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.

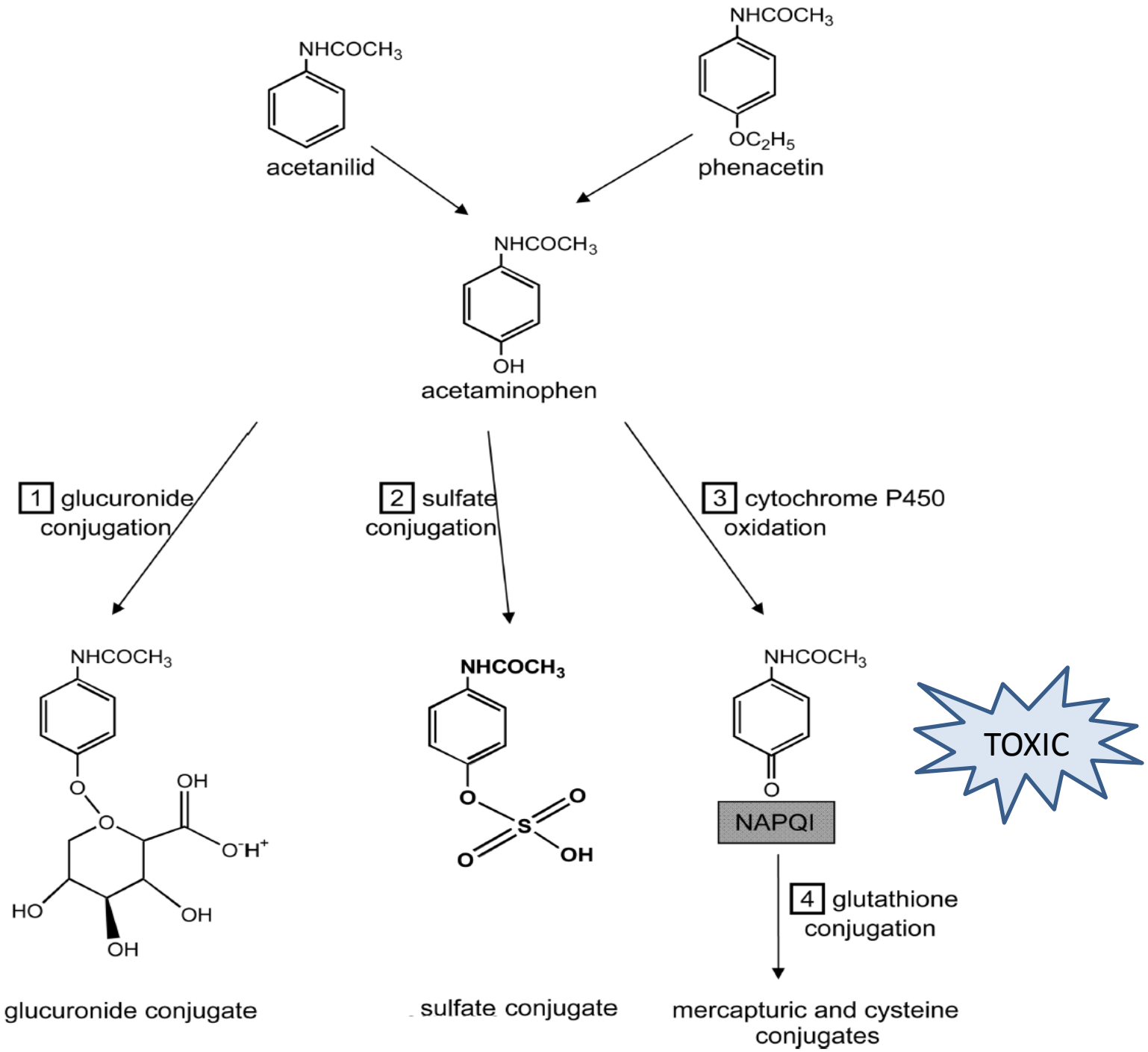
- The **result** is the production of the reactive **intermediate**, N-acetyl-p-benzoquinoneimine (NAPQI) **metabolite**.

- **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**.


NHCOCH3
acetanilid
NHCOCH3
OC2H5
phenacetin
NHCOCH3
OH
acetaminophen
1 glucuronide conjugation
2 sulfate conjugation
3 cytochrome P450 oxidation
NHCOCH3
O
O
OH
O-H+
HO
OH
OH
glucuronide conjugate
NHCOCH3
O
S
O
O
OH
sulfate conjugate
NHCOCH3
O
NAPQI
4 glutathione conjugation
mercapturic and cysteine conjugates
TOXIC

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 8 12 24	≥150 ≥75 ≥35 ≥5	Anorexia, nausea, vomiting, pallor, diaphoresis, malaise, confusion, hypotension, arrhythmias	Hepatic transaminases (AST, ALT) rising
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, arrythmias, 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.

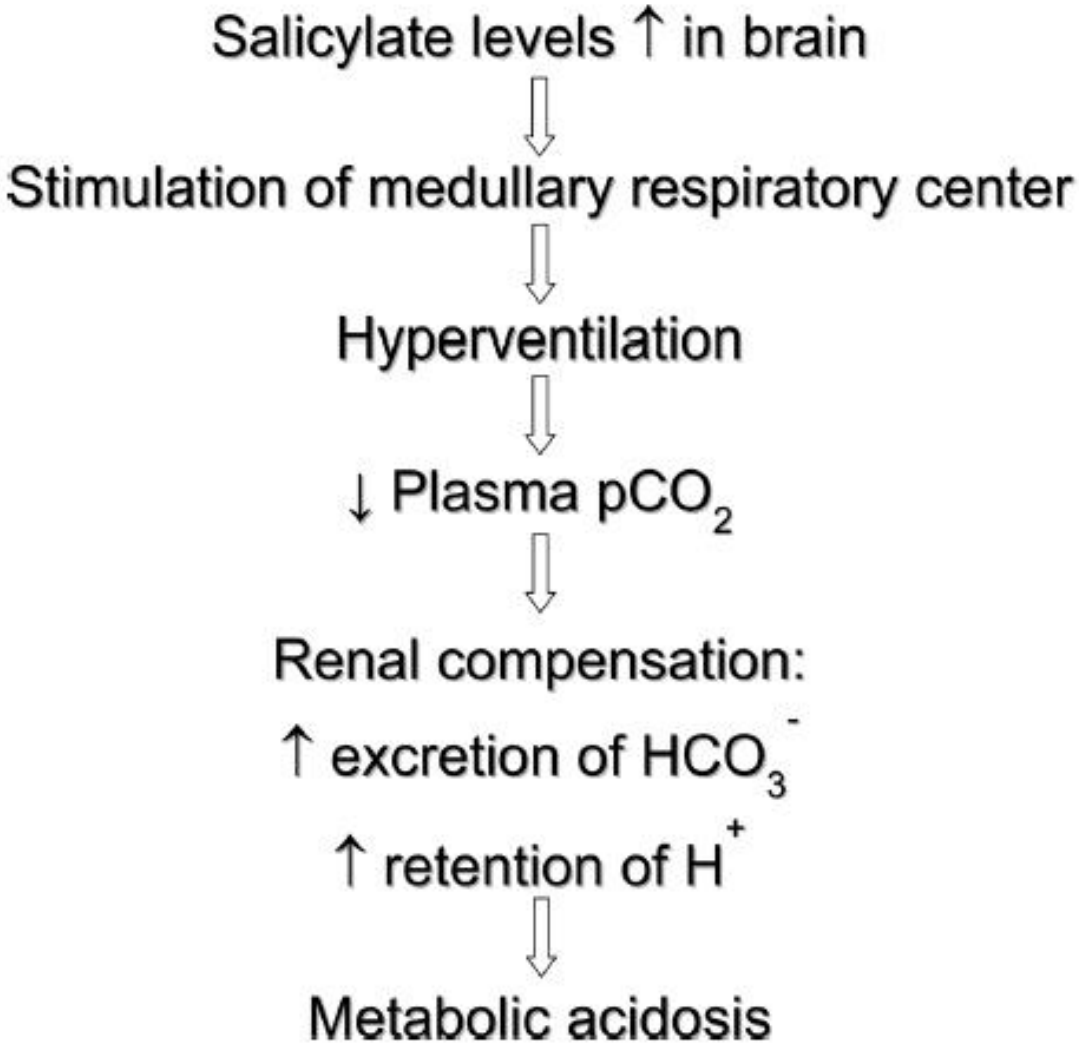
- **Aspirin** has **shown** some success as an **antiplatelet** agent in patients with **thromboembolic** disease.

- **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 Kreb'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
- Acetylsalicylic acid (aspirin)
- Amoxiprin
- Benorylate/Benorilate
- Choline magnesium salicylate
- Diflunisal
- Ethenzamide
- Faislamine
- Methyl salicylate
- Magnesium salicylate
- Salicyl salicylate
- Salicylamide

Arylalkanoic acids
- Diclofenac
- Aceclofenac
- Acemethacin
- Alclofenac
- Bromfenac
- Etodolac
- Indomethacin
- Nabumetone
- Oxametacin
- Proglumetacin
- Sulindac
- Tolmetin

2-Arylpropionic acids (profens)
- Ibuprofen
- Alminoprofen
- Carprofen
- Dexibuprofen
- Dexketoprofen
- Fenbufen
- Fenoprofen
- Flunoxaprofen
- Flurbiprofen
- Indoprofen
- Ketorolac
- Loxoprofen
- Naproxen
- Oxaprozin
- Pirprofen
- Suprofen
- Tiaprofenic acid

N-Arylanthranilic acids (fenamic acids)
- Mefenamic acid
- Flufenamic acid
- Meclofenamic acid
- Tolfenamic acid

Pyrazolidine derivatives
- Phenylbutazone
- Ampyrone
- Azapropazone
- Clofezone
- Kebuzone
- Metamizole
- Mofebutazone
- Oxyphenbutazone
- Phenazone
- Sulfinpyrazone

Oxicams
- Piroxicam
- Droxicam
- Lornoxicam
- Meloxicam
- Tenoxicam

[COX]-2 inhibitors
- 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**.