

**ACETAMINOPHEN, SALICYLATES
&
NONSTEROIDAL ANTI-INFLAMMATORY
DRUGS**

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- Are found alone and in combination with other analgesic/antipyretic compounds in OTC and prescription formulas.
- These agents are routinely reported as products responsible for acute and chronic overdose.
- Analgesic, antipyretic, and anti-inflammatory agents are used in the household management of non-narcotic relief of mild to moderate pain, for inflammation associated with a variety of rheumatic conditions, and for reduction of fever.

ACETAMINOPHEN

- Poisoning cases with APAP exceed those of all other agents in this category (five times greater incidence than with aspirin).
- It is the most common drug involved in OD, registering approximately 60% of all analgesic exposures, and the second most common cause of liver failure in the United States.
- The U.S. Food and Drug Administration (FDA) reports that over 56,000 emergency department visits per year are due to acetaminophen OD alone, resulting in about 100 deaths each year.
- One-fourth of these visits are intentional.

Medicinal Chemistry and Pharmacology

- Acetaminophen is the major hydroxylation metabolite of two potent analgesic parent compounds, acetanilid and phenacetin.
- The antipyretic activity of the molecules resides in the aminobenzene structure.
- APAP reduces fever by a direct action on the heat-regulating centers in the hypothalamus, dissipating heat via vasodilation and increased sweating.
- Analgesic and antipyretic properties are equivalent to that of aspirin. Its inhibition of central prostaglandin synthetase is more effective than its peripheral action, rendering it a weak anti-inflammatory agent compared to aspirin.

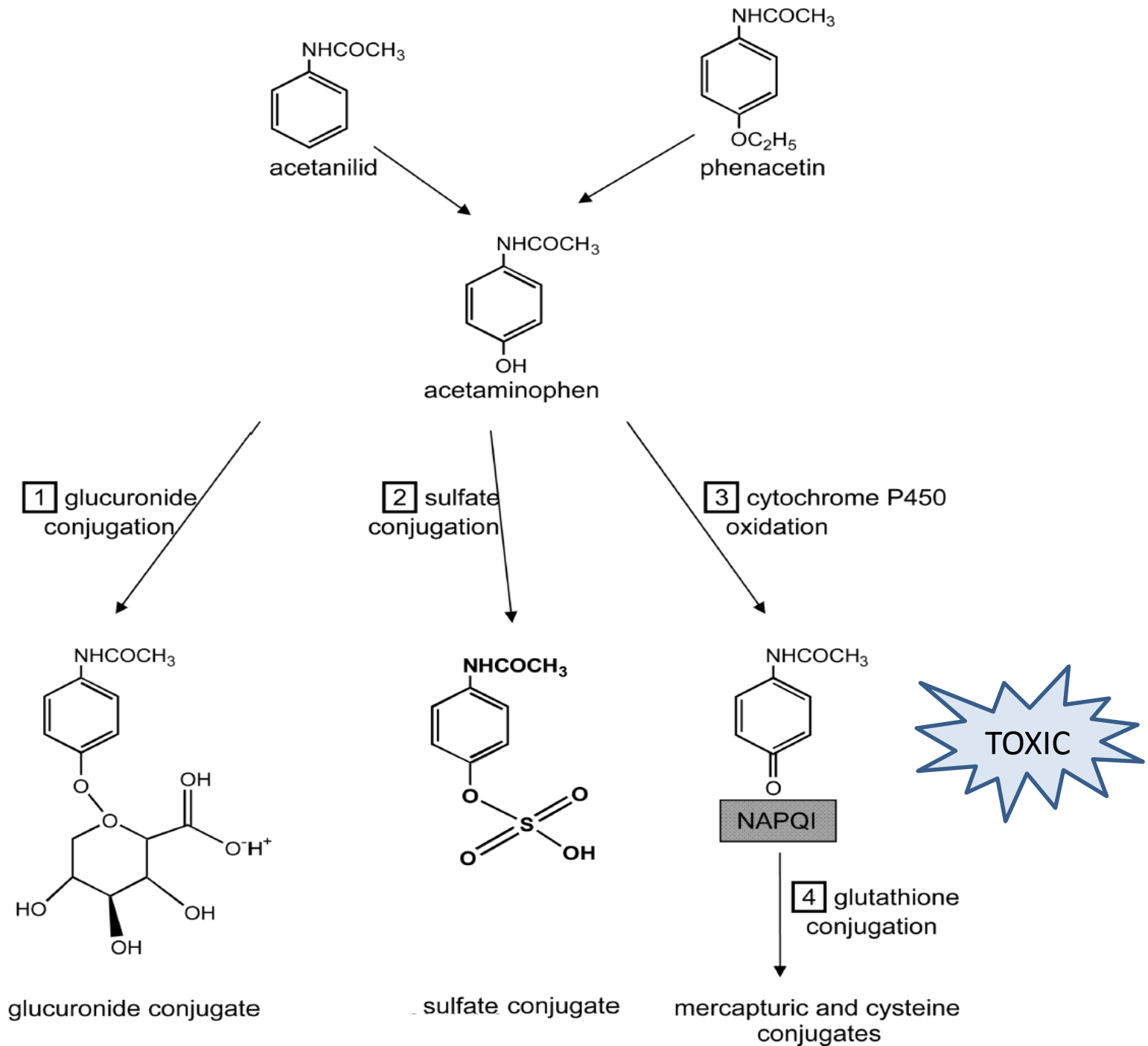
Clinical Use

- APAP is recommended as an analgesic/antipyretic:
 - in the presence of aspirin allergy.
 - in patients who demonstrate blood coagulation disorders.
 - in children.
 - in patients who receive oral anticoagulants.
 - who demonstrate upper (GI) disease.
- It is also useful in a variety of arthritic and rheumatic conditions, including musculoskeletal disorders, headache, and other minor pain, and for the management of fever associated with bacterial and viral infections.

Metabolism and Mechanism of Toxicity

- Acetaminophen is rapidly absorbed from the GI tract and uniformly distributed, with peak plasma levels achieved by 0.5 to 2 hours.
- Hepatic glucuronide and sulfate conjugation produce the inactive corresponding conjugates that account for 95% of metabolism and eliminated in urine.
- In addition, at therapeutic acute doses, the remaining 4% to 5% of the product is detoxified and eliminated in the minor cytochrome P450 oxidase pathway.

- The result is the production of the reactive intermediate, N-acetyl-p-benzoquinoneimine (NAPQI) metabolite.
- Further conjugation by cellular glutathione results in the production of mercapturic acid and cysteine conjugates.
- With chronic use or with large doses, the glucuronide and sulfate conjugation metabolic routes (1 and 2) are saturated and, more importantly, glutathione stores are depleted (reaction 4).
- This leaves the cytochrome P450 oxidase pathway (reaction 3) to accumulate toxic NAPQI metabolite.
- Binding of NAPQI to hepatocytes membranes and sulfhydryl proteins accounts for the hepatotoxic consequences.



Signs and Symptoms of Acute Toxicity

Stage	Time post ingestion (hr)	APAP plasma concentration (mg/dL) ^a	Signs & symptoms	Laboratory findings
1. Preclinical toxic effects	4	≥150	Anorexia, nausea, vomiting, pallor, diaphoresis, malaise, confusion, hypotension, arrhythmias	Hepatic transaminases (AST, ALT) rising
	8	≥75		
	12	≥35		
	24	≥5		
2. Hepatic injury	24–72	≥1 (at 72 hr)	Clinical improvement, right upper quadrant pain; hepatic and renal function deterioration	Transaminases peaking; bilirubin and PT ^b elevated
3. Hepatic failure	72–96	≥1	Hepatic centrilobular necrosis; jaundice, coagulopathy, encephalopathy (coma); reappearance of nausea & vomiting, arrhythmias, acute renal failure, death	Peak levels of AST (20,000 U/mL) and ALT
4. Recovery	4–14 days	≥1	Resolution of hepatic dysfunction and recovery if liver damage reversible	Return to baseline levels

Clinical Management of Acute OD

- Early treatment and careful evaluation of clinical history leading to the emergency event is paramount in treatment.
- Activated charcoal is beneficial if administered to an individual who presents within one to two hours post ingestion.
- An acetaminophen level obtained four hours later determines follow up treatment with the antidote.
- At eight hours post ingestion, activated charcoal, emetics, and gastric lavage are not necessary.
- Typically, a toxic dose is about 150 mg/kg, or 15 g in an otherwise normal 70-kg adult.

Antidote

- NAC is the antidote for acetaminophen poisoning.
- In its conversion to cysteine, NAC restores glutathione reserves by providing sulfhydryl donors for the eventual detoxification of NAPQI.
- In addition, NAC increases sulfate conjugation, thereby preventing excess NAPQI production.
- NAC also acts as an antioxidant, enhancing oxygen utilization; this effect may be of benefit in patients with fulminant hepatic failure.
- NAC is administered as a 10% or 20% solution for oral administration or through nasogastric (NG) instillation.

- It should be delivered within eight hours of ingestion and whenever a potentially toxic acetaminophen concentration is measured above the toxic level.
- Protection against hepatotoxicity is 100% within eight hours of APAP ingestion. Efficacy decreases when administered beyond 8 hours, although NAC therapy may be beneficial even 36 hours post ingestion.
- The protocol is 140 mg/kg oral loading dose followed by doses of 70 mg/kg every 4 hours, for a total of 1330 mg/kg over 72 hours, until the acetaminophen assay reveals a nontoxic level.
- If the patient vomits the loading or maintenance dose within one hour of administration, the dose is repeated.
- Antiemetics, such as metoclopramide, may be helpful in retaining the NAC.

SALICYLATES AND ACETYLSALICYLIC ACID

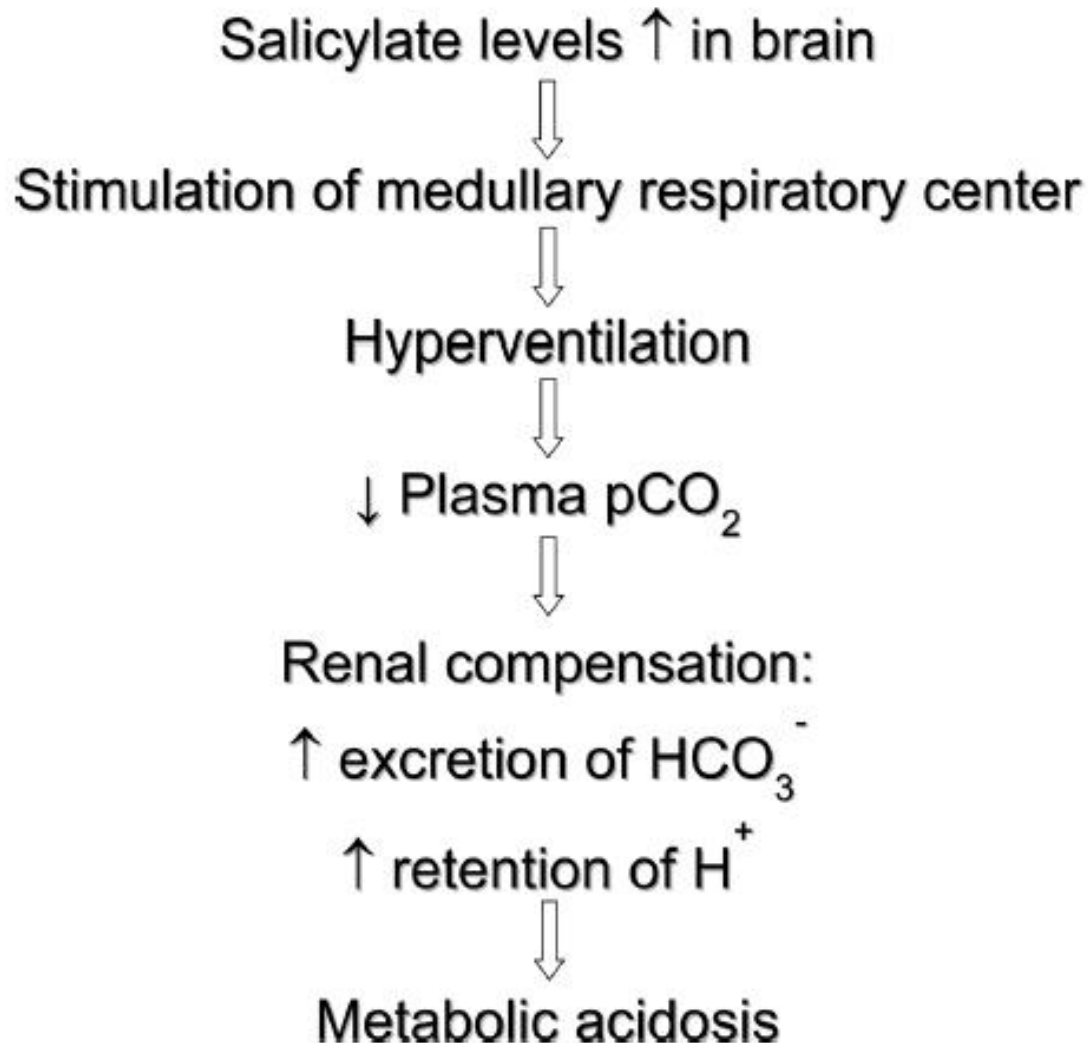
- Synthesized and identified sodium salicylate for use as an antipyretic (for rheumatic fever) and analgesic (for gout).
- By 1815, the inception of the aspirin tablet established.
- Today, salicylates and related analgesics are one of the major sources of pediatric drug product poisoning in the United States.
- At a pediatric toxic dose level of 150 to 200 mg/kg, as little as 10 to 12 adult 325-mg tablets of aspirin produce mild toxicity in an average five-year-old (20-kg) child.

- Oil of wintergreen (betula oil) is an older product traditionally used as an analgesic liniment for the relief of sore muscles and stiff joints.
- It is a methyl salicylate concentrate (530 mg/mL) that produces severe toxicity in children with a 5mL dose.
- Aspirin has shown some success as an antiplatelet agent in patients with thromboembolic disease.
- ASA products are used as analgesics, antipyretics, and anti-inflammatory (arthritis) agents and in cough/cold, antihistamine, and decongestant formulations.

Toxicokinetics

- Salicylates are rapidly and completely absorbed but distributed unevenly throughout body tissues after oral use.
- Metabolism follows first-order kinetics (dose dependent) to form oxidized and conjugated metabolites.
- Renal clearance accounts for most of the compound's elimination and is enhanced from 2% to more than 80% as pH and ionization increases.

Diagram outlining schematic of mechanism of aspirin toxicity



Pathology and Mechanism of ASA Toxicity

Mechanism of toxicity	Pathological consequence	Metabolic compensation	Signs and symptoms
Elevated ASA serum concentration (acidic substance)	Decrease in serum pH	Contributes to metabolic acidosis; alters platelet function (hypoprothrombinemia)	Increased bleeding time
Stimulation of medullary respiratory center	Hyperventilation	Decreases plasma P_{CO_2} with respiratory alkalosis	Tachypnea, pulmonary edema, tachycardia, dehydration
Renal compensation for respiratory alkalosis	Excretion by kidneys of more bicarbonate ions; retention of more hydrogen ions	Contributes to compensatory metabolic acidosis; CNS toxicity	Irritability, restlessness, tinnitus, dehydration, seizures, coma
Inhibition of Krebs's cycle enzymes	Accumulation of organic acids (oxaloacetate)	Contributes to metabolic acidosis and lactic acidosis	Gastric irritation, nausea, vomiting
Oxidative uncoupling of electron transport chain	Prevention of combination of phosphate with ADP	Decreases formation of ATP; enhances glycolysis, lactic acid, pyruvic acid; contributes to metabolic acidosis	Hyperthermia, tachycardia, dehydration, cardiovascular collapse, hypoglycemia
	Increases peripheral demand for glucose	Stimulates lipid metabolism, releases fatty acids, contributes to metabolic acidosis	

Signs and Symptoms of Acute Toxicity

- Onset of symptoms are usually one to two hours but may be delayed four to six hours due to absorption of sustained release preparations or the formation of gastric concretions.
- Severity of symptoms peak between 12 and 24 hours.
- At low doses, elimination half-life is constant at three to four hours and follows first order kinetics (dose dependent).
- With higher doses, or with chronic ingestion, elimination half-life shifts from first-order to zero-order kinetics (dose independent) as metabolic enzymes become saturated.

- More severe ASA toxicity, especially the development of metabolic acidosis, is associated with chronic ingestion and with children less than five years old (the progression is dose related).
- Although a single large dose of aspirin results in signs and symptoms, death is more likely in patients with chronic poisoning and is usually a result of pulmonary or cerebral edema.
- Unlike acetaminophen concentrations, ASA blood levels do not correlate well with acute or chronic signs and symptoms.
- Treatment decisions therefore rely on empirical observations and clinical laboratory function tests.

Clinical Management of Toxicity

- Although serum salicylate concentrations are not dependable for guiding treatment, the change in serum concentrations that is a drop of 10% every three to four hours is a good indicator of recovery.
- In addition, lack of symptoms six hours after ingestion is associated with mild to moderate (less than severe) complications.
- In general, serum salicylate levels are used as a gauge for moderate (50 mg/dL), severe (75 mg/dL), and potentially lethal (100 mg/dL) poisoning.

- Complete clinical laboratory tests, especially for blood glucose, serum electrolytes (determination of the anion gap) and liver function, are important in calculating the risk of metabolic acidosis.
- Administration of emetics is not recommended, as vomiting can induce aspiration of stomach contents and corrosion of esophagus, and will not remove all stomach contents nor sustained release preparations.
- Activated charcoal and cathartics are recommended to effectively bind salicylates and to prevent intestinal obstruction due to concretions, respectively.
- Sodium bicarbonate administration enhances ASA elimination by alkalinizing the urine (maintains the salicylic acid as a polar molecule) while simultaneously reversing metabolic acidosis.

- Other supportive measures include correcting the dehydration, maintaining kidney function (forcing fluids), rectifying electrolyte imbalance (especially potassium for hypokalemia that may result from bicarbonate infusion), and instituting supportive measures for hyperthermia, seizure control, and pulmonary edema.
- Hemodialysis may be useful but is only indicated in salicylate-poisoned patients who present with severe acidosis or hypotension refractory to optimal supportive care, evidence of end-organ injury (i.e., seizures, pulmonary edema), renal failure, or high serum aspirin concentrations (>100 mg/dL) despite a relatively stable metabolic picture.
- Specific antidotes are not available for salicylate poisoning.

NONSTEROIDAL ANTI-INFLAMMATORY AGENTS

- The search for potent anti-inflammatory agents similar to aspirin led to the discovery of phenylbutazone in 1849.
- It was initially used as an anti-inflammatory agent and subsequently for its analgesic and antipyretic actions.
- Because of the serious adverse hematologic reactions associated with phenylbutazone (agranulocytosis), the search for safer drugs with anti-inflammatory properties began.
- The acetic acid derivatives, including indomethacin, were introduced for the treatment of rheumatoid arthritis and related disorders.

Classification, Pharmacology, and Clinical Use

- NSAIDs exhibit antipyretic, analgesic, and anti-inflammatory activities resulting from inhibition of prostaglandin synthesis.
- In particular, NSAIDs inhibit cyclooxygenase (COX), an enzyme that catalyzes the synthesis of prostaglandins from arachidonic acid.
- COX-1 isoenzyme activity produces prostaglandins that are important in maintaining platelet aggregation, regulation of kidney and gastric blood flow and gastric mucus secretion. The COX-2 isoenzyme is expressed during pain and inflammation.
- NSAIDs nonselectively inhibit both enzymes, inhibition of COX-1 has antiplatelet activity, an effect that may be of benefit in prevention of cardiovascular disease.
- The newer selective COX-2 inhibitors avoid GI upset associated with nonselective inhibitors.

Classification of NSAIDs

Salicylates <ul style="list-style-type: none">• Acetylsalicylic acid (aspirin)• Amoxiciprin• Benorylate/Benorilate• Choline magnesium salicylate• Diflunisal• Ethenzamide• Faislamine• Methyl salicylate• Magnesium salicylate• Salicyl salicylate• Salicylamide	Arylalkanoic acids <ul style="list-style-type: none">• Diclofenac• Aceclofenac• Acemethacin• Alclofenac• Bromfenac• Etodolac• Indomethacin• Nabumetone• Oxametacin• Proglumetacin• Sulindac• Tolmetin	2-Arylpropionic acids (profens) <ul style="list-style-type: none">• Ibuprofen• Alminoprofen• Carprofen• Dexibuprofen• Dexketoprofen• Fenbufen• Fenoprofen• Flunoxaprofen• Flurbiprofen• Indoprofen• Ketorolac• Loxoprofen• Naproxen• Oxaprozin• Pirprofen• Suprofen• Tiaprofenic acid	N-Arylanthranilic acids (fenamic acids) <ul style="list-style-type: none">• Mefenamic acid• Flufenamic acid• Meclofenamic acid• Tolfenamic acid
Pyrazolidine derivatives <ul style="list-style-type: none">• Phenylbutazone• Ampyrone• Azapropazone• Clofezone• Kebuzone• Metamizole• Mofebutazone• Oxyphenbutazone• Phenazone• Sulfinpyrazone	Oxicams <ul style="list-style-type: none">• Piroxicam• Droxicam• Lornoxicam• Meloxicam• Tenoxicam	[COX]-2 inhibitors <ul style="list-style-type: none">• Celecoxib (FDA alert)• Etoricoxib (FDA withdrawn)• Lumiracoxib TGA cancelled registration• Parecoxib FDA withdrawn• Rofecoxib (withdrawn from market)• Valdecoxib (withdrawn from market)	

- Guidelines to assist in selecting the appropriate agent are mostly empirical and based on experience, occurrence of ADRs, convenience and cost.
- The highest incidence of ADRs includes the following disturbances:
 - GI (gastritis, heartburn)
 - Cardiovascular (hypertension, peripheral edema)
 - CNS (dizziness, psychic disturbances)
 - Dermatologic (rash)
 - Hematologic (decreased hemoglobin and hemtaocrit)
 - Hepatic (elevated liver enzymes)
 - Renal (urinary tract infection)
 - Respiratory (dyspnea)

Signs and Symptoms of Acute Toxicity

- Most OD exposures of NSAIDs are asymptomatic or produce self-limiting (24 hr) lethargy.
- Nausea, vomiting, drowsiness, and potential renal ischemia and renal failure are possible, however, as a result of decrease in renal prostaglandin.
- Some consequences involve gastric erosion, CNS toxicity, and hemorrhage, although this toxicity requires up to 20 times the therapeutic blood concentrations.

Clinical Management of Acute OD

- The ABCs of supportive care are generally warranted.
- Gastric lavage and administration of emetics are of benefit, as well as forced oral fluids and renal function tests.

METHODS OF DETECTION

- Salicylates (acidic compounds) and acetaminophen (a neutral compound) are routinely monitored in suspected poisoning or cases involving toxicity.
- The methods of choice for both drugs include the urine screening color test, gas chromatography, capillary electrophoresis, and solid-phase extraction (SPE) by a methylcellulose-immobilized-strong-anion-exchanger (MC-SAX) high performance liquid chromatography (HPLC) system.
- In addition, testing for acetaminophen is also routinely performed if codeine, oxycodone, hydrocodone or propoxyphene is detected on initial urine screening.