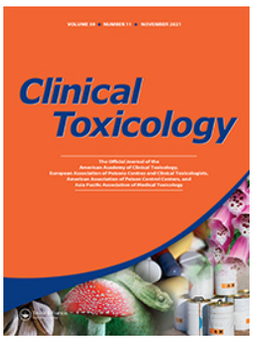

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CLINICAL RESEARCH

Fomepizole as an adjunct in acetylcysteine treated acetaminophen overdose patients: a case series

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ABSTRACT

Acetaminophen (N-acetyl-para-aminophenol or APAP) is the leading cause of acute liver failure worldwide. Standard therapy for APAP overdose is with IV N-acetylcysteine (NAC). However, overdose patients treated with NAC can still incur hepatotoxicity in some circumstances. Fomepizole has proven safety in methanol and ethylene glycol poisoning and is a potent CYP2E1 and c-Jun-N-terminal Kinase (JNK) inhibitor that is effective even in the metabolic phase. We present a case series of 14 patients who had elevated APAP levels after overdose who were treated with fomepizole as an adjunct to standard IV-NAC. Fomepizole adjunctive therapy either completely prevented any hepatotoxicity, mitigated the effects, or reversed significant hepatocellular injury.

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Acetaminophen; APAP; acetylcysteine; fomepizole; hepatotoxicity

Introduction

Acetaminophen (APAP) toxicity is the leading cause of acute liver failure worldwide [1]. Despite standard therapy with IV N-acetylcysteine (NAC), patients can still incur hepatocellular injury and prolonged hospitalizations [2]. A recent review by Mullins et al. discussed the adjunctive treatments for APAP overdose [3]. Fomepizole (4-MP) is a potent alcohol dehydrogenase and cytochrome 2E1 inhibitor with biologic plausibility to treat APAP overdose [4,5]. This case series of 14 patients treated with standard therapy and 4-MP as an adjunct to IV NAC had no significant liver injury despite persistently elevated APAP levels. Some patients had a multiplication product of acetaminophen concentration (APAP)* aminotransferase (AT) [ALT or AST, whichever value is highest] greater than 10,000 which predicts a high risk of hepatoxicity [6]. The original 6 cases were presented in a 2020 paper by Rampon et al. in Toxicology Communications [7].

APAP became first widely available in the United States (US) in the 1950s; it was marketed as the first aspirin free pain reliever. Currently APAP is the most common drug ingredient in America and is found in more than 600 different prescription and over the counter medications. Fifty million Americans use APAP each week [8]. APAP is widely available in multiple forms including capsules, suppositories, and intravenous. The maximum recommended therapeutic dose of APAP in adults is 4 grams per day or less and approximately 50 to 75 mg/kg/day in children [9]. The metabolism of APAP involves converting APAP to nontoxic sulfate and glucuronide conjugates, and a small portion is converted to the potentially toxic N-acetyl-p- benzoquinone imine (NAPQI). NAPQI is a highly reactive species that causes hepatotoxicity in APAP overdose when it cannot be bound by cytosolic glutathione and eliminated as the mercapturate [10]. Once glutathione is depleted, mitochondrial protein adducts may be formed which can lead to cell death *via* a mitogen activated protein (MAP) kinase cascade dependent process that activates c-Jun N-terminal kinase (JNK) *via* phosphorylation in the cytosol. This activated JNK allows for translocation to the mitochondria resulting in further reactive oxygen species, mitochondrial swelling, and other events which leads to hepatotoxicity [11].

In APAP overdose the standard treatment is NAC, which increases glutathione stores, acts as a glutathione substitute, binds NAPQI, and enhances sulfate conjugation. Unfortunately, despite the use of NAC, hepatoxicity can still occur especially in massive overdoses, delayed administration of NAC and potentially patients with genetic anomalies [12,13].

Fomepizole is a known inhibitor of alcohol dehydrogenase in methanol and ethylene glycol poisoning and multiple studies have demonstrated its safety [14]. Fomepizole is also a potent CYP2E1 inhibitor and been shown to reduce conversion of APAP to NAPQI *via* this mechanism [11]. Additionally, fomepizole inhibits c-Jun-N-terminal Kinase (JNK) preventing further toxicity during the metabolic phase. We present the data of 14 patients plotted on the Rumack-Matthew nomogram [17]. The purpose of this data is to determine the safety of fomepizole when used in APAP overdose.

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Case series

The cases presented occurred between 2017 and 2021. All of these cases have been treated within the same medical institution at our tertiary care pediatric and adult hospitals. We received Institutional Review Board (IRB) approval and followed guidelines per our institutions. No funding was provided. Patients in these cases presented with APAP overdose. All patients were treated with standard NAC therapy utilizing the one bag method for IV NAC dosing which consists of 30 g of NAC in one liter of IV fluid with a loading dose of 150 mg/kg over 1 h followed by a continuous infusion of 12.5 mg/kg/hour [13]. Patients were also treated with fomepizole. As we utilized fomepizole in these patients we developed a much less rigid requirement for use and were willing to administer it to patients who we thought might benefit from it. The rationale for administering fomepizole is to inhibit the NAPQI formation and mitigate the JNK cascade. The fomepizole dosing utilized in these cases is the same dosing that has been used for over 20 years in methanol and ethylene glycol poisoning [15]. The protocol for toxic alcohols/glycols is a loading dose of 15 mg/kg IV over 30 min followed by 10 mg/kg every 12 h. In our cases most patients received only one loading dose of 15 mg/kg but at the discretion of the medical toxicology service, some received a second dose of 10 mg/kg intravenously. Additional doses were utilized in known or suspected high-risk situations that could alter the half-life kinetics of APAP. This will decrease the NAPQI formation further and reduce the risks of additional toxicity. One patient who was also on continuous renal replacement therapy (CRRT) received a third dose of 10 mg/kg due to removal of fomepizole during CRRT. Cases 1 through 6 have been published in detail and can be seen in Toxicology Communications [7]. Cases 7 through 14 have not been published before and will be discussed below.

Case 7

A 45-year-old man with history of epilepsy and alcohol use disorder presented with acute encephalopathy thought to be a post-ictal state after seizures secondary to medication nonadherence. Computed tomography (CT) scan of the head was unremarkable. He was monitored in the emergency department, and three hours after arrival to the emergency department he remained presumably post-ictal. At this time, he had an episode of emesis and was immediately intubated for airway protection. Initial workup revealed APAP greater than the detectable level of our assay (>377 mcg/mL). Other relevant labs included ethanol level 239 mg/dL, ALT 14 U/L, AST 47 U/L, and mixed metabolic and respiratory acidosis with pH 7.12, pCO2 41 mmHg, HCO3 8 mmol/L. He was administered a loading dose of IV NAC 150 mg/kg over 1 h followed by a continuous infusion of 12.5 mg/kg and a loading dose of fomepizole 15 mg/kg over 30 min. After subsequent standard dilutional correction, the APAP level was reported as 791 mcg/mL. At this time NAC infusion was increased to 18.75 mg/kg and preparations for continuous renal replacement therapy (CRRT) were made. Four hours later, APAP level obtained by dilution was 691 mcg/mL. Due to clearance of NAC and fomepizole with CRRT additional boluses of NAC 75 mg/kg over 1 h and fomepizole 10 mg/kg over 30 min were given. Eleven hours after CRRT was started, APAP level was 116 mcg/mL. CRRT was stopped after twelve hours and a final bolus of fomepizole 10 mg/kg over 30 min was given at that time. NAC was discontinued after 48 h of therapy. ALT and AST peaked at only 23 U/L on day eight and 73 U/L on day five, respectively. He did not sustain any significant liver injury, and liver enzymes returned to his baseline given history of alcohol use. He was successfully extubated, returned to his neurocognitive baseline, and was discharged to inpatient psychiatry on hospital day eight. He reported that the acetaminophen came from a "broccoli and cheese casserole" that was poisoned and left for him at work, despite family endorsing he was fired from work six months prior.

Case 8

A 47-year-old woman presented to a community hospital with "lightheadedness" and confusion. She had hypoglycemia with a blood glucose of 49 mg/dL by finger stick and significantly elevated serum lactate (12.1 mmol/L). There was a delay in obtaining the collateral information about her ingesting 1 gram of acetaminophen every 4 h for 2 to 3 days for a toothache. Initial APAP level of 10.8 mcg/mL was an estimated 16 h post last dose. In this case the APAP*AT level was significantly elevated with a value of 26322. IV NAC was administered at 150 mg/kg loading dose over 1 h followed by 12.5 mg/kg/hour. The patient was transferred to a tertiary care, academic hospital ICU for further management. She presented critically ill and within a few hours was intubated on mechanical ventilation. She was hypotensive and required three vasopressors (norepinephrine, vasopressin, and Angiotensin II). She had AKI with elevating creatinine and was started on was started on CRRT. IV NAC was continued from the referring hospital. At hour 24 she received a stat dose of fomepizole 15 mg/kg over 30 min and a repeat dose 4 h after CRRT. Her transaminases continued to rise, and she was given an additional dose of fomepizole at hour 57 followed by a final dose at hour 70. She made a full recovery and did not have any signs of liver failure at discharge.

Case 9

A 43-year-old woman with a history of HIV, polysubstance abuse (cocaine, alcohol, amphetamines), depression, and epilepsy presented to a community hospital for hemorrhoidal pain. She stated that she took 10 extra-strength Tylenol pills approximately 12 h prior to admission, however, the ingestion history may have been inaccurate, and it is possible that this was a chronic overdose. She had an elevation in her ALT 2014 U/L and AST 9630 U/L, therefore, APAP was checked. Initial APAP level was 18 mcg/mL which was an estimated 19 h after last ingestion. She received a loading dose of IV NAC 150 mg/kg over 1 h followed by a continuous NAC infusion at hour 25. She received a loading dose of fomepizole

15 mg/kg over 30 min at hour 31. Her ALT and AST peaked at 3555 and 12655 respectively. Our Liver Support team would have considered her for hepatic transplantation as her INR and other studies met criteria, but given her history of substance abuse she would have been declined. She made a relatively rapid and full recovery and was discharged without any new impairments. Her transaminases quickly normalized.

Case 10

An 18-year-old woman presented after intentionally ingesting 50 tablets of acetaminophen 500 mg and 12 to 24 tablets of diphenhydramine 25 mg. Her initial APAP level was 159 mcg/mL approximately four hours after ingestion. She was given IV NAC at 150 mg/kg loading dose over 1 h followed by 12.5 mg/kg/hour and transferred to a tertiary care academic hospital. Due to impaired half-life of elimination and altered kinetics of her APAP levels, and prior experience with worse outcomes and nomogram line-crossing in patients co-ingesting diphenhydramine with acetaminophen, she was administered a loading dose of fomepizole 15 mg/kg over 30 min at approximately 8 h post ingestion. Due to elevated APAP levels she received a second dose of fomepizole at hour 21. Peak transaminases were 16 U/L and 16 U/L for AST and ALT respectively. Transaminases remained normal, and the patient was transferred to inpatient psychiatry.

Case 11

A 51-year-old woman with a history of end stage renal disease, diabetes mellitus, COPD, major depressive disorder, and intimate partner violence intentionally took 20–30 pills of Tylenol 325 mg tablets. The first APAP level was 313 mcg/mL which was approximately 4 h after ingestion. The patient received IV NAC at 150 mg/kg loading dose over 1 h followed by 12.5 mg/kg/hour at hour 6. At 16 h post ingestion she was administered a loading dose of fomepizole 15 mg/kg over 30 min. She underwent hemodialysis from hour 20 to 24 to aide with removal of APAP. At hour 27 she received a second bolus of fomepizole 10 mg/kg. Baseline transaminases were ALT 13 U/L and AST 16 U/L. Within 12 h of arrival or 16 h post-ingestion they had increased to 693 U/L and 1450 U/L for ALT and AST respectively. Her transaminases improved remarkably thereafter, and IV NAC was discontinued.

Case 12

A 15-year-old woman with a history of diabetes and self-harming behaviors presented for decreased responsiveness. She went to take a nap, and after she awoke she was altered and asking for help. Several hours after admission her family member discovered a large bag of acetaminophen and unidentified tablets. The first APAP level approximately 18 h after ingestion was 89 mcg/mL. She was started on IV NAC at 150 mg/kg loading dose over 1 h followed by 12.5 mg/kg/hour at hour 21. At 26 h post ingestion she was administered a loading dose of fomepizole 15 mg/kg over 30 min. Baseline transaminases were ALT 12 U/L and AST 18 U/L. Her transaminases rose to ALT 55 U/L and AST 142 U/L four hours later and then declined to normal.

Case 13

A 16-year-old woman with no significant medical history presented to the emergency department after experiencing abdominal pain and vomiting after stating that she took 15 acetaminophen tablets one day prior. It is possible that the patient's report of ingestion time may be inaccurate. Her

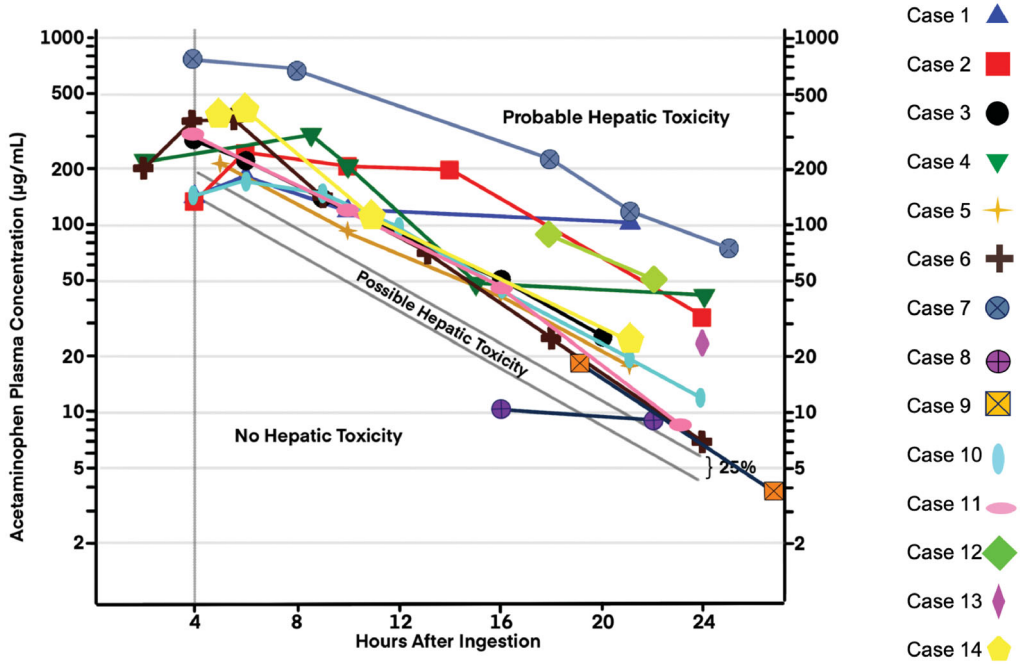

Figure 1. All 14 cases graphed on the Matthew-Rumack nomogram [17].

Table 1. Table of all 14 cases and measurements of transaminases based on time of APAP ingestion.

Case 1			Case 2			Case 3			Case 4			Case 5			Case 6			Case 7		
Peak APAP = 180			Peak APAP = 252			Peak APAP = 281			Peak APAP = 311			Peak APAP = 201			Peak APAP = 361			Peak APAP = 791		
A(140)*T(22) = 3080			A(135)*T(19) = 2565			A(281)*T(30) = 8430			A(311)*T(14) = 4354			A(201)*T(27) = 5427			A(150)*T(18) = 2700			A(691)*T(40) = 27640		
Time	ALT	AST	Time	ALT	AST	Time	ALT	AST	Time	ALT	AST	Time	ALT	AST	Time	ALT	AST	Time	ALT	AST
4	22	20	4	7	19	4	11	30	2	12	13	5	23	27	6	Fomepizole given		6	13	45
6	62	26	6	Fomepizole given		6	Fomepizole given		9	13	14	6	Fomepizole given		9	18	10	6	Fomepizole given	
6	Fomepizole given		27	9	18	20	34	47	9	Fomepizole given		12	29	54	13	19	10	8	13	40
17	61	22	52	7	14	28	37	32	16	15	16	22	21	15	34	14	9	12	13	48
40	66	38	102	12	14	40	41	34	21	12	13	46	19	18				16	Fomepizole given	
62	79	51							35	12	14							18	15	68
86	76	38							54	12	12							25	14	69
110	60	26																35	Fomepizole given	
																		60	16	59

Case 8			Case 9			Case 10			Case 11			Case 12			Case 13			Case 14		
Peak APAP = 11			Peak APAP = 18			Peak APAP = 179			Peak APAP = 313			Peak APAP = 89			Peak APAP = 24			Peak APAP = 412		
A(11)*T(2460) = 26322			A(4)*T(12655) = 50620			A(160)*T(16) = 2560			A(313)*T(16) = 5008			A(89)*T(18) = 1602			A(24)*T(4062) = 97488			A(404)*T(207) = 83268		
Time	ALT	AST	Time	ALT	AST	Time	ALT	AST	Time	ALT	AST	Time	ALT	AST	Time	ALT	AST	Time	ALT	AST
12	110	2398	12	2014	9630	4	16	16	4	13	16	18	12	18	24	2314	4062	5	207	177
16	1289	2460	23	3040	10941	8	Fomepizole given		16	Fomepizole given		22	55	142	32	3812	6222	8	281	201
19	1738	3138	30	3555	12655	16	10	14	18	693	1450	26	Fomepizole given		32	Fomepizole given		11	269	180
24	Fomepizole given		31	Fomepizole given		21	Fomepizole given		23	686	1027	30	49	67	36	3764	5657	13	Fomepizole given	
29	3325	7009	34	2684	8722	24	10	13	27	Fomepizole given		39	39	43	49	3152	2931	21	398	303
36	Fomepizole given		40	1934	5473	48	11	11	34	554	669	43	36	37	64	2244	1045	23	Fomepizole given	
41	3209	9305	51	1772	3728				46	428	356				88	1519	387	30	582	453
53	2791	8590	58	1372	2119				58	449	332				100	1281	251	36	776	678
57	Fomepizole given		71	1779	884				69	346	182				147	654	74	45	1151	1103
65	2255	5534	114	382	64				81	315	126				220	284	32	52	1260	943
70	Fomepizole given								93	240	84							63	1024	478
258	118	77																81	721	160

Time in hours from estimated or confirmed ingestion.
ALT reference range 6-46 U/L.
AST reference range 3-35 U/L.
APAP reference range <3 mcg/mL.
APAP*AT is the first acetaminophen level multiplied by the ALT or AST (whichever value is highest) at the same period in time.

initial APAP level approximately 24 h after ingestion was 24 mcg/mL. Her presenting transaminases were ALT 2314 U/L and AST 4062 U/L. She was started on IV NAC at 150 mg/kg loading dose over 1 h followed by 12.5 mg/kg/hour at hour 30. Two hours after NAC was started her transaminases rose again to ALT 3812 U/L and AST 6222 U/L. She was transferred to a tertiary medical center, and at 32 h post ingestion she was administered a loading dose of fomepizole 15 mg/kg over 30 min. Transaminases were improving 4 h post fomepizole at ALT 3764 U/L and AST 5657 U/L. She also had elevated INR 2.5 and was administered 10 mg IV vitamin K. Serum ammonia was 119 umol/L, and she was given lactulose. The patient made a full recovery and transaminases significantly improved after treatment.

Case 14

A 64-year-old woman with a history of alcohol use was found unresponsive in her bedroom with broken furniture scattered about. A large bottle of Tylenol was nearly empty when she was found and she was intubated on scene. Her first APAP level approximately 5 h after ingestion was 404 mcg/mL. Repeat APAP level an hour later was 411.6 mcg/mL at the referring community hospital. Her presenting transaminases were ALT 207 U/L and AST 177 U/L. She was started on IV NAC at 150 mg/kg loading dose over 1 h followed by 12.5 mg/kg/hour at hour 6. She was transferred to our tertiary medical center and 13 h post ingestion she was administered a loading dose of fomepizole 15 mg/kg over 30 min after GI/Liver Support consult who contacted Medical Toxicology for advice on employing fomepizole. Transaminases continued to rise and at hour 23 she was given a second dose of fomepizole 10 mg/kg over 30 min. At hour 81 her transaminases had improved and she did not show any signs of deterioration.

Discussion

In this case series, we describe the adjunctive use of fomepizole in acute APAP overdose for prevention of hepatotoxicity. In each case, the decision to employ fomepizole was based on the physiologic plausibility of fomepizole to prevent hepatocellular injury by methods of CYP2E1 inhibition preventing conversion to NAPQI and subsequent inhibition of JNK-induced development of reactive oxygen species [16]. In most cases APAP levels were in the high-risk category of hepatotoxicity when plotted on the Rumack-Matthew nomogram (Figure 1) [17]. In case 8, fomepizole was employed due to concerns of continued JNK-mediated hepatocellular injury. We utilized the standard dosing for fomepizole used for toxic alcohol/glycol ingestion (15 mg/kg IV over 30 min) with repeated doses of 10 mg/kg every 12 h at the discretion of the medical toxicology service in the setting of persistently elevated APAP levels. The APAP*AT multiplication product, calculated by multiplying the serum aminotransferase (ALT or AST, whichever value is higher) activity and the APAP concentration [18,19] are shown in Table 1. Retrospective analysis of over 3800 APAP cases at two tertiary centers indicated that patients with a multiplication product less than 1500 were unlikely to develop hepatoxicity, while multiplication products greater than 10,000 were predictive of high risk [6]. Cases 8 and 9 had AST:ALT ratio greater than 2 which is considered a high-risk feature for death [20]. All patients received standard of care therapy with IV-NAC and renal replacement therapy when indicated. Limitations of this observational case series include that this was not an organized clinical trial designed to investigate the effectiveness of fomepizole in preventing hepatotoxicity. There was no formalized protocol for administration of fomepizole, and the decision to administer fomepizole was at the discretion of the primary physician and the consulting medical toxicologist. The attending toxicologist utilized clinical judgement to determine the use of fomepizole in high-risk patients, especially if APAP levels persisted due to altered half-life or risk factors for toxicity. To that extent it was systematic, and the patients were consecutive with high-risk factors. There were no unfavorable outcomes in any patient. Despite these limitations, this case series demonstrates the safety of fomepizole in acute acetaminophen overdose with better-than-expected outcomes.

Conclusions

The efficacy of fomepizole needs to be further elucidated through controlled clinical trials on a larger scale. In a subset of patients that presented within 8 h of an APAP overdose where levels were greater than 300 mcg/mL, nine percent of cases still experienced hepatoxicity [21]. In massive APAP overdoses, fomepizole should be considered as an adjunct due to the known failure rate of NAC and the safety profile of fomepizole. This case series has demonstrated the safety with no observable side effects and possible efficacy and a potential pivotal role in APAP overdose. We postulate that the combination of inhibiting NAPQI production and JNK activity contributed to the better-than-expected outcomes in our patients. Further work in a controlled trial will determine the effectiveness of this adjunctive treatment.

Disclosure statement

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