Fomepizole as an Adjunctive Treatment in Severe Acetaminophen Poisoning

Alexander Kusnik, MD; Mostafa Reda Mostafa, MD, Rutwik Sharma MD , Hera Jamal MS, Mazin Hameed MD
Unity Hospital of Rochester/ Rochester Regional Health
Rochester, NY, USA

ROCHESTER REGIONAL HEALTH
Unity Hospital

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Background

Acetaminophen (APAP) is the leading cause of acute liver failure (ALF) in the Western World. N-Acetylcysteine (NAC) is considered the primary antidote for acetaminophen toxicity. Recent case series raised the question of adding fomepizole to existing NAC in acetaminophen poisoning, especially for patients with a high risk of worsening liver injury despite using NAC.

Case

A 58-year-old female with fibromyalgia and chronic alcoholism presented confused after recently ingesting large amounts of extra-strength acetaminophen. The exact timing of the last ingestion of acetaminophen could not be precisely determined but was likely 6-18h before admission. Furthermore, the patient was chronically on acetaminophen and recently increased her intake secondary to ongoing pain. The patient denied suicidal ideation. There were no signs of alcohol withdrawal.

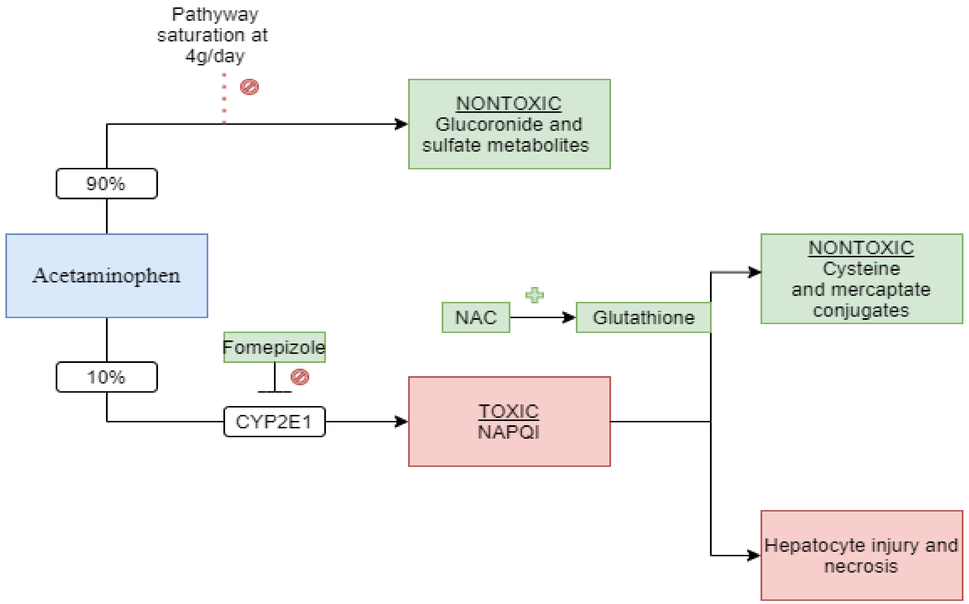
General chemistry obtained throughout the hospitalization is visualized in Table 1. Further relevant labs on admission indicated Ethanol < 0.01 gm/dl %, lactic acid 3.9 mmol/L, phosphorus 2.5 mg/dl. NAC rescue was initiated during the admitting process. In the following days, the transaminitis worsened to AST 34,665 U/l and ALT 13,995 U/l. Creatine kinase was in the regular range. Other causes for such significant transaminitis, including thrombosis or viral hepatitis, were excluded. Additionally, there was a decrease in the synthetic hepatic function with a rise in INR to 4.8 and bilirubin to 8.3 mg/dl. Furthermore, the kidney function worsened with an increase in creatinine to 2.6 mg/dl.
State poison control recommended adding fomepizole to the existing NAC regimen secondary to worsening transaminitis. The addition of fomepizole was approx. 36-48 hours after the last ingestion of acetaminophen.

The acute oliguric kidney injury (AKI), which developed between hours 34 to 40 after admission, improved slowly after 90h. The patient's liver and kidney parameters returned to baseline four weeks after admission.

TIME	0h	15h	40h	48h
ALT (U/L)	896	3117	13995	9610
AST (U/L)	2175	10400	34665	24280
Total bilirubin (mg/dl)	2.6	4.7	7.5	7.6
Creatinine (mg/dl)	0.6	0.5	1.43	1.84
Acetaminophen	126.3	33.7	<10	/
INR	1.6	3.4	4.3	3.6

Administration of Fomepizole during admission

Table 1. General chemistry obtained during the course of the hospitalization and timing of administration of Fomepizole. Last ingestion of Acetaminophen before admission was estimated to be between 6 to 18 hours



Algorithm 1. Metabolism of Acetaminophen and mechanism of action of fomepizole and NAC

Discussion

NAC is the primary antidote for acetaminophen toxicity. Existing data suggest a potential benefit in adding fomepizole to NAC.[1] The majority (90%) of acetaminophen is metabolized to nontoxic glucuronide and sulfate metabolites. The other pathway includes metabolism via CYP2E1 to a toxic metabolite called N-acetyl-p-benzoquinone imine (NAPQI). NAPQI is further metabolized to nontoxic cysteine and mercaptan conjugates via glutathione. Acetaminophen depletes glutathione stores. Hence NAC proves to be beneficial in repleting these stores. Fomepizole seems to be protective by inhibition of CYP2E1, which results in a decrease of the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). Wong et al.[2] highlighted that the multiplication of the acetaminophen concentration (µg/mL) and ALT (IU/L) correlates with the probability of developing significant hepatotoxicity. As a value of >10,000 µg/mL * IU/L predicts hepatotoxicity with a very high likelihood, adding fomepizole could be considered and discussed with state poison control.

Conclusions

Current evidence is still scarce, and randomized clinical evidence is desperately needed to authenticate the results. The decision to add fomepizole should be made by an experienced toxicologist in agreement with the patient.

Conflict of Interest

The authors have no financial conflicts of interest to disclose concerning the presentations.

References

[1] Link SL, Rampon G, Osmon S, Scalzo AJ, Rumack BH. Reply to Comments on Fomepizole as an adjunct in acetylcysteine treated acetaminophen overdose patients: a case series. *Clin Toxicol (Phila).* 2022;60(5):668-669.
[2] Wong A, Sivilotti ML, Dargan PI, Wood DM, Greene SL. External validation of the paracetamol-aminotransferase multiplication product to predict hepatotoxicity from paracetamol overdose. Clin Toxicol (Phila). 2015;53(8):807-814