SALICYLATES

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Overview: Salicylates

Found in Willow bark (*Salix alba vulgaris*)

Widely used analgesic/anti-inflammatory agent

Multitude of preparations

- Prescription (percodan)
- Over-the-counter (pepto-bismol, aspirin)
- Topical preparation (wart removal)
- Combinations (excedrin, fiorinal)
- Other (oil of wintergreen)
Overview: Salicylate Formulations

Aspirin (acetylsalicylic acid)  325 - 650 mg/tab
  BASA                              81 mg/pill
  Suppository                       120 - 600 mg

Fiorinal/Soma or Darvon Compounds 325 mg of ASA

Oil of Wintergreen (methyl salicylate)  5 g/5 cc
Overview: Salicylate Pharmacokinetics

Absorption

With therapeutic use: Rapidly absorbed

In overdose:
- SAL impairs gastric emptying
- Enteric coating produces delayed absorption
- Toxic [SAL] may be delayed for > 6 hrs

Topical application have been assoc with deaths
Salicylate Ion

\[ pK_a = 3.5 \]
Overview: Salicylate Pharmacokinetics

Distribution

Decrease pH favors un-ionized state:
At pH 7.4, 98% of SAL is ionized
At pH 7.2, 96% of SAL is ionized

Unionized SAL distributes into tissues
Overview: Salicylate Pharmacokinetics

Distribution

Salicylate-albumin binding is saturable:

Serum Concentration: Protein Binding:

8 mg/dL  83%
92 mg/dL  40%

From: Br J Clin Pharmac 1981; 11:625-626
Overview: Salicylate Pharmacokinetics

Distribution

Salicylate exists in plasma in equilibrium between:

\[ \text{H}^+ + \text{SAL}^- \leftrightarrow \text{SALH} \]

\[ \text{ALBUMIN-SAL}^- \leftrightarrow \text{ALBUMIN + SAL}^- \]

The unbound unionized salicylate diffuses into tissues
Overview: Distribution

Un-ionized & Non-protein bound Sal
Favors distribution into tissue
Salicylate Neurotoxicity

Figure 1. Post-Mortem Blood and Tissue Salicylate Levels Obtained from Rats as Soon as Possible after Death from Salicylate Overdoses.

The dashed lines include all the brain levels.
Overview: Salicylate Pharmacokinetics

**Elimination**

$T_{1/2} = 3 \text{ hrs} \ (36 \text{ hrs in overdose})$

Bio-elimination via **first-order** (at very low body burden) and then **zero-order** kinetics (in overdose)

Glucuronide and Glycine Conjugation
Microsomal Oxidation
Renal Excretion
outer membrane

intermembrane space

inner membrane; cristae

matrix

citric acid cycle

DNA
Electron Transport Chain

intermembrane space

matrix

I

II

III

IV

CytC
$\Delta p\text{H} \approx 0.5$

$\Delta pH \approx 0.5$

$\text{citric acid cycle}$

$\text{matrix}$

$\text{DNA}$
I

$4H^+ \rightarrow Q$

$Q$

II

$4H^+ \rightarrow III$

$III$

$2H^+$

CytC

$IV$

$3H^+$

$O_2 \rightarrow H_2O$

$succinate \rightarrow NADH + H^+$

$NADH + H^+ \rightarrow N$-

$\Delta \psi - 200 \text{ mv}$

$ADP + Pi + H^+ \rightarrow ATP + H_2O$

$\text{matrix}$

$P$
Generic Acid Uncoupler

\[ \text{pH} \quad H^+ \quad H^+ \quad H^+ \quad H^+ \quad H^+ \quad H^+ \quad H^+ \quad H^+ \quad H^+ \]

intermembrane space

\[ \text{R-COO}^- \quad \text{R-COOH} \]

matrix

\[ \text{pH} \quad H^+ \quad H^+ \quad H^+ \]

N
Generic Acid Uncoupler

\[ \text{pH} \quad H^+ \quad H^+ \quad H^+ \quad H^+ \quad H^+ \quad H^+ \quad H^+ \quad H^+ \quad H^+ \]

intermembrane space

\[ R-\text{COO}^- \quad \leftrightarrow \quad R-\text{COOH} \]

matrix

\[ \text{pH} \quad H^+ \quad H^+ \quad H^+ \]

N
Generic Acid Uncoupler

\[ \text{pH} \quad \text{H}^+ \quad \text{H}^+ \quad \text{H}^+ \quad \text{H}^+ \quad \text{H}^+ \quad \text{H}^+ \quad \text{H}^+ \quad \text{H}^+ \]

intermembrane space

\[ \text{R-COO}^- \quad \text{R-COO}^+ \quad \text{R-COO}^- \quad \text{R-COO}^+ \]

matrix

\[ \text{H}^+ \quad \text{H}^+ \quad \text{H}^+ \]

\[ \text{pH} \quad \text{H}^+ \quad \text{H}^+ \quad \text{H}^+ \quad \text{H}^+ \quad \text{H}^+ \quad \text{H}^+ \quad \text{H}^+ \quad \text{H}^+ \]
The electron transport chain (ETC) plays a crucial role in cell respiration, allowing for the sequential oxidation of substrate molecules and the subsequent transfer of electrons through a series of redox proteins. These proteins are embedded in the inner mitochondrial membrane, facilitating the generation of a proton gradient across the membrane.

1. **NADH + H+** is oxidized to **O2** and **H2O** in complex I.
2. **4H+** are transferred to the intermembrane space, creating a proton gradient.
3. **4H+** are then transferred to complex II (Q), which releases **2H+** to the matrix space.
4. **2H+** are transferred to complex III, releasing **4H+** to the intermembrane space.
5. **4H+** are transferred to complex IV (Cyt C), releasing **2H+** to the matrix space.
6. **2H+** are transferred to the final electron acceptor, **O2**, in complex IV, releasing **3H+** to the intermembrane space.
7. **O2** and **H2O** are produced.

The proton gradient generated across the inner mitochondrial membrane drives the synthesis of **ATP** from **ADP** and **Pi** in a process catalyzed by ATP synthase (complex V). The proton gradient is also coupled with the production of **heat**.

**Coupler**

**Uncoupler**

**Matrix**
Salicylate: Mechanisms of Toxicity

Major (recurrent) toxic effects:

- Metabolic Acidosis
- Hypoglycemia
- Decreased energy production
# Salicylate: Mechanisms of Toxicity

<table>
<thead>
<tr>
<th>MECHANISMS</th>
<th>MANIFESTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncouples Ox-Phosphorylation</td>
<td>Metabolic Acidosis, Decrease ATP, Increased Heat, Hypoglycemia</td>
</tr>
<tr>
<td>Inhibition of Krebs Cycle (TCA)</td>
<td>Hypoglycemia/Metabolic acidosis</td>
</tr>
<tr>
<td>Inhibition of Amino Acid Metabolism</td>
<td>Hypoglycemia/Metabolic Acidosis</td>
</tr>
<tr>
<td>Stimulates Respiratory Center</td>
<td>Tachypnea, Respiratory Alkalosis, Renal Excretion of HCO(_3)^{-}/Fluids</td>
</tr>
<tr>
<td>Stimulation of Glycogenolysis</td>
<td>Hyperglycemia (Early, Transient)</td>
</tr>
<tr>
<td>Inhibit Vitamin K(_1) 2,3-epoxide</td>
<td>Prolonged PT</td>
</tr>
<tr>
<td>Stimulation of Lipid Metabolism</td>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>GI Corrosive</td>
<td>Nausea / Vomiting</td>
</tr>
<tr>
<td>Increased Capillary Permeability</td>
<td>Third Spacing/Pulmonary Edema</td>
</tr>
</tbody>
</table>
Salicylate Neurotoxicity

Brain is most energy dependant organ

Glucose quickly spent during SAL toxicity

Severe hypoglycorrhachia = Death

Mortality correlates best with [SAL] in brain
<table>
<thead>
<tr>
<th>Toxicity Level</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic Range</td>
<td>10–15 mg/kg</td>
</tr>
<tr>
<td>Mild Toxicity</td>
<td>&lt; 150 mg/kg</td>
</tr>
<tr>
<td>Moderate Toxicity</td>
<td>150-300 mg/kg</td>
</tr>
<tr>
<td>Severe Toxicity</td>
<td>&gt; 300 mg/kg</td>
</tr>
</tbody>
</table>

* Approximate ranges
Serum Salicylate Levels

Effect

Complications
Renal and respiratory failure
Vasomotor collapse
Coma
Hypoprothrombinemia
Fever, dehydration
Metabolic acidosis
Central hyperventilation
Tinnitus
Anti-inflammatory
Uricosuric
Rheumatoid arthritis
Analytactic
Antipyretic
Antiplatelet
Gastric intolerance, bleeding
Hypersensitivity reactions
Impaired hemostasis
## Acute Salicylate Toxicity

### Physical Exam

<table>
<thead>
<tr>
<th>Subjective</th>
<th>Depressed, Abdominal pain, N/V, Tinnitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Ill-appearing, Diaphoretic, Febrile, ALOC</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Tachycardia, Hypotension (Dehydrated)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Tachypnea, Kussmaul’s, Rales</td>
</tr>
<tr>
<td>Gastric</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Agitation, Lethargy, Seizures or Coma</td>
</tr>
</tbody>
</table>
Acute Salicylate Toxicity

**Labs**

- **BMP**: Hypokalemia, Ketones, Anion Gap
- **UA**: pH, Ketones, Rhabdomyolysis
- **ABG**: Respiratory Alkalosis and Metabolic Acidosis
- **Coags**: Elevated PT
- **CXR**: Pulmonary Edema, ARDS, Aspiration
- **CTH**: Cerebral Edema
Acute Salicylate Toxicity

Must quantitate serum SAL level
Initial [Sal] don’t correlate with severity.


Fig. 1. Relationship between serum level at time of admission and clinical severity of salicylate intoxication.
Treatment Strategies for Salicylate Poisoning

- Initial Stabilization
- Limit Absorption
- Limit Distribution
- Enhance Elimination
Treatment of Salicylate Poisoning

Initial Stabilization

Obtain detailed history

Central Line, Arterial Line

Aggressive IVFs (Usually 4-6 L volume depleted)

Maintain Respiratory Drive
Treatment of Salicylate Poisoning

Limit Absorption

Activated Charcoal

1 gm/Kg

Best decontamination method

No GI lavage

No Ipecac
Treatment of Salicylate Poisoning

Limit Distribution

Salicylic acid has a $pK_a$ 3.5 (weak acid)
At physiologic pH exists mostly in ionized form
Treat with large doses of IV Bicarbonate:
Keep blood pH 7.50 – 7.55

??Can protein binding be increased??
Effect of Intravenous Albumin Infusion on Brain Salicylate Concentration

Steven C. Curry, MD, Anthony F. Pizon, MD, Bradley D. Riley, MD, Richard D. Gerkin, MD, Dale S. Bikin, PharmD

Acad Emerg Med 2007;14: 508-514
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p=0.07
Treatment of Salicylate Poisoning

Enhanced Elimination

Aggressive IV Hydration

NSS or LR
Maintain brisk urine output

Alkalization of Blood (7.50 – 7.55) and Urine (>8.0)

Sodium Bicarb boluses (1 mEq/kg until blood pH > 7.5)
Indications for Hemodialysis

Signs of Neurotoxicity

Severe Acid-Base/Electrolyte Abnormality (despite appropriate therapy)

Acute Salicylate Level > 100 mg/dL

Chronic Salicylate Level > 40 mg/dL
Indications for Hemodialysis

Renal Failure

Congestive Heart Failure

Hepatic Dysfunction with Coagulopathy

Noncardiogenic Pulmonary Edema
Chronic Salicylate Toxicity

Risk Factors

Daily Aspirin Use
Nursing Home Patient
Psychiatric Comorbidity
Dehydration
Renal Failure
Diuretics (Carbonic Anhydrase Inhibitors)
### Acute vs. Chronic Salicylate Toxicity

<table>
<thead>
<tr>
<th></th>
<th><strong>ACUTE</strong></th>
<th><strong>CHRONIC</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INCIDENCE</strong></td>
<td>85%</td>
<td>15%</td>
</tr>
<tr>
<td><strong>AGE</strong></td>
<td>YOUNG</td>
<td>OLD</td>
</tr>
<tr>
<td><strong>INTENTION OD</strong></td>
<td>OFTEN</td>
<td>RARE</td>
</tr>
<tr>
<td><strong>COINGESTION</strong></td>
<td>OFTEN</td>
<td>RARE</td>
</tr>
<tr>
<td><strong>PSYCH. HX</strong></td>
<td>COMMON</td>
<td>UNCOMMON (UNRELATED)</td>
</tr>
<tr>
<td><strong>COMORBIDITY</strong></td>
<td>RARE</td>
<td>COMMON</td>
</tr>
<tr>
<td><strong>TIME TO DX</strong></td>
<td>EARLY</td>
<td>LATE</td>
</tr>
<tr>
<td><strong>ABNORMAL PROTIME</strong></td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td><strong>RENAL FXN</strong></td>
<td>NORMAL</td>
<td>OFTEN ABNORMAL</td>
</tr>
<tr>
<td><strong>HEPATIC FXN</strong></td>
<td>NORMAL</td>
<td>OFTEN ABNORMAL</td>
</tr>
<tr>
<td><strong>NEUROLOGIC SYMPTOMS</strong></td>
<td>OCCASIONALLY</td>
<td>COMMON</td>
</tr>
<tr>
<td><strong>PULMONARY SYMPTOMS</strong></td>
<td>RARE</td>
<td>COMMON (50%)</td>
</tr>
<tr>
<td><strong>GI SYMPTOMS</strong></td>
<td>VERY COMMON</td>
<td>RARE</td>
</tr>
<tr>
<td><strong>MORBIDITY</strong></td>
<td>16%</td>
<td>30%</td>
</tr>
<tr>
<td><strong>MORTALITY</strong></td>
<td>2%</td>
<td>25%</td>
</tr>
</tbody>
</table>
Salicylate Therapy Pearls

Failing to consider the diagnosis
Underestimating toxicity and not treating 
aggressively

A falling serum levels means pt is getting better

Failing to follow and correct serum Potassium

Sedating a pt with Salicylate toxicity and not 
hyperventilating
Questions?

On Call Medical Toxicologist 24/7

or

Med Call 412-647-7000

or

Poison Center 1-800 222-1222