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Predictors of Death and Prolonged Renal Insufficiency in Ethylene Glycol Poisoning

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Abstract

Background: We assessed the predictive value of selected factors on the outcomes of death and prolonged renal insufficiency (RI) from ethylene glycol poisoning. **Methods:** Retrospective, observational California Poison Control System study, over a 10-year period (1999-2008). We compared 2 groups. The first group (D/RI) included 59 patients who died (9 patients) or had prolonged RI (50 patients). Prolonged RI was defined as kidney injury in which dialysis was required for greater than 3 days after presentation. The second group (RECOV) of 62 patients had an uncomplicated recovery. Secondarily, we evaluated the association of time to antidote (ethanol and/or fomepizole) and time to dialysis with these outcomes. **Results:** The D/RI group was more likely than the RECOV group to present comatose, have seizures, and require intubation. The D/RI group had a lower mean initial arterial pH of 7.03 (standard deviation [SD] 0.20), compared to 7.27 (SD 0.14) for the RECOV group. The D/RI group had a higher initial creatinine (1.7 mg/dL, SD 0.71) than that of the RECOV group (1.0 mg/dL, SD 0.33). Patients with a time to antidote greater than 6 hours had a higher odds of dying or having prolonged RI (OR 3.34, 95% CI: 1.21-9.26) Patients with a time to dialysis greater than 6 hours had a lower odds of dying or having prolonged RI (OR 0.36, 95% CI : 0.15-0.87). **Conclusion:** Compared to survivors with an uncomplicated recovery, patients poisoned with ethylene glycol who died or had prolonged RI were more likely to exhibit clinical signs such as coma, seizures, and acidosis. Antidote administration within 6 hours is associated with better outcomes, unlike earlier time to dialysis.

Keywords

ethylene glycol, fomepizole, dialysis, renal failure, mortality

Introduction

Ethylene glycol is a toxin, most commonly found in vehicle antifreeze, which causes significant morbidity and mortality in overdose. Toxicity is caused by metabolism of ethylene glycol to glycolic and oxalic acids by the enzymes alcohol dehydrogenase and aldehyde dehydrogenase. These toxic acid metabolites can produce profound acidosis leading to death from cardiovascular collapse and dysrhythmia. Acidosis, prolonged cerebral hypoperfusion, and possibly calcium oxalate deposition have also been observed to cause cerebral edema and brain death.[1] Survivors often have prolonged, but mostly reversible, renal insufficiency (RI) attributed to renal precipitation of calcium oxalate crystals.[2]

Diagnosis of ethylene glycol poisoning is challenging. Often, clues to ingestion are not available and immediate laboratory confirmation is not generally available at most health care facilities. Additionally, acidosis and osmol gap may be attributed to a number of other more common illnesses such as sepsis and diabetic ketoacidosis.[3]

Despite the prevalence and severity of ethylene glycol poisoning, there is a paucity of studies that analyze prognostic factors. Although it is intuitive that earlier antidotal blockade of alcohol dehydrogenase and extracorporeal removal of toxin will lead to better outcomes, it is not clear what window of opportunity exists. This study aims to determine the predictive value of initial arterial pH (pH_I), initial serum creatinine (Cr_I), and peak serum creatinine in the first 24 hours of hospitalization (Cr_{24}), time–to–antidote administration, and time-to-dialysis on the outcomes of death and prolonged RI.

Methods

Study Design and Setting

This was a retrospective cohort study of laboratory-confirmed cases of ethylene glycol poisoning that was reported to

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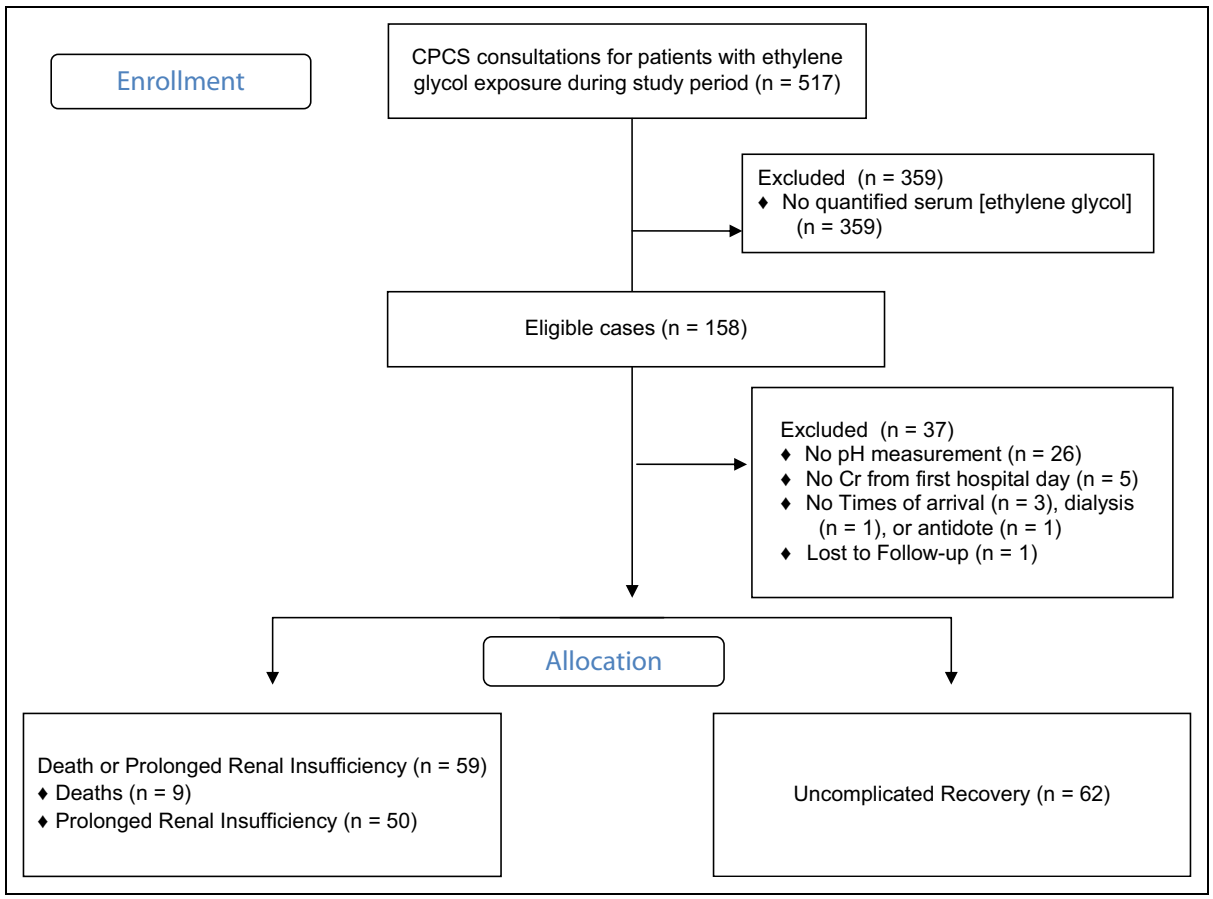

Figure 1. Case inclusion and exclusions.

the California Poison Control System (CPCS) during the 10-year period of January 1, 1999 to December 31, 2008. The CPCS receives approximately 320,000 consultations annually from patients and health care providers in the state of California and is available 24 hours per day. Calls are managed by specialists in poison information (SPI) who are licensed pharmacists or nurses with specialized training in clinical toxicology. Medical toxicologists are available for consultation on complex cases. Cases judged by the SPI to have potentially significant toxicity are followed until the outcome is known. For each consultation, a detailed electronic case record is created in Visual Dotlab (VDL, WeBeMe Software, Fresno, CA) according to the guidelines of the American Association of Poison Control Centers (AAPCC), which includes text-based notes of the case as well as coded entries for demographic and clinical variables including age, sex, reason for exposure, symptoms, treatments, and medical outcome. Every note entered in VDL is permanent and automatically time stamped.

Study Population

We searched 10 years of data in VDL from January 1, 1999 through December 31, 2008. We searched the VDL database for cases coded with AAPCC generic codes and POISINDEX product identification codes for "ethylene glycol." We included all ingestions regardless of intent. This yielded a total of 517 consultations for ethylene glycol exposure.

Of these, 158 cases included a documented serum measurement of ethylene glycol. We further limited the cases to include only those that recorded a pH_I measurement, a serum creatinine measured within the first 24 hours of hospitalization, and text notes of the case detailed enough to determine the timing and duration of antidotal and dialysis treatments. One further case was excluded because it was lost to follow-up. This yielded a total of 121 cases for analysis (Figure 1).

Variables

We extracted the following information from the VDL charts: age, gender, estimated time of health care presentation after ingestion, estimated time of initiation and duration of antidotal treatment (ethanol and/or fomepizole) and dialysis treatments, pH_I measurement, Cr_I, Cr_{24}, notable clinical events (eg, seizures and cardiac arrest), and outcomes of survival, death, and prolonged RI. Peak creatinine during the first 24 hours was also analyzed because it is well known that elevated creatinine is a delayed serologic manifestation of acute renal injury.[4] From the

times of health care presentation and initiation of antidotal and dialysis therapies, we derived door-to-antidote (D2A) and door-to-dialysis (D2D) times.

We broadly interpreted text notations of altered mental status (AMS) as either somnolence or coma. Any altered mental state but exhibiting some verbal or physical responsiveness was categorized as somnolence. Any notation of a state of unresponsiveness was categorized as coma.

We arbitrarily defined prolonged RI as a state of renal function requiring >3 days of dialysis. We assumed that dialysis performed for the purpose of elimination of the parent compound ethylene glycol or its metabolites would be completed within the first 24 hours and certainly before 3 days. We defined prolonged RI as the need for clinical treatment rather than the creatinine measurement: we felt this was a more clinically relevant outcome than a discrete creatinine measurement.

Using estimated times of patient arrival and initiation of antidotal and/or dialysis therapy, we recorded D2A and D2D times. We decided to broadly categorize these times into arbitrary ranges of times (eg, 0-3 hours and >24 hours) instead of examining discrete times because we recognize that many factors likely obscure the precise recording of these times. Exact times were rarely recorded. Also, any number of events might have occurred between the actual initiation of treatment by the treating health care providers and the time the CPCS specialist logged their VDL text note. Our time ranges are more narrow earlier in the clinical course because CPCS specialists commonly correspond with the treating provider multiple times within the first 24 hours of these cases due to the many nuances and complexities of treating these poisonings.

Data Analysis

We divided the 121 cases of confirmed ethylene glycol poisoning into 2 groups for comparison. The first group included 59 patients who died (9 patients) or had prolonged RI (50 patients; D/RI). Prolonged RI was defined as kidney injury in which dialysis was required for greater than 3 days after hospital presentation. The remaining 62 patients had uncomplicated recovery (RECOV). Descriptive statistics were used to compare the 2 groups. Primary outcome measures were the incidence of prolonged RI and death. Other significant clinical effects were compared between the groups. Descriptive statistics were used for categorical data. Student *t* test was used for continuous variables and Fisher exact test for bivariate variables. Additionally, to evaluate the association of time to antidote and time to dialysis with dying or prolonged RI, we estimated odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression models. To consider potential confounding, we took into account age and gender. We attempted to adjust for pH_I, as discrete and categorical variables, but the logistic regression model failed, given the strength of pH_I as a predictor of outcome. SPSS (v20, IBM Corp, Armonk, New York) was used for data collection and descriptive statistics analysis. SAS (v9.2, SAS Institute Corp, Cary, North Carolina) was used for logistic regression analysis.

This study was approved by the University of California, San Francisco Committee on Human Research and by the CPCS Research Committee.

Results

Descriptives

Of the 517 consultations to the CPCS for possible ethylene glycol exposure during the study period, we analyzed 121 laboratory-confirmed cases of ethylene glycol poisoning that met our inclusion criteria. Descriptive statistics comparing D/RI (59 patients) and RECOV (62 patients) are represented in Table 1. Patients in D/RI and RECOV groups were of similar age, but males appeared to be more likely than females to have prolonged RI or death. Males represented 78% of D/RI and 58.1% of RECOV. Although D/RI presented with a higher mean ethylene glycol level of 240.4 mg/dL (standard deviation [SD] 307) than that of RECOV with 171.8 mg/dL (SD 168.3), this was not statistically significant ($P = .13$). No difference between the type of antidote (ethanol and or fomepizole) was found between D/RI and RECOV. Finally, dialysis was much more likely to be used in D/RI (98.3%) than in RECOV (69.4%).

As would be expected, D/RI was more symptomatic than RECOV. Patients in the D/RI group were more likely than the RECOV group to present with somnolence or coma (OR 29.71, 95% CI: 3.8-229.7), require intubation (OR 20.23, 95% CI: 8.03-51.0), and have seizures (40.7% compared to none). Patients in the D/RI group were nonsignificantly ($P = 0.12$) more likely than RECOV to require vasopressor support (OR 3.09, 95% CI: 0.78-12.25).

Table 2 provides succinct descriptions of the 9 deaths. These patients were severely symptomatic on arrival. Most were comatose and had an initial pH measurement under 7.0. Eight patients had a creatinine greater than 1.0 mg/dL on arrival. Interestingly, 6 of these patients were noted to have a serum calcium measurement under 8.0 mg/dL during their clinical course. Finally, it is notable that in the majority (6 patients) of these cases, antidotal and dialysis therapies were delayed for more than 12 hours from patient presentation or were incompletely administered.

Initial arterial pH, Cr_I, and Cr_{24}

Initial arterial pH, Cr_I, and Cr_{24} measurements appear to provide some prognostic information.

Patients in the D/RI group presented with a lower mean pH_I of 7.03 (SD 0.20) than those of the RECOV group with a pH_I of 7.27 (SD 0.14). Based on a receiver–operating characteristic (ROC) curve, a pH_I of 7.37 or less had a sensitivity of 94.9% and a specificity of 75.8% for the outcomes of RI or death. A pH_I under 7.0 produced a sensitivity of 35.6% and a specificity of 95.2% for RI or death. The area under the ROC was 0.85 (95% CI: 0.77-0.92; Figure 2).

Patients in the D/RI group had a higher Cr_I (1.7 mg/dL, SD 0.71) than those of the RECOV group (1.0 mg/dL, SD 0.33). Based on an ROC curve, a Cr_I of 0.95 or higher had a

Table 1. Clinical and Laboratory Characteristics of 121 Patients With Ethylene Glycol Poisoning.

	All Patients (121)	D/RI (59)	RECOV (62)	*P* Value[a]	OR (95% CI)
Age, years	42.0 (15-89), SD 16.3	43.1 (16-84), SD 13.9	40.9 (15-89), SD 18.3	.47	
Gender, male	82 (67.8%)	46 (78%)	36 (58.1%)	***.021***	***2.56 (1.15-5.66)***
EG, mg/dL	202.2 (3-1540), SD 247.3	240.4 (5-1540), SD 307.0	171.8 (3.0-675), SD 168.3	.13	
pH	7.16 (6.6-7.6), SD 0.21	7.03 (6.6-7.6), SD 0.20	7.27 (6.70-7.43), SD 0.14	***<.01***	
Cr, initial, mg/dL	1.4 (0.6-3.7), SD 0.65	1.7 (0.6-3.7), SD 0.71	1.0 (0.6-2.2), SD 0.33	***<.01***	
Cr, peak 24 hours, mg/dL	1.8 (0.6-5.3), SD 1.0	2.4 (1.0-5.3), SD 1.0	1.1 (0.6-3.7), SD 0.5	***<.01***	
Antidote	118 (97.5%)	57 (96.6%)	61 (98.4%)	.61	0.47 (0.041-5.29)
EtOH	29 (24.0)	16 (28.1)	13 (21.3)	.52	1.40 (0.61-3.24)
4-MP	65 (53.7)	30 (52.6)	35 (57.4)	.59	0.80 (0.39-1.63)
Both	24 (19.8)	11 (19.3)	13 (21.3)	.82	0.85 (0.35-2.08)
Door-to-antidote					
<3 hours	60 (49.6)	27 (47.3)	33 (54.1)	.47	0.74 (0.36-1.52)
3-6 hours	31 (25.6)	11 (19.3)	20 (21.9)	.099	0.48 (0.21-1.12)
6-12 hours	22 (18.2)	15 (26.3)	7 (11.5)	.059	2.68 (1.00-7.14)
12-24 hours	4 (3.3)	3 (5.3)	1 (1.6)	.36	4.44 (0.48 to 40.9)
>24 hours	1 (0.8)	1 (1.7)	0		
Dialysis	102 (84.3)	58 (98.3)	43 (69.4)	***<.01***	***25.63 (3.3-198.9)***
Door-to-dialysis					
<3 hours	13 (10.7)	11 (19.0)	2 (4.7)	***<.01***	***6.88 (1.45-32.5)***
3-6 hours	28 (23.1)	19 (32.8)	9 (20.9)	***.03***	***2.80 (1.15-6.83)***
6-12 hours	38 (31.4)	17 (29.3)	21 (48.8)	.56	0.79 (0.37-1.71)
12-24 hours	19 (15.7)	9 (15.5)	10 (23.3)	1.0	0.94 (0.35-2.50)
>24 hours	3 (2.5)	2 (3.4)	1 (2.3)		
AMS (any)	99 (81.8)	58 (98.3)	41 (66.1)	***<.01***	***29.71 (3.8-229.7)***
Somnolence	57 (47.1)	24 (40.7)	33 (53.2)	.20	0.60 (0.29-1.24)
Coma	42 (34.7)	34 (57.6)	8 (12.9)	***<.01***	***9.18 (3.72-22.7)***
Intubated	59 (48.8)	48 (81.4)	11 (17.7)	***<.01***	***20.23 (8.03-51.0)***
Seizures	24 (19.8)	24 (40.7)	0	***<.01***	
Vasopressors	11 (9.1)	8 (13.6)	3 (4.8)	.12	3.09 (0.78-12.25)
Prolonged renal insufficiency (dialysis > 3 days)	52 (43.0)	52 (88.1)	0		
Death	9 (7.4)	9 (15.2)	0		

Abbreviations: D/RI, died or had prolonged RI; EG, ethylene glycol; RECOV, recovery; OR, odds ratio; Cr, creatinine; 4-MP, fomepizole; EtOH, ethanol; AMS, altered mental status; Boldface and italicized results are statistically significant.
[a]*t* test for continuous variables or Fisher exact test for bivariate variables.

sensitivity of 93.2% and a specificity of 46.8% for the outcomes of prolonged RI or death. A Cr_I of 1.65 or higher produced a sensitivity of 40.7% and a specificity of 96.8% for RI or death. The area under the ROC was 0.86 (95% CI: 0.79-0.93; Figure 3).

A pH_I of <7.0 and a Cr_I of >1.0 had a sensitivity of 33.9% and a specificity of 98.4% for the outcomes of RI or death.

The D/RI group had a higher peak Cr_{24} (2.4 mg/dL, SD 1.0) than that of the RECOV group (peak Cr 1.1 mg/dL, SD 0.5). Based on a ROC curve, a Cr_{24} of 1.25 or higher had a sensitivity of 94.9% and a specificity of 25.8% for the outcomes of prolonged RI or death. A Cr_{24} of 2.15 or higher produced a sensitivity of 52.5% and a specificity of 95.2% for RI or death. The area under the ROC was 0.92 (95% CI: 0.86-0.97; Figure 3).

Antidotal and Dialysis Therapies

Although the overall proportions of D/RI and RECOV who received antidotal therapy did not differ, when stratified by time-to-antidote administration, we found an association between earlier administration of antidote and better outcomes. Compared to patients with a D2A within 3 hours, patients with a D2A greater than 6 hours had a higher odds of death or RI (OR 3.34, 95% CI: 1.21-9.26; Table 3).

Dialysis was utilized in a higher proportion by D/RI than that by RECOV. In addition, dialysis administered 6 hours or later was associated with a lower odds of death or RI (OR 0.36, 95% CI: 0.15-0.87). We iterate that the logistic regression model was unable to include pH_I, either as a discrete or as a categorical variable, because of its strength as a predictor of outcome. However, notably, patients who received dialysis (101 patients), compared to those who did not (20 patients), had worse indices of illness. Patients who received dialysis had a lower initial pH (mean 7.13, SD 0.21) than those who did not (mean 7.30, SD 0.12; $P = .001$). Patients who received dialysis had a higher Cr_I (mean 1.4, SD 0.68) than those who did not (mean 1.1, SD 0.37; p = .006). Patients who received dialysis also had a higher

Table 2. Description of 9 Deaths from Ethylene Glycol Poisoning.

Age, years/Gender	TAI, Hours	Antidote	D2A, Hours	D2D, Hours	pH_I	Ca_{LOW}, mg/dL	Cr_I, mg/dL	Cr_{24}, mg/dL	EG, mg/dL	Clinical Description
20/M	6-12	4-MP	>12	>12	7.01	8.6	3.1	3.1	23.2	"Comatose," developing status epilepticus requiring thiopental; diagnosed with brain death
29/M	20	EtOH, 4-MP	<3	<6	6.92	6.9	1.9	3.3	29	"Obtunded," developing seizures; diagnosed with brain death
42/M	Unknown	EtOH, 4-MP	>24	>24	6.67	7.1	1.3	3.9	5	"Stumbling and became unresponsive" with a [EtOH] 600 mg/dL, developing seizures; diagnosed with brain death
46/F	Unknown	4-MP	>6	>12	6.83	6.1	1.8	2.4	83	"Altered level of consciousness," developing myocardial infarction and hypotension; diagnosed with brain death
46/M	Unknown	4-MP	<3	<6	7.13	6.6	1.3	1.6	916	"Found down," developing hypotension; diagnosed with brain death
46/M	11-16	EtOH	<3	<6	6.76	9.7	2.8	3.1	79	"Unresponsive," developing seizures and SVT; received single po dose of EtOH prior to hospital transfer; fatal cardiac arrest during initial dialysis session 6 hours after arrival
48/M	12	EtOH	Unknown	<6	6.76	8.5	1	1.9	1262	"Obtunded" with a [EtOH] 30 mg/dL, developing seizures, upper GI bleeding, and hypotension; received a single oral dose of EtOH prior to hospital transfer; fatal cardiac arrest during initial dialysis session 20 hours after presentation
51/F	6-12	4-MP	>6	None	6.89	7.0	1.4	3.8	17	"Completely unresponsive" after a suspected polysubstance ingestion, developing seizures; family refused dialysis; fatal cardiac arrest HD #5 when care was withdrawn
56/M	Unknown	4-MP	>6	<12	7.26	6.6	1.1	2.0	1540	"Unresponsive"; frequent problems with 4-MP dosing and dialysis catheter; death on HD #7, manner not specified

Abbreviations: M, male; F, female; TAI, time after ingestion; Ca_{LOW}, lowest recorded serum calcium; EtOH, ethanol; 4-MP, fomepizole; D2A, door-to-antidote; D2D, door to dialysis; pH_I, initial arterial pH; Cr_I, initial serum creatinine; Cr_{24}, peak serum creatinine in the first 24 hours; SVT, supraventricular tachycardia; GI, gastrointestinal; EG, ethylene glycol; po, oral administration; HD, hospital day.

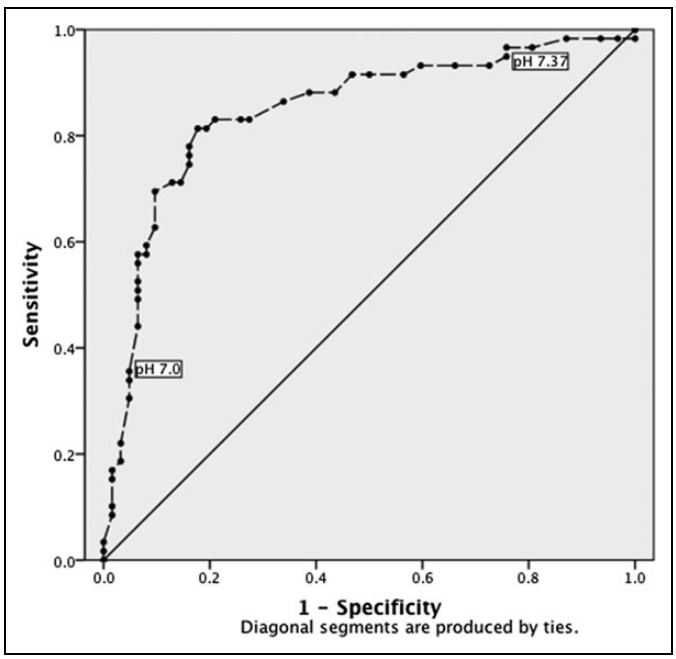

Figure 2. Receiver–operating characteristic (ROC) for initial arterial pH (pH_I).

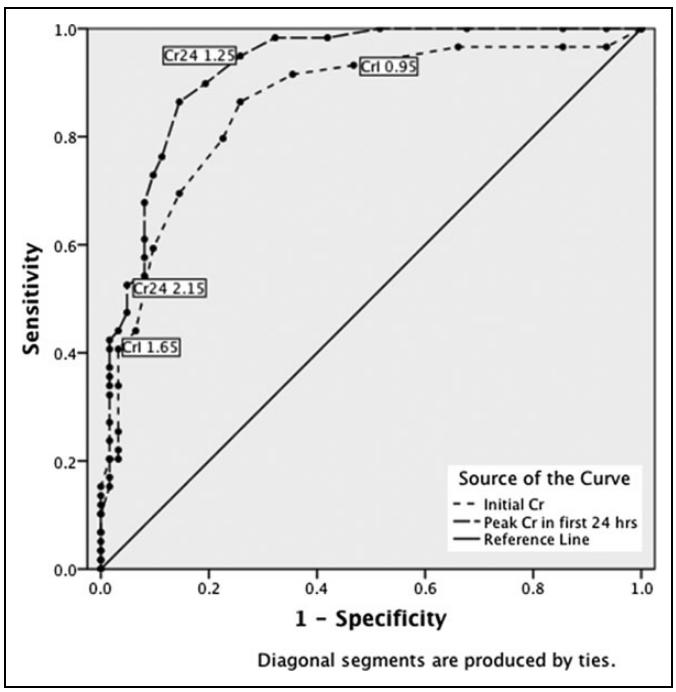

Figure 3. Receiver–operating characteristic (ROC) for initial serum creatinine (Cr_I) and peak serum creatinine in the first 24 hours (Cr_{24}).

Table 3. Logistic Regression Results

	All patients (121)	D/RI (59)	RECOV (62)	Logistic Regression, OR (95% CI)[a]
Door-to-antidote[b], %				
0-<3 hours	60 (49.6)	27 (47.3)	33 (54.1)	1.00 (ref)
3-<6 hours	31 (25.6)	11 (18.6)	19 (30.6)	0.70 (0.28-1.79)
≥6 hours	27 (22.3)	19 (32.2)	8 (12.9)	***3.34 (1.21-9.26)***
Door-to-dialysis[c], %				
0-<6 hours	41 (33.8)	30 (50.8)	11 (17.7)	1.00 (ref)
≥6 hours	60 (49.6)	28 (47.5)	32 (51.6)	***0.36 (0.15-0.87)***

Abbreviations: D/RI, died or had prolonged RI; RECOV, recovery; OR, odds ratio; CI, confidence interval; ref, reference; Boldface and italicized results are statistically significant.
[a]Adjusted for age and gender.
[b]3 patients did not receive an antidote.
[c]20 patients did not receive dialysis.

Cr_{24} (mean 1.85, SD 1.02) than those who did not (mean 1.34, SD 0.91; $P = .034$).

Discussion

The present study is one of the only a few attempts to analyze prognostic factors in ethylene glycol poisoning and the first to attempt analysis of the influence of time to initiation of therapy on outcomes. Our study validates a single prior study's finding that patients with ethylene glycol poisoning who exhibit signs of advanced toxicity (eg, coma, seizures, and severe acidosis) are more likely to have poor outcomes. Our study also appears to validate a few prior studies' inference that laboratory markers of toxicity (eg, pH and Cr) can be used for prognosis.

Hylander and Kjellstrand published the only consecutive case series in which they compared 11 survivors to 6 deaths.[5] Similar to our findings, the presence of coma and seizures was more likely to be present in fatal cases than in survivors ($P = .049$ and .027, respectively). Intubation was almost significantly different between the groups ($P = .054$). Initial potassium levels were higher in fatal cases (6.1 ± 1.2 mmol/L) than in survivors (4.4 ± 0.9 mmol/L; $P = .011$). Initial pH was found to be significantly lower in fatal cases (6.9 ± 0.2) than in survivors (pH 7.2 ± 0.1; $P = .024$). However, the study did not find a difference between Cr measurements at presentation, 24, 48, and 72 hours. This group of patients likely had a greater degree of toxicity than our patient sample since the mean Cr at 24 hours among their survivors was 3.2 ± 1.5 mg/dL. This study's contemporary applicability is somewhat limited now that fomepizole is an alternative antidote to ethanol.

Coulter et al published the only other study that attempted to describe prognostic factors in ethylene glycol poisoning among published cases in the literature.[6] They analyzed 87 published cases with an initial pH measurement, which included 19 deaths. This analysis, however, did not find a significant difference between the initial pH of survivors (mean pH 7.08, range 6.46-7.39) and fatal cases (mean pH 6.98, range 6.5-7.16; $P = .072$). Their area under the ROC for pH was only 0.64 (CI 0.52-0.76). This nonsignificant result is not surprising since it would be expected that published case reports would highlight particularly ill or unusual patients.

Our study supports the observations of Hylander and Kjellstrand that patients who exhibit clinical signs of end-organ toxicity will more likely have worse outcomes such as prolonged RI or death. Specifically, we found that AMS, the need for intubation, and seizures were associated with a higher likelihood of RI or death. Seizures appear to be particularly predictive as all patients with seizures had RI or death.

Three chosen indices of toxicity, pH_I, Cr_I, and Cr_{24}, appear to be helpful in prognostication. Assuming appropriate clinical care, patients presenting with no serologic signs of advanced toxicity (ie, a pH_I and Cr_I within the normal range) are unlikely to have RI or death. A pH_I of 7.37 or less had a sensitivity of 94.9% and a specificity of 75.8%. A Cr_I of 0.95 or higher had a sensitivity of 93.2% and a specificity of 46.8%. Conversely, patients presenting with serologic signs of advanced toxicity (ie, a very low pH_I and high Cr_I) are very likely to have RI or death: a pH_I less than 7.0 had a sensitivity of 35.6% and a specificity of 95.2%. Since serum creatinine is a delayed marker of acute renal injury, we expected to find that Cr_{24} would have better prognostic characteristics than that of Cr_I. However, the ROC curves were not significantly different. In any event, we believe it is worth noting that a Cr_I of 1.65 or higher was quite specific for severe illness (sensitivity 40.7% and specificity of 96.8%). Overall, we expected better sensitivity and specificity of pH and Cr as markers of toxicity but these may have been influenced by interventions (eg, bicarbonate and dialysis), delays in diagnosis and/or treatment, and time of blood sampling in relation to these.

Our study suggests that initiating antidotal therapy within 6 hours may result in a significant improvement in outcome. Intuitively, earlier cessation of toxic acid production will limit end-organ injury; however, no one has attempted to specifically describe a time period in which this should be done.

Unexpectedly, we found that earlier dialysis was associated with worse outcomes. This appears counterintuitive since earlier removal of ethylene glycol and its toxic metabolites should be beneficial. This may be explained by the observation that in our

retrospective sample, patients who received dialysis were more ill than those who did not received dialysis and thus would be expected to have worse outcomes. Patients who received dialysis (101 patients) had significantly lower pH_I and higher Cr_I and Cr_{24} than patients who did not (20 patients) received dialysis. We were unable to construct a statistical model to account for the effect of D2D stratified by pH because of our low numbers and the high predictability of pH on outcome.

Although we did not structure our study to evaluate the safety of antidotal monotherapy, our data are consistent with prior work, which suggests that patients who present with normal or near-normal initial pH and renal function might be safely managed without dialysis. Twenty of our patients who received antidotal therapy but not dialysis had a mean pH_I of 7.30 (SD 0.12) and mean Cr_I of 1.1 mg/dL (SD 0.37). Of these patients, only 1 patient experienced oliguric RI; this patient had exhibited early signs of severe toxicity, including an initial pH of 6.89 and seizures. These numbers are roughly similar to those of 2 other studies. Levine et al described 40 patients with confirmed ethylene glycol poisoning that were managed successfully with fomepizole and without dialysis.[7] None of these patients died. Only 1 patient developed nonoliguric RI with a peak Cr of 2.1. These patients had an initial pH of 7.37 (interquartile range 7.33-7.4, range 7.29-7.43) and a Cr_I of 0.97 (IQR 0.8-1.1, range 0.5-1.54). Hovda et al described a single patient who survived 154 episodes of ethylene glycol poisoning, receiving antidote monotherapy on 81 of these presentations.[8] The patient usually had only mild acidosis with a median initial pH of 7.31. The patient had only 10 episodes of ''renal impairment'' with a Cr_I of 0.9 to 1.75 mg/dL that always ''seemed to normalize'' afterward.

Finally, our study results may have implications for multivictim exposures to ethylene glycol. Although mass poisonings are more common with methanol, it is not inconceivable that a single hospital or region might be faced with multiple poisonings from ethylene glycol.[9] The difficult decision of allocating limited medical and human resources (eg, antidotes, dialysis, and intensive care unit beds) may be made somewhat easier with the prognostic data that we have collected. It seems clear that patients with profound acidosis and early signs of renal injury are at high risk of death or prolonged RI. Additionally, patients requiring intubation and/or experiencing seizures are particularly ill and have a dire prognosis. These patients could ideally receive immediate antidote and dialysis therapies. On the other hand, patients with near-normal initial pH and creatinine are candidates for antidote-only treatment. With appropriate antidote and supportive treatments, these patients will likely survive without serious sequelae.

Since a randomized controlled trial of antidotal and/or dialysis therapy in ethylene glycol poisoning would never be ethical, ideally, a prospective observational study could be repeated with a larger, more complete data set. Besides pH, Cr, and time to intervention, other less understood prognostic factors such as serum calcium or novel serologic markers of acute kidney injury would be useful for the analysis.[4,10]

Limitations

Our study has the inherent limitations of any retrospective, poison center study. Our patient population consists of a convenience sample of patients that were referred to the CPCS by health care providers. Since the CPCS does not capture all consecutive exposure cases at all health care facilities, this patient population may misrepresent the true incidence of exposure and clinical effects. The CPCS cannot capture unreported or undiagnosed cases of ethylene glycol poisoning. Unless voluntarily provided during the course of a specific case, hospital and clinic medical records were not available for review, limiting our observations to verbal reports provided to our telephone hotline staff by family members and health care providers. The SPIs and other personnel responsible for documenting poison control center cases were not under protocol to collect specific, additional information that might be relevant to this study but not necessary for patient management. Because of this, the poison center record might underreport signs, symptoms, clinical events, and treatments. Additionally, as an observational study, laboratory testing and treatments were not controlled. For example, when not explicitly stated, we assume that the pH reported reflects an arterial pH, rather than capillary or venous, especially since point-of-care pH testing was not widely utilized during the study period.

Further selection bias may be present since our patient sample consists only of cases with laboratory verification of ethylene glycol poisoning. The ability of a health care provider to access onsite, regional, or referral laboratory ethylene glycol testing may vary and could overrepresent health care facilities with greater critical care resources.

We decided to categorize D2A and D2D times instead of reporting them as discrete numerical values, because we recognize that any number of events might have occurred between the actual initiation of treatment by the treating health care providers and the time the CPCS specialist logged their VDL text note. Although our analysis lacks the precision granted by discrete times, we believe it is a more accurate description given the inherent imprecision of the CPCS electronic medical record.

Conclusion

Compared to survivors without any prolonged toxic sequelae, patients poisoned with ethylene glycol who died or had prolonged RI were more likely to have exhibited severe clinical signs such as coma, seizures, and acidosis at the time of presentation. Earlier time-to-antidote administration was associated with better outcomes. Benefit from earlier time to dialysis could not be demonstrated.

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