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CASE REPORT

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Late *N*-acetylcysteine for successful recovery of acetaminophen-related acute liver failure: A case report

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Abstract

Acetaminophen toxicity is one of the leading causes of liver failure. Although *N*-acetylcysteine (NAC) is generally successful in preventing acetaminophen hepatotoxicity when given in a timely manner, if not prescribed in the early golden time, the only practical way to save the patient might be liver transplantation. The case presented was a 20-year-old female with an acetaminophen overdose (30 g), for which more than 24 h had passed since the ingestion. Despite the critical clinical condition, loss of consciousness (Glasgow Coma Score of 4) of the patient, and passing the golden time of antidote administration, the decision was made by the healthcare team to administer NAC. After transferring the patient to the intensive care unit, the three-bag NAC regimen was initiated and appropriate monitoring was performed. After this, the regimen of 3 g q8h was continued for the patient. The patient's condition began to improve slowly on the second day and then she was extubated on the fourth day. Finally, she was discharged on the tenth day. Although the golden period of antidote administration had passed outwardly, there was no need for a liver transplant and the patient recovered successfully with late NAC administration. Hence, clinicians can benefit from the use of NAC even in the late phases of acetaminophen liver toxicity.

KEYWORDS

acetaminophen, hepatotoxicity, liver failure, *N*-acetylcysteine

1 | INTRODUCTION

Acetaminophen toxicity is among the most common medication-related overdoses. Given the large number of over-the-counter and prescription acetaminophen-containing products available, it is not surprising that acetaminophen-related toxicity is a concern all over the world.[1]

Management consists of gastric decontamination and early administration of *N*-acetylcysteine (NAC). NAC is considered the gold-standard antidote for acetaminophen poisoning.[2] The multiple mechanisms of protection are the reasons for the extended therapeutic window of NAC. As a rich glutathione precursor with antioxidant activity, NAC aids in the detoxification of *N*-acetyl-*p*-benzoquinone imine (NAPQI) within the

hepatocyte. Improving hepatic perfusion and oxygen delivery in patients with acetaminophen-induced fulminant hepatic failure is another mechanism for this agent.[3] Other beneficial effects include scavenging of reactive oxygen and nitrogen species and improved mitochondrial energy production.[4] This agent will have the most protective effects when given within 8 h after ingestion. NAC will consider when the acetaminophen level is potentially toxic on the Rumack–Matthew acetaminophen treatment nomogram.[5] Although it seems that in severely ill patients who present 24 h after the ingestion of acetaminophen, NAC administration may have some benefits, in these conditions, liver transplantation is considered standard management.

Our case here is a 20-year-old female with hepatic failure due to acetaminophen toxicity and more than 24 h had passed since the ingestion. By administering NAC, it became possible to recover from liver injury and survive the patient.

2 | CASE DESCRIPTION

2.1 | Patient information

The case was a 20-year-old (60-kg) female who was transferred by ambulance from a primary care center to the poisoning emergency department of Baharloo Hospital, a referral poisoning center at Tehran University of Medical Sciences, Tehran, Iran, under supportive care and ventilation. According to history, she had an acetaminophen overdose, with a dosage of 30 g >24 h before the admission. She was living in the North of Iran, where after 3 days of ingestion referred to a medical center with complaints of icterus and abdominal pain. She became a candidate for liver transplantation and was referred to Baharloo Hospital in Tehran. Her vital signs upon arrival were as follows: blood pressure of 128/71 mmHg, heart rate of 85 bpm, temperature of 37°C, and respiratory rate of 16 bpm. Her Glasgow Coma Score was 4. She was immediately transferred to the intensive care unit (ICU).

Initial investigations included the following: complete blood count (white blood cells [WBC] 28.9 cell 10^3/mm^3, hemoglobin [Hg] 6.8 g/dL, hematocrit [HCT] 23.2%, platelet counts [PLT] 319 cell 10^6/mm^3), urea 40 mg/dL (normal range [NR] 15–45), creatinine 1.1 mg/dL (NR 0.6–1.3), electrolytes (sodium [Na] 140 meq/L, potassium [K] 3.6 meq/L, phosphorus [P] 4.3 mg/dL, magnesium [Mg] 2.83 mg/dL, calcium [Ca] 10.5 mg/dL), creatine phosphokinase (CPK) 93 IU/L (NR <170), lactate dehydrogenase (LDH) 1764 U/L (NR 230–460), aspartate aminotransferase (AST) 3700 U/L (NR <32), alanine aminotransferase (ALT) 1420 U/L (NR <40), alkaline phosphatase (ALP) 245 U/L (NR 64–306), prothrombin time (PT) 19 s (NR 12–14), partial thromboplastin time (PTT) 33 s (NR 25–40), international normalized ratio (INR) 2.4 (NR: 1), total bilirubin 34 mg/dL (NR 0.3–1.2), direct bilirubin 27 mg/dL (NR <0.4), ammonia 90 μmol/L (NR 11–48), serum albumin 3.94 gr/dl (NR 3.5–5), and β-HCG 1.2 mg/dL (non-pregnant NR <5). Viral markers (HCV Ab, HBS antigen, and HBC Ab) for hepatitis were negative. Acetaminophen level was also equal to 7 mg/L.

2.2 | Clinical findings

Based on physical examinations, the patient had mild to moderate peripheral extremities edema, her icterus appearance was predominant, and she had a comatose state and agitation. Abnormal findings were not seen in the electrocardiogram (ECG) upon admission. Some evidence in favor of aspiration pneumonia was seen in the chest X-ray. Hence, appropriate antibiotics were started. Her arterial blood gas analysis was as follows: pH 7.4, pCO_2 42 mmHg, and HCO_3 27.9 mmol/L.

2.3 | Therapeutic interventions

The first critical decision was made when the patient's chance of receiving an emergency liver transplant was very low. Considering that more than 24 h had passed since the overdose, the first dose of NAC was prescribed to the patient, 9 grams (150 mg/kg) infused over 15 min. As the acetaminophen level was 7 mg/L after >24 h, the treatment was continued. The second bag was equivalent to 3 g (50 mg/kg) NAC, infused over 4 h. Finally, the third bag containing 6 g (100 mg/kg) NAC was infused over 16 h. After these three doses, the 50 mg/kg regimen (3 g q8h) was continued.

The patient's condition began to improve after 48 h of NAC administration. Liver transaminase values decreased without high acetaminophen levels. Lab data related to liver function on the fourth day were as follows: AST 588 U/L, ALT 95 U/L, ALP 186 U/L, PT 13 s, PTT 29 s, INR 1.3, total bilirubin 31 mg/dL, and direct bilirubin 15 mg/dL. The patient was extubated and then discharged from the ICU with stable hemodynamic parameters after 4 days. Further, ultrasonography of the liver and biliary system revealed no concerning findings at this time and the clinical condition of the patient improved significantly.

Finally, the patient was discharged from the hospital on the 10th day with mildly elevated liver enzymes (AST 221 U/L, ALT 69 U/L, ALP 292 U/L, PT 12 s, PTT 33 s, INR 1.2, total bilirubin 12 mg/dL, and direct bilirubin 8.2 mg/dL) which was resolved in subsequent follow-up.

Two weeks after discharge, the results were reported as follows: AST 91 U/L, ALT 39 U/L, ALP 213 U/L, PT 15 s, PTT 30 s, INR 1.1, total bilirubin 3.2 mg/dL, and direct bilirubin 1.6 mg/dL. All the laboratory values at different time points are described in Table 1.

3 | DISCUSSION

Classically, clinical acetaminophen poisoning is described in four stages. In the first 12–24 h after ingestion, patients present with non-specific symptoms commonly gastrointestinal discomforts such as nausea, vomiting, and abdominal pain. After this stage, the hepatic injury becomes apparent with elevated liver transaminase concentrations. In the third stage, patients can progress to fulminant hepatic failure (presence of encephalopathy and/or coagulopathy). Patients will become candidates for receiving a liver transplant, recover, or die.[2]

With therapeutic dosing, acetaminophen is metabolized primarily via glucuronidation and sulfation to nontoxic metabolites. With supratherapeutic ingestions, up to 50% of absorbed acetaminophen is metabolized by CYP2E1, leading to the production of NAPQI, the hepatotoxic metabolite. In therapeutic doses, NAPQI quickly binds to hepatic glutathione stores, producing additional nontoxic metabolites. However, in toxic ingestions with the increase of NAPQI levels, hepatic necrosis goes further and further leading to hepatic failure which is irreversible.[6] It is of importance that acetaminophen-induced hepatotoxicity can lead to hyperammonemia, as observed in our case. However, it has been shown that there was no correlation between hepatic encephalopathy and elevated ammonia concentrations since it had low specificity and sensitivity for the prediction of encephalopathy, while it had a small significant positive likelihood ratio for the development of hepatic encephalopathy.[7]

Late NAC administration in acetaminophen toxicity may be considered in situations like our presented case, where more than 24 h had passed from ingestion, especially in cases where urgent liver transplantation is not available.[8] Also, other strategies such as using fomepizole and other strategies have been used in addition to NAC to treat some cases.[9]

In cases who receive NAC within the first 8 h after an acute overdose, the risk of hepatotoxicity is as low as 5% whereas delays are associated with an increased risk of fulminant hepatic failure.[10–12] In one retrospective cohort study which included 727 admissions for acute acetaminophen toxicity, the dose–response relationship between paracetamol concentration and acute liver injury was demonstrated even in patients treated with NAC within 8 h of overdose.[13]

Patients who have serum acetaminophen concentration above the "treatment line" of the Rumack–Matthew nomogram are candidates for NAC administration. Likewise, the nomogram has been validated for use only to 24 h after acute overdose.[10,12] The nomogram is not valid for patients who present beyond 24 h after an acute overdose. The serum level of acetaminophen in our patient could not be assessed in the nomogram. In one small series, more than 40% of patients presenting with an acetaminophen overdose could not be assessed using the Rumack–Matthew nomogram.[14]

Delayed initiation of NAC treatment is the main reason for treatment failure and death after acetaminophen overdose. However, several case reports have highlighted the development of acute liver injury and acetaminophen-related death despite appropriate treatment with NAC especially in the setting of massive acetaminophen ingestion.[13,15,16]

There is a case report of successful treatment with late NAC administration in an 18-year-old man, although in that case very high doses of NAC and a longer period

TABLE 1 Laboratory findings of the case at different times.

	At admission	After 48 h	After 10 days (discharge)	Two weeks after discharge
AST (U/L)	3700	588	221	91
ALT (U/L)	1420	95	69	39
ALP (U/L)	245	186	292	215
PT (s)	19	13	12	15
PTT (s)	33	29	33	30
INR	2.4	1.3	1.2	1.1
Total bilirubin (mg/dL)	34	31	12	3.2
Direct bilirubin (mg/dL)	27	15	8.2	1.6

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time.

regimen (a week) than the standard regimen were used.[17] This case report revealed that while NAC has been suggested to be an effective antidote for early phases, the use of it in late toxicity is also gaining importance.[18] Furthermore, successful treatment with prolonged infusion of NAC was reported in a 22-year-old female with encephalopathy due to acetaminophen toxicity.[19] Meanwhile, our reported case was recovered with the standard regimen. NAC administration may improve survival even at this stage. Diminishes hepatic necrosis, decreasing neutrophil infiltration, improving microcirculation, and increasing oxygen delivery are the reasons that support this approach.[20,21] Although it seems like an opportunity for individuals with late presentation acetaminophen toxicity, many patients still need a liver transplant as the only way to survive.[22]

Based on the cases of successful treatment of NAC in acetaminophen liver toxicity, clinicians can benefit from the administration of it. NAC is relatively safe with minimal and transient side effects reported for that,[23,24] which can be easily managed if the patient is under observation, resulting in its benefits outweighing the risks. Since the exact estimation of overdose timing is always challenging, NAC seems to be a useful agent even if there is a doubt between early and late acetaminophen toxicity.

4 | CONCLUSION

Late presentation of the patients and delayed initiation of NAC treatment are the main reasons for acute liver failure and death after acetaminophen overdose. Our report can be a glimmer of hope for the treatment of similar patients despite the loss of the golden time of antidote administration or in cases where liver transplantation is not possible.

AUTHOR CONTRIBUTIONS

Nafiseh Alizadeh: Writing – original draft; writing – review and editing. **Amir-Mohammad Yaryari:** Writing – original draft; writing – review and editing. **Amir Hossein Behnoush:** Writing – review and editing. **Kosar Raoufinejad:** Writing – review and editing. **Behnam Behnoush:** Conceptualization; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

Not applicable.

ETHICS STATEMENT

Not applicable.

CONSENT

Written informed consent was obtained from the patients for publication of this case series.

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