"And should there be a sudden loss of consciousness during this class, oxygen masks will drop from the ceiling."

Salicylates

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Learning Objectives: After studying this material, the student should:

1. Know the **four** basic therapeutic uses for aspirin.

2. Know the major routes of absorption for salicylates and the **plasma half-life of aspirin** and of salicylic acid.

3. Know the **basic reaction** by which aspirin is inactivated.

4. Understand how **urine pH** can affect the excretion of free salicylic acid.

5. Understand the **basic mechanisms** or proposed mechanisms by which salicylates produce their four therapeutic activities.
6. Understand how aspirin and salicylates can produce effects on respiration, electrolyte and acid/base balance, especially know the difference in these factors as the dose increases from normal therapeutic to toxic levels.

7. Know the most predominant undesirable side-effects of salicylates.

8. Be able to define the term "salicylism".

9. Understand the possible implications of aspirin use in those with hypersensitivity responses or in children who have chicken pox or flu.

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I. Introduction

A. Use - anti-inflammatory, anti-pyretic, analgesic - non-narcotic, anti-thrombotic

B. Prevalence - estimated U.S. annual consumption as high as 25-50 million lbs., over 200 drug products contain aspirin

8 million people consult GPs each year with some form of arthritic disorder

Between 2 and 4% of the GP registered population receive intermittent or maintenance long-term NSAIDs

C. History - Salicin - from the willow and the rose-like spirea
II. CHEMISTRY

Salicylic acid (SA) irritating, keratolytic, external use

Aspirin (acetylsalicylic acid, ASA)

Methyl salicylate - oil of wintergreen, caustic, flavorings, rubefacient

Sodium salicylate

III. ASPIRIN Absorption, Distribution, Biotransformation, Excretion

A. Absorption - passive diffusion

1. stomach and upper sm. intestine, generally rapid ($t_1/2 = 20-30$ min), influenced by disintegration, dissolution, gastric emptying time and especially gastric pH.

Ionization increases ASA solubility in watery stomach contents but slows transport across GI membranes. Ionization of aspirin in mucosal cells causes concentrating effect and damage to cells.

2. rectal absorption - poor

3. skin - salicylic acid - rapid, methylsalicylate - rapid
B. Distribution - 160 ml/kg

1. extracellular distribution - rapid, thorough, slow across blood brain barrier
2. intracellular distribution - variable
3. 50-90% SA bound to plasma protein
   !! Effects binding of other drugs
4. little ASA bound to plasma protein

C. Biotransformation -

plasma ASA rapidly deacetylated to salicylic acid by liver and blood
1. $\text{ASA} + \text{HOH} \rightarrow \text{SA} + \text{acetic acid}$

2. plasma ASA $t1/2 = 20-30$ min, plasma SA $t1/2 = \text{hrs}$ (increases with dose)

3. ASA acetylates some proteins

4. SA does not acetylate protein, including cyclooxygenase, therefore no platelet effect
D.  Excretion in urine -
form influenced by urine pH

1.  normal urine pH 6
   a)  free SA - 10%
   b)  salicyluric acid (a glycine conjugate) - 75% [water soluble]
   c)  other metabolites - 15%

2.  alkaline urine pH - up to 30% free SA [ionized and excreted]
3.  acidic urine pH - as low as 2% free SA [un-ionized and reabsorbed]

IV. Pharmacologic Activity

Anti-inflammatory -
likely due to ASA's acetylation of cyclooxygenase, the enzyme necessary for the synthesis of prostaglandins (PGs) and thromboxanes.

PGs are produced by inflamed tissue and can cause hyperemia, increase capillary permeability and leukocyte migration.

Potency and efficacy to inhibit PG synthesis correlates with clinical potency and efficacy.
Aspirin (acetyl salicylic acid)

Aspirin and salicylic acid, at millimolar (high) concentrations, also inhibit induction of nuclear factor kappa B (NFκB), which stimulates formation of pro-inflammatory molecules.

The capacity for salicylate to inhibit NFκB formation may explain why it is anti-inflammatory despite not being an inhibitor of cyclooxygenase at normal therapeutic doses.
B. Antipyretic -

lowers body temp. only if body temp. abnormally high.

Mechanisms may include:

1) resetting hypothalamic temp. reg. center
2) competing with pyrogens for receptor sites
3) inhibition of synthesis of pyrogenic prostaglandins
C. Analgesia -

relieves mild-moderate intensity pathological pain arising mainly from integumental structures, but not hollow organs.

Mechanism uncertain but may involve peripheral and central neural actions.

May include inhibition of PGs, which sensitize pain receptors to cause hyperalgesia.

Central actions may also be via salicylic acid.

Prostaglandins & Pain (COX-1 & -2)

![Diagram showing Prostaglandins & Pain (COX-1 & -2)]

- Nociceptor
- Stimulus
- \( \text{PgE}_2 \) Facilitates
D. Anti-thrombotic -

prolongs bleeding time by decreasing platelet aggregability, works via inactivation of platelet cyclooxygenase and thus prevents formation of the platelet aggregator substance, thromboxane.

Synthesis of Thromboxane A$_2$ (TxA$_2$) in Platelets

- Arachidonic acid
- Prostaglandin G$_2$
- Prostaglandin H$_2$
- Other Pg’s
- TxA$_2$

Aspirin
Acetylation of NH$_2$-terminal serine of cyclooxygenase (irreversible) 

Permanent loss of TxA$_2$ production 

Permanent defect in platelet clot formation 

Protection from thrombotic disorders

**Aspirin's Antiplatelet Effect Is Antagonized by Ibuprofen**

The concomitant administration of ibuprofen but not Celebrex, or acetaminophen antagonizes the irreversible platelet inhibition induced by aspirin. Treatment with ibuprofen in patients with increased cardiovascular risk may limit the cardioprotective effects of aspirin

E. Respiration, Electrolyte, Acid-base balance

1. Metabolic effect (low dose ASA) -

uncouple ox. phos., get ↑ O₂ use, ↑ CO₂ prod.

therefore ↑ ventilation depth

2. Central neural effects - dose dependent, in toxic range

   a. Stimulation (higher dose) - acidosis increases ventilation depth and rate,

      But if the dose is very high, respiratory alkalosis occurs. -
      MORE CO₂ is generated than you can exhale so the CO₂ builds up;

      and the body compensates by increases in bicarb., Na & K excretion (compensated resp. alk.)

3. Metabolic acidosis (toxic high dose) due to decreased renal function, increase production of organic acids, salicylic acid itself
Salicylates (treatment for poisoning)

Strategy: cardiovascular and respiratory support, correction of acid-base imbalances, speed excretion

obtain blood levels of salicylate
activated charcoal to prevent further absorption from GI tract.
i.v. fluids to prevent dehydration
acidosis: give bicarbonate solution
give appropriate cations if necessary
hemorrhagic occurrence: blood transfusion and vitamin K
rid body of salicylate rapidly: forced diuresis with alkalinizing solution

F. Gastrointestinal -

most predominant side effect of salicylates is epigastric distress.
Also nausea and vomiting.

ASA can cause gastric ulceration and ↑ tendency toward ulcers.

Minor to major gastric bleeding.
Effects may be due to ↓ formation of cytoprotective PGs.
Other Adverse Effects

Renal Failure

Congestive Heart Failure

Raised Blood Pressure

G. Hepatic and Renal -

Salicylates may exacerbate problems in those with existing liver or renal problems.

In 1980 epidemiological evidence showed that salicylates were a factor in the severe hepatic injury and encephalopathy observed in childhood Reyes Syndrome, a rare but often fatal consequence of infection with chicken pox and various influenza strains.
While there is strong association, the mechanism of causality by salicylates has not been established. **It is now standard practice to not use salicylates in children with chicken pox or influenza and many completely avoid aspirin use in children.** The generally used alternative to aspirin is acetaminophen.

- **Reye’s Syndrome**
  - *children with acute febrile viral illnesses*
  - *aspirin for fever*
  - *hepatic failure*
  - *very high mortality*
  - *Particular risk of bronchospasm*

Since 1980 the incidence of Reyes Syndrome in those under 18 years old has decreased precipitously and is now a rare occurrence (N. Engl. J. Med. 340: 1377, 1999).

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### V. Salicylate Intoxication

**Salicylism** - mild chronic salicylate intoxication.

Syndrome consists of:

- headache, dizziness, tinnitus, difficulty hearing, dim vision, mental confusion, lassitude, drowsiness, sweating, thirst, hyperventilation, nausea, vomiting and occasionally diarrhea.

These symptoms subside upon stopping or lowering salicylate dose.
VI. Aspirin Hypersensitivity

Uncommon but may be severe or fatal.

Occurs mostly in middle aged and females.

Warning signs are previous history of hypersensitivity to chemicals, asthma or especially nasal polyps.

May occur with small dose of ASA or other PG synthesis inhibs.

Effects include rhinorrhea, urticaria, bronchospasm, hypotension, and vasomotor collapse.

Treat with epinephrine.

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Recent Considerations in Nonsteroidal Anti-inflammatory Drug Gastropathy*

hospitalizations NSAID-related GI complications: 107,000 patients
NSAID-related deaths among arthritis patients: 16,500
(1) OA and RA patients are 2.5-5.5 times more likely than the general population to be hospitalized for NSAID-related GI events
(2) the absolute risk for serious NSAID-related GI toxicity remains constant and the cumulative risk increases over time
(3) there are no reliable warning signals- >80% of patients with serious GI complications had no prior GI symptoms
(4) risk factors for serious GI events were age, prednisone use, NSAID dose, disability level, & previous NSAID-induced GI symptoms
(5) antacids and H2 antagonists do not prevent NSAID-induced gastric ulcers, and high-risk NSAID users who take gastro-protective drugs are more likely to have serious GI complications than patients not taking such medications

VII. Therapeutic Uses

analgesia

antipyresis

colds - symptomatic relief

rheumatoid arthritis

acute rheumatic fever

keratolytic agent - salicylic acid

counter-irritant - methylsalicylic acid, sprains

anti-thrombotic - antiplatelet, TIAs, angina, as little as 80 mg (1/4 of 1 ASA tablet) per day is effective

VIII.
### Other Salicylates

#### A. Diflunisal -

difluorophenyl derivative of salicylic acid.

**Competitive inhibitor of cyclooxygenase.**

**Not converted to salicylic acid in vivo.**

More potent anti-inflammatory agent than aspirin

has **no anti-pyretic effects**, perhaps due to poor CNS penetration.

Used for sprains, osteoarthritis, rheumatoid arthritis (RA).

No auditory side effects (unlike ASA)

**Less GI upset and less anti-platelet effects than aspirin.**
B. **Sulfasalazine** -

A sulphonamide anti-microbial used for ulcerative colitis and regional enteritis.

Poorly absorbed in GI tract.
Broken down by intestinal bacteria to sulfapyridine, an **active sulphonamide, and 5-aminosalicylate**, which is thought to be the effective anti-inflammatory agent when used to treat inflammatory bowel disease.

Sulfasalazine has been empirically found to be helpful in RA and ankylosing spondylitis.

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C. **Olsalazine** -

A dimer of 5-aminosalicylate, which is the active anti-inflammatory agent produced by metabolism of sulfasalazine.
Learning Resources:

Drugs to Remember:
1. Salicylic acid
2. Aspirin
3. Diflunisal
4. Sulfasalazine

Recommended Reading:
1. Basic and Clinical Pharmacology,
   B.G. Katzung (ed), 10th ed.