CASE REPORT

Acute Fulminant Liver Failure Secondary to Yellow Phosphorus Poisoning: Role of Extended N-acetylcysteine Therapy

Shivakumar Shivanna[1], Pavitra Pushpa[2], Indira Menon[3], Deepa Das[4], Swapna M Babu[5], Deepak I Tauro[6]

Received on: 03 November 2022; *Accepted on:* 10 December 2022; *Published on:* 07 March 2023

Abstract

Yellow phosphorus is widely used in agricultural applications as well as a rodenticide. Poisoning from unintentional consumption and suicidal intent is common in the Indian subcontinent. Acute fulminant liver failure caused by yellow phosphorus intoxication is fatal. Treatment options include early intervention with supportive care, N-acetylcysteine (NAC), plasmapheresis, and liver transplantation. We used an extended NAC therapy, which resulted in a favorable outcome for our patient.

Keywords: Drug-induced, Fatal toxicity, Intensive care unit.

Indian Journal of Critical Care Case Report (2023): 10.5005/jp-journals-11006-0033

Case Description

A 21-year-old male presented to the emergency department with an alleged history of rodenticide paste (Ratol) containing 3% yellow phosphorus. He had 3–4 episodes of hematemesis. There was no history of loss of consciousness, seizures, or abdominal pain. Following consumption, he was given a stomach wash in a local hospital and was referred to our center.

Upon admission to the intensive care unit (ICU), the patient was conscious and oriented with no apparent distress. A general and systemic examination did not reveal any abnormal findings. There was no further bleeding manifestation, jaundice, or no other signs of acute liver failure (ALF). Screenings for hepatitis were negative. Initial laboratory evaluation revealed deranged coagulation parameters and mild thrombocytopenia, and his liver function tests (LFT) were within normal limits (Table 1). He has initiated on intravenous (IV) hydration, IV magnesium sulfate, and NAC infusion at 150 m/kg over 20 minutes, followed by 50 mg/kg over 4 hours and 100 mg/kg over 16 hours. Other supportive measures were commenced as per our ICU protocol.

Within 24 hours of ICU admission, his platelet count dropped to 68,000, which was associated with transaminitis, worsening of coagulation profile, and dyselectrolytemia (hypokalemia, hypoglycemia); hence ALF was considered. On examination, he had a subconjunctival hemorrhage. He received fresh frozen plasma and random donor platelets. On day 3 of his ICU stay, he had fever spikes associated with worsening transaminitis, coagulation parameters, hypoglycemia, and altered sensorium. His serum ammonia was 108 µ/dL.

He was commenced on hepatoprotective measures with rifaximin, lactulose, and broad-spectrum antibiotics, pending culture reports. He continued to receive 100 mg/kg of IV NAC over 16 hours per day. A chest X-ray revealed bilateral mid and lower-zone opacities suggestive of bronchopneumonia, which progressed to respiratory failure requiring high-flow nasal oxygen support. In view of desaturation and worsening sensorium (hepatic encephalopathy grade III), he was intubated and initiated on lung protective ventilation. His computed tomography brain and electroencephalogram were found to be normal. The urine culture showed *Escherichia coli*, for which antibiotics were escalated to meropenem. Ultrasound abdomen (USG) showed hepatomegaly, mild ascites, and bilateral pleural effusion. The model for end-stage liver disease (MELD) score was 34 and a King's College Hospital criterion for non-acetaminophen poisoning was met. A medical gastroenterology opinion was obtained and advised on the need for liver transplantation with a guarded prognosis. Due to financial constraints, the patient's family opted for conservative management.

He continued to receive NAC infusions at 100 mg/kg over 16 hours in view of worsening liver functions. Over a period of 7 days, the patient's sensorium improved, and he was gradually weaned off from mechanical ventilation and extubated. Sputum culture showed pan-drug resistance to klebsiella, and antibiotics escalated to colistin. In view of abdominal pain and raised amylase and lipase (195.2 µ/L) levels, the USG abdomen was repeated, which revealed features of acute pancreatitis, mild hepatomegaly, moderate pleural effusion, and ascites.

His LFT and coagulation parameters started to improve, showing a downward trend. The patient received an NAC infusion

[1–6]Department of Critical Care (ICU), Bangalore Baptist Hospital (BBH), Bengaluru, Karnataka, India

Corresponding Author: Shivakumar Shivanna, Department of Critical Care (ICU), Bangalore Baptist Hospital (BBH), Bengaluru, Karnataka, India, Phone: +91 9611988538, e-mail: shivanna03@gmail.com

How to cite this article: Shivanna S, Pushpa P, Menon I, *et al.* Acute Fulminant Liver Failure Secondary to Yellow Phosphorus Poisoning: Role of Extended N-acetylcysteine Therapy. Indian J Crit Care Case Rep 2023;2(1):11–13.

Source of support: Nil

Conflict of interest: None

Patient consent statement: The author(s) have obtained written informed consent from the patient for publication of the case report details and related images.

Table 1: LFT and coagulation parameters

Parameters	*Day 1*	*Day 2*	*Day 3*	*Day 4*	*Day 5*	*Day 6*	*Day 7*	*Day 8*	*Day 9*	*Day 10*	*Day 11*	*Day 12*
Platelet count	1,18,000	68,000	66,000	35,000	42,000	23,000	9,000	36,000	35,000	32,000	45,000	97,000
INR	1.79	3.19	5.81	4.86	4.64	3.48	1.64	2.39	1.66	1.94	1.89	1.51
Total bilirubin	1.0	1.1	2.1	5.3	4.8		14.0				29	29.7
Direct bilirubin	0.1	0.3	1.2	3.0	2.6		8.7				23	24
Serum glutamic-oxaloacetic transaminase	26	63	159	1090	3280	483	200	133		110	94	129
Serum glutamic pyruvic transaminase	15	32	113	820	1910	700	510	395		283	104	214
Alkaline phosphatase	106	62	122	138	216		113				218	126

for a period of 12 days till the normalization of his international normalized ratio (INR). He was discharged from the ICU stay and returned home after 19 days of hospitalization. He was followed up for a period of 3 weeks upon discharge and showed improvement in LFT and coagulation parameters (Table 2).

Table 2: LFT and coagulation parameters on the follow-up period

Parameters	*1 week*	*2 weeks*	*3 weeks*
Total bilirubin (mg/dL)	6.5	1.07	1.34
Direct bilirubin (mg/dL)	2.8	0.28	0.31
Serum albumin	3.5	2.64	2.90
Serum glutamic-oxaloacetic transaminase/aspartate aminotransferase (U/L)	114	100	45
Serum glutamic pyruvic transaminase/ALT (U/L)	201	80	63
Alkaline phosphatase (U/L)	130	87	80
INR	1.50	1.0	0.7

Discussion

Warfarin and related substances (coumarins), inorganic substances (thallium, arsenic), and convulsants (strychnine) are the three main classes of rodenticides. Phosphorus exists as two elements—yellow and red. Red phosphorus is not harmful since it is not soluble or absorbable. Yellow phosphorus is a protoplasmic toxin that readily gets absorbed in the digestive tract. Ratol paste is composed of 3% yellow phosphorus. Ingesting a lethal dose of 1 mg/kg results in circulatory collapse and death from ALF. After ingestion of yellow phosphorus, phosphine and proton undergo a reaction to make phosphonium, which directly enters into the small intestine, duplicates phosphine, and exerts its harmful effects on hepatocytes.

Yellow phosphorus causes necrobiosis, most notably in the liver, which leads to ALF and massive hepatocyte death. The brain, striated muscles, and kidneys may also be affected by toxins. The clinical disease typically develops in three stages—mild gastrointestinal symptoms for the first 24 hours, followed by an asymptomatic period for the next 24–72 hours, and then a delayed presentation of fulminant liver failure with a high death rate at 72 hours. To delay gastrointestinal tract absorption, early gastric lavage is recommended. Gastric lavage with 1:5000 potassium permanganate, followed by activated charcoal and mineral oil cathartically, is used as an initial form of decontamination. Gastrointestinal symptoms, liver dysfunction, renal failure, arrhythmias, seizures, coma, and circulatory collapse are among the consequences of intoxication. Since there is no antidote to reverse the toxic effects on the liver, the modality to treat ALF is a liver transplant.

Nalabothu et al.,[1] observed a 28% mortality rate that most correlated with the MELD score. Death was associated with MELD scores greater than 40, while survivors showed MELD scores of <12. The highest MELD score for our patient was 34. McCarron et al.[2] observed 23–73% mortality in yellow phosphorus toxicity based on clinical symptoms. Those with early central nervous system manifestations had a worse prognosis.[2] Recently, the MELD score has also been used to predict outcomes in patients with acute liver impairment caused by acetaminophen and other drugs. In patients with non-acetaminophen-induced-ALF (NAI-ALF), comparing the MELD score and King's College Hospital criteria, high mortality was observed in patients with a mean MELD score of 35.35.[3] NAI-ALF is associated with a significant death rate in the absence of widely accepted therapy other than liver transplantation. NAC is often used off-label for NAI-ALF though the Food and Drug Administration has only approved it for the treatment of acetaminophen overdose.

Intravenous (IV) NAC improves transplant-free survival in patients with non-acetaminophen-related ALF and early-stage hepatic encephalopathy, particularly those with coma grades I–II at admission.[4] Advanced coma grades prevent patients from benefiting from NAC, and they often need an urgent liver transplant instead. In this study, NAC was administered intravenously at doses of 150 mg/kg for the 1st hour, 12.5 mg/kg/hour for the next 4 hours, and 6.25 mg/kg/hour for the following 67 hours. IV NAC group showed a significantly higher transplant-free survival rate. This was especially true for the subgroups of patients with low-grade encephalopathy, drug-induced liver injury, and ALF linked to the hepatitis B virus.[4] The timing of IV NAC treatment influences the survival rates for all rodenticide poisonings with liver failure, and early NAC use improves outcomes.[2] The survival percentage in this context was 76% if NAC was given on day 1, 40% on the 2nd day, and 23% after the 3rd day following the rodenticide consumption.[2] In our situation, continued IV NAC therapy was employed for a total of 12 days until the normalization of hepatic indicators, particularly targeting INR of <1.5.

Prolonged IV NAC therapy was described in two observational studies in patients with NAI-ALF,[5,6] and therapy was continued for a median of 5 and 8 days, respectively. Additionally, an ongoing IV NAC regimen for up to 7 days was described in a randomized controlled trial in pediatric patients with NAI-ALF.[7] Therefore, no clear data is available concerning the extended duration of IV NAC administration in patients with NAI-ALF. In a pediatric population, IV NAC was administered in children with NAI-ALF until the INR was <1.5, until death, or until the time of liver transplant.[5] The median time of IV NAC administration in this trial was 5 days. Compared to a historical cohort, the administration of IV NAC significantly improved transplant-free survival rates (43 vs 22%; $p = 0.05$).[5] Similarly, Darweesh et al.,[6] in their observational trial on NAI-ALF, continued IV NAC until INR was <1.3. The average duration of IV NAC administration was 8 days. When compared to controlled trials, this technique was also linked to a greater transplant-free survival rate (96.4 vs 23.3%, $p = 0.01$).[6]

NAC administration hastens the healing process after hepatic injuries, as evidenced by declining trends in alanine transaminase (ALT) and bilirubin.[7] NAC may act through a variety of mechanisms, including improved peripheral tissue oxygen delivery and microcirculatory dysfunction, antioxidant activity, and cytokine storm reduction.[8] NAC also reduces IL-17 production, which has been linked to the worsening of hepatic encephalopathy and a poor prognosis. The timing of NAC treatment influences the survival rate for all rodenticide poisoning with liver failure, and early NAC use improve use improves outcomes. Prognosis is grave in patients with early onset hepatic encephalopathy, grade III encephalopathy, serum lactates >5.8, sequential organ failure assessment score >14.5, and MELD score >35.35.[9]

Conclusion

The cornerstone of treatment is liver transplantation. Plasmapheresis has been used as a bridge to transplantation with limited response. In our patient, early initiation of NAC followed by extended infusion until normalization of liver biomarkers, particularly INR, may have been beneficial in reversing the ALF caused by non-acetaminophen poisoning. NAC has been proven safe in patients with NAI-ALF. It can prolong patients' survival without liver transplantation and after transplantation. More research is required to determine the liver biomarkers that would guide the length of NAC therapy. There is also a need to define which subpopulations of patients with NAI-ALF would benefit from extended treatment duration, either as a bridge to transplant or to spontaneous recovery.

Orcid

Indira Menon https://orcid.org/0000-0002-6244-2088
Swapna M Babu https://orcid.org/0000-0001-9269-158X

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