Toxicity of Analgesics, Antipyretics, and Non-steroidal anti-inflammatory drugs

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References:

- Oxford Desk Reference Toxicology, D. Nicolas Bateman, Robert D. Jefferson
- Principles of Clinical Toxicology; Thomas A. Gossel, J Douglas Brickers
Background

- NSAIDs are considered among the most commonly used and prescribed medications in the world.
- An estimated *one in seven patients* with rheumatologic diseases is given a prescription for NSAIDs.
- And *one in five* people in the USA use NSAIDs for *acute common complaints*. Ibuprofen, naproxen, and ketoprofen are currently the only non-prescription NSAIDs in the USA.
Clinical Manifestations of NSAIDs Toxicity

- More *moderate and severe* findings are *rare*
- Massive NSAID ingestions may lead to *multisystem organ failure and death.*
Clinical Manifestations of NSAIDs Toxicity

- Initial clinical manifestations are usually **mild and predominantly include GI symptoms** (nausea, vomiting, or abdominal pain),

  Long-term use of NSAIDs can lead to stomach ulcers and gastrointestinal bleeding.
Gastrointestinal Toxic Effects

- Although the most common adverse GI effect of therapeutic NSAID use is *dyspepsia*, most patients with dyspepsia do not have ulcers.
- The most serious adverse GI effect is *ulcer formation*, which has the potential for *life-threatening perforation and hemorrhage*, and numerous studies reported an increased risk of these effects with *therapeutic use of NSAIDs*.
- Acute NSAID overdoses cause *bloody emesis, fecal occult blood loss*, and severe, life-threatening *GI hemorrhage*. 
Clinical Manifestations of NSAIDs Toxicity

- or *neurologic symptoms* (drowsiness, headache, tinnitus, blurred vision, diplopia, and dizziness).
Neurologic Toxic Effects

- Drug-induced *aseptic meningitis* is reported with several NSAIDs, including tolmetin, rofecoxib, naproxen, sulindac, piroxicam, and diclofenac, but *ibuprofen is more commonly implicated*, perhaps because of its *widespread use*. 
Studies suggest an *immunologic mechanism* behind NSAID-induced aseptic meningitis.
Renal and Electrolyte Toxic Effects

Both *acute overdose* and *chronic therapeutic dosing* of NSAIDs may have deleterious effects on *kidney function*, most of which are reversible.

These include *sodium retention* and *edema*, *hyperkalemia*, *acute kidney injury* (AKI), *membranous nephropathy*, *nephrotic syndrome*, *interstitial nephritis*, and both *acute and chronic renal papillary necrosis.*
Renal and Electrolyte Toxic Effects

- *Acute tubule-interstitial nephritis* (ATIN) is one of the more common forms of NSAID-induced renal impairment, and it may occur with **short-term therapeutic dosing**.

- Significant elevations in blood urea nitrogen (**azotemia**) may occur in elderly patients within **5 to 7 days** of initiating NSAID therapy and usually return to baseline within 2 weeks of discontinuation.
NSAID-induced hepatotoxicity

- NSAID-induced **hepatotoxicity** is a well-known adverse effect that has prompted the removal of several NSAIDs from the market.

- Hepatotoxicity can be quite **difficult to diagnose** because many patients on chronic NSAID therapy have underlying conditions, such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA), which may cause hepatotoxicity.

- NSAID-induced hepatotoxicity is an **idiosyncratic reaction** primarily causing hepatocellular injury and **does not depend on the chemical class**.

- E.g: *Diclofenac* and *Sulindac* are most commonly implicated.
The non-immunologic anaphylactoid and the IgE-mediated anaphylactic reactions that are reported with the use of NSAIDs are clinically indistinguishable from one another, producing flushing, urticaria, bronchospasm, edema, and hypotension.

Evidence for anaphylactic reactions includes the presence of NSAID-specific IgE antibodies, positive wheal-and-flare skin reactions.
The most common skin reactions include **angioedema** and **facial swelling**, **urticaria** and **pruritus** and **photosensitivity**.
Hematologic Effects

- NSAIDs are frequently implicated in the development of *drug-induced thrombocytopenia, agranulocytosis, aplastic anemia, hemolytic anemia, methemoglobinemia, and pancytopenia*.

- *Phenylbutazone* in chronic, therapeutic doses was associated with agranulocytosis and aplastic anemia, prompting its removal from the US market in the 1970s.
Cardiovascular Effects

- Although no evidence supports a direct cardiotoxic effect of NSAIDs or their metabolites, acute and massive NSAID overdoses may be complicated by:
  - Persistent and severe hypotension;
  - Myocardial ischemia; and
  - Cardiac conduction abnormalities and dysrhythmias, including bradycardia, ventricular tachycardia or fibrillation, and prolonged QT interval.

- The cause of these findings is yet to be elucidated, although these effects are reported only in severely ill patients with acid-base abnormalities and multisystem organ involvement.
Pulmonary Effects

- Although there is no evidence of *direct pulmonary toxicity*, some *case reports* describe the development of *acute respiratory distress syndrome*. 

- **Signs & Symptoms**
  - Tachypnea
  - Dyspnea
  - Retractions
  - Hypoxia
  - Tachycardia
  - ↓Pulmonary Compliance

- **Causes**
  - *Trauma*
  - *Pulmonary Infection/Aspiration*
  - *Prolonged Cardiopulmonary Bypass*
  - *Shock*
  - *Fat Emboli*
  - *Sepsis*

- **ABG’s**
  - ↓Po2, ↑Dyspnea
    *(Po2 is NOT getting better, even with ↑FiO2)*

- **My heart is racing and I can’t catch my breath**

- www.NursingGuide.ph
Management of NSAIDs Toxicity

- Management of a patient with an *NSAID overdose* is largely *supportive* and guided by the clinical signs and symptoms.

- Most asymptomatic patients with *intentional overdose* and those with *normal vital signs* require observation for 4 to 6 hrs and determination of a serum drug concentration before being medically cleared.
Management of NSAIDs Toxicity

- Children with **ibuprofen ingestions** of less than 100 mg/kg can be **observed at home**, but those who ingest greater than 400 mg/kg are at **high risk for toxicity** and require medical evaluation.

- **GI decontamination** with **activated charcoal** (AC) should be considered for an **asymptomatic patient** with the potential for a large ingestion,

- **Gastric lavage** for massive overdose **followed by AC** should be considered, and multiple-dose AC may be useful for patients with massive overdoses of sustained-release preparations.
Management of NSAIDs Toxicity

- Patients who develop *severe, life-threatening manifestations* usually present with lethargy or unresponsiveness. Aggressive, supportive care is indicated in these patients, including *stabilization of the airway* and *IV fluid therapy*.

- An early ECG is essential to detect any significant electrolyte abnormalities or conduction disturbances. Electrolyte imbalances should be corrected and *sodium bicarbonate* therapy considered for life-threatening *metabolic acidosis*.

- Hypotension should be treated initially with *IV fluid* therapy followed by *direct-acting vasopressors* if necessary.
Management of NSAIDs Toxicity

- Due to **high protein binding**, NSAIDs do not appear to be responsive to extracorporeal removal methods; however, in cases of **refractory metabolic acidosis** or **kidney failure**, hemodialysis or continuous renal replacement therapies may be useful to correct the acid–base status.

- Patients with **seizures**, which are characteristic of **mefenamic acid** overdose, should be treated with **IV benzodiazepines**.
Acetaminophin (Paracetamol) poisoning:

- Acetyl-para-aminophenol or acetaminophene (APAP) is proved to be a remarkably safe xenobiotic at appropriate dosage, which has led to its popularity.
- The safety of appropriate APAP dosing results from the availability of electron donors such as reduced GSH and other thiol (S-H)-containing compounds.
- After therapeutic APAP dosing, GSH supply and turnover are far more than that required to detoxify N-acetyl- \( p \) – benzoquinoneimine (NAPQI).
Scheme for acetaminophen metabolism.
Acetaminophin (Paracetamol) poisoning:

- *After overdose*, the rate and quantity of NAPQI formation *exceed* the supply and turnover of GSH.

- Resulting in the *release of NAPQI within the cell.*

- NAPQI then rapidly *binds to hepatocyte constituents*, including the cysteine portion of proteins, producing protein adducts within the liver that *result in cell death.*
Acetaminophin (Paracetamol) poisoning:

- **Covalent binding and arylation occur rapidly after GSH depletion.**
- Both covalent binding and GSH deficiency are necessary for hepatotoxicity.
- The final pathway of hepatic cell death is predominantly *cellular necrosis.*
Acetaminophin (Paracetamol) poisoning:

- Kidney injury after acute overdose is typically **acute tubular necrosis** (ATN) that may be caused by **local production of NAPQI** by **renal CYP2E1** enzymes. However, several other nephrotoxic mechanisms have been proposed.
Clinical Manifestations:

- The first symptoms after APAP overdose may be those of *hepatic injury*, which develop *many hours after the ingestion*, when antidotal therapy will have diminished efficacy.
Clinical Manifestations: Acute toxicity has 4 stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>Time Postingestion (h)</th>
<th>APAP Plasma Concentration (mg/dl)</th>
<th>Signs and Symptoms</th>
<th>Laboratory Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>≥150</td>
<td>Anorexia, nausea, vomiting, pallor, diaphoresis, malaise, confusion, hypotension, arrhythmias</td>
<td>Hepatic transaminases (AST, ALT) rising</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>≥75</td>
<td>(Perceived recovery)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>≥35</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>≥5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>24–72</td>
<td>≥1 (at 72 h)</td>
<td>Clinical improvement, right upper quadrant pain, renal function deterioration</td>
<td>Transaminases peaking; bilirubin &amp; PT elevated</td>
</tr>
<tr>
<td>3</td>
<td>72–96</td>
<td>≥1</td>
<td>Hepatic centrilobular necrosis: jaundice, coagulopathy, encephalopathy (coma); reappearance of nausea &amp; vomiting, arrhythmias, acute renal failure, death</td>
<td>Peak levels of AST (20,000 U/ml) &amp; ALT</td>
</tr>
<tr>
<td>4</td>
<td>4–14 days</td>
<td>≥1</td>
<td>Resolution of hepatic dysfunction and recovery if liver damage is reversible</td>
<td>Return to baseline levels</td>
</tr>
</tbody>
</table>

*Note: AST = aspartate aminotransferase, ALT = alanine aminotransferase, PT = prothrombin time; other laboratory tests include blood urea nitrogen (BUN), creatinine, electrolytes, and blood glucose.*
Doses of 7.5 g in an adult or 150 mg/kg in a child are widely disseminated as the lowest acute dose capable of causing toxicity.

However, it is more likely that doses of at least 12 g in an adult or 200 mg/kg in a child are necessary to cause hepatotoxicity in most patients.
The effects of ethanol on APAP toxicity are complex and are best described by clearly separating acute ethanol use from chronic heavy ethanol use or alcoholism, and single from repeated supra therapeutic (RST) APAP dosing.
Ethanol and Risk Determination

- Both animal and human data suggest that acute ethanol co-ingestion with APAP may be hepatoprotective. Ethanol co-ingestion decreases NAPQI formation presumably by inhibiting CYP2E1 in both humans and animals.

- However, chronic ethanol administration increases the risk of hepatotoxicity from APAP dosing in animals. This may be a consequence of ↑ NAPQI formation due to induction of CYP2E1 metabolism once the ethanol is metabolized or ↓ mitochondrial GSH supply or regeneration.
CYP Inducers and Risk Determination

- Several medications, including phenytoin, carbamazepine, and phenobarbital, are reported to ↑ APAP toxicity because of nonspecific CYP induction activity.
Management:

- **Gastrointestinal Decontamination:**
  - In cases of very early presentation or co-ingestion of xenobiotics that delay GI absorption, gastric emptying may be appropriate for some patients.

- In general, however, *gastric emptying is not appropriate for patients with isolated APAP overdose* because of the very rapid GI absorption of APAP and the availability of an effective and safe antidote.
Management

- Activated charcoal-if present within 1 hr of ingestion
- N-acetylcysteine (NAC)- most efficacious if given within 8hrs of ingestion. (Dose of NAC?) but current management guidelines recommend use in patients with severe paracetamol poisoning at any time after ingestion because it is effective for preventing mortality (2014).

  (concomitant oral administration of NAC and AC not recommended).

- Antiemetics-ondansetron is preferred; avoid antiemetics with sedative properties or that are metabolized by the liver.
Supportive Care:

- General supportive care consists primarily of controlling nausea and vomiting and managing the hepatic injury, acute kidney injury, and other manifestations.

- Monitoring for and treatment of hypoglycemia are critical because hypoglycemia is one of the most readily treatable of the life-threatening effects of hepatic failure. If adequate viable hepatocytes are present, vitamin K may produce some improvement in coagulopathy.

- Administration of fresh-frozen plasma (FFP) should be based on specific indications rather than PT and INR alone.
Supportive Care:

- Supportive therapy for *cerebral edema*, including *cooling*, *hypertonic saline*, *elevation of the head*, and support of the *cerebral perfusion pressure*, are all indicated.
Antidotal Therapy with N-Acetylcysteine

- N-Acetyl cysteine (NAC): During the metabolism of APAP to NAPQI, NAC prevents toxicity by *limiting the formation of NAPQI*. It ↑ the capacity to detoxify NAPQI that is formed.
- NAC may be administered via the oral or IV routes.
- The two most common regimens are a *21 hr IV infusion and a 72 hr oral dosing* protocol.
- Start NAC when the patient is at risk of toxicity, continue NAC while the patient remains at risk or has hepatotoxicity, and stop NAC when that risk or toxicity is gone.
Rumack-Matthew nomogram for assessing the extent of acetaminophen toxicity

![Graph showing acetaminophen levels and hours after ingestion for assessing hepatic toxicity.](image_url)
Management of Patients at Risk for APAP Toxicity

- **Hemodialysis**: Both intermittent hemodialysis (HD) and continuous hemodialysis increase elimination of APAP. HD has been used early after overdose to eliminate highly elevated plasma APAP level, typically above 500 µg/mL, and in patients with slow clearance of APAP late after overdose.

- **Plasmapheresis and Plasma Exchange**: Plasmapheresis removes small amounts (5%) of APAP with therapeutic dosing, but few data exist with regard to overdose. Plasmapheresis may be useful in patients with acute liver failure to correct coagulopathy, but it does not reliably correct encephalopathy.
Management of Patients at Risk for APAP Toxicity

- Patients with **hepato-renal syndrome** are commonly treated with **continuous renal replacement therapy**, and among those who survive, kidney failure generally resolves within one month.
Salicylates

- The term salicylate refers to any of a group of chemicals that are derived from salicylic acid. The best known is acetylsalicylic acid (aspirin).
- Acetylsalicylic acid is metabolized to salicylic acid (salicylate) after ingestion.
- The salicylates originally were derived from salicin, the active ingredient in willow bark, which Hippocrates used it 2500 years ago for treating pain and fever. Salicylates also occur naturally in many plants such as strawberries, almonds, and tomatoes.
Willow tree
Salicylates

- Children are most susceptible to toxicity.
- Fatal outcome enhanced when the child is febrile and/or dehydrated. When the child has a minor infection and taking aspirin, the child may be lethargic (not eating or drinking adequately).

- The dose of aspirin for children at which symptoms of toxicity are likely to occur is 150mg/kg.
- A healthy 20kg child ingesting 36 children aspirin (81mg per tablet), or only 9 adult tablet (325mg per tablet) will experience toxicity.
Salicylates

- Aspirin is a serious cause of poisoning in children under 5 years of age, although the concern for a possible association between it and Reye’s syndrome may eventually reduce the overall incidence of aspirin poisoning in children.

- Methyl salicylate (Oil of Wintergreen) is used in topical liniments (less viscous than ointment); and is used alone as an analgesic rub; smells like wintergreen candy, is another source of salicylate intoxication in children. One teaspoonful oil of wintergreen contains 7gm salicylate, or approximately 22 adult aspirin tablet. 4 ml of methyl salicylate is fatal.
Mechanism of Toxicity:

The pathophysiologic consequences can be summarized by:

- CNS effects
- Metabolic effects
Mechanism of toxicity

CNS effect and metabolic effect:

- The respiratory center is stimulated directly by salicylates, and indirectly by an increase in pCO$_2$ production as it enhances O$_2$ consumption by increasing metabolic rate which lead to hyperthermia and accumulation of CO$_2$ and this cause hyperpnea.

- Increase of respiratory rate will increase the expiration of CO$_2$, which result in less plasma CO$_2$. 
Mechanism of toxicity

- The reactions of the Bicarbonate buffer system for maintaining blood pH:
  \[ \text{H}_2\text{O} + \text{CO}_2 = \text{H}_2\text{CO}_3 = \text{H}^+ + \text{HCO}_3^- \]
  Blood pH is dependent on the bicarbonate/carbonic acid ratio according to Henderson-Hasselbalch equation:

- Since less \( \text{CO}_2 \) available, less carbonic acid (\( \text{H}_2\text{CO}_3 \)) is formed resulting in a deficit of \( \text{H}_2\text{CO}_3 \) with a subsequent decrease in [\( \text{H}^+ \)], Normally the ratio is 20/1, and the pH is 7.4

- The kidney compensate for the acid-base imbalance.
A. CNS Effects of Salicylate Intoxication

- Salicylate level increases in the brain
- Stimulates the respiratory center
- Hyperventilation
- ↓ $\text{Pco}_2$

**RESPIRATORY ALKALOSIS**

B. Metabolic Effects of Salicylate Intoxication

- Uncoupling oxidative phosphorylation
  - ↓ ATP
  - ↑ Glycolysis
  - ↑ Lactic acid
  - ↑ Pyruvic acid
- Increased peripheral glucose demand
- Stimulation of lipid metabolism
- ↑ Ketone bodies

**METABOLIC ACIDOSIS**

- Inhibition of Kreb’s cycle enzymes
- Inhibition of amino acid metabolism
- Renal compensation by excreting more $\text{HCO}_3^-$ and retaining more $\text{H}^+$

**FIG. 12.1. Pathophysiologic consequences of salicylate intoxication.**
Salicylate uncoupling oxidative phosphorylation
### Pathology and Mechanism of ASA Toxicity

<table>
<thead>
<tr>
<th>Mechanism of Toxicity</th>
<th>Pathological Consequence</th>
<th>Metabolic Compensation</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated ASA serum concentration (acidic substance)</td>
<td>Decreases serum pH</td>
<td>Contributes to metabolic acidosis; alters platelet function (hypoprothrombinemia)</td>
<td>Increases bleeding time</td>
</tr>
<tr>
<td>Stimulation of medullary respiratory center</td>
<td>Hyperventilation</td>
<td>Decreases plasma PCO₂ with respiratory alkalosis</td>
<td>Tachypnea, pulmonary edema, tachycardia, dehydration</td>
</tr>
<tr>
<td>Renal compensation for respiratory alkalosis</td>
<td>Kidneys excrete more bicarbonate ions; retain more hydrogen ions</td>
<td>Contributes to compensatory metabolic acidosis; CNS toxicity</td>
<td>Irritability, restlessness, tinnitus, dehydration, seizures, coma</td>
</tr>
<tr>
<td>Inhibition of Kreb’s cycle enzymes</td>
<td>Accumulation of organic acids (oxaloacetate)</td>
<td>Contributes to metabolic acidosis and lactic acidosis</td>
<td>Gastric irritation, nausea, vomiting</td>
</tr>
<tr>
<td>Oxidative uncoupling of electron transport chain</td>
<td>Prevents combination of phosphate with ADP</td>
<td>Decreases formation of ATP, enhanced glycolysis, lactic acid, pyruvic acid; contributes to metabolic acidosis</td>
<td>Hyperthermia, tachycardia, dehydration, cardiovascular collapse, hypoglycemia</td>
</tr>
</tbody>
</table>

- Increases peripheral demand for glucose
- Stimulates lipid metabolism, releases fatty acids, contributes to metabolic acidosis
Interference with oxidative phosphorylation by salicylate has impact on glucose homeostasis negatively, this increases tissue demand for glucose oxidation. The brain seems sensitive to this effect and CNS glucose depletion (neuroglycopenia) can occur in the presence of normal blood glucose.

Consequently glycogen depletion, gluconeogenesis, and catabolism of proteins and free fatty acids can occur and the end result being low serum glucose levels and central nervous system (CNS) hypoglycemia relative to serum glucose levels.
Pharmacokinetics

- The pharmacokinetic profile of aspirin is unique and explains the unique characteristics of clinical poisoning.
- In an acidic environment like the stomach, more of the drug will be absorbed compared with tissues at a higher pH.
- Salicylates are rapidly and completely absorbed, but distributed unevenly throughout body tissues after oral use.
Pharmacokinetics

- Metabolism follows first-order kinetics (dose dependent) to form oxidized and conjugated metabolites.
- In therapeutic doses, the major route of salicylate biotransformation is conjugation in the liver. A small amount of aspirin is excreted unchanged in the urine and it follows first order kinetics.
- In overdose, the liver’s ability to metabolize the drug is overwhelmed, and unchanged salicylate excretion through the kidney becomes a much more important elimination route and it follows zero-order kinetics.
Characteristics of poisoning

Clinical manifestations of salicylate poisoning can be arranged in increasing order of severity which related to amount ingested and blood salicylate concentration

1. Asymptomatic  blood concentration < 45mg/dl.
3. Moderate toxicity ..............65-90mg/dl.
4. Sever toxicity .................90-120mg/dl.
5. Lethal toxicity ..................120mg/dl.
A useful way to evaluate the degree of toxicity after acute oral ingestion is to correlate blood salicylate concentration with patient’s clinical status.

Blood salicylate concentration ranges were selected from the Done nomogram (valuable in evaluation acute salicylate poisoning)
Management of poisoning

- There is no specific antidote for salicylate so the treatment is supportive:
  1. Gastric decontamination.
  2. Correction of:
     - Metabolic acidosis by I.V infusion of Sodium bicarbonate 50-100 mmol.
     - Dehydration.
     - Hyperthermia.
     - Hypoglycemia → Glucose
     - Hypokalemia → pot. Replacement
     - Seizures → Diazepam
     - Convulsion.
     - Coagulation defect → Vit K
     - Hypocalcemic tetany by calcium supplement
  3. In severe salicylate toxicity with renal failure hemodialysis used to enhance drug elimination.
Use of elimination techniques

- Urine alkalination: should be undertaken in patients with plasma salicylate conc. higher than 500mg/L (50mg/dl) + acidosis.

- Hemodialysis, when salicylate conc. > than 900mg/L (90mg/dl) and unresponsive to urine alkalination, persisting severe metabolic acidosis, renal failure, non-cardiogenic pulmonary oedema, coma, convulsions, or other CNS effects not resolved by correction of acidosis.

- Forced alkaline diuresis, no longer used because it does not increase salicylate excretion and may precipitate pulmonary oedema.
Review Question

- During salicylate toxicity the pH become more than 7.4, Why?
- Salicylate poisoned patients may become febrile? Why?
  Uncoupling OP → heat production
- Dehydration is another serious consequence of salicylate toxicity? How?
- How does salicylate interfere with normal blood glucose level?