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34. Outcomes of acute acetaminophen poisoned patients treated with and without fomepizole: A ToxIC Database Study

Peter Akpunonu[a,b], Jordan Woolum[b], Nena Bowman[c], Yana Feygin[d], Kory Heier[d], Caitline Phan[d] and on Behalf of the Toxicology Investigators Consortium (ToxIC)

[a]Kentucky Poison Control Center, Lexington, KY, USA; [b]UK HealthCare, Lexington, KY, USA; [c]Tennessee Department of Public Health, Nashville, TN, USA; [d]University of Kentucky, Lexington, KY, USA

Background: Acetaminophen overdose remains the leading cause of acute hepatic failure in the United States. Despite the effectiveness of N-acetylcysteine (NAC) therapy when used early in a patient's poisoning timeline, patients presenting later after an acute overdose or those who have ingested a large amount of the substance may be at risk for traditional NAC therapy failure. Fomepizole, an inhibitor of cytochrome P450 2E1 and JNK-mediated peroxynitrite formation, has been suggested to improve outcomes in case reports involving acetaminophen-poisoned patients. The purpose of this study was to evaluate whether fomepizole, when used in conjunction with standard-of-care NAC therapy, improves mortality and other clinical outcomes in acetaminophen-poisoned patients.

Methods: This was a secondary analysis of cases reported to the Toxicology Investigators Consortium (ToxIC) Core Registry between January 1, 2010, and October 28, 2024. Mono-substance acetaminophen-poisoned patients who were managed with NAC therapy were initially identified. Patients were excluded if they were reported as having a chronic or parenteral acetaminophen exposure or did not receive NAC therapy. Patients were then stratified into two groups: those receiving NAC therapy alone or NAC therapy in combination with fomepizole. The primary outcome of the study was in-hospital mortality. Secondary endpoints included the presence of any of the following during a patient's hospital course: metabolic acidosis (pH < 7.2), AST or ALT > 1000, coagulopathy (PT > 15), acute kidney injury (creatinine > 2 mg/dL), vitamin K administration, vasopressor use, transfusion, and hepatic transplantation. A subgroup analysis of high-risk poisoned patients was also conducted. Frequencies and percentages were reported. Odds ratios (OR) and 95% confidence intervals (CI) were calculated, and Chi-squared or Fisher's Exact tests were used to assess differences in proportions. Statistical significance was determined using two-sided P-values < 0.05.

Results: Cases of acute acetaminophen poisoning managed with NAC therapy (N = 3,789) were identified and divided into two cohorts: the NAC cohort (n = 3,665) and the NAC + fomepizole cohort (n = 124). Patients receiving combination NAC and fomepizole therapy were more likely to have received renal replacement therapy (1.6% vs. 12.1%, P < 0.001) and were more often classified as high-risk ingestions (5.9% vs. 12.1%, P = 0.005). Overall, no mortality improvement was seen with combination

therapy compared with NAC monotherapy (OR 3.59, P = 0.01). Metabolic acidosis, AST/ALT > 1000, coagulopathy, vitamin K use, vasopressor use, and transfusion were also more common in the combination group. Fifteen patients were identified as high-risk and receiving combination therapy, compared to 218 monotherapy patients. No deaths were identified in the combination group, compared to three patients in the monotherapy group. No significant differences in secondary outcomes were found between high-risk groups.

Conclusion: In this large database study of acute, mono-substance acetaminophen poisoning, routine use of fomepizole with NAC therapy was not associated with improvements in mortality or other clinical endpoints. Within a high-risk poisoned population, additional investigation is needed to determine the potential utility of this combination therapy.