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Acetaminophen Intoxication with Fulminant Hepatic Failure Salvaged by Plasmapheresis

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Abstract

Introduction: Acetaminophen-induced liver injury is the most common cause of acute liver failure, where multiple ingestions or a delay in the presentation may lead to a poor prognosis. N-acetylcysteine (NAC) is the conventional antidote used to treat acute acetaminophen toxicity, and plasmapheresis can be used as an adjunct, though there are no systematic studies to prove its effectivity.

Case Presentation: An 18-year-old girl was admitted with reduced responsiveness for one day with a few episodes of diarrhea. On admission, she was febrile and had a GCS of 10/15, otherwise normal neurology. She had marked right hypochodrial tenderness, deep icterus, and a pulse of 120 beats per minute, with a blood pressure of 80/50 mmHg; fluid resuscitation with inotropic support was done. Initial investigations revealed severe metabolic acidosis, hemoglobin of 9.5 g/dL, white blood cell count 13,500/mm3, and platelet 119,000 per µL. The prothrombin time (PT) international normalized ratio (INR) was 4.7, and the activated partial thromboplastin time (APTT) was 38.6. The alanine aminotransferase (ALT) level was 8118 U/L, and aspartate aminotransferase (AST) was 3883 U/L with a total bilirubin of 107 µmol/L. The diagnosis of acute liver failure following acetaminophen intoxication was made and managed with intravenous NAC, pantoprazole cover, intravenous ceftriaxone, metronidazole, thiamine, and vitamin K. Fresh frozen plasma and platelets were given for severe coagulopathy. She was started with plasmapheresis at the intensive care unit (ICU), where she had a significant improvement, though she developed hospital-acquired pneumonia, which was successfully managed. Subsequently, her liver functions returned to the baseline, and she was discharged after a psychiatric assessment.

Conclusion: A high degree of suspicion needs to be adopted to diagnose acetaminophen-induced acute liver failure when a patient presents with hepatic encephalopathy, and plasmapheresis can be considered a life-saving measure adjunct to the NAC.

Keywords: acetaminophen; fulminant hepatic failure; acute liver failure; plasmapheresis; n-acetyl cysteine

Abbreviations

NAC: N-acetylcysteine; GCS: Glasgow Coma Scale; NCCT: Non-contract Computed Tomography; PT: Prothrombin Time; INR: International Normalized Ratio; APTT: Activated Partial Thromboplastin Time; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ICU: Intensive Care Unit; NAPQI: N-acetyl parabenzoquinone imine

Introduction

Acetaminophen is the most widely used analgesic – antipyretic agent since its clinical introduction in 1965. In therapeutic doses, it is considered safe, but its overdose could cause fatal and nonfatal hepatic necrosis. Nevertheless, in susceptible individuals like alcoholics, therapeutic or slightly excess doses can be hepatotoxic [1]. The other reported risk factors for hepatotoxicity of acetaminophen include chronic malnutrition, advanced age, genetic factors, and use of cytochrome P450 inducers [2]. In the United States, 20% of liver transplantations are due to acetaminophen-induced acute liver failure [1].

In managing acetaminophen toxicity, serum acetaminophen concentration is measured after four hours of single ingestion, and the values plotted in a Rumack-Matthew nomogram are used for therapeutic decision-making. N-acetylcysteine (NAC) is the antidote that will be started based on this nomogram [2]. In cases of multiple ingestions or when there is a delay in presentation, the prognosis is poor. Those patients may require intensive care management and anticipate the possibility of liver transplantation [3]. Though the mainstay of treatment in acetaminophen intoxication is

NAC, extracorporeal removal can be used as an adjunctive method. There are no systematic studies to prove the effectiveness of this treatment [4]. We report a case of an adolescent who presented with fulminant hepatic failure following high dose acetaminophen consumption fully recovered following plasmapheresis, without the need for liver transplantation.

Case Report

An 18-year-old girl was transferred from a local hospital due to reducing responsiveness over a one-day duration. As the patient was drowsy, she was unable to provide any information. Therefore initial history was taken from the mother. Before this incident, she was admitted to the local hospital three days before due to recurrent vomiting and dyspeptic symptoms, managed as acute gastroesophageal reflux disease, and discharged on the following day. According to the mother, she also had a few episodes of diarrhea at home, and she was having her regular menstruation. The was no history of deliberate self-harm or psychiatric illness in the past, and she denied the use of alcohol or illicit drugs. Although the mother denied any possibility of an overdose with paracetamol or any other drugs, the patient's sister admitted that the patient had a boyfriend, and the parents forced the patient to terminate it, causing psychological distress.

Upon arrival to our hospital, her Glasgow Coma Scale (GCS) was 10/15, with no evidence of meningism, but she was febrile to touch. The pupils were equally reacted to light, and there was deep icterus with dry mucus membranes noted. She was not pale or plethoric. She had tachycardia with a rate of 120 beats per minute, and blood pressure was recorded as 80/50 mmHg. Lungs were clear on auscultation, and respiratory rate was 20 breaths per minute. Peripheral blood oxygen saturation was 96% with 2 L of oxygen via nasal prongs. She also had marked right hypochondrial tenderness and flapping tremors. Except for the drowsiness, the limited neurological examination was unremarkable.

Initial fluid resuscitation was done with 2 liters of crystalloids followed by inotrope support with intravenous noradrenaline infusion. Arterial blood gas showed severe metabolic acidosis with a lactate level of 4 mmol/L. After stabilizing the patient. we did an urgent non-contrast CT (NCCT) scan of the brain, which came as normal

Her initial investigations revealed hemoglobin of 9.5 g/dL, white blood cell count 13,500/mm3, and platelet 119,000 per µL. The serum electrolyte levels were normal, but the blood urea level was 40 mg/dL with a creatinine level of 0.9 mg/dL. The prothrombin time (PT) international normalized ratio (INR) was 4.7, and the activated partial thromboplastin time (APTT) was 38.6. The liver enzyme levels were markedly elevated with alanine aminotransferase (ALT) of 8118 U/L and aspartate aminotransferase (AST) of 3883 U/L. The total bilirubin was 107 µmol/L.

The diagnosis of acute liver failure following acetaminophen intoxication was made with the clinical features and available investigations. Intravenous NAC 100 mg per hour infusion and pantoprazole 8 mg per hour infusion were started. Concomitantly intravenous ceftriaxone 2 g daily, metronidazole 500 mg 8 hourly, thiamine 250 mg daily, and vitamin K 10 mg were given. As there was a severe coagulopathy, four units of fresh frozen plasma and one adult dose of platelets were transfused. Urgent ultrasound of the abdomen showed evidence of acute liver parenchymal disease. As she was clinically deteriorating, the patient was transferred to the intensive care unit (ICU).

At the ICU, she was commenced on plasmapheresis. The following day the blood acetaminophen level was available, and it was 58.89 mg/dL, which was significantly high and confirmed our diagnosis. In the septic screening, the C-reactive protein level, serum procalcitonin, urine full report, urine culture, and blood culture were within normal limits. There were negative screening for hepatitis A, hepatitis B surface antigen,

hepatitis C antibody, dengue antibodies, and cytomegalovirus antibodies. She received a total of five cycles of plasmapheresis. Additionally, she was given Rifaximin and lactulose orally.

Her ICU stay was prolonged due to hospital-acquired pneumonia. She needed intubation and ventilation subsequently. She was managed with intravenous teicoplanin and piperacillin-tazobactam for 14 days, and she was extubated after one week. Once she had recovered from the acute stage, she admitted that she took 48 tablets of paracetamol due to some conflicts with her boyfriend.

She recovered fully with the management inward and in ICU, where liver functions returned to the baseline, and she was discharged after psychiatric assessment.

Discussion

Acetaminophen is a common antipyretic and an analgesic where its toxicity was first noted in the 1960s. Since then, the incidence of poisoning has been increased, making paracetamol the most common drug in self-poisoning, with a high rate of morbidity and mortality in the world [4,5]. In Sri Lanka, the number of cases has been widely increased, to the extent of 50% of admissions related to poisoning at the National Hospital of Sri Lanka due to acetaminophen toxicity [6].

Acetaminophen is metabolized by glucuronidation and sulfonation pathways and is usually tolerated well by healthy individuals. Nevertheless, supratherapeutic doses of acetaminophen cleared by cytochrome-mediated oxidative metabolism primarily by hepatocytes may lead to hepatocellular damage [7]. A highly reactive metabolite generated in this process, namely N-acetyl parabenzoquinone imine (NAPQI), is considered the cause of liver damage in acetaminophen toxicity [2]. Excess NAPQI causes significant liver injury via overwhelming oxidative stress, protein adducts formation, and cellular malfunction [7].

The clinical course of acetaminophen toxicity is divided into four stages. During the first stage (30 min to 24 hours), the patient may be asymptomatic or may have emesis. There may be emesis, right upper quadrant pain, and hypotension in the second stage (18 to 72 hours). Liver dysfunction is significant in the third stage (72 hours to 96 hours) with renal failure, coagulopathies, metabolic acidosis, and encephalopathy. Gastrointestinal symptoms reappear, and death is most common at this stage [8]. In our patient, she had right upper quadrant pain, hypotension, liver dysfunction, metabolic acidosis, and encephalopathy, suggesting that she may have probably been in the third stage. The fourth stage (4 days to 3 weeks) is marked by recovery [8].

Late presentation of acetaminophen intoxication will be challenging to diagnose, especially when the patient is in encephalopathy and the history is unreliable. A patient presenting with an altered mental state could be due to many causes, such as neurologic, infectious, toxicologic, metabolic, and psychiatric [9]. Therefore, it is essential to exclude the other possibilities in this patient by doing an NCCT brain and other supportive laboratory tests. In critical circumstances of acetaminophen toxicity, treatment decisions must be made following presumptive diagnosis. It can be either empirical or based on the data available at the time. We suspected acetaminophen toxicity in this patient based on the clinical features and available investigations with an unreliable history.

The management of acetaminophen toxicity depends on the time of presentation. If the patient presents within 8 hours of ingestion, the blood paracetamol level should be measured and then plotted in a Rumack-Matthew nomogram to decide whether to start NAC. If the patient delays more than 8 hours to present or if the time of ingestion is uncertain, NAC should be started indefinitely before measuring the blood paracetamol level [9,10]. The Rumack-Matthew nomogram was of limited value in

this patient because of the uncertain time of ingestion. NAC should be immediately started in any patient with the slightest suspicion of intoxication with acetaminophen, as we did in our patient [10]. NAC has several mechanisms for preventing liver toxicity. It can detoxify NAPQI, increase tissue oxygenation via non-specific ways and reduce tissue free radical formation [9]. The definitive diagnosis of acetaminophen toxicity is made with the high blood acetaminophen level, which is not routinely practiced in Sri Lanka. However, in this case, we were able to get the level which is 58.89 mg/dl.

Acute liver failure is a fatal complication of acetaminophen toxicity. It is defined by the presence of hepatic encephalopathy, jaundice, and coagulopathy in individuals without any history of cirrhosis occurring for less than 26 weeks [11]. The main reasons behind fulminant hepatic failure and death following acetaminophen intoxication are delay in seeking medical attention, delay in recognition of poison or delay in institution of appropriate therapy, and the existence of preexisting comorbidities [3,4]. The key to diagnosing fulminant hepatic failure, in this case, was the presence of deep icterus, hepatic encephalopathy characterized by flapping tremors, coagulopathy characterized by high INR, and low blood pressure.

Even though liver transplantation is the cornerstone of managing fulminant hepatic failure, the progression is halted by the early initiation of plasmapheresis. However, the clinical applicability of plasmapheresis is yet to be proven by randomized clinical trials [12]. Nevertheless, this patient with a severe deteriorating fulminant hepatic toxicity achieved a significant improvement with plasmapheresis.

Very few studies have looked at plasmapheresis treatment in acute liver failure due to specific etiologies. However, it has been reported to positively affect survival over molecular adsorbent recirculating system therapy for liver failure secondary to acetaminophen toxicity [13]. Karvellas and Stravitz have also demonstrated a conclusive improvement in transplant-free survival in patients with acute liver failure and consistent improvements with biochemical, immunological, and clinical features with plasmapheresis [14]. However, future studies are needed to evaluate the efficacy of plasmapheresis over other treatment modalities in acetaminophen-induced acute liver failure.

Conclusion

Acetaminophen ingestion is a significant cause of poisoning globally, with a generally better outcome, leading to fatal complications like a fulminant hepatic failure. In developing countries like Sri Lanka, a high degree of suspicion needs to be adopted to diagnose acetaminophen-induced acute liver failure when a young patient presents with hepatic encephalopathy. In such instances, early recognition and prompt treatment is key to a better outcome. Even though there is no concrete evidence for the use of plasmapheresis, it can be considered a life-saving measure as an adjunct to the NAC, especially in countries like Sri Lanka, where liver transplantation is not widely available.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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