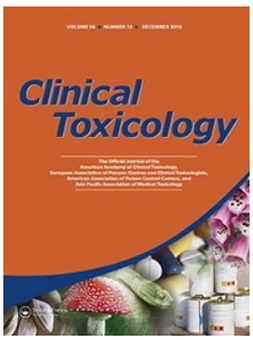

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CLINICAL RESEARCH

Single versus continued dosing of fomepizole during hemodialysis in ethylene glycol toxicity

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ABSTRACT

Background: In cases of ethylene glycol (EG) toxicity requiring hemodialysis (HD), fomepizole is dosed every four hours. HD efficiently clears EG and its toxic metabolites, and it's unclear if multiple doses (MD) of fomepizole improve patient outcomes or whether a single dose (SD) prior to initiation of HD is sufficient.

Methods: We reviewed cases of EG toxicity at a toxicology referral center from 2008 to 2018. Patients treated with HD with EG levels greater than 20 mg/dL were included. Duration of dialysis, creatinine at discharge, hospital length of stay (LOS), and complications were analyzed. We compared patients who received a single dose of fomepizole prior to HD to those who received continued dosing during and after HD.

Results: Twenty-five patient encounters were identified (MD: 20; SD: 5). Initial bicarbonate (11 [SD] vs. 9 mg/dL [MD]) and pH (7.1 vs. 7.1) were similar between the groups; however, there was a trend toward a greater proportion of patients with renal dysfunction in the MD group: 11 (55%) vs. 1 (20%). HD was initiated a median interval of 5.2 h [SD] vs. 5.7 h [MD] after a dose of fomepizole. There was one death in the MD group and none in the SD group. Median creatinine on the day of discharge was 0.7 mg/dL (IQR: 0.57–3.8) in the SD group and 2.0 mg/dL (0.90–7.0) in the MD group. LOS was similar (5.8 days [95% CI 3.6–8.0] vs. 7.6 days [5.3–9.9]) ($p = .61$).

Conclusion: Patients with moderately severe EG toxicity (acidosis and no initial renal dysfunction) treated with a single dose of fomepizole prior to HD had similar outcomes to those receiving continued dosing of fomepizole during or after HD. This raises the possibility that a single dose of fomepizole may be sufficient if HD is initiated quickly.

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Ethylene glycol; fomepizole; hemodialysis

Background

Ethylene glycol (EG) ingestions continue to be a source of poisoning in the US with 6411 poison center calls in 2018, about a third of which were for hospitalized patients [1]. Toxicity is characterized by encephalopathy, progressive metabolic acidosis, and renal failure. In order to prevent end organ damage, inhibition of alcohol dehydrogenase by fomepizole or ethanol (used historically or in resource poor settings) is needed [2,3]. These agents block the conversion of ethylene glycol into glycolic acid and oxalic acid, the primary causes of metabolic acidosis and renal failure with toxicity [4]. With fomepizole, extended treatment is possible and may obviate the need for hemodialysis [2,5]. However, hemodialysis (HD) is required in order to remove ethylene glycol's toxic metabolites, treat metabolic acidosis, and clear EG in the setting of renal dysfunction. During hemodialysis, recommendations are to continue fomepizole, but at an increased dosing frequency of every 4 h as opposed to every 12 h in order to compensate for increased fomepizole clearance [3]. Hemodialysis removes toxic metabolites efficiently, and therefore although recommended it is unclear if continued dosing of fomepizole is needed.

In this study, we sought to compare patient outcomes between those treated with continued dosing of fomepizole during hemodialysis to those who only received a single dose prior to HD. We hypothesized that a single dose of fomepizole prior to HD would lead to similar outcomes as the administration of continued dosing during HD.

Methods

This is a retrospective review of patients treated for ethylene glycol toxicity. Our institution's IRB approved the study [STUDY19010015]. We included patients from 2008 to 2018 who underwent toxic alcohol testing, had EG levels >20 mg/dL, and were managed at one of three academic hospitals within our hospital system. Only those patients in whom hemodialysis was initiated were included. Exclusion criteria included patients with elevated levels of other toxic alcohols (methanol, isopropyl alcohol), those receiving initial therapy

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with continuous modalities (CVVH/HD), and those in whom documentation was limited and the number of doses of fomepizole or the duration of hemodialysis was not recorded. Patients were divided into two groups – those receiving a single dose of fomepizole (SD) prior to the initiation of HD, and those receiving multiple doses (MD) of fomepizole with administration during or after HD. Baseline characteristics including pH, creatinine (Cr), age, and initial EG level were recorded. Duration of hemodialysis was also recorded. Outcome variables included peak Cr, discharge Cr, need for hemodialysis upon discharge, hospital length of stay, and any other major complications identified during hospitalization. Two reviewers, JVM and AS, independently reviewed patient charts and compiled the data into a shared database using a standardized form. All data was pulled directly from patient charts. If any discrepancies occurred, the patient chart was re-reviewed, and the two reviewers reached a conclusion after discussion. Baseline characteristics were compared between the groups. Median levels or means were calculated for continuous data when appropriate and to characterize the data interquartile ranges or 95% confidence intervals were used. Data between groups was compared using a Fisher's exact test for categorical variables and a two-tailed Mann-Whitney *U* test for continuous variables. A *p*-value $<.05$ was deemed to be significant.

Results

Twenty-five patient encounters were ultimately included after an initial screen identified 124 hospitalizations with positive ethylene glycol levels. Out of these, 105 patients had an initial level greater than 20 mg/dL. We excluded 29 patients who were treated with fomepizole alone (no HD) and 44 who were managed outside our medical center (no records apart from EG levels were available). Seven additional patients were excluded for receiving CVVH/HD as an initial treatment ($N = 3$), inadequate medical records ($N = 2$), or for having a co-ingestion of methanol ($N = 2$) (Figure 1). Of the 25 patient encounters, three patients were included twice given multiple overdoses. Of these, two received multiple doses of fomepizole each hospitalization and the other patient had one visit included in the SD group and the other in the MD group. Records on the initiation of fomepizole prior to hemodialysis were present in 4/5 patient in the SD group and 17/20 in the MD group. In the four remaining patients, the exact timing was unknown due transfer from an outlying hospital.

Baseline characteristics between the two groups were similar. These are included in Table 1. Ethylene glycol levels ranged widely between the groups with a median level of 292 mg/dL (IQR: 84–1740) in the SD group and 170 mg/dL (65–270) in the MD group. All patients had metabolic acidosis upon arrival. Bicarbonate (mg/dL) (median: 11 [IQR: 9–12] vs. 9 [6–10]), pH (mean: 7.1 [range: 6.9–7.17] vs. 7.1 [6.6–7.19]) and creatinine (mg/dL) (median: 0.9 [IQR: 0.9–2.2] vs. 1.6 [1.0–1.8]) [$p = .23$] were similar between the SD and MD group.

Despite these apparent similarities, there was a trend toward a greater proportion of patients in the MD group having renal dysfunction (defined as a creatinine (Cr) >1.5 mg/dL) on presentation. Eleven (55%) patients in the MD group vs. one (20%) in the SD group had renal dysfunction prior to the initiation of HD ($p = .32$). Duration of dialysis tended to be higher in the MD group as well, but statistically was no different (median: 6.0 h [IQR: 5.0–10] vs. 8.1 h [5.6–11]), with 2/5 [SD] and 10/20 [MD] receiving HD for >8 h. An average of five doses of fomepizole was given amongst the patients in the MD group (range: 2–7). Fomepizole was initiated at least 12 h prior to HD for all patients in whom records on the exact timing was available ($N = 21$). The time interval from dosing of fomepizole to the initiation of HD was similar between the groups (median: 5.2 h [SD] vs. 5.7 h [MD]).

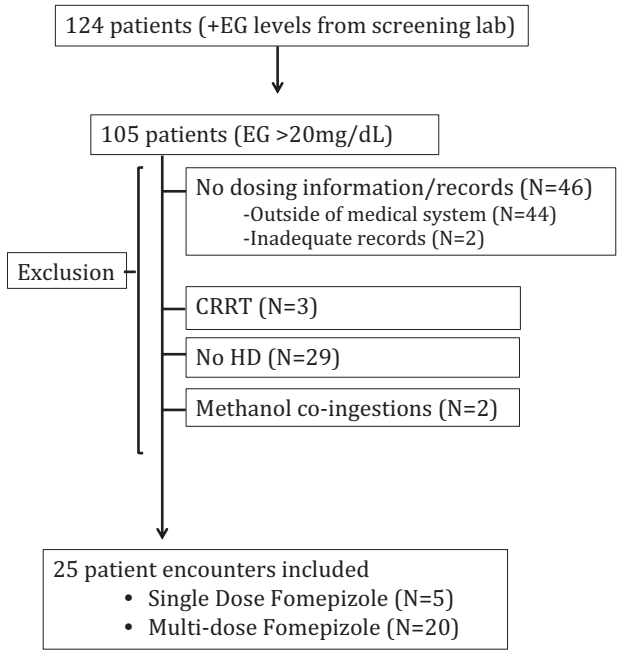


Figure 1. Inclusion and exclusion flowchart. Abbreviations: CRRT: continuous renal replacement therapy; EG: ethylene glycol; HD: hemodialysis.

Table 1. Baseline characteristics and initial laboratory results.

	Single dose (SD) [$N = 5$]	Multi-dose (MD) [$N = 20$]
Sex		
Men	4 (80%)	11 (55%)
Age (year)		
Mean:	66	51
Range:	45–79	38–76
Initial creatinine (mg/dL)		
Median:	0.9	1.6
IQR:	0.9–2.2	1.0–1.8
Renal dysfunction		
N (%):	1 (20%)	11 (55%)
Bicarbonate (mMol/L)		
Median:	11	9
IQR:	9–12	6–10
pH		
Median:	7.1	7.1
Range:	6.9–7.17	6.6–7.19
Ethylene glycol (mg/dL)		
Median:	292	170
IQR:	84–1740	65–270

Table 2. Treatment and outcomes.

	Single dose (SD) [$N = 5$]	Multi-dose (MD) [$N = 20$]	p-Value
Discharge creatinine (mg/dL)			
Median:	0.7	2.0	.06
IQR:	0.57–3.8	0.90–7.0	
Peak creatinine (mg/dL)			
Median:	0.96	4.9	.09
IQR:	0.90–3.8	1.6–8.2	
Duration of HD (h)			
Median:	6.0	8.1	.68
IQR:	5.0–10	5.6–11	
Dialysis $>$ 8 h			
N (%):	2 (40%)	10 (50%)	1.0
Interval from Fomepizole to HD (h)			
Median:	5.2	5.7	.75
Range:	2.6–10	0–11	
Length of stay (days)			
Mean:	5.8	7.6	.61
95% CI:	3.6–8.0	5.3–9.9	

For the patients receiving multiple doses of fomepizole, 18 (90%) had an initial dose of fomepizole followed by initiation of HD with additional dosing during or after HD. In the two patients who did not, one was given their first dose at the onset of HD and another had two doses prior to HD due to delays in transfer to our tertiary care center. Seventeen patients (85%) received fomepizole during HD (median doses: 2; IQR: 1–3). Three patients received all of their additional doses after HD. In one case this was due to a short course of HD with ethylene glycol levels remaining elevated afterwards. In the remaining two cases, an additional dose of fomepizole was given at the end of dialysis as a precaution due to a lack of rapid serum testing to guide the length of treatment.

In the SD group, all patients survived and one required HD (20%) on discharge. In the MD group, one patient died and seven (35%) required temporary HD after discharge. Two patients had additional complications during their hospitalization. One developed bilateral lower extremity deep vein thromboses and another developed aspiration pneumonia and received a tracheostomy for prolonged ventilatory needs. Out of the patients presenting with no renal dysfunction (Cr $<$ 1.5 mg/dL) in the SD group ($N = 4$), none developed renal injury. Overall, there was a non-significant trend toward a lower Cr on discharge in the SD group compared to the MD group: 0.7 mg/dL vs. 2.0 mg/dL. Mean hospital LOS between the two groups was similar: 5.8 days vs. 7.6 days (Table 2).

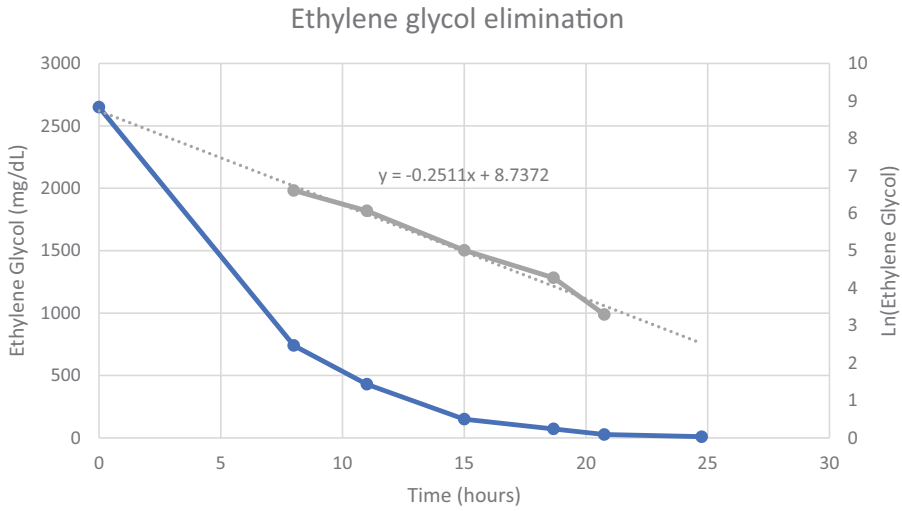
In the patient with the highest ethylene glycol, 2650 mg/dL (also the highest reported in the literature), treatment consisted of a single dose of fomepizole followed by hemodialysis. No renal dysfunction or metabolic acidosis developed during hospitalization. The first-order elimination rate constant during hemodialysis was 0.25 h^{-1} which is similar to patients treated with fomepizole during hemodialysis [6].

Discussion

During HD, recommendations are to increase the frequency of fomepizole dosing. Hemodialysis removes fomepizole efficiently with a reported clearance of 117–137 mL/min. Therefore, in order to maintain a level that adequately blocks metabolism of ethylene glycol, 10 μmol/L, re-dosing every four hours is needed [3,7]. An additional determination is made whether to re-dose fomepizole at the start of HD depending on the length of time from the preceding dose. This increased dosing frequency has been recommended by the US manufacturer of fomepizole but is based on the pharmacokinetics of fomepizole during HD rather than proven benefit.

Detailed pharmacokinetics of ethylene glycol metabolites during HD is limited, but information on glycolate is available. Glycolate accumulates to the highest degree after an ingestion of EG and is largely responsible for the metabolic acidosis [4]. The half-life of glycolate during hemodialysis has been reported as 2.4, 2.6, and 3.9 h in various case reports with clearances ranging from 137 to 170 mL/min [8,9]. This data suggest glycolate is cleared at about the same rate as ethylene glycol which has a half-life of 2.4 h during HD [8]. Therefore, by the time alcohol dehydrogenase inhibition is ineffective, a large proportion of EG metabolites will have been cleared. In Brent et al. no patient in whom initial glycolate levels were less than 76.8 mg/dL developed renal injury when treated with fomepizole, and glycolate levels did not rise prior to repeat doses of fomepizole [2]. Given this, we suspect HD clears and prevents these metabolites from reaching toxic levels capable of causing renal injury even with continued production of these metabolites.

The potential harm from failing to maintain alcohol dehydrogenase inhibition during HD would be the accumulation of EG metabolites which could then produce end organ damage. We therefore sought to analyze measures that would serve as proxies for a failure of hemodialysis to adequately clear EG metabolites without ADH inhibition. We found a non-significant trend toward an increased LOS, a higher creatinine upon discharge, and more adverse effects in the MD group. No increase in adverse effects were found in the SD group. These findings were likely driven by the fact that the MD group was potentially more delayed in presentation. There was a trend toward more renal dysfunction on presentation and longer durations of HD in the MD



Graph 1. Ethylene glycol concentrations over time in patient with highest reported initial concentration. All measured concentrations are shown in blue, on a linear scale (left-sided *y*-axis), while intra-dialysis concentrations are shown in gray, on a logarithmic scale (right-sided *y*-axis) and are used to estimate first-order elimination during hemodialysis (dotted line fit using least squares regression).

group, which may have affected the number of doses of fomepizole given and made it difficult to directly compare outcomes between the groups.

Nevertheless, we found that administering only a single dose of fomepizole in a small number of patients who had already developed moderate to severe acidosis did not lead to them developing renal dysfunction during hospitalization. Since a pH $<$ 7.3 has been linked to an increased risk of renal failure and all of the patients in the SD group had a significant acidosis upon presentation (median pH: 7.1), but did not progress to renal failure, the suspected harm from withholding fomepizole may be unwarranted, but certainly requires further investigation [10]. It is possible that in a select group – those requiring hemodialysis but without renal dysfunction on presentation – a protocol of administering a single dose of fomepizole followed by hemodialysis is safe and not associated with any increased risk.

This study did not analyze the patient cohort in whom it would be safe to treat with fomepizole alone. Prior work has shown that fomepizole alone has led to good outcomes in patients without initial renal dysfunction and with no or minimal acidosis [5]. The exact cutoff pH in which it would be safe to forgo hemodialysis has not been studied. Usually this is made on a case-by-case basis. In the Levine et al. [5] analysis on treatment of EG with fomepizole alone, one patient who had an initial pH of 7.3 and an anion gap of 29, developed transient renal dysfunction. However, three patients with mild metabolic acidosis (pH 7.28–7.29) did well. No patients with more severe acidosis were included. In our study, no patient had a pH $>$ 7.19 indicating that this was a distinct patient population, one with more severe toxicity on presentation.

The limited number of patients and lack of randomization certainly allows for confounding effects. The small sample size in the SD group potentially minimized the chance of finding adverse effects with this method of treatment. The presence of a greater number of patients with renal dysfunction at baseline would add to our confidence in the findings and lead to a more representative sample. One potential counterargument to a single dose protocol would be that continued dosing of fomepizole may be needed with higher EG concentrations, as hemodialysis would need to be continued for an extended period of time and the potential for accumulation of metabolites exists. Anecdotally however, in the patient with the highest EG level in this study and highest reported in the literature, 2650 mg/dL, a single dose of fomepizole was given prior to hemodialysis and no renal dysfunction nor any other adverse effects developed.

Conclusion

Continued dosing of fomepizole once dialysis is initiated may be unnecessary in a select group of patients as hemodialysis theoretically removes toxic metabolites as they are produced, but further evidence is needed to ensure the safety of this approach.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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