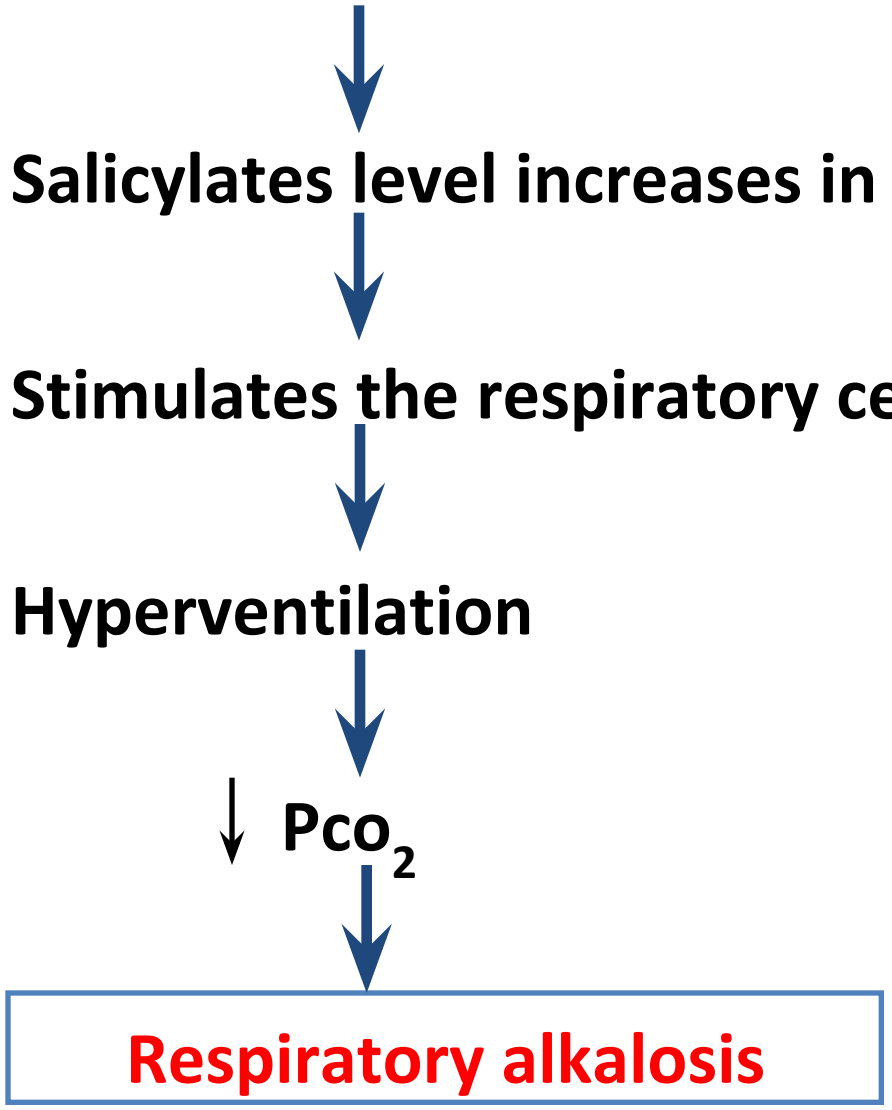
- The earliest signs & symptoms of salicylate toxicity, which include nausea, vomiting, diaphoresis, & tinnitus, typically develop within 1 to 2 hours of acute exposure.

- Other early CNS effects may include vertigo & hyperventilation manifested as hyperpnea or tachypnea, hyperactivity, agitation, delirium, hallucinations, convulsions, lethargy, & stupor.

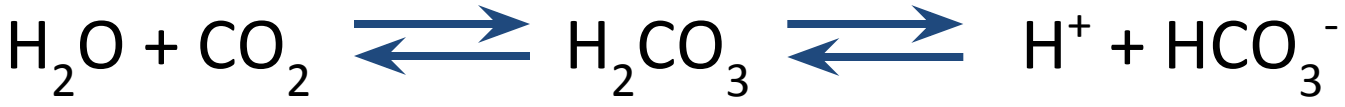
- Coma is rare & generally it occurs only with severe acute poisoning.

- A marked elevation in temperature resulting from the uncoupling of oxidative phosphorylation caused by salicylate poisoning is one indication of severe toxicity.

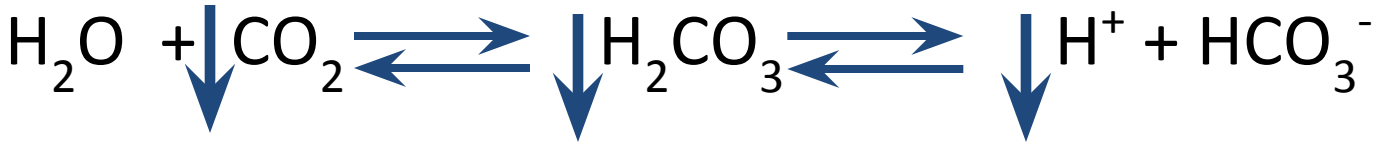
CNS effect of salicylate intoxication:



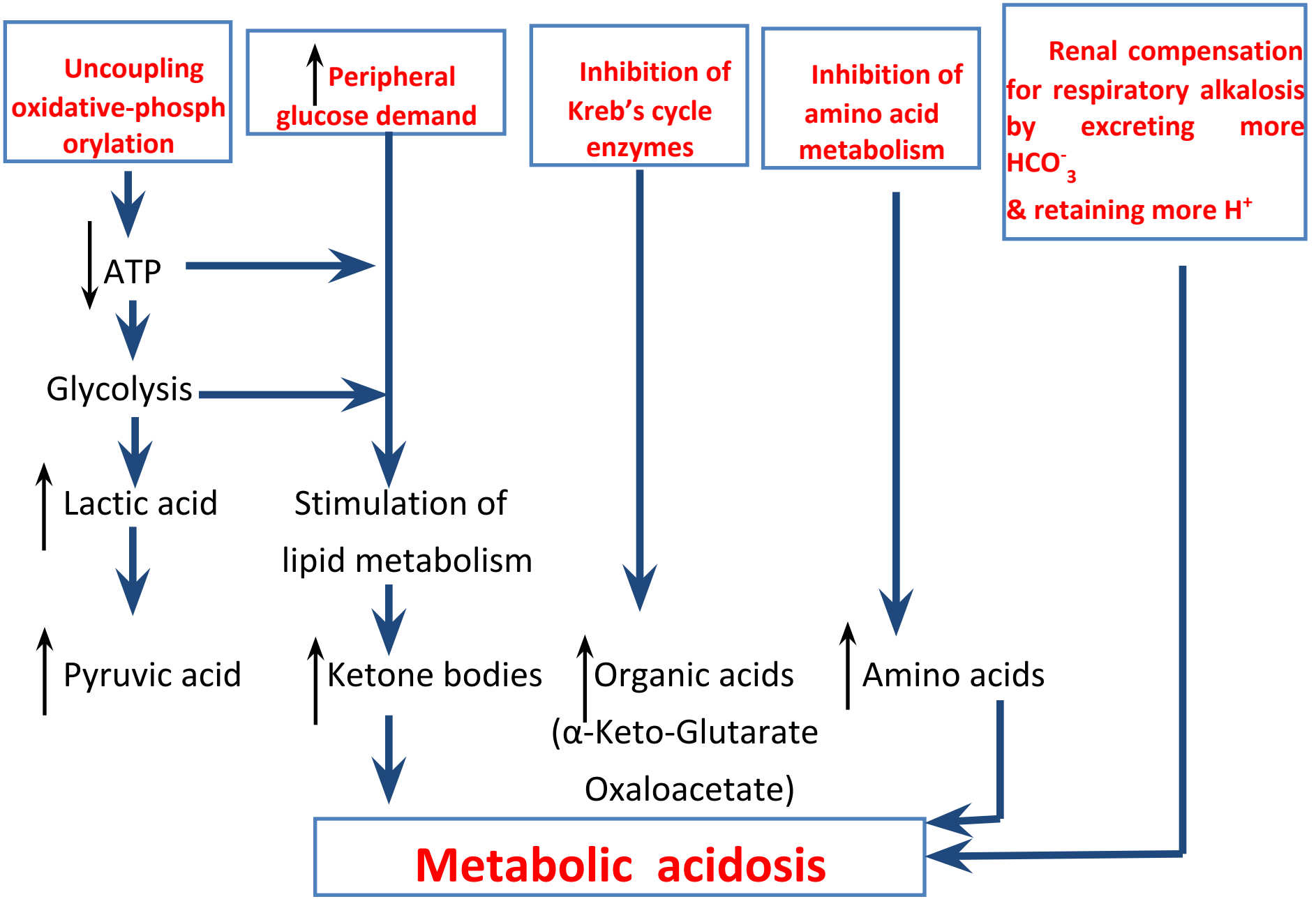
Reactions of the bicarbonate buffer system for maintaining blood pH:



In hyperventilation:



Metabolic effects of salicylate intoxication



Clinical manifestations & diagnostic testing results 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 (vomiting)
- Hypokalemia

Central nervous system:

- Tinnitus
- Diminished auditory acuity
- Vertigo
- Hallucinations
- Agitation
- Hyperactivity
- Delirium
- Stupor
- 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
- Hyperglycemia
- 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 requires an extremely careful approach if death is to be avoided.

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

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Case Report

Hypercapnea and Acidemia despite Hyperventilation following Endotracheal Intubation in a Case of Unknown Severe Salicylate Poisoning

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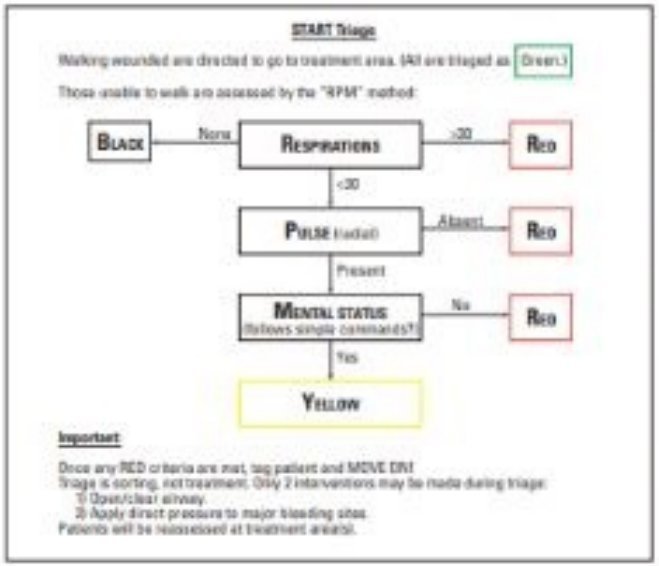
Salicylates are common substances for deliberate self-harm. Acute salicylate toxicity is classically associated with an initial respiratory alkalosis, followed by an anion gap metabolic acidosis. The respiratory alkalosis is achieved through hyperventilation, driven by direct stimulation on the respiratory centers in the medulla and considered as a compensatory mechanism to avoid acidemia. However, in later stages of severe salicylate toxicity, patients become increasingly obtunded, with subsequent loss of airway reflexes, and therefore intubation may be necessary. Mechanical ventilation has been recommended against in acute salicylate poisoning, as it is believed to take away the compensatory hyperpnea and tachypnea. Despite the intuitive physiological basis for this recommendation, there is a paucity of evidence to support it. We describe a case of a 59-year-old male presenting with decreased level of consciousness and no known history of ingestion. He was intubated and experienced profound hypercarbia and acidemia despite mechanical ventilation with high minute ventilation and tidal volumes. This case illustrates the deleterious effects of intubation in severe salicylate toxicity.

1. Introduction

Severe, acute salicylate toxicity remains a common presentation to the Emergency Department (ED) and is associated with a significant degree of mortality [1]. In its unionized form, salicylate can move across cell membranes into tissues to exert toxic effects. In the presence of acidemia, salicylate will shift to this unionized form, which allows it to cross the blood-brain barrier, and cause central nervous system toxicity (cerebral edema, seizures, and coma). Therefore, the presence of acidemia is seen as a poor prognostic indicator. Classically, salicylate toxicity is initially associated with a respiratory alkalosis, secondary to direct stimulation of the medulla, and subsequent tachypnea and hyperpnea as a response to metabolic acidosis. For this reason, intubation and mechanical ventilation have been commonly recommended against in severe salicylate poisoning, as it is believed that this intervention may take away this protective respiratory drive [2, 3]. Other sources suggest that intubation may be safely performed, as long as apneic time during induction is minimized, and the patient is hyperventilated adequately on the ventilator [3]. Unfortunately, very little evidence exists on this topic, and there are multiple reasons that a patient with salicylate toxicity may require intubation, including decreased or altered level of consciousness, failure to protect airway, and respiratory distress from pulmonary edema. Taken together, there is very little understanding regarding the approach to intubation of patients with severe salicylate overdose. We present a case of a patient with unknown severe salicylate toxicity, who was intubated upon arrival, but immediately hyperventilated several minutes later once initial blood gas levels revealed the diagnosis. To our knowledge, we are the first to publish pre- and postintubation blood gas data in the context of ventilator settings that should have resulted in hyperventilation and improving acidemia.

Figure (Rozenman).
Summary/adaptation of the START triage system. The Web version of this figure is available in color



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Deleterious Effects of Endotracheal Intubation in Salicylate Poisoning

Severe salicylate intoxication is typically associated with metabolic acidosis and a concomitant respiratory alkalosis.[1] Confusion may arise because this respiratory alkalosis is not a simple compensatory response to the developing metabolic acidosis. Rather, this phenomenon represents a primary central nervous system effect of salicylate in the central nervous tissue.[1] The clinical importance of this principle is illustrated by the following case, wherein we provided consultation.

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 and tachypneic, and the initial salicylate level was reported to be 111 mg/dL. An arterial blood gas measurement revealed pH of 7.5, a Pco_2 of 17 mm Hg, and a bicarbonate level of 13 mmol/L. The patient was treated with orally administered activated charcoal, intravenous fluids, and intravenous sodium bicarbonate. The attending physician noted marked tachypnea and thought that the patient might tire. Consequently, the patient was endotracheally intubated. Immediately after intubation, the patient's pH was 7.07, and he died 40 minutes later.

It is important to remember that salicylates in solution have a pK_a of approximately 3.5.[2] Consequently, an acidic environment favors the nonionized state for this molecule, and thus facilitates the ability of the molecule to cross biologic membranes. In the case described here, once intubated, the patient could not be ventilated rapidly enough to maintain the pH at alkaline levels. Thus, almost immediately after intubation, the patient's pH declined substantially, facilitating entry of salicylate from the serum into central nervous tissue.

We were unable to identify medical literature that directly addresses this critical clinical phenomenon. We are concerned that physicians who may be called on to treat salicylate intoxication be aware that endotracheal intubation, usually a life-saving procedure, may have deleterious effects in the setting of severe aspirin poisoning. Because suppression of the patient's respiratory drive can be rapidly life threatening in this setting, we recommend that endotracheal intubation in similar cases be withheld unless cardiorespiratory arrest has occurred. Even in these cases, it is essential that the patient be manually ventilated as rapidly as possible to try to prevent a precipitous decline in serum pH and consequent rush of salicylate into the brain. Mechanical ventilation simply cannot be provided at rates rapid enough to accomplish this.

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- 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.

- Theoretical support may be found for the use of whole-bowel irrigation (WBI) consisting of polyethylene glycol electrolyte lavage solution (PEG-ELS) in addition to AC to reduce systemic absorption.

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

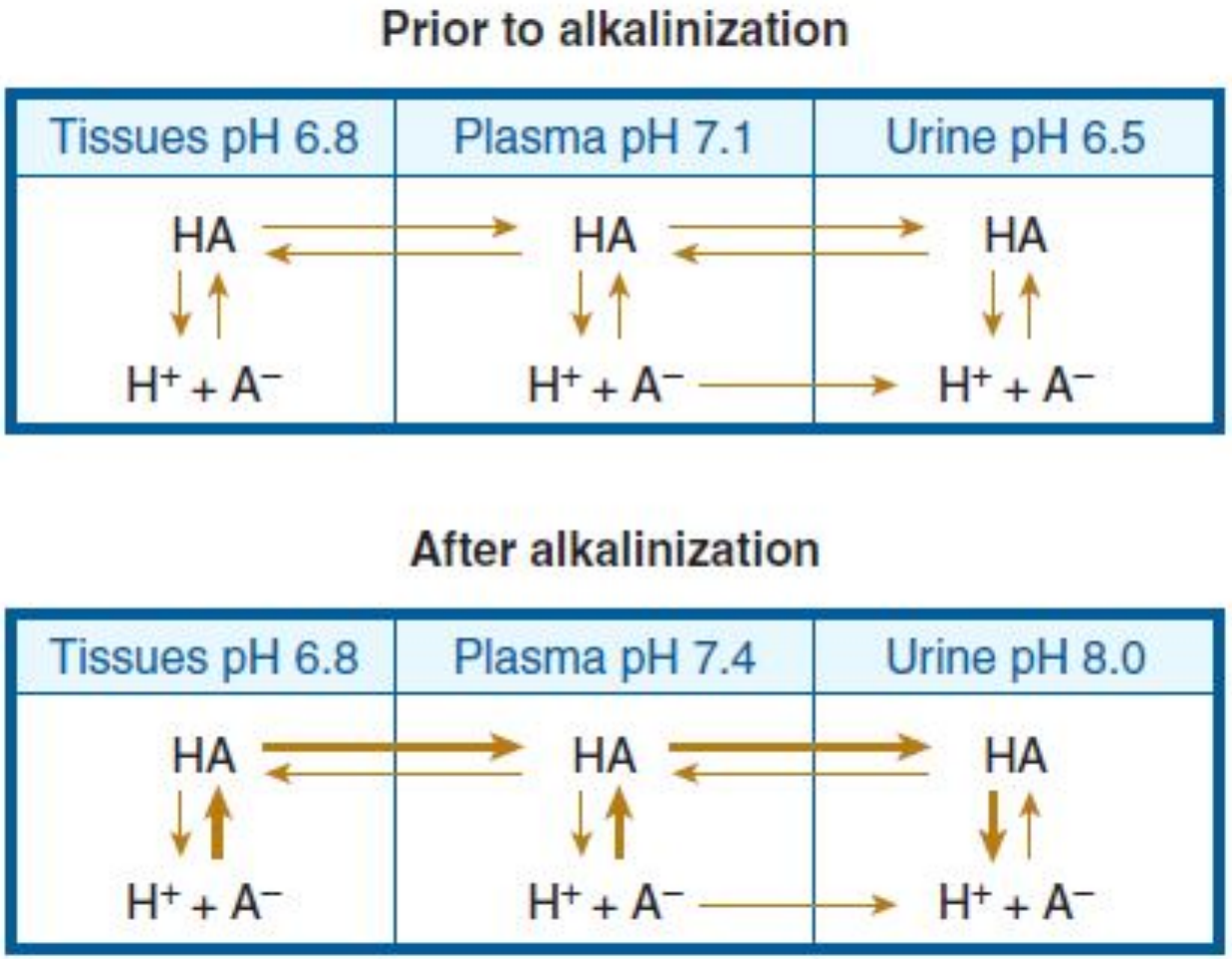

Figure 1. Rationale for alkalinization. Alkalinization of the plasma with respect to the tissues and alkalinization of the urine with respect to plasma shifts the equilibrium to the plasma and urine and away from the tissues, including the brain.

- 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, or is unable to eliminate the salicylates.

  In most In most instances of severe salicylate poisoning, HD is the extracorporeal technique of choice,

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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