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RESEARCH ARTICLE

Acetaminophen Induced Hepatotoxicity: Mechanism, Symptoms and Treatment

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ABSTRACT

Acetaminophen (N-acetyl-p-aminophenol, APAP, or Paracetamol, PARA) is widely used for its analgesic and antipyretic properties in many over-the-counter formulations in both adults and children. At the most usual therapeutic adult dose of 1–2 g/day, oral APAP is indicated for fever and for the relief of mild to moderate acute pain. Administration of acetaminophen via the intravenous route has become increasingly widespread and has been used as a safe and effective antipyretic and analgesic agent. The maximum recommended therapeutic dose of APAP is 4 g/day in adults and 50–75 mg/kg/day in children. Consumption of a single dose greater than 7.5 to 10 grams in an adult and 150 mg/kg in a child is considered potentially toxic to the liver and kidneys due to the highly active metabolite, N-acetyl-p-benzoquinone imine (NAPQI). In the present study we are going to learn about a review of Acetaminophen induced Liver toxicity (Hepatotoxicity).

KEYWORDS

N-acetyl-p-benzoquinone imine, Hepatotoxicity, Glucuronidation, Acetaminophen, Cytochrome P450, N-acetylcystine.

INTRODUCTION

Acetaminophen is one of the most common medications found in households. It is used for the treatment of pain and to lower fever. Over many years, it has been used countless times by many people, and it has proven to be a safe and effective medication.

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However, if taken in excess amounts (overdose, whether on purpose or by accident), acetaminophen can cause life-threatening illness. Acetaminophen in overdose can seriously damage the liver. If the damage is severe, a liver transplant may be necessary in order to save someone's life. In this literature, the mechanism, symptoms and treatment of acetaminophen induced hepatotoxicity are descried.

Description of Acetaminophen

Acetaminophen is a White, crystalline powder. Its Molecular formula is C8H9NO2, Molecular Weight is 151.2 and IUPAC name is N-(4-Hydroxyphenyl) acetamide. It is sparingly soluble in water, freely soluble in alcohol, very slightly soluble in methylene chloride. Melting point of Acetaminophen is 168 °C to 172 °C. It is a widely used as an analgesic and antipyretic agent. It is available in market in syrup as well as tablet dosage form [1].

Pharmacokinetics of Acetaminophen

Acetaminophen has a high oral bioavailability (70%-90%) and it is well absorbed in the gastrointestinal tract. Acetaminophen reaches the peak blood concentrations within 90 minutes after ingestion. Rectal administration of Acetaminophen is also feasible and rectal bioavailability is 30%-70%. Administration of acetaminophen via the intravenous route has

become increasingly widespread and has been used as a safe and effective antipyretic and analgesic agent [9]. When administered through the oral route, Acetaminophen is distributed throughout the body fluids in a homogeneous way. Volume of distribution is 65 Liter. Acetaminophen is not widely bound to plasma proteins and has a plasma half-life of 1.5–2.5 hours at the recommended doses. Acetaminophen is essentially metabolized in the liver but after an overdose, its metabolism is impaired and hence the half-life is prolonged to 4–8 hours and is directly related to the extent of the liver injury. Metabolites are excreted through the kidneys in the urine and Clearance is 20 Liter/hour [2, 3, 4, 5].

Mechanism of Acetaminophen Metabolism

The liver is the main site where Acetaminophen is metabolized. Acetaminophen is also metabolized in the kidney and intestine to a lesser extent [6].

After normal dose, about 5% of acetaminophen is excreted unchanged in urine, whereas most acetaminophen is metabolized through various pathways in the liver [10]. The pathways responsible for acetaminophen metabolism can be described as follows-

A. Glucuronic Conjugation Pathway or Glucuronidation

It accounts for approximately 60% of acetaminophen hepatic metabolism. It results in non-toxic Glucuronide conjugate which is called as Glucuronic Acid (GlcA) Conjugate. This conjugate is then excreted through urine.

B. Sulphate Conjugation Pathway or Sulfation

It accounts for approximately 30% of acetaminophen hepatic metabolism. It results in non-toxic Sulphate (HSO_4^-) conjugate. This conjugate is then excreted through urine.

C. Cytochrome P450 2E1 Pathway It accounts for approximately 5-10% of acetaminophen hepatic metabolism. Here acetaminophen is oxidized to form the reactive intermediate metabolite NAPQI (N-acetyl p-benzoquinone imine).

NAPQI in turn conjugate with Glutathione (GSH) in Glutathione Conjugation to produce non-toxic Mercapturic Acid Cystine metabolite which is the excreted through urine.

Mechanism of Acetaminophen Induced Hepatotoxicity

As far as the acetaminophen metabolism in adults is concerned, Sufficient Glutathione is available to conjugate the amount of NAPQI produced when acetaminophen is taken at recommended doses.

However, in uncommon setting of acetaminophen overdose for example injection of 7.5 to 10 grams in 8 hours or less, the amount of NAPQI produced may increase markedly and the amount of glutathione available may become insufficient to conjugate NAPQI.

It is estimated that when the amount of Glutathione is reduced to about 30% of normal, un-conjugated NAPQI may rapidly and irreversibly bind to proteins throughout the hepatic cell micro molecules inducing a cascade of events that culminate in cell death leading to hepatic injury or hepatotoxicity [10].

Phases of Hepatotoxicity with Symptoms

Acetaminophen toxicity is typically described in four phases. The phases and their symptoms can be described as-

Phase I: The first phase occurs a few hours after ingestion of a toxic dose and lasts 12 to 24 hours. The patients are relatively asymptomatic. If symptoms are present, they are usually mild and nonspecific and include and include nausea, vomiting, diaphoresis, anorexia, and lethargy, the severity will depend size of the dose administered [11, 12].

Phase II: The second phase occurs up to 24 to 48 hours after ingestion. It shows symptoms like, abdominal pain or right upper quadrant tenderness. In addition, laboratory values will begin to show evidence of hepatotoxicity, hepatic enzymes, lactate, phosphate, prothrombin time, and international normalized ratio (INR) will increase dramatically [11, 12, 13, 14]. If the antidote N-acetylcysteine is administered, the toxicity does not progress [11, 12, 14].

Phase III: Very few patients will enter this stage. This phase occurs 3 to 5 days after ingestion. The symptoms are reappearance or worsening of nausea and vomiting along with malaise, jaundice, confusion, somnolence, and coma [11, 13]. Serious and possibly fatal hepatic necrosis may occur. As a result of acetaminophen-induced

tubular necrosis, renal insufficiency, as demonstrated by oliguria, can manifest but it is less common [11, 12, 13, 14]. Hepatic enzyme levels will reach their peak, measuring as high as 10,000 IU/L. Jaundice, hypoglycemia, bleeding and coagulation abnormalities, and hepatic encephalopathy can also be seen [11, 12, 14]. Death may occur as a consequence of complications associated with hepatic failure, including multi-organ system failure, cerebral edema, and sepsis [11, 15].

Phase IV: It is the last phase. This phase involves survival and recovery. It involves return of full liver function and no long-term effects. Approximately 70% of patients in this phase recover completely, while 1% to 2% of patients develop fatal hepatic failure. If acetaminophen toxicity remains untreated, it will result in death within 4 to 18 days after ingestion [11, 13].

Acetaminophen Toxicity Diagnosis

A doctor's first step in diagnosing acetaminophen toxicity is to get a complete history, including the time the medication was ingested, the amount of medication that was ingested, and what form of the medication was ingested. A diagnosis of acetaminophen toxicity is usually confirmed through diagnostic tests, including an acetaminophen level, electrolytes, kidney function tests, amylase, lipase, liver function tests, complete blood count, and coagulation factors. Imaging studies, such as an ultrasound may be used to assess liver enlargement. A liver biopsy may also be ordered.

Management of Acute Acetaminophen Overdose

Acetaminophen toxicity can be managed by the Timely assessment / appropriate monitoring of serum acetaminophen levels and Selective use and timely administration of N-acetylcystine (NAC), when indicated.

General management: General management of acetaminophen toxicity involves supportive care and initiation of antidotal therapy. Gastrointestinal decontamination with activated charcoal (without sorbitol) can be considered within 1-2 hours after exposure and may decrease the need for antidotal therapy [24]; however, because of the availability of highly effective antidote and the rapid absorption of acetaminophen, activated charcoal use should not be widespread [10].

Acetylcysteine: The main drug used in the treatment of acetaminophen toxicity is N-acetylcysteine. This agent prevents accumulation of NAPQI, replenishes hepatic glutathione stores and increases sulfate conjugation [18]. Acetylcysteine improves hemodynamic and oxygen use, decreases cerebral edema, and improves mitochondrial energy production. Due to this Acetylcysteine may be beneficial in patients with acetaminophen-induced hepatic failure, as it [4, 16, 17].

If Acetylcysteine is administered within 8-10 hours following an acute overdose, it may prevent hepatic failure from an acetaminophen overdose. It may also be of value up to 48 hours after ingestion [4, 13, 16, 18, 19]. To determine the likelihood of serious liver damage, the standard acetaminophen toxicity nomogram, the Rumack-Matthew nomogram, can be utilized. However, it is rendered ineffective when evaluating possible toxicity due to multiple ingestions over time, when time of ingestion is unknown, or when altered metabolism occurs. Taking this into consideration, acetylcysteine should be administered in any case of acute liver failure or when there is any evidence of liver toxicity in which acetaminophen overdose is suspected [19].

Acetylcysteine is can be administered orally and intravenously; according to the clinical scenario [20]. Oral administration may be beneficial for patients with preclinical toxic effects or hepatic injury, although the presence of altered mental status and vomiting may limit its use [17]. The dosing regimen for oral acetylcysteine is a loading dose of 140 mg/kg, followed by 17 doses of 70 mg/kg every 4 hours for a total of 72 hours [19]. Patients with hepatic failure should receive IV therapy [17]. Continuous IV infusion is recommended at a loading dose of 150 mg/kg IV in 200 ml D5W infused over 60 minutes followed by a maintenance dose of 50 mg/kg over 4 hours, followed by a second maintenance dose of 100 mg/kg in 1,000 ml D5W administered over 16 hours [19]. If the patient is under 40 kg, fluid should be adjusted as per guidelines to avoid fluid overload, hyponatremia, and seizures. If the patient is doing well yet has not fully recovered after the recommended dosing, acetylcysteine therapy can be continued using either the last

oral dose or the last IV infusion rate. Until acetaminophen concentrations are undetectable, serum AST has normalized or significantly improved, and there is resolution of any evidence of hepatic failure Acetylcysteine should be continued beyond the protocol length [21].

Vomiting frequently occurs with oral acetylcysteine administration, because of its unpleasant taste and smell [18, 22]. Adverse effects associated with IV acetylcysteine include anaphylactoid reactions, including rash, pruritus, angioedema, bronchospasm, tachycardia, and hyper-tension [18, 22].

Other agents: Dimercaprol and D-penicillamine appear to offer a little or no protection against acetaminophen toxicity in man [25, 26, 27, 28].

Summary

Acetaminophen (Paracetamol) is the most widely used over-the-counter analgesic agent in the world. At therapeutic doses, acetaminophen (APAP) is a safe and effective analgesic and fever reducer. However, overdose of APAP can cause severe liver injury [29]. Acetaminophen is metabolized through various pathways like Glucuronic Conjugation Pathway, Sulphate Conjugation Pathway and Cytochrome P450 2E1 Pathway in the liver. After a therapeutic dose of Acetaminophen, metabolites produced are excreted through urine.

However, in uncommon setting of acetaminophen overdose for example injection of 7.5 to 10 grams in 8 hours or less, the amount of NAPQI produced in Cytochrome P450 2E1 Pathway may increase markedly. The un-conjugated NAPQI may rapidly and irreversibly bind to proteins throughout the hepatic cell micro molecules inducing a cascade of events that culminate in cell death leading to hepatic injury or hepatotoxicity [10].

Acetaminophen overdose can be effectively managed by focusing on few basic principles. As in all cases of poisoning, healthcare providers should obtain a careful history and should have a high index of suspicion. When acetaminophen overdose is a possibility, an acetaminophen level should be obtained, and antidotal therapy should be initiated. When Acetylcysteine is administered soon after an overdose occurs, morbidity is significantly reduced, and mortality virtually eliminated.

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