Fulminant hepatorenal syndrome due to Acetaminophen toxicity: A case report

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Abstract:

Hepatorenal syndrome is a rare life-threatening complication of acetaminophen toxicity. It is not responsive to fluid therapy and need performing an emergent liver transplantation. Here, we introduce a 24-year-old woman with a history of chronic high doses of acetaminophen consumption, presenting with nausea, vomiting, lethargy, oliguria, and severe metabolic acidosis.

Keywords: Acetaminophen, Hepatorenal syndrome, metabolic acidosis

Introduction

Acetaminophen [(N-acetyl-p-aminophenol or APAP], also known as Paracetamol is used for its antipyretic and analgesic properties [1]. It is widely available as single-ingredient or combination formulations with other medications for over the counter use which accounts for its high prevalence of toxicity [2]. Although acetaminophen is safely used in therapeutic doses, severe and life-threatening toxicities including renal injury and acute liver failure (ALF) potentially may occur with doses higher than recommended [3,4].

Acetaminophen dose-dependent hepatotoxicity is the most frequent cause of ALF(about 50 %) in the United States [5]. With doses less than 4 g/day, about 97% of acetaminophen metabolized by glucuronidation and sulfation to eliminate safely through the kidney [6]. When larger doses ingested, the acetaminophen metabolism pathway primary change to cytochrome P450 system in which acetaminophen metabolized to [N−acetyl−p−benzoquinone imine] (NAPQI), a reactive metabolite leading to irreversible hepatocellular damage [7,8].

Acute kidney injury (AKI) is another complication of acetaminophen toxicity that happens in less than 2 % of cases and may occur either in the presence or absence of ALF. While necrosis is responsible for cell death in AKI, it seems that apoptosis is the major cause of hepatocellular damage in acetaminophen-ALF. ALF-related hepatorenal syndrome also may be involved in acute kidney injury (AKI) in acetaminophen overdose [9,10].

1. Case presentation

This study was conducted according to the declaration of Helsinki principles. Also, CARE guidelines and methodology have been followed in this study. A 24-year-old woman with nausea, vomiting, dizziness, and anorexia was referred to the emergency room (ER) of Imam Khomeini Hospital, Sari, Iran; on December 20, 2020. She had no history of underlying disease. Due to emotional problems, she had been taking 50 to 100 tablets of clonazepam 1 mg and alprazolam 0.5 mg daily for two years. Eight months ago, regardless of the importance of tapering down, she stopped taking these drugs straight off and started to take 50 to 60 tablets of acetaminophen/codeine 300/20 mg and 500 mg daily. Almost from the same time, she gradually became weak and lethargic leading to the hospital admission. According to the history of acetaminophen overdose, she consulted a clinical toxicologist.

In the clinical examination, the conjunctiva and skin were pale. The heart rate of 110 beats per minute, blood pressure of 80/50 mmHg, respiratory rate of 24 per minute, and arterial O2 saturation of 97% were recorded. On physical examination, the abdomen was soft with tenderness in the right upper quadrant. There was bleeding from the mucosa of the mouth. She was oliguric and underwent urine catheterization. Hydration was started and a blood sample was sent to the laboratory for routine tests on admission and evaluation of the

acetaminophen plasma level. On ultrasound sonography, an increase in the size of the spleen was notable. Space-occupying lesions were not seen in the parenchyma of the liver, spleen, kidneys, and pancreas. Liver echography and bile ducts were normal. No mass and free fluid was visible inside the abdomen. On ECG, sinus tachycardia was detected. Viral markers including HIV, HBsAg, HCV Ab were negative. ABG showed severe metabolic acidosis. Other laboratory data are in table 1.

She was immediately transferred from the emergency room to the ICU. She had hematemesis consisting of acetaminophen tablet residues which explained upper gastrointestinal bleeding. Tachypnea and loss of consciousness secondary to the hepatic encephalopathy resulted in intubation. According to the metabolic acidosis and raised creatinine, the three hours hemodialysis was performed. Treatment was started with N-Acetylcysteine (NAC), pantoprazole, norepinephrine, albumin, fresh frozen plasma, packed cell, vitamin K, magnesium sulfate, and sodium bicarbonate. Dextrose water 50% was also administered to improve her hypoglycemic state. Based on the impaired LFT profile and her coagulopathy, she consulted a gastrointestinal specialist and a surgeon for an urgent liver transplantation. Despite the intensive supportive therapy during the first 24 hours and efforts to correct the metabolic acidosis and electrolyte disorders, no response was detected, and unfortunately, she .died. The patient gave verbally informed consent in this regard

2. Discussion

Acetaminophen, a safe and effective analgesic, and antipyretic agent can cause irreversible, even fatal damage to the liver and kidney with chronic high doses consumption. Early presentation and diagnosis of acetaminophen overdose are critical for successful management. Acetaminophen is rapidly absorbed after oral administration with the onset of action 30 minutes to 2 hours. Peak plasma levels reach 4 hours after overdoses, which could be prolonged in gastrointestinal hypomotility or administration of extended-release formulation [1,11]. in acute situations, during the first 4-6 hours after consumption, oral activated charcoal reduce the gastrointestinal absorption and subsequent acetaminophen plasma level. A free radical scavenger, NAC, is also effective against the replenishing glutathione stores caused by oxidative metabolite of acetaminophen and could prevent or reduce the severity of acetaminophen hepatotoxicity [12].

The normal elimination half-life of 2 hours could prolong to 17 hours in severe hepatic dysfunction [13]. It is well known that in acute ingestion of acetaminophen, Rumack-Matthew nomogram is used to make decisions about initiation and to evaluate the treatment trend. This nomogram cannot be used in chronic toxicity to predict the time of treatment

initiation due to the lack of correlation between plasma levels and the degree of acetaminophen ingestion. However, treatment is indicated in such patients with concurrent elevated transaminases regardless of acetaminophen plasma level. It has been recommended to treat patients either in acetaminophen plasma level of more than 20 mcg/mL or rises in transaminases [1]. Accordingly, NAC was started for this case, with acetaminophen plasma level of 84.7 mcg/mL, but it could not be effective based on the extensive liver and kidney oxidative injuries.

Late presentation, like our case, may manifest as a rise in alanine transaminase (ALT), aspartate transaminase (AST), and bilirubin that represents the hepatic phase of acetaminophen toxicity [14]. Actually this case was on chronic acetaminophen abuse and presented by both liver and kidney dysfunction which did not respond to any treatment options. About this patient, chronic consumption of acetaminophen had led to the impairment of hepatic metabolism pathways; therefore, prolonged half-life of acetaminophen had been caused further hepatic injury.

She also became oliguric with a creatinine level of 3 mg/dl, representing acetaminophen renal injury. Acetaminophen related renal injury is more occurred in chronic users with significant elevation in liver transaminases [15]. Acute tubular necrosis (ATN) is the most common type of acetaminophen-induced nephrotoxicity which is important to be differentiated from hepatorenal syndrome (HRS) in the case of its durability. (Acetaminophen-Induced Nephrotoxicity: pathophysiology, clinical manifestations, and management) in overdoses, the acetaminophen metabolic pathway shifted to how more oxidative NAPQI metabolite was produced and could be excreted in urine. As a result, glutathione stores of the kidney will be reduced and tubular injury occurs [16]. Kidney involvement in the present case was not related to any other known causes of renal failure; so, among her liver failure, increased serum creatinine, oliguric state, lethargy, and non-fluid responsiveness, HRS could be considered as a consequence of chronic acetaminophen hepatotoxicity. HRS is described as a progressive reduction in renal function resulting from severe liver failure, which often happens in cirrhotic patients. HRS has a poor prognosis, particularly in type 1 and its mortality rate is high within 2 weeks unless performing an urgent liver transplantation [17]. This case was also a candidate for liver transplantation but unfortunately died before any preparations.

3. Conclusion

It is important to distinguish HRS from ATN that is the most reported cause of acetaminophen-induced nephrotoxicity, to select a certain treatment strategy. HRS is a rare and poor prognosis complication of chronic acetaminophen toxicity, which presents by progressive decline in renal function secondary to liver failure. The curable treatment option in this situation may be the liver transplantation, the same as HRS in cirrhotic patients.

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Authorships

ZZ involved in interpretation and collecting of data, and editing the manuscript. MM involved in drafting first version of manuscript and editing. ZN involved in writing, editing and preparing the final version of manuscript. MF involved in critical revising. RT is responsible for collecting data and submitting the manuscript. All authors reviewed the paper and approved the final version of the manuscript**.**

CONFLICT OF INTEREST

.The authors confirm that this article content has no conflict of interest

Table 1. Baseline laboratory data	
Hemoglobine	7.9 g/dL
White blood cells	9000/mm^3
Platelet	142000/mm^3
Sodium	143 mmol/L
Potassium	3.5 mmol/L
ALT	2030 IU/L
AST	1691 IU/L
ALP	303 IU/L
Bilirubin Total Direct	 2.3 mg/dL 0.8 mg/dL
Lactate dehydrogenase	5400 IU/L
PT	39.2 sec
PTT	58 sec
INR	4.8
Albumin	2.5 g/dL
Calcium	7.9 mg/dL
Magnesium	1.6 g/dL
Blood urea nitrogen	16.82 mg/dL
Creatinine	3 mg/dL
pH	7.19 mmHg
HCO3	9.6 mmol/L
PCO2	24.7 mmHg
Base excess	-18.6 mmol/L
Blood sugar	50 mg/dL

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