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Acute Paracetamol Toxicity - A Case Report

KEYWORDS: Paracetamol, Acetylcysteine

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ABSTRACT *Paracetamol toxicity is caused by excessive use or overdose of the analgesic drug paracetamol, mainly causing liver injury. Paracetamol toxicity is one of the most common causes of poisoning worldwide as it is the most popular over the counter analgesic.*

INTRODUCTION:

Paracetamol toxicity is caused by excessive use or overdose of the analgesic drug paracetamol. Paracetamol toxicity is one of the most common causes of poisoning worldwide as it is the most popular over the counter analgesic. Recommended dose of paracetamol is 650 to 1000 mg .in adults & 10 to 15 mg/kg in children, every 6-8 hours. Recommended total daily dose is 4gm in adults & 75mg/kg in children.

Many individuals with paracetamol toxicity may have no symptoms at all in the first 24 hours following overdose. Others may initially have nonspecific complaints such as vague abdominal pain and nausea. With progressive disease, signs of liver failure may develop; these include_hypoglycemia, acidosis, bleeding tendency, and hepatic encephalopathy. Some will spontaneously resolve, although untreated cases may result in death. Treatment is aimed at removing the paracetamol from the body and replacing glutathione. Activated_charcoal can be used to decrease absorption of paracetamol if the patient presents for treatment soon after the overdose; the antidote acetylcysteine acts as a precursor for glutathione, helping the body regenerate enough to prevent damage to the liver. N-acetylcysteine can neutralize NAPQI by itself as well. A liver_transplant is often required if damage to the liver becomes severe. Patients treated early have a good prognosis, whereas patients that develop major liver abnormalities typically have a poor outcome. Efforts to prevent paracetamol overdose include limiting individual sales of the drug and combining paracetamol with Methionine, which is converted into glutathione in the liver.

CASE REPORT

A 19year old female 2nd year engineering student weighing 45kg came to hospital casualty with alleged history of intake of 25 tablets of combiflam (ibuprofen 400mg +paracetamol 325mg) & 6 tablets of cyclopam(dicyclomine20 mg+paracetamol 500mg) 10 hour prior to admission. She had vomiting 3-4 times & was feeling drowsy. She had no other medico surgical premorbid illness in past. On physical examination vital parameters were normal except for borderline hypotension of 100/64 mm of hg. Her hydration was poor & was drowsy but oriented. her lab reports on day of admission were normal. Serum acetaminophen level sent to lab. Ryle's tube no 16 inserted & stomach content preserved for medico legal purpose. She was treated with gastric lavage, inj pantoprazole, inj ondensetron & inj acetylcysteine. Inj acetylcysteine given as 6.75gm iv diluted in 500cc of NS over 1hour followed by 2.25gm iv over next 4hour followed by 4.5gm iv over next 16 hour. Antacids & antiemetic continued for next 5 days. Recovery was uneventful & was discharged on 7th day without any complaints.

DISCUSSION:

The toxic dose of paracetamol is highly variable. In general the recommended maximum daily dose for healthy adults is 4 grams. Higher doses lead to increasing risk of toxicity. In adults, single doses above 10 grams or 200 mg/kg of bodyweight, whichever is lower, have a reasonable likelihood of causing toxicity. Toxicity can also occur when multiple smaller doses within 24 hours exceeds these levels. Damage to the liver, hepatotoxicity, results not from paracetamol itself, but from one of its metabolites, N-acetyl-p-benzoquinoneimine (NAPQI). It depletes liver's natural antioxidant glutathione and directly damages cells in the liver, leading to liver failure. Risk factors for toxicity include excessive chronic alcohol intake, fasting or anorexia nervosa, and the use of certain drugs such as isoniazid,Carbamazepine, phenytoin, and barbiturates. The signs and symptoms of paracetamol toxicity occur in four phases. The first phase begins within 24 hours of overdose, and patients often have no specific symptoms or only mild symptoms like anorexia, nausea, vomiting, pallor, and sweating. Rarely, after massive overdoses, patients may develop symptoms of metabolic_acidosis and coma early in the course of poisoning. The second phase occurs between 24 and 72 hours following overdose and consists of signs of increasing liver damage. In general, damage occurs in hepatocytes as they metabolize the paracetamol. The individual may experience right-upper-quadrant abdominal pain. The increasing liver damage also alters biochemical markers of liver function; International_normalized ratio (INR) and alanine transaminase and aspartate transaminase rise to abnormal levels. Acute kidney failure may also occur during this phase, typically caused by either hepatorenal syndrome or multiple organ dysfunction syndrome.

The third phase follows at 3 to 7 days, and is marked by complications of massive hepatic necrosis leading to fulminant hepatic failure with complications of metabolic acidosis coagulation defects, hypoglycemia, kidney failure, hepatic encephalopathy, cerebral edema, sepsis, multiple organ failure, and death. If the third phase is survived 2-3 weeks, hepatic necrosis runs its course, and liver and kidney function typically return to normal in a 1-3 months.

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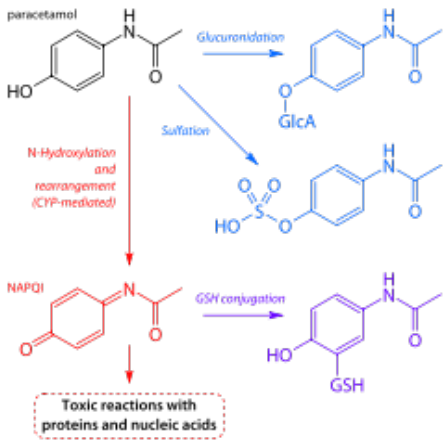
Pathophysiology



Main pathways of paracetamol metabolism.

Following a therapeutic dose, it is metabolized to nontoxic metabolites via Phase II metabolism by conjugation with sulfate (20%-40%) and glucuronide(40%-60%), with a small portion being oxidized via the cytochrome P450 enzyme system. Cytochrome P450 2E1 and 3A4 convert approximately 5% of paracetamol to a highly-reactive intermediary metabolite, N-acetyl-p-benzoquinoneimine (NAPQI). Under normal conditions, NAPQI is detoxified by conjugation with glutathione to form cysteine and mercapturic acid conjugates.

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. As a result, hepatocellular supplies of glutathione become depleted, as the demand for glutathione is higher than its regeneration. NAPQI therefore remains in its toxic form in the liver and reacts with cellular membrane molecules, resulting in widespread hepatocyte damage and death, leading to acute hepatic necrosis. In animal studies, hepatic glutathione must be depleted to less than 70% of normal levels before hepatotoxicity occurs.

Diagnosis

A toxic exposure to paracetamol is suggested when an adult ingests

(1) >10 grams or 200 mgs/kg as asingle ingestion
(2) >10 grams or 200 mgs/kg over 24 hour period
(3) >6 grams or 150 mgs/kg/24 hour period for at least 2 consecutive days

The most effective way to diagnose poisoning is by obtaining a blood paracetamol level. A drug normogram developed in 1975, called the Rumack-Matthew normogram, estimates the risk of toxicity based on the serum concentration of paracetamol at a given number of hours after ingestion.

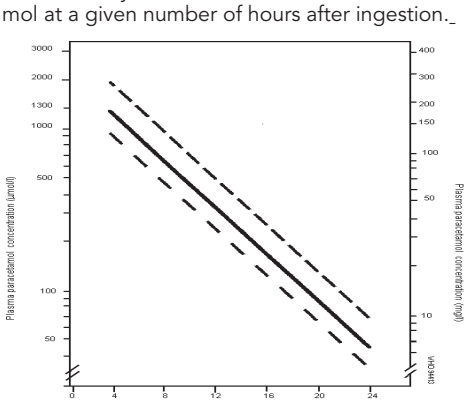


Fig. 1. Treatment nomogram for paracetamol posioning. The solid line represents the "treatment line". The upper broken line defines the patients at more than 90% risk of developing liver damage. The lower broken line represents the treatment nomogram line used in many American studies (see text).

Treatment

Gastric decontamination Gastric lavage with Activated charcoal is the most common gastrointestinal decontamination procedure as it adsorbs paracetamol, reducing its gastrointestinal absorption.[1] It appears that the most benefit from activated charcoal is gained if it is given within 30 minutes to two hours of ingestion. Administering activated charcoal later than 2 hours can be considered in patients that may have delayed gastric emptying due to co-ingested drugs or following ingestion of sustained- or delayed-release paracetamol preparations. Activated charcoal should also be administered if co-ingested drugs warrant decontamination. Inducing vomiting with syrup of ipecac has no role in paracetamol overdose because it delays the effective administration of activated charcoal and oral acetylcysteine.

Acetylcysteine

Acetylcysteine / N-acetylcysteine or NAC is the antidote for paracetamol toxicity. It replenishes body stores of the antioxidant glutathione. Glutathione react with the toxic NAPQI metabolite so that it does not damage cells and can be safely excreted. If the patient presents less than eight hours after paracetamol overdose, then acetylcysteine significantly reduces the risk of serious hepatotoxicity and guarantees survival. If acetylcysteine is started more than 8 hours after ingestion, there is a sharp decline in its effectiveness because the cascade of toxic events in the liver has already begun, and the risk of acute hepatic necrosis and death increases dramatically. Although acetylcysteine is most effective if given early, it still has beneficial effects if given as late as 48 hours after ingestion by acting as an antioxidant, decreasing neutrophil infiltration. Improving microcirculatory blood flow, increasing tissue oxygen delivery & extraction. Oral acetylcysteine is given as a 72-hour regimen as 140 mg/kg loading dose followed by 70 mg/kg every four hours for 17 more doses. Oral acetylcysteine may be poorly tolerated due to its unpleasant foul rotten egg taste, odor, and its tendency to cause nausea and vomiting. 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 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. 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, occurring in 4 to 23% of patients. Rarely, severe life-threatening reactions may occur in predisposed individuals, such as patients with asthma.

Liver transplant In patients who develop fulminant hepatic failure the mainstay of management is liver transplantation.

CONCLUSION

Acute paracetamol poisoning is becoming common now a days because of easy availability & over the counter medicine. If untreated or delayed treatment, mortality can occur. The mortality rate from paracetamol overdose increases two days after the ingestion, reaches a maximum on day four, and then gradually decreases.

Prevention of paracetamol poisoning is possible with following steps

Combination with acetylcysteine.

Limitation of availability & to make paracetamol a prescription-only medicine.

Paracetamol ester prodrug with L-pyroglutamic acid (PCA), precursors of glutathione,

Increasing awareness about paracetamol toxicity

Inclusion of warnings on packs of paracetamol

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