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# Fomepizole as an Adjunctive Treatment in Severe Acetaminophen Toxicity

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ABSTRACT

A 33-year-old male presented to the emergency department with a chief complaint of abdominal pain after taking #50 500 mg acetaminophen tablets over the preceding two days. He was tachycardic and tachypneic, and the initial labs were notable for acetaminophen level, 337 mg/L; AST, 137 IU/L; ALT, 194 IU/L; ABG pH, 7.24; and lactate, 4.1 mmol/L. The patient was started on IV N-Acetylcysteine (NAC) as well as given a single dose of 15 mg/kg fomepizole. The patient did remarkably well, with a peak AST of 198 IU/L, peak ALT of 301 IU/L, and peak INR of 3.1. Biochemical and animal data support fomepizole having hepatoprotective effects in acetaminophen poisoning. To our knowledge, this is the first human case of an intentional dual NAC/fomepizole regimen for severe acetaminophen toxicity.



A 33-year-old male presented to the emergency department with a chief complaint of abdominal pain without vomiting after taking #50 500 mg acetaminophen (APAP) tablets over the preceding two days for pain; he denied self-harm. Past medical history was significant for alcohol abuse; routine medications were quetiapine and gabapentin. Vital signs were HR, 102 bpm; RR, 26 breaths/min; BP, 145/60 mmHg; and SpO2, 98%. His initial labs were notable for APAP level, 337 mg/L; AST, 137 IU/L; ALT, 194 IU/L; and undetectable salicylate and ethanol levels. Initial EKG revealed sinus rhythm with ventricular rate 85 bpm; PR, 154 ms; QRS, 98 ms; QTC, 506 ms. An arterial blood gas three hours after arrival revealed pH, 7.24; pCO2, 23 mmHg; pO2, 71 mmHg; and bicarbonate, 10 mEq/L. Other laboratories drawn 4 h after arrival were lactate, 4.1 mmol/L; creatinine, 1.1 mg/dL; anion gap, 16 mEq/L; and INR, 2.2. Toxic alcohol level testing was neither recommended nor performed.

IV N-acetylcysteine (NAC) was started nine hours after arrival, with 150 mg/kg given over 1 h, 12.5 mg/kg/hour for 4 h, and then 6.25 mg/kg/hour for 9 h, after which the rate was switched to 15 mg/kg/hour. Fomepizole IV 15 mg/kg was given 11 h after arrival as an antidotal adjunct for the expected severe APAP toxicity. The patient was admitted to the hospital floor, and his INR peaked the following day at 3.1; no blood products were administered. His acetaminophen was 134 mg/L approximately 19 h after arrival and was still detectable (20 mg/L) 42 h after arrival. Peak transaminases were two days after admission, with an AST of 198 IU/L and an ALT of 301 IU/L. N-acetylcysteine was discontinued three days after admission and he was medically cleared.

The patient had multiple markers for a poor expected clinical outcome. The patient's cross product (multiplication of his higher transaminase and APAP level) was over 10,000 mg/L × IU/L, corresponding to a positive likelihood ratio of 250 for hepatotoxicity (defined as peak transaminase > 1000 IU/L) [1]. He had a history of chronic ethanol use with a negative ethanol level, which was concerning for a higher risk of hepatotoxicity due to CYP 2E1 upregulation [2]. There was a delay to NAC administration of over eight hours, which is another marker of elevated risk of hepatotoxicity [2]. His serum APAP half-life was 10.2 h; a value well above 4 h and corresponding to hepatotoxicity [3]. Finally, his vital signs met systemic inflammatory response syndrome criteria, his ABG pH was < 7.3 several hours after arrival, and his lactate several hours after arrival was > 3.5 mmol/L, all of which are correlated to death without liver transplant [4–6]. With such severe expected morbidity and mortality, fomepizole was administered for hepatoprotection. Despite so many factors working against him, his peak transaminases remained well below 1000 IU/L and his INR normalized within 3 days.

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There is only one human case report published that utilized fomepizole, unintentionally, with IV NAC for severe acetaminophen toxicity [7]; however, strong biochemical data and animal data exist supporting fomepizole use. Acetaminophen's hepatotoxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI), is produced primarily via CYP 2E1. Mice with CYP 2E1 genetic "knockout" show a survival benefit for the same acetaminophen dose [8]. Fomepizole binds in the active site of 2E1 [9], and at a dose of 15 mg/kg, it achieves a concentration of 100 μmol/L for 24 h [10], which is sufficient to inhibit the majority of NAPQI creation from CYP 2E1 [11]. Animal studies show significantly decreased transaminases with fomepizole use [12,13]. Moreover, in addition to CYP 2E1 inhibition, data suggests fomepizole decreases c-jun N-terminal kinase signaling, a second pathway in acetaminophen toxicity which amplifies mitochondrial oxidative damage and leads to mitochondrial membrane collapse [14]. Finally, fomepizole has an impressive safety profile, especially at a single dose of 15 mg/kg [15].

This is now the second human case report of fomepizole use without extracorporeal elimination as an adjunctive therapy to NAC for severe acetaminophen toxicity. Limitations of this case report include the lack of testing for other causes of liver injury, such as via a hepatitis panel, and the higher dose of IV NAC that was eventually given 23 h after arrival. The patient's initial transaminitis may have been related to chronic ethanol use because we do not have baseline transaminases. However, the overall history and clinical course are classic for acetaminophen, with multiple markers for severe toxicity present. In the rare patient whose treatment with NAC is delayed, and who presents with both significant parent compound remaining as well as concerning features for severe morbidity and mortality, such as someone with an acetaminophen > 75 mg/L, pH < 7.3, lactate > 3.5 mmol/L, and a significantly elevated cross product, a single dose of 15 mg/kg fomepizole may be an option as an adjunctive treatment to NAC, but further human research needs to be done before this is routine practice.

## Declaration of Competing Interest

The authors report no conflicts of interest and have no funding to disclose.

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