Original Article

Evaluation of the Role of Emergency Physician in Diagnosis and Management of Acetaminophen in the Emergency Department

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Abstract

Background: Acetaminophen abuse is known since its advent, as patients and non-patients would self-prescribe and often overdose. This drug is utilized in many ways including analgesia, antipyrexia, and unfortunately, in suicidal attempts. Acetaminophen is majorly hepatotoxic; as it is metabolized mainly in the liver. If not urgently diagnosed and treated before the development of liver failure, around one-third would develop liver failure, and one-third of them would need a new liver. **Objective:** In this review, we discuss acetaminophen toxicity focusing on clinical pathophysiology and emergency management. **Methodology:** PubMed database was used for articles selection, papers on acetaminophen toxicity were obtained and reviewed. **Conclusion:** The maximum daily dose for acetaminophen should be no greater than four grams. In patients taking larger amounts, and often within the allocated daily dosage, severe adverse effects may occur — the most important of which is hepatotoxicity. Risk factors may include alcohol misuse and the presence of underlying hepatic illness. The period elapsed since ingestion is important with patients initially being asymptomatic, reduced nausea, and vomiting but the appearance of tenderness and elevated liver enzymes; at three days, they would appear jaundiced, confused, and overtly deteriorating before recovering if they persevere. When a patient is diagnosed with acetaminophen poising, the physician should start NAC treatment as it can help in the prevention of hepatotoxicity. A multidisciplinary team including Psychiatry, Intensive Care Unit, and Digestive Department is important, especially in the case of attempted autolysis and severe liver failure.

Keywords: Acetaminophen, Management, Emergency Department

Introduction

Acetaminophen, also known as paracetamol or N-acetyl-p-aminophenol (APAP), has been one of the most commonly used analgesic and antipyretic medications since it was the commercial introduction in the United States (US) back in 1950 [1, 2]. Although it has been used by millions and millions of people since then and helped alleviate the suffering of many, it has also damaged and even taken the lives of many people. These damages are mainly due to the availability of this drug as an over-the-counter medication, people's underestimation of its toxicity, people's unawareness of the active ingredient of this drug in multiple medications, and the use of this medication as a means of suicide [3, 4]. The major toxicity of acetaminophen is hepatic [5, 6], and if not diagnosed and treated before the development of liver failure, the mortality might reach to 28% and about 33% will require liver transplantation [7]. In this review, we shall discuss acetaminophen toxicity, from pathophysiology to emergency management. The clinical manifestations of acetaminophen toxicity and their severity depend on the dose that was ingested, and the time elapsed since ingestions.

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Methodology

PubMed database was used for articles selection, and the following keys used in the MeSH ((“Acetaminophen"[MeSH]) AND (“Toxicity”[MeSH]) And (“Pathophysiology”[MeSH]) OR (“Manifestation”[MeSH]) OR (“Diagnoses”[MeSH]) OR (“Management ”[MeSH])). In regards to the inclusion criteria, the selection of the articles was based on the inclusion of one of the following topics; acetaminophen and toxicity, pathophysiology, manifestations, diagnosis, and management. Exclusion criteria were all other articles that did not have one of these topics as their primary endpoint.

Discussion

The maximum daily dose allowed for acetaminophen for an adult is 4,000 mg and considering that commercially available acetaminophen contains 500 mg, the maximum daily intake allowed in 8 pills [8]. Nevertheless, some degree of hepatotoxicity might develop at lower doses in susceptible individuals [9, 10]. A Canadian retrospective review looked into all cases of acetaminophen toxicity reported in the Calgary region between 1995 and 2004. They found that 4.5% developed hepatotoxicity, and risk factors, other than increased dose, included alcohol abuse, and the presence of underlying liver disease [11].

Understanding of acetaminophen metabolism is essential for understanding its hepatotoxicity. It is primarily metabolized in the liver. At therapeutic doses, 90% of the drug is converted into glucuronide and sulfate conjugates via UDP-glucuronosyl transferases (UGT) and sulfotransferase (SULT) respectively, which then get excreted in the urine. The remaining are either eliminated unchanged in the urine (about 2%) or undergoes oxidation via the cytochrome P450 mixed-function oxidase pathway (about 8%) into a toxic, highly reactive substance with a fancy chemical name; N-acetyl-p-benzoquinone imine (NAPQI) [12].

When in small amounts, NAPQI is conjugated with hepatic glutathione (GSH), forming harmless cysteine and mercaptate compounds to be eliminated via the urine. At increasing doses, however, more acetaminophen is metabolized into NAPQI, and when about 75% of GSH gets saturated, NPAQs start accumulating and reacting with cellular proteins causing cell damage that is clinically manifested as an acute liver failure if not recognized and managed early [13].
Chun et al. summarized the mechanisms of acetaminophen hepatotoxicity into 3 parts [14]:

• *Toxic Metabolite Generation*

As mentioned earlier, NAPQI is generated after acetaminophen overdose. Firstly, more than 90% of the therapeutic dose of acetaminophen is metabolized in the liver by glucuronyltransferases and sulfotransferases. It will be converted to phenolic glucuronide and sulfate. Then, it will be excreted in the urine. Approximately 2% of the remaining acetaminophen will be excreted unmetabolized. Regarding the rest amount of acetaminophen will be metabolized by cytochrome P450, mainly the enzyme CYP2E1, to NAPQI.

NAPQI is a highly reactive, electrophilic molecule that causes harm by the formation of covalent bonds with other intracellular proteins. This reaction is prevented by conjugation with glutathione and subsequent reactions to generate a water-soluble product that is excreted into the bile.

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 the 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.

• *Mitochondrial Dysfunction*

Acetaminophen overdose can also cause mitochondrial dysfunction either by covalent binding to mitochondrial proteins or by other mechanisms. It can depress mitochondrial respiration and adenosine triphosphate (ATP) synthesis and induce mitochondrial oxidant stress with increased production of peroxynitrite. Peroxynitrite is a potent oxidant and nitrating agent. It can generate additional covalent bonds with cellular proteins, causing further mitochondrial dysfunction. Eventually, there are alterations in membrane permeability leading to the collapse of mitochondrial membrane potential, disruption of ATP synthesis, and release of mitochondrial proteins into the cell cytoplasm and oncotic necrosis of hepatocytes [15].

• *Alteration of Innate Immunity*

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

The clinical manifestations of acetaminophen toxicity and their severity depend on the dose that was ingested, and the time elapsed since ingestions. However, the earliest manifestations are nonspecific and cannot aid in the diagnosis unless the assessing physician kept this differential in mind [16]. Hence, taking a detailed history that includes questioning the patient about drug intake and assessing him/her for possible suicidal ideation or tendency is paramount for making the diagnosis. The clinical course of acetaminophen toxicity can be described in chronologically sequential stages (see Table 1) [17]:

- **Stage I** represents the first 24 hours post-intake and it is either asymptomatic or manifests nonspecific symptoms such as pain in the right hypochondrium, nausea, vomiting, and general malaise. Laboratory studies are normal. The severity of the first stage depends on the dose ingested by the patient.
- **Stage II** represents 24-72 hours post-intake; patients may show pain in the right hypochondrium and moderate involvement of the general condition, some degree of nephrotoxicity and rarely pancreatitis. Laboratory studies reveal an increase in transaminases and a decrease in prothrombin time, and antithrombin III.
- **Stage III** represents 72-96 hours post-intake; hepatocellular failure is completely clinically evident. The patient may have hepatic encephalopathy, pancreatitis, coma, renal failure, coagulation disorder, and metabolic acidosis.
- **Stage IV** represents 4-14 days post-intake; it could be recovery and improvement or deterioration of the patient's condition. The resolution of clinical manifestations may appear after 2-3 months of intoxication, but the histologic recovery period may take several months longer. Chronic hepatic failure has not been reported as a complication of Acetaminophen hepatotoxicity [18].

Table 1: stages of Acetaminophen hepatotoxicity

Stage	Period elapsed since ingestions	Manifestations
I	0 – 24 hours	• **Clinical**: asymptomatic or nonspecific (e.g. nausea, vomiting, sweating, and lethargy). • **Lab**: normal.
II	24 – 72 hours	• **Clinical**: might initially improve, but later develop right upper quadrant tenderness and liver enlargement. • Some might develop nephrotoxicity or pancreatitis. • **Lab**: elevations of liver aminotransferases (ALT and AST).
III	72 – 96 hours	• **Clinical**: jaundice, confusion, and bleeding diathesis. • **Lab**: deteriorate further and peak.
IV	4 days – 2 weeks	• ***Recovery*** (that is if survive stage III).

Organ failure begins to appear between 3 and 5 days after ingestion. Given this, and considering such a progressive nature of acetaminophen toxicity, timely diagnosis is essential in order to initiate management and prevent acute liver failure. However, as previously mentioned, unless stated by the patient or actively assessed by the clinician, the diagnosis of this toxicity is quite challenging. Acetaminophen toxicity should be evaluated when a patient is presented in ER with toxic ingestion of an unknown substance, altered mental status, and/or suspicion of the intent of self-harm. For that, acetaminophen blood concentrations should be measured in suspected patients and this should remain the basis of diagnosis [19]. Other laboratory parameters such as arterial blood gas (to investigate acid/base status), coagulation profile, basic metabolic panel, hepatic function tests, and urine drug screen (to determine possible co-ingestions) are essential to evaluate the general condition of the patient [17, 20].

Acetaminophen poisoning management includes the following:

- Gastric lavage, which should be done in the first 2h post-intake. If the physician is unsure of the exact time of ingestion, gastric lavage should be performed [21].
- Activated charcoal (dose of 1 g/kg), should be done within 6 hours post-intake or when the time is unknown. No harm will occur in the case of administration with NAC. Patients with GCS <9 airway level must be maintained by intubation, and then activated charcoal can be given via nasogastric tube.
- In the case of nausea and vomiting, Metoclopramide or Ondansetron agents can be given.
- In the case of renal insufficiency, coma, acidosis, and plasma concentrations of Acetaminophen greater than 1000 µg/ml hemodialysis may be considered [22].

N-Acetyl cysteine (NAC) is a hepatic *Glutathione* precursor and an acetaminophen antidote and should be given for any patient suspected with acetaminophen poisoning. NAC administration for patients will reduce the mortality of acetaminophen poisoning from 5% to 0.7%. NAC helps in improving hepatic perfusion and oxygen delivery, which refine mitochondrial energy metabolism [23]. NAC can be given orally or IV (See Table 2) [17].

NAC treatment indications in the case of acetaminophen poisoning [17]:

- Initiation of NAC within 24 hours of acetaminophen ingestion
- Serum acetaminophen levels from 140 mg/L in 4 hours to 50 mg/L in 10 hours
- Acute poisoning with no ingestion of sustained-release formulations
- Baseline normal hepatic enzymes and INR
- Used ideally within the first 8-10 hours with the risk of hepatotoxicity being <5%
- Empirical use when acetaminophen levels cannot be obtained within 8 hours of ingestion

Table 2. NAC treatment attending to it is via (oral or intravenous).

Oral NAC treatment

Initial dose: 140 mg/kg diluted to 5% in a liquid (usually fruit juice)
Posterior doses: 70 mg/kg in the same concentration every 4h for 17 times
Total administered dose: 1330 mg/kg
Duration of treatment: 72 hours

Intravenous NAC treatment

Initial dose: 150 mg/kg in 250 ml of 5% glucose serum in 1 hour
Posterior doses: 50 mg/kg in 500 ml of glucose 5% serum in 4 hours. 100 mg/kg in 500 ml of 5% glucose serum in 16 hours
Total administered dose: 300 mg/kg
Duration of treatment: 21 hours

After the treatment, it must be prolonged (150 mg/kg/24h) if there has been important cytolysis or signs of liver failure. This perfusion of NAC should be prolonged for the necessary time until the improvement of liver function is achieved or until the transplant or death.

Conclusion

In conclusion, acetaminophen is one of the most commonly used over-the-counter medication that has alleviated a lot of suffering. Yet, it is also a medication that has caused a great deal of morbidity and mortality when overdosed due to its hepatotoxicity. So, when used, patients should be always warned not to exceed the prescribed dose, and when a patient is presented to the ER, the possibility of overdose should be always kept in mind.

In the case of suspected acetaminophen poising, a comprehensive medical history should be done to estimate the taken dose, time passed since taken and patient's risk factors.

In the case of normal liver enzymes, the physician may wait for the assessment of the acetaminophen level in the blood to begin NAC treatment. However, when there are increases in liver enzymes or doubts about acetaminophen overdose, NAC treatment can be started to avoid the risk of hepatotoxicity.

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