Paracetamol

The major manifestation of paracetamol poisoning is hepatotoxicity, although the kidneys and heart may also be affected in severe poisoning. N-acetylcysteine prevents toxicity if given within the first eight hours but is also of benefit in patients presenting late or with established hepatotoxicity. Decisions about treatment are based on the plasma concentration in patients who present early and the dose ingested and/or clinical signs in those presenting late.

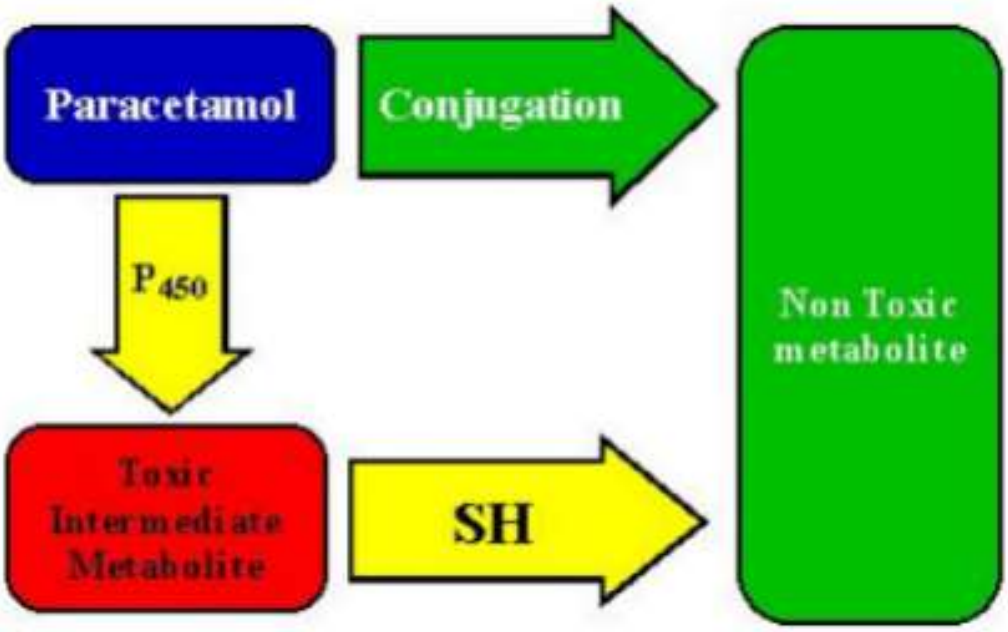
Uses:

Paracetamol (known as acetaminophen in the US and Canada) is found in multiple combined analgesic and antipyretic preparations and the strengths vary considerably.

Toxicity Level:

- About 20 to 25 grams. However doses as low as 10 grams can cause serious hepatotoxicity. Ingestion of even 150 mg/kg or 7.5 grams has caused liver injury
- Children under the age of 10 years appear to be more resistant to the toxic effects of paracetamol. It has been suggested that the toxic dose for a 5-year-old child, based on liver size ratio compared to an adult, is 187.5 mg/kg. Predicted toxic dose for a younger child would be even higher.

There are a number of variables, which potentially influence the risk of toxicity. These are best appreciated by understanding the toxicokinetics of paracetamol.



Theoretically, toxicity is more likely if the P450 enzymes are induced by chronic alcohol ingestion, anticonvulsants, or barbiturates.

Inhibition of P450 enzymes at the time of the overdose may reduce the production of toxic metabolites. This occurs with acute alcohol ingestion (4-6 drinks) and may occur with coingestion or chronic medication with drugs that inhibit these enzymes (e.g. cimetidine).

Patients who are depleted of glutathione are also at theoretically increased risk of toxicity. This may occur in a number of situations, such as chronic ingestion of paracetamol, malnutrition, and eating disorders.

Patients who have increased sulphation enzymes (people on the oral contraceptive and children) will have lower bioavailability and faster clearance of paracetamol.

Mechanism:

Paracetamol can produce multiorgan failure via the production of an intermediate toxic metabolite. Minor oxidative pathways (P450 enzymes, mainly CYP2E1) produce the intermediate toxic metabolite N-acetyl-p-benzoquinonimine that requires glutathione for further metabolism to non-toxic metabolites. After glutathione supplies are exhausted, the toxic metabolite binds to sulphydryl-containing proteins in the liver cell and causes lipid peroxidation disrupting the cell membrane. These events eventually lead to cell death. Any organ that has P450 enzymes can suffer toxicity (i.e. liver, kidneys, heart, and pancreas).

Clinical (Toxic) Symptoms:

1. **Acute Poisoning:**

- Stage I (1/2 hr to 24 hrs): Anorexia, vomiting, sweating, malaise.
- Stage II (24 to 72 hrs): Relatively symptom-free. There may be right upper quadrant pain. Liver function tests may be abnormal
- Stage III (72 to 96 hrs): Hepatic necrosis sets in with coagulation defects, jaundice, and encephalopathy. Nausea and vomiting reappear. Renal failure and myocardial damage are frequently present. Death is usually due to hepatic failure and is preceded by coma.

- Stage IV (4 days to 2 wks): If the patient survives the IIIrd stage, complete resolution of hepatic damage is the rule rather than the exception.

2. Chronic Poisoning:

- Hepatic effects - Hepatotoxicity is the major clinical effect. A rise in the transaminases (ALT, AST) occurs within 24 hours and will usually peak 3-4 days later.
- Patients may complain of anorexia, nausea, vomiting, and hepatic tenderness.
- Renal effects - Acute renal failure with acute tubular necrosis is usually reversible and occurs in only a small proportion of patients with hepatotoxicity. It appears to correlate with a history of chronic alcohol use. It may, on rare occasions, occur in individuals with little hepatotoxicity.

Investigations/Diagnosis:

- Evidence of hypoglycaemia, metabolic acidosis.
- Blood concentrations - Plasma paracetamol should be estimated urgently in any patient who has paracetamol poisoning or presents unconscious with a drug overdose. The purpose of this is to determine the potential severity of the poisoning using the nomogram.
- Biochemistry - Patients with hepatotoxicity will require daily measurement of electrolytes and creatinine. This is to detect renal failure, acidosis and electrolyte abnormalities due to hepatic failure.
- Blood glucose - Patients who develop hepatotoxicity require regular measurement of their blood glucose, particularly in

those patients who are unable to eat. Patients may become hypo- or hyperglycaemic.

- Liver enzymes - An early rise (at 24 hours) in transaminases (ALT, AST) is an indicator of potentially serious hepatotoxicity. Almost all patients who will go on to develop hepatotoxicity (ALT or AST > 1,000 IU) will have abnormal transaminases at 24 hours.
- The prothrombin time is the best prognostic indicator.

Management:

- GI Decontamination - Oral activated charcoal should be given to all adults and older children ingesting more than 150 mg/kg of paracetamol standard release tablet or capsule preparations presenting within 2 hours. For children 1-5 years of age, the at risk dose is > 225 mg/kg.
- Stomach wash - useful only in cases of very early presentation (<1 hour), or in concomitant ingestion of other drugs which delay GI absorption.
- Anti-emetic, if the patient is vomiting repeatedly
- Supportive measures - dextrose for hypoglycaemia, Vitamin K if PT is elevated, Fresh-frozen plasma if there is overt bleeding and Mannitol for cerebral oedema.

Salicylates

Salicylate poisoning is a potentially life threatening condition which is characterised by extreme acid-base disturbances, electrolyte disturbances and decreasing level of consciousness. There is a wide variation in the clinical spectrum of toxicity. There are differences between acute and chronic toxicity and a varying clinical picture which is dependent on the age of the patient and renal function.

Uses:

1. Sodium salicylate and acetyl salicylic acid:

- Antipyretic
- Analgesic
- Treatment of rheumatoid arthritis
- Low-dose aspirin is used in the prophylaxis of cerebrovascular ischaemic events, angina pectoris, and is also recommended by some authorities for the prevention of colon cancer, and migraine.

2. Sodium aminosalicylate:

- Tuberculosis

3. Bismuth subsalicylate:

- Diarrhea
- Prophylaxis for travellers diarrhea

4. Mesalamine

- Suppository or rectal suspension enema for its local effects in the treatment of inflammatory bowel disease

- Ulcerative colitis

5.Locally acting salicylates:

- Methyl salicylate used as a flavouring agent for candy.
- Homomenthyl salicylate is a sunscreen agent.

Toxicity Level:

Initial assessment of the severity of toxicity the four following areas should be considered

- Dose ingested
- Salicylate concentration
- Clinical grading of toxicity
- Acid-base grading of severity

➢ **Ingested Dose**

The assessment of ACUTE salicylate intoxication based on dose

Ingested Dose mgs/kg	Estimated Severity
< 150	No toxic reaction expected
150-300	Mild to moderate toxic reaction
300-500	Serious toxic reaction
500	Potentially Lethal

➢ **Salicylate concentration**

Conversion factor

- mg/L x 0.0072 = mmol/L
- mmol/L x 138 = mg/L

➢ **Clinical grading of toxicity**

- **Mild -** Nausea, vomiting, tinnitus
- **Moderate -** Confusion, hyperventilation
- **Severe -** Hallucinations, seizures, coma, cerebral or pulmonary oedema.

➢ **Acid-base grading of severity**

Stage	Blood pH	Urine pH	Comment
I	>7.4	>6	Respiratory alkalosis , Increased urinary excretion of NaHCO3, K+ & Ca++
II	>7.4	<6	Metabolic acidosis with compensating respiratory alkalosis. Intracellular K+ depletion, urine H+ excretion.

III	<7.4	<6	Severe hypokalaemia and metabolic acidosis

Mechanism:

- Salicylates stimulate the respiratory centre in the brainstem leading to hyperventilation and respiratory alkalosis. They also interfere with Krebs cycle, inhibit production of ATP, and increase lactate production, leading to ketosis and a wide anion-gap metabolic acidosis. In children, respiratory alkalosis is quite transient, and metabolic acidosis is the predominant feature. Respiratory acidosis in salicylate overdose indicates grave prognosis and is seen in salicylateinduced pulmonary oedema, CNS depression from mixed overdose, or severe fatigue due to prolonged hyperventilation.
- Salicylates are extremely irritating to the GI mucosa, and overdose often results in haemorrhagic gastritis. In the US, the FDA requires an alcohol warning on all over-the-counter pain relievers, which includes aspirin, other salicylates, paracetamol, ibuprofen, ketoprofen, and naproxen sodium, due to a potential drug interaction resulting in upper GI bleed or liver damage.
- Aspirin is commonly involved in allergic reactions, ranging in severity from urticaria or angioedema to acute anaphylaxis

Clinical (Toxic) Symptoms:

In children hyperventilation, dehydration and neurological dysfunction are greater in chronic overdoses compared with single acute ingestions.

Symptoms can occur with declining salicylate concentrations because of CNS trapping of ionised salicylate.

- Acid-base disturbance - Respiratory alkalosis is the earliest acid-base disturbance in salicylate poisoning.
- Electrolyte imbalance - Patients are often significantly dehydrated (chronic > acute). Electrolyte abnormalities are common which include hyponatraemia, hypernatraemia, hypokalaemia and hypocalcaemia.
- Mild pyrexia is common and is due to increased metabolic activity.
- Nausea and vomiting are common. Less common are epigastric pain and haematemesis. Vomiting contributes significantly to electrolyte imbalance and dehydration.
- Rises in transaminases occur not uncommonly, are usually not clinically significant, and resolve over several days.
- Non-cardiogenic pulmonary oedema and renal failure occur occasionally and always in association with other signs of significant poisoning.

Investigations/Diagnosis:

The following investigations should be done in all patients

- FBC, coagulation profile
- Electrolytes, calcium, creatinine, glucose
- Arterial blood gas
- Urinalysis and urine pH
- Plasma salicylate concentration

- Biochemistry - Patients with moderate or severe poisoning (by any measure) will need 2nd hourly measurement of electrolytes and glucose. CSF glucose concentrations may be low despite normal plasma concentrations.
- Blood concentrations - Plasma salicylate should be estimated urgently in any patient who has a potentially serious poisoning, electrolyte or acid-base disturbance.
- Differential diagnosis - Poisonings can present with a metabolic acidosis and impaired concentration or consciousness.

Management:

1. In patients with severe poisoning, examine the urine for calcium oxalate crystals. Also, monitor calcium and renal function (BUN, creatinine).
2. Local treatment with cold milk or ice cream as a demulcent is sufficient in most cases. Cold water or sucking on crushed ice will also relieve oral pain. Remove all visible evidence of plant debris from the oropharynx.
3. In severe cases, parenteral opioids, corticosteroids, IV fluids, and endotracheal intubation may be required. Tetany should be treated with intravenous calcium gluconate.
4. Ocular exposure to sap resulting in chemical conjunctivitis and corneal abrasions must be treated with copious irrigation, systemic analgesics, and expert ophthalmologic consultation.