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Ananalyzed Review on Paracetmol and Salicylate Toxicity

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ABSTRACT

Paracetamol is widely available and yet is substantially more toxic than other analgesics available without prescription and Paracetamol is one of the most used medicines worldwide and is the most common importantpoisoning in high-income countries. In overdose, paracetamol causes dose-dependent hepatotoxicity. Large overdosesand those involving modified-release paracetamol are high-risk and can be targeted through legislative change Toxicitycan occur following dosing errors, accidental exploratory ingestions in children, and deliberate self-harm overdose. This review summarizes paracetamol overdose and toxicity (including mechanisms, treatment) A literature search onPubMed for poisoning epidemiology and mortality from 1 January 2017 to 26 October 2022 was performed to estimate rates of paracetamol overdose, liver injury, and deaths worldwideAnd Salicylates are found in a myriad of prescription and over-the-counter medicinal preparations, including acetylsalicylic acid tablets and analgesic mixtures. On the basis of data from 2014 through 2018, approximately 25,000 exposures to acetylsalicylic acid are reported annually to poison control centres in the United States.8,9 In 2018, acetylsalicylic acid alone was involved in 17,380 cases of salicylate poisoning, with unintentional exposure more common than intentional exposure. Moderate or severe toxic effects occurred in 1761 of the 17,380 cases; 26 additional patients died Given the wide range of signs and symptoms and the high rates of death and complications associated with a toxic overdose ofsalicylate, this article highlights the risk factors for salicylate toxicity, reviews the pathophysiological effects, and discusses treatment strategies.Especially during the current pandemic, clinicians should beaware of the potential for salicylate poisoning,1whichoccurred in the 1918–1919 pandemic of Spanish influenza.

Keywords: Paracetamol, Acetylcysteine, Hepatotoxicity, Mitochondrial toxin, Acetanilide, Overdose, NAPQI, Poisoning, Aspirin, Metabolic disorders, Fatal dose, Haemodialysis.

PARACETMOL:

INTRODUCTION

Paracetamol is one of the most used medicines worldwide and is the most common important poisoning in high-income countries. In overdose, paracetamol causes dose-dependent hepatotoxicity. Acetylcysteine is an effective antidote, however despite its use hepatotoxicity and many deaths still occur. [1]

Paracetamol (acetaminophen) is one of the most widely used medicines worldwide and is readily available without prescription in most countries.It is listed on the World Health organization.[2]

It is recommended as a first-line treatment for most cases of pain and fever and is safe to use in children as young as one-month old as well as women who are pregnant.[3]

Compared to other analgesics accessible **without a prescription**, paracetamol has a relatively **narrow therapeutic index**. Paracetamol can cause **severe hepatotoxicity** with as little as 10 g (or 200 mg/kg for patients under 50 kg) in an acute overdose.

There is an effective antidote to paracetamol (N-acetylcysteine or NAC).

Synonyms:[4]
Acetaminophen; N-acetyl-p-aminophenol; 4-hydroxyacetanilide.

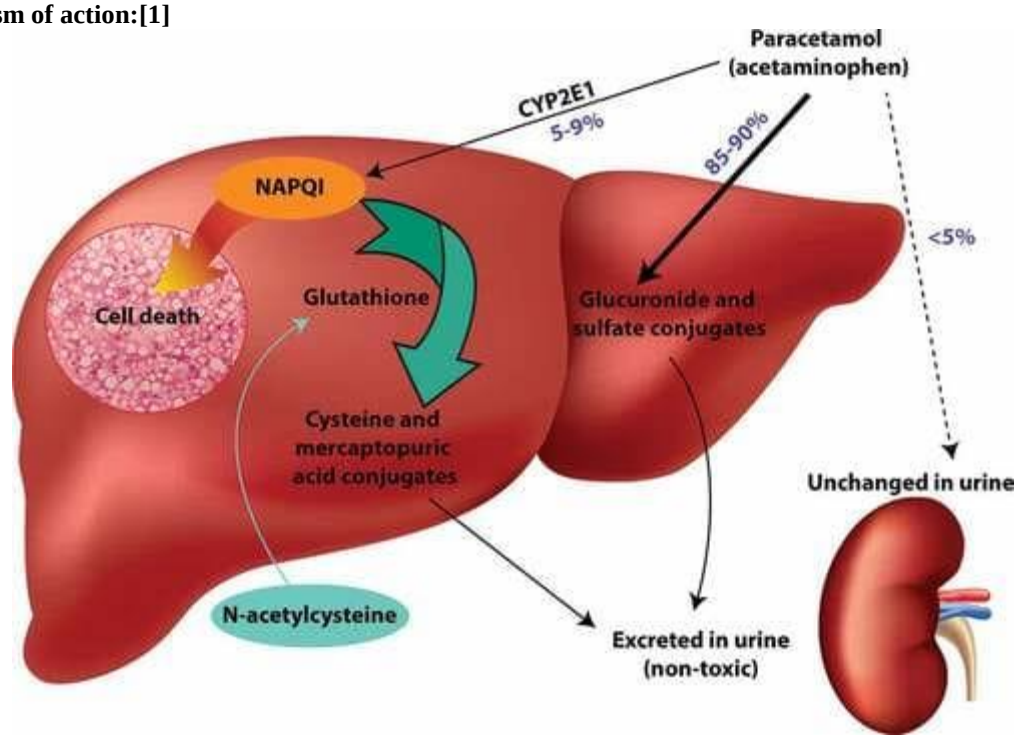
Physical Appearance:[4]
- Paracetamol exists as white, odourless, bitter tasting crystals or crystalline powder.
- It comes in a variety of forms and strengths including oral tablets, capsules, and liquid formulations as well as rectal suppositories.

Clinical uses:[5]
- Antipyretic & Analgesic.

Discovery and use
Paracetamol is an aniline derivative. Acetanilide was the first aniline derivative to be used as an antipyretic and analgesic in 1886[6]. However, it was found to have frequent toxic effects (particularly methemoglobinemia) [7]and so exploration of further aniline derivatives commenced. This led to the discovery of phenacetin and paracetamol in the late 1800s.Phenacetin was deemed safer and was used frequently for around 50 years. However, in the late 1940s it was discovered that paracetamol was the less toxic major metabolite of phenacetin and acetanilide, and that it did not cause methemoglobinemia. This combined with a low risk of nephrotoxicity resulted in paracetamol becoming available.

Fatal dose:[4]
- 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.

Mechanism of action:[1]



Toxic mechanism of paracetamol and mechanism of action of acetylcysteine. Paracetamol is primarily detoxified by glucuronide and sulfate conjugates which are then excreted in the urine. A small percentage is metabolizedby CYP2E1 to the reactive intermediate NAPQI. Under normal conditions, NAPQI can be detoxified by reactionwith glutathione to form cysteine and mercaptopuric acid conjugates. If glutathione is depleted (e.g., inparacetamol overdose), NAPQI binds to cell macromolecules causing hepatocyte cell death. The antidoteacetylcysteine replenishes cysteine, which is the rate-limiting factor for glutathione synthesis.

Toxicokinetics:
- Acetaminophen is rapidly absorbed from the gastrointestinal (GI) tract and reaches therapeutic levels in 30minutes to 2 hours. Overdose levels peak at 4 hours unless other factors could delay gastric emptying,

such asa co-ingestion of an agent that slows gastric motility or if the acetaminophen is in an extended-release form.[8]

- Acetaminophen has an elimination half-life of 2 hours but can be as long as 17 hours in patients with hepaticdysfunction. It is metabolized by the liver, where it is conjugated to nontoxic, water-soluble metabolites thatare excreted in the urine.[9]

Mechanism and manifestations of toxicity:

- The main toxic effect of paracetamol is hepatoxicity.
- Paracetamol isa 'pro-poison' that exerts its toxic effect through the toxic reactive metabolite, NAPQI. This metabolite is formed by cytochrome P−450 (CYP) enzymes, primarily CYP2E1 and CYP3A4.
- NAPQI is formed in small amounts in therapeutic doses where it is readily detoxified by conjugation with glutathione [10]. In overdose, there may be insufficient glutathione to detoxify NAPQI, causing it to bind to cellular proteins (adduct formation).
- NAPQI primarily binds to cysteine residues but can potentially also damage proteins at methionine, tryptophan, and tyrosine residues. The mitochondria are a key target for NAPQI adduct formation. Formation of reactive oxygen species causes oxidative stress and leads to activation of c-Jun N-terminal kinase (JNK). [11]
- The JNK enzyme translocates to the mitochondria, leading to mitochondrial dysfunction, cessation of ATP formation, and mitochondrial membrane rupture. This leads to cellular necrosis.
- The role of mitochondria in paracetamol hepatotoxicity has been reviewed extensively. Severe liver injury leads to loss of hepatic synthetic function and coagulopathy and hypoglycaemia. Loss of hepatic metabolic functions leads to encephalopathy and lactic acidosis [12]. The clinical manifestations of hepatotoxicity are delayed, with peak serum transaminase levels occurring two to three days after the overdose.
- Approximately 12–13% of acute overdoses result in hepatotoxicity even with treatment, with 2–5% progressing to liver failure and 0.2–0.5% resulting in death. Acute kidney injury can also occur, even in the absence of liver failure, and may be delayed. Nephrotoxicity may be direct due to tubular necrosis from renal NAPQI production or indicate hepatorenal syndrome.[12]
- Paracetamol is also a direct mitochondrial toxin and at very high concentrations can result in central nervous system (CNS) depression. Coma may occur in the absence of hepatotoxicity or other drugs causing CNS depression and may lead to delayed diagnosis and treatment of paracetamol overdose.[13]

Clinical features:[4]

Acute toxicity

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):

- Jaundiceand encephalopathy.
- Nausea and vomiting reappear.
- Renal failure
- Myocardial damage
- Hepatic failure
- Coma &death

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. There are no reported cases of chronic hepatic dysfunction from paracetamol.

Additional Manifestations:

- Hypotension and shock with hypothermia.
- Myocardial injury.
- Coma and metabolic acidosis.

Chronic toxicity

- Anorexia
- Vomiting

- Lethargy
- Low body temperature
- Hepatomegalyand oliguria.

Diagnosis:[4]

1. Evidence of hypoglycaemia, metabolic acidosis.
2. Evidence of hepatocellular injury.
    a. Elevated AST, ALT, bilirubin, and prothrombin time.
    b. Hypophosphatemia is often present (greater than 1.2 mmol/L), occurring48 to 96 hours after the overdose.
    c. Decreased serum interleukin-6 (IL-6) or C-reactiveprotein.
    d. Fatal cases of paracetamol overdose usually havea bilirubin level greater than 4 mg/100 ml and a prothrombin time greater than twice the control or a prothrombin time ratio of 2.2 or greater on the third to the fifth day.
3. Evidence of renal damage:Proteinuria, phosphaturia.
4. Evidence of myocardial damage:ECG changes indicative of arrhythmias.
5. Serum paracetamol level: The lowest acute dose of paracetamol capable of toxicity is generally regarded as 7.5 grams in an adult and 150 mg/kg in a child, though it is more likely that the actual figures may be 15 grams and 250 mg/kg respectively.

Treatment:

1. Charcoal [14]

Activated charcoal binds paracetamol and thus may reduce the amount of paracetamol absorbed from the gastrointestinal tract. It may be useful in acute paracetamol overdoses that present to primary care facilities within 2 h of ingestion (or 4 h for ‘massive’ overdoses or exposures to MR/ER preparations). However, it is not useful in patients who ingest liquid formulations due to the rapid absorption. It is also not recommended after repeated supratherapeutic ingestions. Charcoal may reduce peak paracetamol concentrations, the need for NAC and decrease the risk of hepatotoxicity.

2. N-acetylcysteine (NAC) [15]

NAC restores glutathione by replenishing cysteine, the rate-limiting factor for glutathione synthesis. This allows for the detoxification of NAPQI and prevents hepatotoxicity in most cases. The risk of developing hepatotoxicity is substantially reduced when NAC is given within 8 h of ingestion.

3. Methionine [16]

Similar to NAC, methionine is an antidote used to increase glutathione and treat or prevent hepatotoxicity. Althoughprimarily administered orally, it has been administered intravenously. Methionine may cause gastrointestinal,neurological, or cardiovascular side effects which limit its acceptability and so it is no longer routinely recommended.

4. Cimetidine

Cimetidine is a histamine−2 receptor antagonist and an inhibitor of CYP2E1. Based on this inhibition, it has been proposed as a potential treatment for paracetamol overdose.

5. Fomepizole[17]

Fomepizole has recently been proposed as a treatment to prevent hepatotoxicity following paracetamol overdose.Fomepizole inhibits CYP2E1, reducing conversion of paracetamol into NAPQI. Secondly, it can also prevent theactivation of the JNK enzyme and resultant mitochondrial dysfunction.

6. Liver transplant - patients with severe liver failure.

SALICYLATES

Introduction:

Salicylate toxicity is a medical emergency. Intentional ingestion or accidental overdose can cause severe metabolic derangements, making treatment difficult. Co-ingestion of other medications can further complicate management. Salicylates are widely available over the counter medications. They are commonly used for their analgesic, antipyretic, and anti-thrombotic properties, and toxicity can occur due to acute ingestion or from chronic ingestion. Salicylate poisoning is characterized as either acute or chronic. The acute form of salicylate intoxication generally occurs in young adults.[18]

These compounds are derivatives of salicylic acid and include acetyl salicylic acid, sodium salicylate, and methyl salicylate. Salicin, a naturally occurring salicylate is a constituent of several plants but is present in highest concentration in the willow tree (Salix alba vulgaris), which grows near lakes and rivers in temperate climates.[4]

Examples:[4]

- Acetaminosalol
- Aloxiprin
- Aluminium aspirin
- Ammonium
- salicylate
- Antipyrine salicylate
- Aspirin
- Benorylate
- Bismuth subsalicylate
- Bromosalicylic acid acetate
- Calcium amino salicylate
- Calcium carbaspirin

Clinical uses:[19]

1. Analgesics
2. Anti-inflammatory
3. Antipyretics
4. Keratolytic
5. Antiplatelets
6. To treat rheumatoid arthritis and osteoarthritis

Physical appearance:[4]

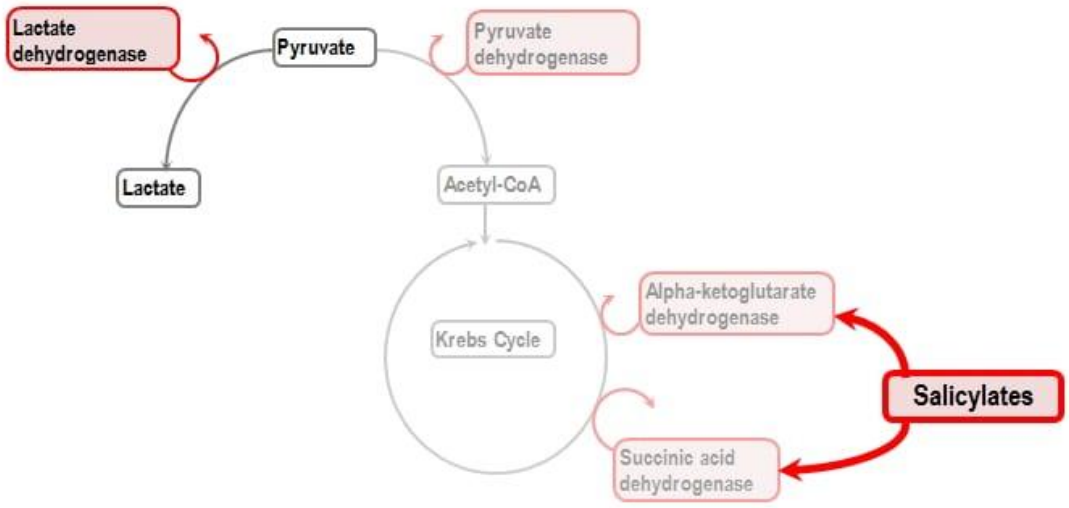
- It appears as an odourless, white, crystalline powder with an unpleasant saline taste.
- Salicylates for therapeutic use are available as tablets, capsules, powders, effervescent tablets and liquidpreparations for ingestion; rectal suppositories; and as liniments, creams and lotions for topical application.

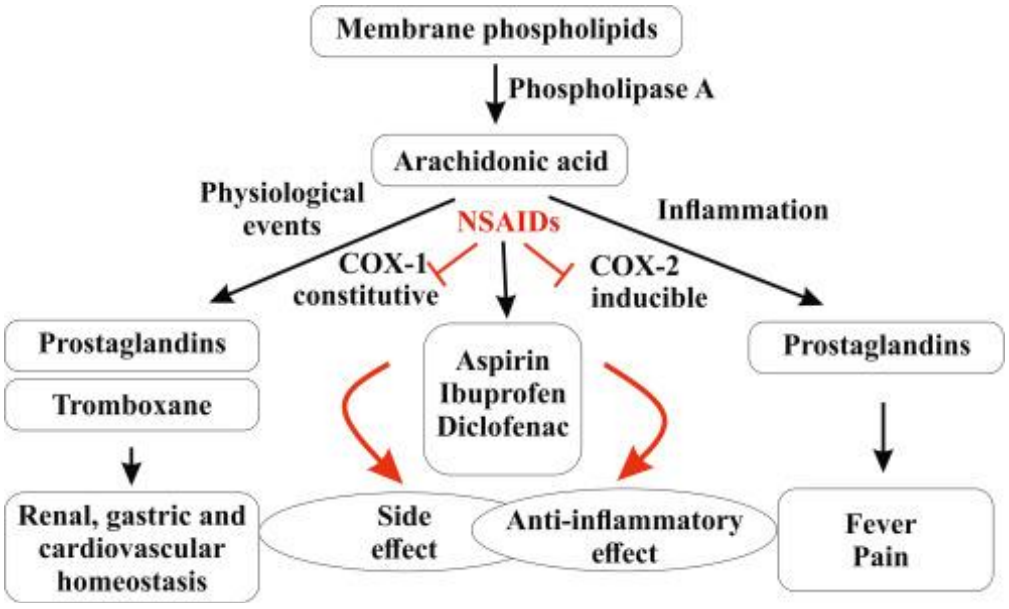
Fatal dose:[20]

- Toxic dose-150 mg/kg.
- Minimal lethal dose = 450 mg/kg Dose.
- Less than 150 mg/kg of aspirin - no symptoms to mild toxicity.
- Ingestions of 150-300 mg/kg - mild to moderate toxicity.
- Ingestions of 300-500mg/kg – Serious toxicity Greater than 500mg/kg – potentially lethal.

Mechanism of action:[21]

Salicylate poisoning causes a variety of metabolic disorders. Direct stimulation of the cerebral medulla causes hyperventilation and respiratory alkalosis. As it is metabolized, it causes an uncoupling of oxidative phosphorylation in the mitochondria. Lactate levels then increase due to the increase in anaerobic metabolism. The lactic acid along with a slight contribution from the salicylate metabolites result in metabolic acidosis. Hyperventilation worsens in an attempt to compensate for the metabolic acidosis. Eventually, the patient fatigues and is no longer able to compensate via hyperventilation, and metabolic acidosis prevails. This results in hemodynamic instability and end-organ damage.





Toxicokinetics:[4]

1. Salicylates are rapidly absorbed from the stomach, and to a slightly lesser extent from the small intestine.
2. Salicylates distribute well into plasma; saliva; milk; and spinal, peritoneal and synovial fluid and into body tissues including kidney, liver, lung and heart.
3. Metabolism occurs chiefly in the liver, where salicylates are broken down into salicyluric acid, ether glucoronide, ester glucoronide, and gentisic acid. Excretion is mainly through urine.
4. The half-life of salicylates is 2 to 4 hours at therapeutic levels, but may increase to 20 hours at toxic levels.
5. Plasma salicylate is 50 to 80% protein bound.

Clinical features:[4]

Acute toxicity

Early

- Nausea& vomiting
- Sweating
- Tinnitus (ringing or hissing)
- Vertigoand hyperventilation due to respiratory alkalosis
- Irritability

Late

- Deafness
- Hyperactivity
- Agitation
- Delirium
- Convulsions
- Hallucinations
- Hyperpyrexia
- Coma is unusual.

Chronic toxicity

- Slow onset of confusion
- Agitation
- Lethargy
- Disorientation
- Slurred speech
- Hallucinations
- Convulsionsand coma
- There may also be tinnitus, hearing loss, nausea, dyspnoea, tachycardia and fever.

    - Thrombocytopenia, hypofibrinogenemia, elevation of fibrin degradation products, and red blood cell fragmentation has developed in some patients with multiorgan system failure associated with chronic salicylate toxicity.

Diagnosis:

1. Monitor serum salicylate level, glucose and electrolytes every 2 hours until the salicylate level is consistently falling and acid base abnormalities are improving. [4]
2. Abdominal X ray.
3. Liver function test,Kidney function test, Complete blood count.
4. Laboratory Findings:[22]
   a) Anion-gap acidosis.
   b) Hypokalaemia (acidosis may mask it).
   c) Hypocalcaemia.
   d) Hypoglycaemia.

Drug Interactions: [4]

Salicylate and/or acetazolamide toxicity may occur inpatients taking salicylates chronically when acetazolamideis added to drug regimen. The syndrome of effects reportedare confusion, fatigue, hyperchloremic metabolic acidosis, incontinence, lethargy, and somnolence shortly after theintroduction of acetazolamide in patients chronicallyreceiving aspirin.

Treatment:[4]

Supportive therapy

- Correction of fluid and electrolyte imbalance (watch out for fluid overload!).
- Correct dehydration with 0.9% saline 10 to 20 ml/kg/hr over 1 to 2 hours until a good urine flow is obtained (at least 3 to 6 ml/kg/hr).
- Hypoprothrombinaemia can be corrected by 2.5 to 5 mg of vitamin K IV every day.
- Correction of metabolic acidosis with NaHCO3.
- Treatment of convulsions with benzodiazepines.
- Mild cerebral oedema and elevated intracranial pressure (ICP) can be managed by head elevation and administration of mannitol; hyperventilation should be performed.

1. Whole bowel irrigation:

Stomach wash may be beneficial up to 12 hours after ingestion, since toxic doses of salicylates often cause pylorospasm and delayed gastric emptying. Whole bowel irrigation might be useful in patients with bezoars, or patients who have ingested enteric coated or sustainedrelease products.

2. Activated charcoal:

It is said to be very efficacious in the treatment of salicylate poisoning The initial dose of AC can be combined with a cathartic to enhance elimination.

3. Haemodialysis:

It is very effective in salicylate poisoning and must always be considered in the presence of cardiac or renal failure, intractable acidosis, convulsions, severe fluid imbalance, or a serum salicylate level more than 100 mg/100 ml. Patients with evidence of cerebral oedema require immediate dialysis. Charcoal hemoperfusion produces better salicylate clearance than haemodialysis, but does not correct fluid and electrolyte balance like haemodialysis.

Table-1: Treatment of salicylate poisoning [23]

Treatment	Indications	DosingandTreatmentConsiderations
Activatedcharcoal	Gastrointestinaldecontamination	1–2g/kgofbodyweighttomaximumof100ginadults; Mosteffectiveifgivenwithin2hrs.after ingestion;1g/kg to amaximum of 50g in children†;multiple dosetreatmentismosteffectiveforbezoarsandfor enteric-coatedorsustained-releasepreparations.
Whole-bowelirrigation‡	Gastrointestinaldecontamination	Polyethyleneglycolthroughnasogastrictubeata dose of 20–40ml/kg/hruntilrectaleffluentisclear (usually4–6 hr)
IVfluids	Restorationandmaintenanceofextracellular fluidvolume;forceddiuresisnotrecommendedbecauseofriskof pulmonaryedema.	Lactated Ringer's solution or isotonic saline: 10–20 ml

Mechanicalventilation	Endotrachealintubationwhenrespiratory effortsarefaltering,toprotectairwayin obtundedordeliriouspatients;sedationfor dialysis-accessplacement	$NaHCO_3$at adose of 2mmol/kg to improveplasma pHbeforeintubation

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CONCLUSION

In this article we represented about paracetamol and salicylates poisoning. As these two are OTC drugs and availabilityof these drugs are more common. The incidence of overdosing is high due its availabilityand due to frequent usage. We came here with this article by explaining in detail how its leads to toxicity& some supportive measures andtreatment indication for the paracetamol and salicylate overdose condition.

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