Paracetamol Poisoning in Children

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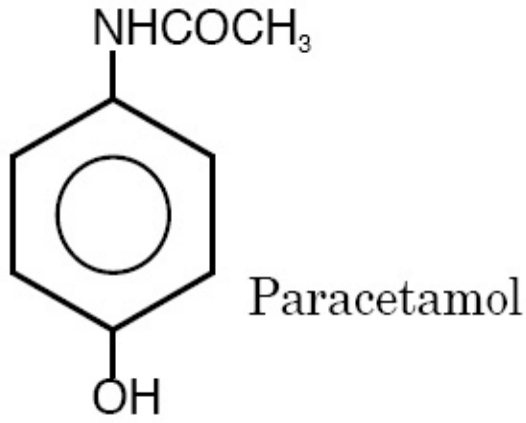
Introduction

Paracetamol is one of the most commonly used drug world wide. It is the deethylated active metabolite of phenacetin. Paracetamol (acetaminophen) was discovered in Germany at the end of the 19th century and has come into common clinical use since 1950.1 Paracetamol is contained in many preparations, in many forms either alone or in combination with other drugs (usually opiates) for analgesia and in other mixtures its analgesic and antipyretic properties and is available as both over-the-counter and as prescription-only medications. Because of its wide availability paired with comparably high toxicity, (compared to ibuprofen and aspirin) there is a much higher potential for overdose especially in children.[1,2]

Structure of Paracetamol



Paracetamol toxicity,accidental or suicidal or part of child abuse is one of the most common causes of poisoning worldwide. The major organ affected by the damage is liver and can lead to acute liver failure. Renal tubular damage and hypoglycemic coma also can occur. Adolescent is 6 times more likely to develop hepatotoxicity than children less than 6 years. Paracetamol toxicity should be suspected in any child with unexplained liver failure.

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Pathophysiology

Paracetamol is well absorbed orally and produces peak plasma level in half hour and only 1/3 is protein bound in plasma . In over dose absorption may take 4 hours.plasma half life is 2-3 hours and effect of an oral dose last 3-5 hours.3

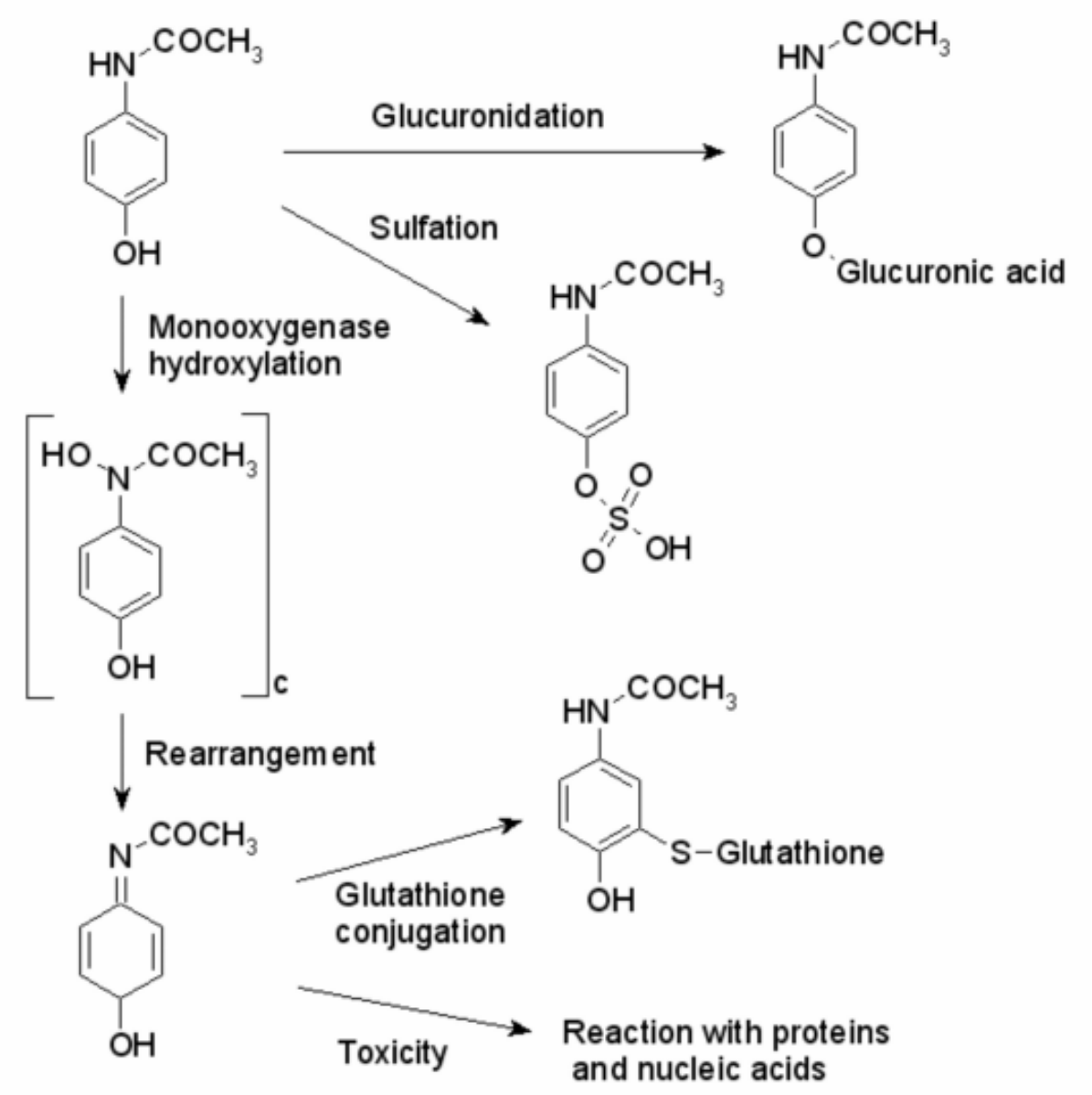
When taken in normal therapeutic doses, paracetamol is converted to nontoxic metabolites via Phase II metabolism by conjugation with sulfate and glucuronide, with a small portion being oxidized via the cytochrome P450 enzyme system. Cytochromes P450 2E1 (CYP2E1) and 3A4 (CYP3A4) convert approximately 5% of paracetamol to a highly-reactive intermediary metabolite, N-acetyl-p-benzoquinoneimine (NAPQI)Under normal conditions, NAPQI is a highly reactive arylating minor metabolite which is detoxified by conjugation with glutathione to form cysteine and mercapturic acid conjugates.4,5

In cases of paracetamol overdose, the sulfate and glucuronide pathways become saturated, and more paracetamol is shunted to the cytochrome P450 system to produce NAPQI.Hepatic glutathione stores get depleted and this metabolite covalently bind

to protein in liver cells and renal tubules and cause necrosis. The lower incidence of toxicity in young children may be due to lesser metabolism via p450.4,5,6,7

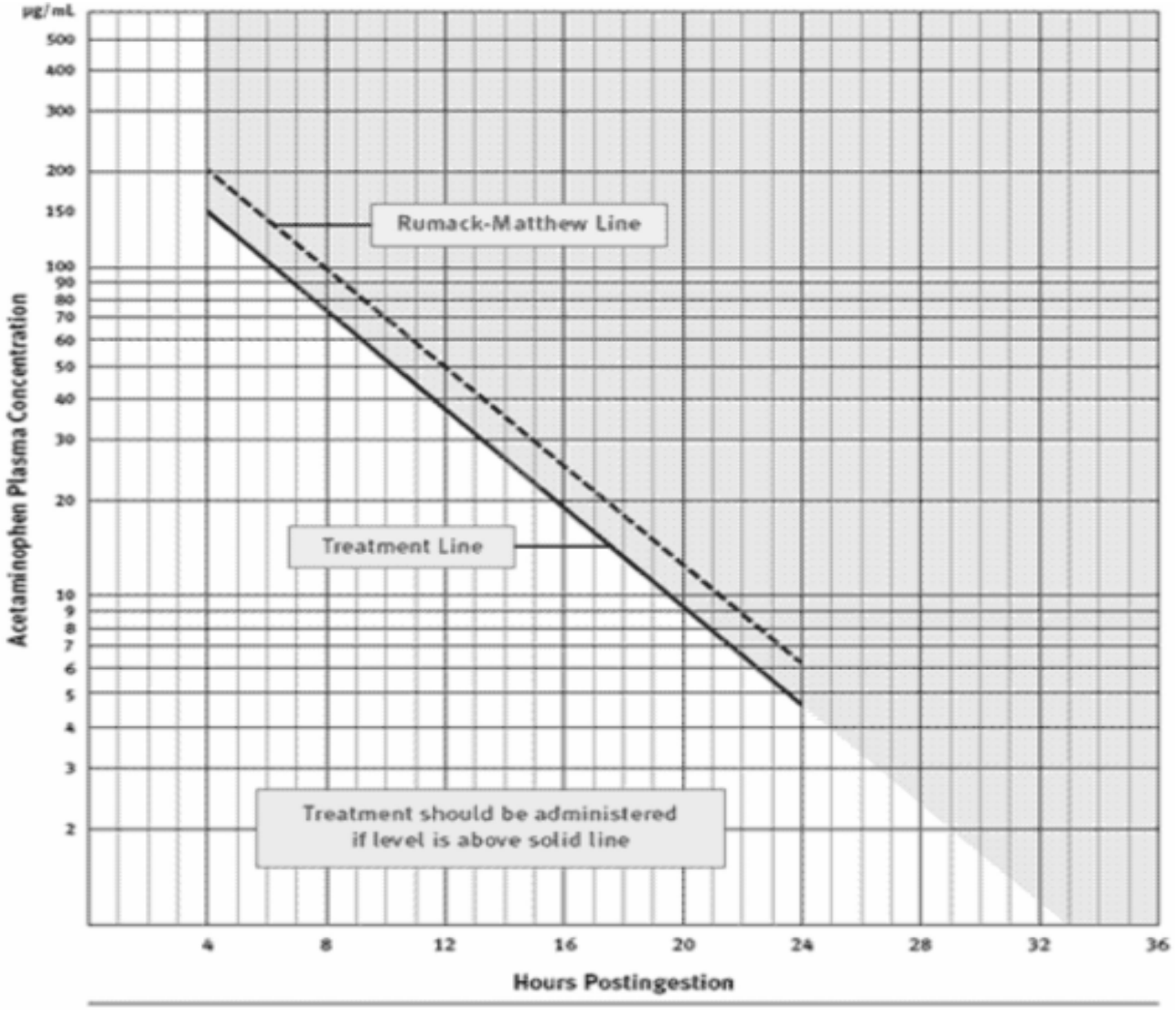
Acute toxic dose is generally considered >200 mg/kg in children younger than 12 yr of age and a single ingestion of more than 7.5 grams is considered a minimum toxic dose in adolescents and adults. Repeated dosage of >60 mg/kg/day may lead to hepatic injury and failure. Fatal period 2-7 days and fatal dose is 20-25 gms.4,5,6,7

Paracetamol metabolic pathway



A drug nomogram developed in 1975, called the **Rumack–Matthew nomogram**, estimates the risk of toxicity based on the serum concentration of paracetamol at a given number of hours after ingestion. To determine the risk of potential hepatotoxicity, the paracetamol level is traced along the nomogram. If a toxic ingestion is suspected then the plasma acetaminophen concentration should be measured 4 hours after ingestion, because during the first four hours after ingestion may underestimate the

amount in the system because paracetamol may still be in the process of being absorbed from the gastrointestinal tract. Normograms predictive strength may not be useful in children with reduced glutathione stores such as malnourishment and prolonged illness. Minimum 2 sampe for the assessment of plasma acetaminophen should be taken one 4 hours after the exposure and second 4-6 hours from the first and if the level exceeds the treatment value patient should receive specific antidote therapy.[4,5]



Clinical Features

The patient usually presents with features of liver cell failure ,renal failure and hyoglycemic coma. The signs and symptoms of paracetamol toxicity occur in 4 stages if left untreated.[4,5,6,7]

Stage 1

The onset of symptoms is within 6 hours after ingestion and patients often have no specific symptoms or only mild symptoms. The clinical features consists of nausea, vomiting, pallor, and sweating. This phase last for the first 24 hours after the ingestion. Laboratory investigations such as AST,ALT, Bilirubin and Prothrombin time are normal at this stage. [4,5,6,7]

Stage 2

The second phase occurs between 24 to 48 hours following overdose. and consists of signs of increasing liver damage.It is

characterised by the resolutions of symtoms of stage1 but child may experience right upper quadrant pain. Mild hepatomegaly and jaundice may be present. In general, damage occurs in hepatocytes as they metabolize the paracetamol. Biochemical parameters show elevated AST, ALT and bilirubin and prolonged prothrombin time. Some children may develop oliguria during this period.

Stage 3

The third phase follows at 48 to 96 hours after ingestion, and is marked by complications of massive hepatic necrosis leading to fulminant hepatic failure with complications of coagulation defects, hypoglycemia, kidney failure, hepatic encephalopathy, cerebral edema, sepsis, multiple organ failure, and death.. The severity of paracetamol toxicity varies depending on the dose and whether appropriate treatment is received. Less than 1% dies of liver failure if not treated specifically. Plasma ALT levels will be usually greater than 1000U/L and prolonged PT and bilirubin value. [4,5,6,7]

Stage 4

This stage last from 4 days to 2 weeks after ingestion. If properly treated If the third stage is survived, the hepatic necrosis runs its course, and liver and kidney function typically return to normal . [4,5,6,7]

Risk Factors

Malnourishment is i a risk factor, possibly because of depletion of hepatic glutathione reserves. The concomitant use of the CYP2E1 inducer isoniazid increases the risk of hepatotoxicity, and antiepileptics including carbamazepine, phenytoin, and barbiturates, which induce CYP enzymes have also been reported as risk factors. [4,5,6]

Management

General measures

If a patient comes with features suggestive of hepatic encephalopathy , among the various cause one should consider paracetamol toxicity as a possibility. Maintain airway, breathing and circulation. Take care of metabolic, coagulation and electrolyte homeostasis as in the management of any acute liver failure.

Specific measures

If the child comes within 4 hours of ingestion gastric decontamination should be done. Gastric lavage with normal saline may be considered if the amount ingested is potentially life-threatening

Activated charcoal is the most common gastrointestinal decontamination procedure as it adsorbs paracetamol, reducing its gastrointestinal absorption.Administering activated charcoal also poses less risk of aspiration than gastric lavage. For maximal effect activated charcoal should be administered within half hour of ingestion at a dose of 10 times the dose of ingested paracetamol. There was reluctance to give activated charcoal in paracetamol overdose, because of the concern that it may also absorb the oral antidote acetylcysteine.[8]

Inducing vomiting with syrup of ipecac has no role in paracetamol overdose because the vomiting it induces delays the effective administration of activated charcoal and oral acetylcysteine

Specific antidote

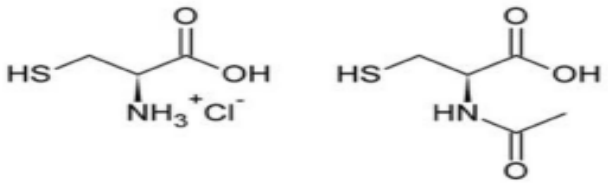
N Acetyl cysteine(NAC) is the specific antidote for the paracetamol poisoning. It reduces paracetamol toxicity by supplying sulfhydryl groups. NAC serve as a precursor for hepatic glutathione and replenishes the stores and glutathione react with the toxic NAPQI metabolite so that it does not damage cells and can be safely excreted.[9,10]

Cysteamine and methionine have also been used to prevent hepatotoxicity.

NAC therapy is most effective when given less than eight hours after paracetamol overdose, but may be value even if started 24-36 hours after ingestion.NAC has no effect in the plasma acetaminophen concentration

and drug elimination from the body. 9,10

Structure of N Acetyl cysteine (NAC)



Dose

Drug can be used orally and intravenous route. 9,10

Oral route

The orally administered NAC can bind to activated charcoal roughly around 30%. However most authorities tend to administer the same dose. [9,10]

Oral acetylcysteine is given as a 140 mg/kg loading dose followed by 70 mg/kg every four hours for 17 more doses. [9,10]

Oral acetylcysteine may be poorly tolerated due to its unpleasant taste, odor, and its tendency to cause nausea and vomiting. It should be diluted to a 5 % solution with soda or fruit juice to minimise vomiting. If repeat doses of charcoal are indicated because of another ingested drug, then subsequent doses of charcoal and acetylcysteine should be staggered. [9,10]

Intravenous route

Intravenous acetylcysteine is given as a continuous infusion over 20 hours for a total dose 300 mg/kg. Recommended administration involves infusion of a 150 mg/kg loading dose over 15 to 60 minutes, followed by a 50 mg/kg infusion over four hours; the last 100 mg/kg are infused over the remaining 16 hours of the protocol. [9,10]

The most common adverse effect to acetylcysteine treatment is an anaphylactoid reaction, usually manifested by rash, wheeze, or mild hypotension. Adverse reactions are more common in people treated with IV acetylcysteine. If anaphylactoid reaction occurs the acetylcysteine is temporarily halted or slowed and antihistamines and other supportive care are administered. [9,10]

Cysteamine and methionine have also been used to prevent hepatotoxicity due to paracetamol. Methionine act by replenishing glutathione stores .More effective when given orally than iv. The initial oral dose is 2.5 gm then 2.5 gm 4 hourly to a total of 10 gms over 12 hours.

In patients who develop fulminant hepatic failure or who are otherwise expected to die from liver failure, the mainstay of management is liver transplantation.[11]

Prognostic indicators

Prognostic indicators in paracetamol induced hepatic failure include pH less than 7.30 renal insufficiency, grade 3 or worse hepatic encephalopathy, a markedly elevated prothrombin time, or an elevated blood lactic acid level. The ratio of factor VIII to factor V of less than 30 indicated a good prognosis (100% survival).Patients with a poor prognosis are usually identified for likely liver transplantation.[12]

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