

Successful Outcome Following a Loading Dose of N-Acetylcysteine to Treat Hepatotoxicity after Repeated Therapeutic Doses of Paracetamol

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Abstract

We describe a case of liver failure in a child with repeated therapeutic doses of paracetamol after being given multiple doses to manage pyrexia during a viral illness. The child was treated successfully with only a single loading dose of N-acetylcysteine. This case highlights the importance of parental advice and physician vigilance in preventing hepatotoxicity paracetamol overdose during viral illnesses.

Keywords Paracetamol; Hepatotoxicity; Child

Abbreviations

NAC: N-acetylcysteine

Case Description

A 22-month-old male was brought to our emergency pediatric hospital by his parents with a history of fever, diarrhea, vomiting, and lower-extremity edema.

Before attending our hospital, the patient was admitted to another hospital with persistent pyrexia, was treated with paracetamol, discharged after 4 days, and advised to continue paracetamol therapy every 4 hours to manage the fever. While at home, the patient's temperature continued to increase; he was given paracetamol orally at dosage 120 mg (98 mg/kg/day) every 3-4 hour for 7 consecutive days. His parents bought the paracetamol at a local pharmacy. After 1 week, the patient's condition had not improved; despite paracetamol therapy, he continued to have a fever and he developed diarrhea, vomiting, and lower-extremity edema. On admission, his parents reported that the patient had no history of chronic disease and had received all of the recommended vaccinations in due time.

The positive findings on physical examination included an enlarged liver 2 cm below the costal margin and edema of both ankles and feet. An initial laboratory investigation within 2 hours of arrival at our hospital revealed alanine aminotransferase (ALT) 4153 IU/L, albumin 13.6 mmol/L, ammonia 55 μ mol/L, paracetamol (acetaminophen) 88 μ mol/L, activated partial thromboplastin time (APTT) 39.6 s, prothrombin time 20 s, and an international normalized ratio (INR) ratio of 1:8. Salicylate, hepatitis B, and PCR were negative; anti-HBs and Epstein-Barr virus IgG and IgM were positive, and an ultrasound of the liver revealed borderline hepatomegaly with fatty infiltration and sludge in the gallbladder. The amylase, lipase, and lactate levels were normal.

Following clinical laboratory confirmation of hepatotoxicity and a paracetamol level of 80 μ mol/L, a loading dose of N-acetylcysteine was initiated at 150 mg/kg over 1 hour. A second dose of N-acetylcysteine

50 mg/kg intravenously was ordered, but the patient was reassessed by the primary team physicians and the second dose was stopped before completion.

In the clinical laboratory analysis repeated on the third day, the ALT was 2224 IU/L and the INR was 1:3. Subsequently, the aminotransferase concentration and coagulation parameters improved progressively, with ALT 1321 IU/L on the fourth day. The patient's condition also improved. After 8 days, the ALT was at 471 IU/L; the patient was discharged on day 9, and his parents were advised to bring him to the outpatient clinic for a checkup. At the first outpatient visit, 4 days after discharge, the ALT was 202 IU/L and no complaints were raised by his parents.

Discussion

Paracetamol (acetaminophen) is among the most frequently prescribed medications for pediatric patients with pyrexia; it is widely believed that such antipyretic treatment reduces pyrexia and pain [1]. The therapeutic use of paracetamol in pediatric patients is generally safe [2]. However, hepatotoxicity can occur regardless of recommended doses if it is repeated [3,4]. This child also had evidence of Epstein-Barr virus infection, which can also contribute to liver dysfunction. Clinical intervention with N-acetylcysteine was necessary to prevent further liver injury.

N-acetylcysteine, an antecedent of reduced glutathione, is recommended for the treatment of acetaminophen toxicity. Glutathione is produced from cysteine in the liver. When N-acetylcysteine is administered in the early stage of paracetamol toxicity, it can restore glutathione levels and prevent the liver damage induced by paracetamol [5-11]. The optimal time to evaluate serum paracetamol levels is 4 hours after ingestion, but when the duration of acetaminophen poisoning is unknown, paracetamol levels should be drawn and N-acetylcysteine should be administered immediately [10]. Paracetamol intoxication is associated with a good outcome if N-acetylcysteine is administered shortly after an overdose has been identified, although this is not always possible because patients might not seek medical assistance immediately [1].

N-acetylcysteine administration prior to measuring the paracetamol concentration has been suggested when acetaminophen toxicity is suspected [5]. Patients in whom presentation is delayed are characterized by a higher rate of hepatotoxicity (5.5% vs. 0.4%; $p < 0.0001$), and an increased likelihood of having a paracetamol concentration above the nomogram line (33.6% vs. 18.2%; $p < 0.0001$) compared with non-delayed cases; late presenters are also more likely to receive N-acetylcysteine (47.6% vs. 23%; $p < 0.0001$) [5]. The optimal dose and duration of N-acetylcysteine administration for repeated therapeutic paracetamol poisoning is unclear and treatment should be continued until the laboratory indices improve [12,13].

Intravenous NAC 300 mg/kg for 20 hours (a loading dose of 150 mg/kg infused for 15 minutes, followed by 50 mg/kg for 4 hours and then 100 mg/kg for 16 hours) has been shown to be effective in counteracting paracetamol poisoning [14]. The singular loading dose (150 mg/kg) of NAC we gave to our patient led to rapid improvement of hepatic enzymes and clinical findings without complete full IV course.

Conclusions

Although paracetamol toxicity is uncommon, it is important that physicians need to provide adequate counseling to parents regarding its use in the management of fever during viral illnesses. The pediatric dose of paracetamol should not exceed 75 mg. Additionally, children treated with frequent doses of paracetamol for more than 3 days should be assessed for possible liver injury. When there is evidence of liver injury, treatment with N-acetyl cysteine should be started immediately. Although we successfully managed paracetamol-induced liver toxicity in our patient using a single loading dose of N-acetylcysteine reversed liver toxicity in our patient, further studies are needed to clarify the efficacy of this modality.

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