Forensic & Toxicology Team

MED 433

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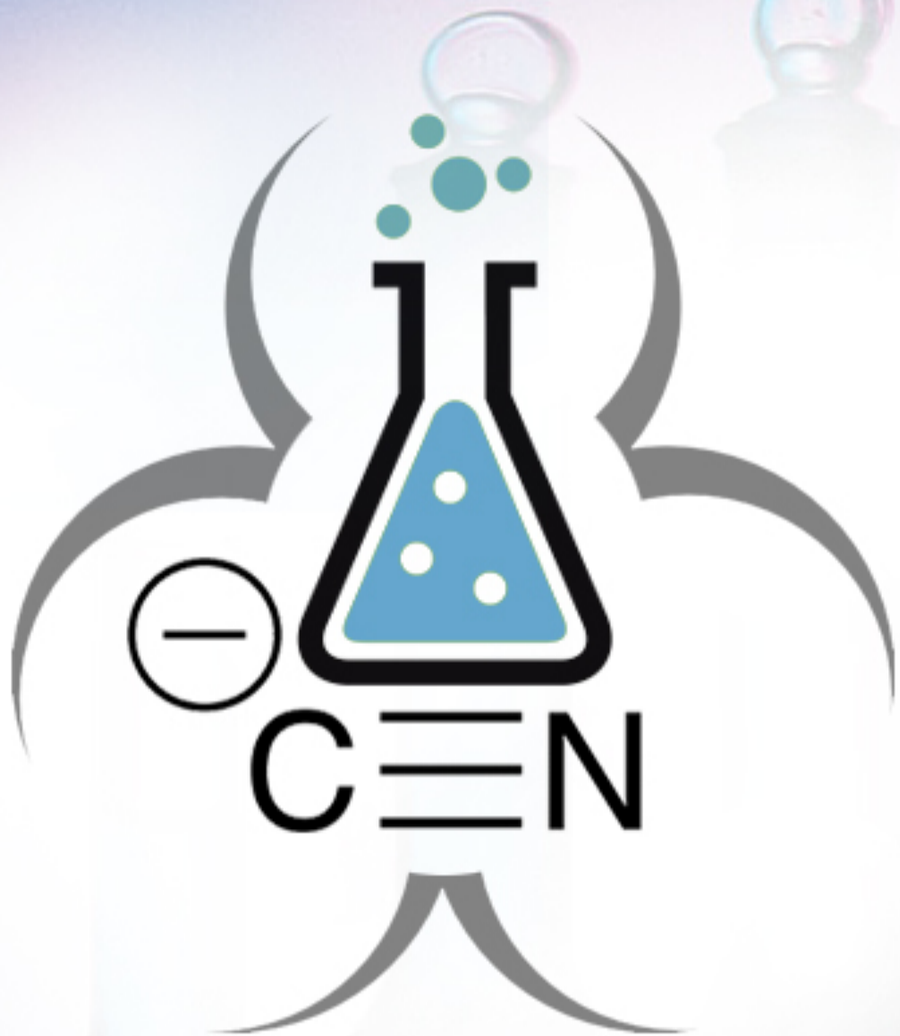
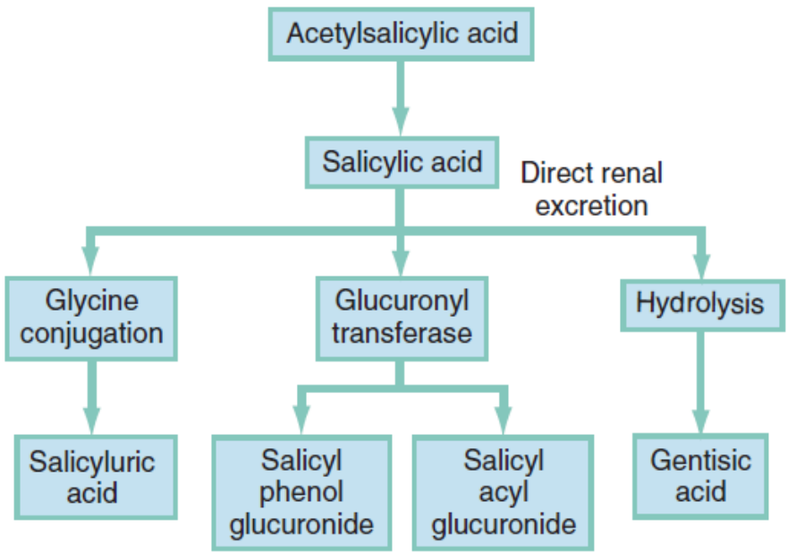



# Lecture 13 : Aspirin Toxicity

# Principles of Disease Pharmacokinetics:

- Aspirin was used in the past as a pain killer, nowadays it's only used as an antiplatelet due to its side effects.
- In dermatology, aspirin is still used to remove excess keratin from the skin. (Locally applied keratolytic agent)
- Salts of salicylic acid are rapidly absorbed intact from the GI tract, with appreciable serum concentrations within 30 minutes.
- Two thirds of a therapeutic dose is absorbed in 1 hour, and peak levels occur in 2 to 4 hours.
- Serum concentrations may rise for more than 12 hours after large ingestions (which may delay gastric emptying) or ingestions of enteric capsules.
- In the intestinal wall, liver, and red blood cells, aspirin is hydrolyzed to free salicylic acid, which reversibly binds to albumin.
- In the liver, salicylate is conjugated with glucuronic acid and glycine.
- A small fraction is hydroxylated.
- Free salicylate and its conjugates are eliminated by renal excretion.



# Principles of Disease Pharmacokinetics:

## Aspirin Metabolism

- At therapeutic salicylate concentrations, elimination follows first-order kinetics*, and excretion is proportional to salicylate concentration.

- When serum salicylate concentrations are greater than 30 mg/dl, however, elimination follows zero-order kinetics*, and the metabolic rate is constant.

- The metabolic pathways become saturated, and the pH-sensitive urinary excretion of salicylic acid determines the half-life (which may approach 15–30hr with toxic doses). [30hrs = observe the patient for two days]

Important
*First-order kinetics = when the concentration of a drug goes high in the serum, the metabolism also goes up. (the metabolism increases as the concentration increases) (proportional).
*Zero-order kinetics = Whatever the concentration of the drug, the metabolism remains the same (constant).

# Pathophysiology

## Acid-Base Disturbances and Metabolic Effects

- Salicylate stimulates the medullary respiratory center early and increases the sensitivity of the respiratory center to pH and carbon dioxide partial pressure (Pco2).

- Hyperventilation develops early, then subsequently becomes a compensatory mechanism to the metabolic acidosis.

- Prolonged high serum concentrations eventually depress the respiratory center.

- Respiratory alkalosis is compensated for by buffering of the hemoglobin-oxyhemoglobin system, the exchange of intracellular hydrogen ions for extracellular cations, and the urinary excretion of bicarbonate.

- Loss of bicarbonate decreases buffering capacity and intensifies the metabolic acidosis.

# Pathophysiology

## Acid-Base Disturbances and Metabolic Effects

- Toxicity results primarily from interference with aerobic metabolism by uncoupling of mitochondrial oxidative phosphorylation.
- Inhibition of the Krebs dehydrogenase cycle increases production of pyruvic acid and increases conversion to lactic acid.
- Increased lipid metabolism increases production of ketone bodies.
- Metabolic rate, temperature, tissue carbon dioxide, and oxygen consumption are increased.
- Tissue glycolysis predisposes to hypoglycemia. (Hepatic gluconeogenesis and release of adrenaline may cause the less common hyperglycemia.)
- Hypoglycemia is more common than hyperglycemia in aspirin toxicity.
- Inefficiency of anaerobic metabolism results in less energy being used to create ATP, and energy is released as heat, causing the hyperthermia frequently seen in salicylate poisoning.
- Only non-ionized particles can cross the cell membrane and accumulate in the brain and other tissues.
- Because ASA has a low pKa, the majority of salicylate is ionized and little salicylate enters tissues at the physiologic pH of 7.4.
- As pH decreases, more particles become un-ionized, cross the cell membrane and blood-brain barrier, markedly increasing the movement of salicylate into the tissues and CNS.

# Pathophysiology

## Fluid and Electrolytes Abnormalities

- **Potassium loss in salicylate toxicity is caused by :**

(1) Vomiting, secondary to stimulation of the medullary chemoreceptor trigger zone.

(2) Increased renal excretion of Na, bicarbonate, and K as a compensatory response to the respiratory alkalosis.

(3) Salicylate-induced increased permeability of the renal tubules with further loss of potassium.

(4) Intracellular accumulation of sodium and water.

(5) Inhibition of the active transport system, secondary to uncoupling of oxidative phosphorylation.

The net result is rapid depletion of potassium stores (Hypokalemia), which is one of aspirin toxicity hallmarks.

- Asalicylate-induced decrease in renal blood flow or direct nephrotoxicity may cause acute nonoliguric renal failure.
- Salicylate-induced secretion of inappropriate antidiuretic hormone may also affect renal function.

# Pathophysiology

## Pulmonary and Cerebral Edema

- The exact mechanism by which salicylate increases alveolar capillary membrane permeability is unknown.
- Any alteration in sensorium is evidence of cerebral edema and is a grave prognostic sign.
- Factors causing cerebral edema are unknown.
- Patients with cerebral or pulmonary edema require immediate dialysis.

## Risk factors for salicylate-induced pulmonary edema

| Risk factors in children | Risk factors in adults (important) |
|---|---|
| • High serum salicylate levels<br>• Large anion gap<br>• Decreased serum potassium concentration<br>• Low Pco2. | • Age older than 30 years<br>• Cigarette smoking<br>• Chronic salicylate ingestion<br>• Metabolic acidosis<br>• Neurologic symptoms<br>• Salicylate concentration greater than 40 mg/dl. |

# Pathophysiology

## Chronic Ingestion Physiology

- Physiologic changes of aging predispose elderly patients to toxicity from chronic therapeutic ingestion.
- Decreased liver blood flow rates decrease biotransformation of salicylate
- Decreased renal function decreases ASA clearance.
- Chronic ingestion of aspirin decreases albumin binding, which increases free salicylate.
- The free salicylate enters the cell, causing significant clinical illness with a relatively low serum salicylate concentration.
- A patient with chronic salicylate toxicity and a serum concentration of 40 mg/dl may be more ill than a patient with an acute ingestion and serum concentration of 80 mg/dl.
  [Because patients with chronic ingestion have more free salicylates, while in acute ingestion the salicylate will bind to albumin]
- Pediatric salicylism from supra-therapeutic dosing may be more serious than acute ingestion.
- Sweating, fever, and tachycardia caused by salicylism may be attributed to underlying infection.
- Other sources of salicylate exposure include breast milk, teething gels, and percutaneous absorption of skin ointments, which have high concentrations of methyl-salicylate.

# Clinical Features

- A toxic dose of aspirin is 200 to 300 mg/kg. While 500 mg/kg is potentially lethal.

## Initial manifestations of acute salicylate:

- Tinnitus
- impaired hearing
- Hyperventilation
- Vomiting
- Dehydration
- Hyperthermia

**Salicylate-induced hyperpnea may manifest as increased respiratory depth without increase in rate. Hyperventilation is more common in adults, who usually have an initial respiratory alkalosis.**

- Young children are predisposed to toxicity due to the metabolic acidosis, which increases tissue and CNS salicylate concentrations.
- Vomiting can occur 3 to 8 hours after ingestion.
- Serious dehydration can occur from hyperpnea, vomiting, and hyperthermia.
- CNS manifestations are usually associated with acidemia.
- SOB caused by pulmonary edema
- Altered sensorium by cerebral edema
- Non-cardiac pulmonary edema may be more common in children

**Asymptomatic:** Occasional subjective but no objective manifestations

**Mild:** Mild to moderate hyperpnea tinnitis, sometimes with lethargy

**Moderate:** Severe hyperpnea, prominent neurologic disturbances, such as marked lethargy or agitation, but no coma or convulsions

**Severe:** Severe hyperpnea, coma, or semicoma, sometimes with convulsions

# Diagnostic criteria

- Serum salicylate concentration should be measured after 6 hours or more, a second sample should be obtained 2 hours later.

(If second is greater, serial concentrations should be obtained to monitor continued absorption)

- Acid-base status can change quickly, and frequent monitoring of arterial pH is necessary to guide treatment.
- ↓ pH and bicarbonate → severe disease.
- The pH begins to drop when the patient is unable to compensate for the acidosis.
- Lactic acid accumulates, and serum bicarbonate is consumed.
- When pH is less than 7.4, and both Pco2 and bicarbonate are low, the patient begins to decompensate hemodynamically.
- In the intubated patient or the acidotic patient with low Pco2 and bicarbonate, hemodialysis should be undertaken.

**Asymptomatic:** Occasional subjective but no objective manifestations

**Mild:** Mild to moderate hyperpnea tinnitis, sometimes with lethargy

**Moderate:** Severe hyperpnea, prominent neurologic disturbances, such as marked lethargy or agitation, but no coma or convulsions

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# Management

## Initial evaluation

- Physical examination → including vital signs (including oxy saturation and a counted respiratory rate and reliable temperature).
- Chest auscultation may provide evidence of pulmonary edema.
- ABG → assess acid-base & compensatory status.

## Aim of management

1- correct fluid deficits & acid-base abnormalities.
2- increase excretion.

- Infuse intravenous fluids: D5 with 100–150 mEq bicarbonate/L.
- Monitor serum pH; do not cause systemic alkalosis.
- Do not attempt forced diuresis.

- Monitor for Coma, Seizure, Renal, hepatic, or pulmonary failure, Pulmonary edema and Severe acid-base imbalance. If at least one is present, patient usually require dialysis.

**Gastric emptying is of no value**

# Management

## Activated charcoal

- There is not sufficient evidence to support the administration of activated charcoal (AC) in acute or chronic salicylate poisoning.
- Even when given within 1 hour of ingestion.

**Gastric emptying is of no value**

## Intravenous fluid

- Dehydration should be treated with intravenous fluid.
- Potassium depletion must be corrected.
- Fluid administration should be guided by the patient's apparent deficit to maintain urine output of 2 to 3 mL/kg/hr and should not exceed the estimated replacement, because excessive fluid administration can worsen cerebral and pulmonary edema.

- Intravenous fluid should contain dextrose, and the serum glucose level should be frequently monitored to prevent hypoglycemia.

- In animal studies, hypoglycemia consistently occurs with death.

# Management

## Urine Alkalization

- Salicylate is renaly excreted, alkaline urine traps the salicylate ion and increases excretion.
- In levels greater than 35 mg/dl, significant acid-base disturbance, or increasing salicylate levels.
- A urine pH of 7.5 to 8.0 is necessary to increase excretion.
- Sodium bicarbonate (1–2 mEq/kg) over 1 to 2 hs, with subsequent dosage adjustment determined by urinary and serum pH.
- However, Urinary alkalization is difficult to achieve because the excretion of salicylic acid in the urine decreases urinary pH.
- Additionally, potassium depletion must be corrected to attain an alkaline urine.
- Alkaline urine should not be produced at the cost of systemic alkalemia.
- Forced diuresis not indicated

# Management

## Hemodialysis

**Indications:**

1- salicylate levels greater100 mg/dl in acute intoxication

2- 50 mg/dl in chronic salicylate poisoning

3- altered mental status

4- endotracheal intubation

5- Coma

6- renal or hepatic failure

7- pulmonary edema

8- severe acid-base imbalance

9- rapidly rising serum salicylate level

10- failure to respond to conservative treatment.

Exchange transfusion can be considered in young infants or unusual cases of congenital salicylism.

## Pregnancy

- Greater salicylate concentration on the fetal side of the placenta and relative fetal acidemia contribute to fetal distress from maternal salicylate poisoning.
- Salicylate poisoning during pregnancy is associated with fetal demise, and delivery of the distressed fetus should be considered if the fetus is viable

# Disposition

- mortality rate is chronic salicylate intoxication →25% , while acute salicylate intoxication → 1%
- Patients should not be discharged unless the serum concentrations are decreasing.
- As in any case of intentional overdose, psychiatric evaluation is essential

- In patients with acute ingestion, a second serum salicylate concentration measurement is essential to determine whether the peak serum concentration has been attained.
- Patients should not be discharged unless the serum concentrations are decreasing.
- As in any case of intentional overdose, psychiatric evaluation is essential.

**KEY CONCEPTS**

- ASA intoxication, especially chronic salicylism, should be considered in the differential diagnosis of altered mental status in the elderly.
- Potassium stores are rapidly depleted in patients with salicylate intoxication.
- The acute toxic dose of ASA is 300 mg/kg, and 500 mg/kg is potentially lethal.
- Acidosis signifies severe salicylism as unbound salicylate is moving into the cell.
- Signs of pulmonary or cerebral edema, coma, hepatic failure, circulatory collapse, refractory acidosis, or levels greater than 100 mg/dL require immediate hemodialysis.
- Hyperthermia, altered mental status, coma, pulmonary edema, and shock may be presenting signs of salicylism.
- Serial salicylate concentrations should be obtained after acute ingestion to ensure that the salicylate concentration is decreasing.
- Consider dialysis in patients with coma, seizures, renal failure, hepatic failure, pulmonary failure, or refractory acidosis or in acute cases in which serum levels are greater than 100 mg/dL.
- NSAID overdose, other than ASA, is usually self-limited, with predominantly gastrointestinal toxicity.
- Pyrazolones and fenamates can cause seizures.

# MCQ’s

**1- Acute Aspirin toxicity causes which of the following electrolyte abnormalities :**

A- hyperkalemia C- hypermagnesemia

B- hypokalemia D- hyperphosphatemia

**2- The metabolism of Aspirin mainly takes place in :**

A- Liver C- Spleen

B- Kidney D- Lungs

**3- In acute Aspirin toxicity hemodialysis is indicated if patient develops:**

A- Pulmonary edema C- Hyperthermia

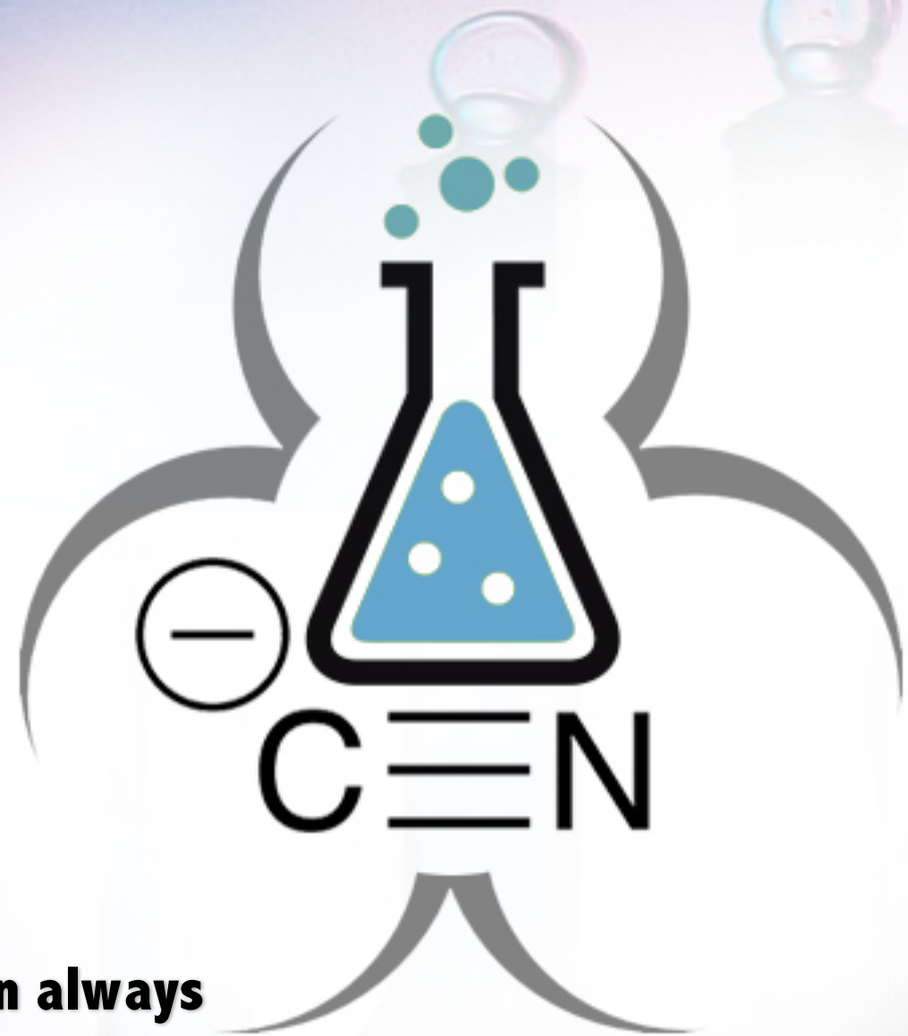
B- Vomiting & diarrhea D- Skin rash

**4- Which dose of Aspirin will produce severe toxicity**

A- 30mg/kg C- 200mg/kg

B- 150mg/kg D- 500mg/kg

1- B 2- A 3- A 4- D

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