Original Article

Evaluation of Recent Updates Regarding Acetaminophen-Induced Acute Liver Failure

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Abstract

Acetaminophen is considered as the most common analgesic and antipyretic over-the-counter drug. It is also considered a very safe medication if used in limited doses. Its index of safety is relatively narrow. Therefore, an overdose of acetaminophen can lead to severe liver damage, which can result in acute liver failure subsequently. The clinical outcome of acetaminophen-induced acute liver failure ranges from full improvement and recovery to the need for liver transplantation or even death. Objective: The study aimed at reviewing the literature that has discussed different aspects of acetaminophen overdose-induced acute liver failure. Methods: PubMed database was used for articles selection and the following keywords were used in the MeSH: acetaminophen-induced acute liver failure, and acetaminophen-induced hepatotoxicity. A total of 35 papers were reviewed and included in the review. Conclusion: Acetaminophen overdose may and may not progress eventually to acute liver failure. Other than the dose, there are several risk factors that can affect the outcomes. The pairing of alcohol and acetaminophen is an issue that needs to spot the light on it. Chronic alcohol ingestion augments acetaminophen hepatotoxicity by enhancing the mechanisms of acetaminophen hepatotoxicity. The goals in treating cases of acetaminophen overdose should be the inhibition of absorption, removal of acetaminophen from the blood, prevention of the conversion of acetaminophen into the toxic metabolite NAPQI, detoxification of NAPQI, and liver transplantation. N-acetylcysteine is the recommended agent to detoxify NAPQI. It is now widely accepted as the antidote best able to reduce the risk of hepatotoxicity.

Keywords: Acute Liver Failure, Acetaminophen, NAPQI

Introduction

Acetaminophen is the most used over-the-counter drug [1, 2]. When used in limited doses, it is very safe but the safety margins are considered narrow. It can cause severe liver damage after an overdose, which can result in acute liver failure subsequently [3, 4]. Patients with acetaminophen-induced acute liver failure are prone to a wide range of outcomes from complete improvement to death [4].

In western countries, acetaminophen-induced overdose is the main cause of acute liver failure [3, 5]. The estimated number of acetaminophen overdose cases is up to 60,000 cases per year [6]. Most of these cases are intentional suicide attempts. Around 26,000 of the overdosed patients are hospitalized each year. Approximately 1% develop encephalopathy or severe coagulopathy and the acetaminophen overdose-related mortality cases account for 500 per year. Around 20% of these deaths happen in patients with non-intentional acetaminophen overdose [7].

In this paper, we aimed to review the recent literature that has discussed the different aspects of acetaminophen overdose-induced acute liver failure.

Methodology

PubMed database was used for articles selection and the following keys were used in the MeSH (("acetaminophen-induced acute liver failure"[MeSH]) AND (“acetaminophen-induced hepatotoxicity"[MeSH])). A total of 35 papers were reviewed and included in the review.

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Inclusion criteria: The articles were selected based on the relevance to the project, which should include acetaminophen-induced acute liver failure/hepatotoxicity.

Exclusion criteria: all other articles that did not have a related aspect to the acetaminophen-induced acute liver failure as their primary endpoint or repeated studies.

Discussion

Acute liver failure is defined as a sudden loss of hepatic function in a person with no previous history of hepatic diseases. It is a rare syndrome but can be very dramatic. There are several conditions that can be the cause behind acute liver failure, for example, viral hepatitis, metabolic errors, drug-induced and toxin-induced liver disease, and ischemia [8-10].

Recently, there has been a gradual increase worldwide in the proportion of cases with acetaminophen overdose-induced acute liver failure, especially in the USA and other western countries. Nevertheless, viral hepatitis is the main cause of acute liver failure in regions like Africa and Asia [11, 12]. Cases with hepatitis E, and also hepatitis A and B, are common [13]. Outcomes of acute liver failure are better in children than in adults [14]. In addition, cases with acetaminophen toxicity and cases with hepatitis A have shown high survival rates (93% and 100%, respectively) [15-17].

After the discovery of the relationship between aspirin and Reye's syndrome in children, reported between 1982 and 1987, Americans started to use acetaminophen as the safe alternative analgesic for adults and children [18]. Then, cases with fatal acetaminophen-induced acute liver failure were reported. Moreover, the association of alcohol with acetaminophen poisoning was assessed for the first time [19, 20].

Nowadays, acetaminophen is considered as a predictable hepatotoxin [21]. The biochemical signs of liver damage may appear after 24 hours since the time of overdose. This damage may lead to dose-related centrilobular liver necrosis [22, 23]. It is believed that 125-150 mg/kg is the lowest dose of acetaminophen for hepatotoxicity [24, 25]. In adults, 10 g of acetaminophen is the threshold dose to cause hepatotoxicity; while, the threshold dose in children is 150 mg/kg [24, 26].

Pathophysiology

Chun et al. [21] summarized the mechanisms of acetaminophen hepatotoxicity into 3 parts. They included the generation of a toxic metabolite, mitochondrial dysfunction, and alteration of innate immunity.

A toxic metabolite called N-acetyl-p-benzoquinone imine (NAPQI) is generated after acetaminophen overdose. Firstly, more than 90% of the therapeutic dose of acetaminophen is metabolized in the liver by glucuronyl transferases and sulfotransferases. It will be converted to phenolic glucuronide and sulfate. Then, it will be excreted in urine [26]. Approximately, 2% of the remaining acetaminophen will be excreted unmetabolized. The remaining amount of acetaminophen will be metabolized by cytochrome P450, mainly the enzyme CYP2E1, to NAPQI [27]. NAPQI is a highly reactive, electrophilic molecule that leads to harm by the formation of covalent bonds with other intracellular proteins. Conjugation with glutathione prevents the reaction that leads to NAPQI formation. Subsequently, this process results in the production of a water-soluble substance that will be excreted into bile [28].

Nevertheless, in cases of acetaminophen overdose, NAPQI will be generated in high amounts and glutathione will not be able to prevent it. Glutathione will be depleted by NAPQI leading to the accumulation of NAPQI in hepatocytes. NAPQI can change the function and structure of the cellular proteins. It can alter the permeability of the cell leading to the loss of cell membrane integrity [23].

Acetaminophen overdose can also cause mitochondrial dysfunction either by covalent binding to mitochondrial proteins or by other mechanisms. It has the ability to depress mitochondrial respiration and the synthesis of adenosine triphosphate (ATP), inducing mitochondrial oxidant stress with increased production of peroxynitrite. Peroxynitrite is a nitrating and potent oxidant agent, which generates additional covalent bonds with cellular proteins, causing further mitochondrial dysfunction. Eventually, there is the alteration of membrane permeability leading to the collapse of mitochondrial membrane potential, disruption of ATP synthesis, release of mitochondrial proteins into the cell cytoplasm, and oncotic necrosis of hepatocytes [28, 29].

It has been shown that the innate immune system of the liver attribute to the progression of liver injury during acetaminophen hepatotoxicity. In acetaminophen overdose, the toxic acetaminophen metabolites will activate Kupffer cells, which are immune cells in the liver [30]. Activated Kupffer cells will release inflammatory cytokines that may activate natural killer thymus lymphocytes that may cause liver damage by cytotoxic activity. This can promote further activation of Kupffer cells, and stimulating the local production of chemokines. Inflammatory mediators, cytokines, and chemokines accumulate neutrophils in the liver and exacerbate the hepatic injury [31].

Risk Factors

Acetaminophen overdose may and may not progress eventually to acute liver failure. Other than the dose, there are several risk factors that can affect the outcomes. Malnutrition, fasting, and chronic liver disease all increase the risk of hepatotoxicity by decreasing glutathione stores [32]. Moreover, there are drugs that can induce liver injury or fulminant hepatic failure such as, isoniazid, rifampin, and phenobarbital. Fibrates and nonsteroidal anti-inflammatory drugs are associated with a higher incidence of death in cases of acetaminophen-induced acute liver failure [33].

Furthermore, chronic use of alcohol increases the production of NAPQI [32].

The pairing of alcohol and acetaminophen is an issue that needs to spot the light on it [34]. Both substances are normally available in many societies. It has been found that the co-ingestion of alcohol and acetaminophen is expected to cause acute hepatotoxicity [35-37]. Chronic alcohol ingestion augments acetaminophen hepatotoxicity enhances the mechanisms of acetaminophen hepatotoxicity by increasing the depletion of glutathione leading to liver necrosis and worsening prognosis [29, 31]. There is another explanation of the poor outcomes of acetaminophen-related hepatotoxicity in chronic alcohol abusers, which is the delay in seeking medical attention after acetaminophen ingestion, which would prolong the activity of toxic metabolites on the liver [34].

In addition, malnourishment has shown an association with acetaminophen hepatotoxicity. In a poor nutritional state, glutathione reserves become easily exhausted. Decreased levels of available glutathione in such cases will lead to hepatocyte damage. Inadequate nutritional status is often associated with chronic alcoholism. Therefore, alcoholic patients with acetaminophen-induced hepatotoxicity experience both decreased body glutathione stores as well as increased activity of hepatotoxic enzymes [38].

According to the US FDA, more than 4000 mg of acetaminophen in 24 hours may lead to severe liver damage. Watkins et al. [39] conducted an RCT on the ingestion of the recommended maximum amount of 4000 mg of acetaminophen daily for 2 weeks. The results showed an elevation of a particular liver function test, which was alanine transaminase, up to three times the normal. These elevations of transaminase showed no clinical manifestations and they were in 40% of patients. However, the transaminase levels went back to their normal values after the acetaminophen was stopped [39].

Clinical Presentation

Acute liver failure is an abrupt onset of hepatic dysfunction in the absence of a previous history of liver disease. It can progress to encephalopathy, jaundice, and coagulopathy [40]. The early stage of acute liver failure can be presented with general nonspecific symptoms, such as abdominal pain, fatigue, anorexia, and fever. Mostly, cases with acetaminophen-induced acute liver failure progress toward hepatic encephalopathy that develops within 0–7 days after the onset of jaundice. Encephalopathy can be divided into 4 grades with higher grades strongly correlating with poor clinical outcomes [32]. The mildest Grade I encephalopathy is characterized by minor changes in the mental status with a normal Glasgow coma score and no EEG changes, with increasing levels of altered mental status and asterixis up to Grade IV, defined as coma with decerebrate posturing and marked EEG abnormalities. Patients with Grades III and IV encephalopathy are at a particularly high risk of developing cerebral edema due to hyperammonemia, inflammation, loss of cerebral blood flow autoregulation, and hyponatremia [32]. Additional sequelae of acute liver failure include vasodilatory shock, pulmonary edema, and acute renal failure [40].

Diagnosis

The diagnosis of acetaminophen hepatotoxicity needs a high index of suspicion. Some cases only show unexplained nausea and vomiting along with just mild elevations of aminotransferase, isolated hypoprothrombinemia, or metabolic acidosis. Acetaminophen hepatotoxicity should be thought of if the elevation of serum aminotransferase levels was up to 400 above the upper limits of normal along with hypoprothrombinemia, metabolic acidosis, and renal failure [7]. In addition, the levels of serum acetaminophen can be a helpful tool in the estimation of the risk of liver injury after single ingestion [27, 41]. Nevertheless, significant overdose cannot be excluded in case of a low acetaminophen level. Serum samples should be repeated every 4-12 h in order to define the hepatic risks [7].

Management

The goals in treating cases of the acetaminophen overdose include the inhibition of absorption, removal of acetaminophen from the blood, prevention of the conversion of acetaminophen into the toxic metabolite NAPQI, detoxification of NAPQI, and liver transplantation [36].

Choosing the interventions is affected by two factors, which are the timing of presentation and the degree of hepatic decompensation [21]. To reduce absorption within the first few hours after ingestion, gastric lavage, activated charcoal ingestion, and induction of vomiting by ipecacuanha are recommended options [42].

Activated charcoal and gastric lavage can be used to prevent the absorption of acetaminophen, but only are effective when used within 1 hour of ingestion for charcoal and 4 hours for gastric lavage.

N-acetylcysteine (NAC) is the recommended agent to detoxify NAPQI. It is now widely accepted as the antidote best able to reduce the risk of hepatotoxicity. It also reduces mortality in patients with acute liver failure [42]. It works by replenishing glutathione stores and directly binds to acetaminophen toxic metabolites. Moreover, it increases nontoxic sulfate conjugation in liver cells [41]. There are other agents, such as methionine and cysteamine that can detoxify NAPQI and reduce liver damage. Nevertheless, they show more adverse gastrointestinal and central nervous system effects when compared with NAC. The overall mortality rate for acetaminophen overdose had declined from as high as 5% to 0.7% with the use of NAC. Liver transplantation is the only intervention that improves survival when there is irreversible liver damage causing acute liver failure [42]. Patients should receive a full course of NAC if they have a questionable history regarding the acetaminophen dose or a non-acute

overdose [24]. The ingested dose and the interval to the presentation are the most important prognostic factors for non-acute overdoses. Presentation later than 24 hours after ingestion is associated with an increased risk of hepatotoxicity. NAC treatment is required for ingestion of more than 150 mg/kg over 24 hours or 75 mg/kg over 24 hours for patients with risk factors that would increase susceptibility to developing acetaminophen-induced hepatotoxicity [25]. Patients with coagulopathy or elevated creatinine level should be admitted for further monitoring including daily measurements of INR and creatinine and should receive NAC treatment at a dose of 150 mg/kg every 24 hours until INR falls below 2. Patients may be discharged from the hospital after they complete a full course of NAC treatment if it was begun within 8 hours of ingestion. For treatment initiated after 8 hours, patients may be discharged only if they are asymptomatic and have normal serum creatinine concentration and liver tests [24]. Management decisions are based partly on serial measurements of INR, but cases exist where INR is increased without liver toxicity, possibly as the consequence of the interaction between clotting factors and NAC [43, 44]. This possibility should be considered as the only sign of hepatotoxicity for patients with increased INR [44].

NAC can be delivered intravenously (IV) or orally (PO). The dose should be calculated depending on the patient's weight in which the maximum dose for oral is 110 kg and 100 kg for IV [34]. The standard formulation of NAC for the IV regimen is a loading dose of 150 mg/kg in 200 ml, given for 15 min. Then, it should be followed by 50 mg/kg in 500 ml over 4 h and after that, 100 mg/kg in 1000 ml over 16 h. Regarding the oral regimen, a loading dose of 140 mg/kg is given, followed by 70 mg/kg every 4 hours for a total of 18 total doses. NAC therapy can be considered complete if acetaminophen levels became untraceable and alanine transaminase level went back to normal [45].

Outcomes

The mortality due to acetaminophen toxicity is less than 2% if the patient is diagnosed and treated quickly. Besides, late presentation and intervention are associated with severe liver failure and high mortality. Liver transplantation is needed in around 1% to 3% of patients with severe liver failure in order to save their lives [34]. Children under 6 years mostly have better outcomes than adults because of their greater capacity regarding acetaminophen detoxification.

Upon discharge, the parents should be given several instructions regarding the storage, frequency, and dosage of acetaminophen. First, the medications should be kept out of the reach of children. They should know the proper dosing for children. They also should be informed that there are pediatric and adult doses of the drug [46]. Moreover, they should be encouraged to read the label of the vial containing the medication. In addition, combining drugs can increase the risk of toxicity. Therefore, this practice should be avoided and the parents should be informed regarding it [46, 47].

Conclusion

Acetaminophen overdose may and may not lead eventually to acute liver failure. Other than the dose, there are several risk factors that can affect the outcomes. The pairing of alcohol and acetaminophen is an issue that needs to spot the light on it. Chronic alcohol ingestion augments acetaminophen hepatotoxicity by enhancing the mechanisms of acetaminophen hepatotoxicity.

The goals in treating cases with acetaminophen overdose include the inhibition of absorption, removal of acetaminophen from the blood, prevention of the conversion of acetaminophen into the toxic metabolite NAPQI, detoxification of NAPQI, and liver transplantation. The recommended agent to detoxify NAPQI is N-acetylcysteine. It is now widely accepted as the antidote best able to reduce the risk of hepatotoxicity.

When patients are discharged, they should be provided with clear instructions on drug dosage, frequency, and route of administration.

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