Predictors of Ethylene Glycol Ingestion Cases Called into a Regional Poison Center

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Abstract Poison center consultations for potential toxic alcohol poisonings are challenging because blood levels are typically not immediately available. The primary objective of this study was to determine whether readily obtainable laboratory values can be used to accurately and rapidly diagnose these poisonings. Over a 15-month period, patients with a history of toxic alcohol ingestion or a metabolic acidemia ($\text{pH} \leq 7.30$ or serum bicarbonate ≤ 18 mEq/L) that prompted a poison center consultation were enrolled. A predictive logistic regression model was used to assess the combined ability of serum pH, calcium, osmolar gap, and anion gap levels to predict a final diagnosis of toxic alcohol poisoning. There were 102 subjects included in the analysis. A total of 44% (45/102) patients had a final diagnosis of ethylene glycol (EG) poisoning. Higher levels of calcium, osmolar gap, and anion gap were independently associated with statistically significant or marginally significant increases in the odds of a final diagnosis of EG poisoning.

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The c-index was estimated at 0.81, indicating that the model showed a reasonable ability to discriminate EG cases from others. The final model had a sensitivity and specificity of 78% and 89%, respectively, and positive and negative predictive values of 84% and 83% respectively. The combination of elevated calcium, osmolar gap, and anion gap is associated with a high likelihood of EG poisoning, but clinician gestalt is still essential for its diagnosis. Further refinement of the model is needed.

Keywords Toxic Alcohol · Ethylene Glycol · Poison Center

Introduction

In 2009, US poison centers (PC) received 5,282 consultations for possible ethylene glycol (EG) exposures and 2,162 possible methanol (ME) exposures [1]. These numbers do not account for all the calls that PCs receive regarding patients with an unexplained metabolic acidemia in which toxic alcohol poisoning is in the differential diagnosis. It can often be difficult for toxicologists and poison center personnel to determine the appropriate diagnosis and treatment recommendations for these potential toxic alcohol poisonings. This is due to several factors: (1) The clinical presentation of toxic alcohol poisoning can be quite variable depending on the interval between time of ingestion and healthcare presentation; (2) Co-ingestions may create a complicated array of clinical signs or symptoms; and (3) Laboratory limitations with serum osmolality and obtaining specific toxic alcohol levels. Taken together, these variables place toxicologists and PCs in the difficult position of making recommendations based on limited and non-specific information. In response to these difficulties, the American Academy of Clinical Toxicology (AACT) formed expert

panels to discuss treatment recommendations for EG and ME poisonings [2, 3]. Because of limited data and lack of human trials, their recommendations for the treatment of toxic alcohol poisoning are currently based on our present understanding of the pathophysiology of toxic alcohol metabolism in combination with existing literature.

In addition to the aforementioned difficulties in diagnosing toxic alcohol ingestions, significant economic costs and resource utilization are involved in the care of patients with potential toxic alcohol ingestions. For example, the treatment of EG poisoning with fomepizole is reported to cost between \$373 and \$533 per dose [4]. The median numbers of fomepizole doses per patient for EG and ME are 3.5 and 4 doses respectively [5, 6]. Since the timely administration of fomepizole for toxic alcohol poisoning is vital, many patients with potential toxic alcohol poisoning are treated empirically while results of confirmatory tests are pending.

Efforts to optimize the timely diagnosis of toxic alcohol poisoning would be expected to improve PC management of patients with both potential and true toxic alcohol poisoning. Moreover, such improvement would be expected to decrease the use of vital healthcare and pharmaceutical resources. Since the results of confirmatory test for EG and ME are often unavailable in the immediate time frame, it is important to investigate other means to aid in the diagnosis. We sought to evaluate the ability of rapidly available laboratory tests to stratify patients with potential toxic alcohol poisoning and to help determine which patients should receive empiric treatment for toxic alcohol poisoning until confirmatory testing returns. The aim of our study was to identify factors predictive of toxic alcohol poisoning on presentation with the goal of identifying a more specific patient population who would benefit from empiric antidote therapy.

Methods

All telephonic consultative cases involving the Georgia Poison Control Center were eligible for enrollment. Over a 15-month period from March 2007 through June 2008, all patients with a history of EG or ME ingestion as reported to the poison center by the treating health care provider, or patients with a metabolic acidemia as defined by a $\text{pH} \leq 7.3$ (venous or arterial) or a serum bicarbonate ≤ 18 mEq/L were included. Patients were excluded if the acidemia was determined to be a respiratory acidosis based on blood gas analysis. Patients were also excluded if the call to the PC was delayed beyond the initial health care presentation as the goal was to evaluate information readily available within the first 6 h after initial presentation. Per our standard operating protocols, subjects who met the enrollment criteria were immediately referred to the on-call toxicologist for

evaluation and recommendations. The following clinical and laboratory data were collected: subject age, sex and vital signs, time of ingestion if known, pH, PCO_2 , and chemistry panel including calcium, acetaminophen level, salicylate level, ethanol level, lactic acid, serum osmolality, and serum ketones. Osmolar gaps were calculated and reported factoring in ethanol and dividing the ethanol level by 4.6. Recommendations for treatment were made on a case by case basis at the discretion of the on-call toxicologist. All enrolled subjects were followed prospectively. Clinical outcomes, final diagnoses, and the results of send out laboratory tests including EG and ME levels were collected with PC follow-up. A final diagnosis of EG or ME poisoning was defined by a detectable EG or ME level.

Data Analysis

A predictive logistic regression model was used to assess the combined ability of pH, serum calcium, osmolar gap, and anion gap (independent variables) to predict a final diagnosis of EG poisoning (dependent variable) among patients for whom a PC consultation for a potential toxic alcohol poisoning was sought. Some subjects had missing data on one or more of the analytes under consideration, and a “complete case” analysis would have reduced our sample size from 102 patients to 38 patients. To avoid the reduced statistical power and possible bias that might result from a complete case analysis, we used multiple imputation to fill in the missing analyte data. Specifically, we used a type of “switching regression” as implemented by the ICE package in STATA (version 10) to create 20 multiply imputed data sets. In conducting the imputation, we assumed that the data were missing at random.

Once the 20 imputed data sets had been created, we performed a three-step process to arrive at a final predictive logistic model. In step 1, we determined whether each analyte was best modeled as a continuous or dichotomous variable. We considered the following dichotomous cut-points for each analyte: $\text{pH} \leq 7.4$, calcium < 8.4 mg/dL, osmolar gap ≥ 10 , and anion gap ≥ 13 . The form of the analyte that led to the higher c-index in the majority of the 20 imputed data sets was then regarded as the most appropriate form to use in modeling the effect of that analyte. The c-index is a measure of the overall ability of the model to discriminate cases from controls, and ranges from 0.5 (no discrimination) to 1.0 (perfect discrimination). In step 2, we determined which of the four analytes should be included in a “final” multivariable model. We ran logistic regression models on each of the 20 imputed data sets in which the four analytes were modeled as simultaneous predictors. If an analyte showed a significant p -value ($p < 0.10$) in the majority of the 20 imputed data sets, it was included in the final model; otherwise, it was excluded from the final model. The

Table 1 Patient characteristics ($n=102$)

Characteristic	Mean $\pm$ SD or n (%)	Percentage of subjects with missing values
Age (years)	41.5 $\pm$ 16.5	0.0
Male	67 (65.7)	0.0
Serum pH	7.2 $\pm$ 0.2	15.7
Serum calcium (mg/dL)	8.9 $\pm$ 1.1	42.2
Osmolar gap (mOsm/kg)	41.9 $\pm$ 31.2	57.8
Anion gap (mEq/L)	17.8 $\pm$ 8.2	5.0
Final Dx of EG poisoning	45 (44.1)	0.0

Dx diagnosis, EG ethylene glycol

choosing of $p < 0.10$ rather than $p < 0.05$ was done because the data set is small and the statistical power to identify predictive analytes would be limited. Thus, when running the backwards elimination procedure on each of the multiply imputed data sets, a decision was made to err on the side of including a variable rather than excluding it, so we used a p -value of 0.10 rather than 0.05 [7]. In step 3, we ran the final model on each of the 20 imputed data sets. The odds ratios and 95% confidence intervals from this set of 20 final models were then combined into summary estimates. Finally, classification statistics were calculated in each of the 20 final models by choosing the linear predictor cut-point in each model that maximized the sum of sensitivity and specificity from that model. Again, we reported the median and range of each of these classification metrics from the 20 final models. All analyses were conducted in Stata Version 10 and R-version 2.7.1. This study was approved by the Emory University institutional review board.

Results

There were 102 subjects enrolled and were included in the analysis. Subject data is summarized in Table 1. Mean pH levels demonstrated an acidemia, mean calcium levels were in the normal range, and mean osmolar and anion gap levels tended to be elevated. A total of 45 (44%) of the 102 subjects had a final diagnosis of EG poisoning. Sixty-four

Table 2 Odds ratios for variables included in logistic regression model

Variable	Odds ratio of EG poisoning (95% CI)	p -Value
Serum calcium (per SD increase)	2.9 (1.3–6.7)	0.01
Osmolar gap (per SD increase)	3.3 (2.9–7.6)	0.03
Anion gap ≥ 13	3.3 (1.0–11.4)	0.06

Data are summary estimates from 20 multiply imputed data sets
EG ethylene glycol

Table 3 Predictive performance of logistic regression model

	Median (range)
c-Index	0.81 (0.76–0.88)
Calibration slope	0.90 (0.82–0.95)
R^2	0.38 (0.26–0.51)

Data are summary estimates from 20 multiply imputed data sets

subjects had some history of a potential toxic alcohol ingestion when calling the poison center, and of these, 39/64 (61%) ended up with a confirmed diagnosis of EG poisoning. None of the subjects were found to have a confirmed diagnosis of ME poisoning. In the 102 subjects enrolled, only 45 had a known time of ingestion. Of those with a known time of ingestion, 24/45 (53%) presented within 6 h of reported ingestion and the remaining 21/45 (47%) all presented between 6 and 12 h. EG poisoning was diagnosed in 21/45 with known time of ingestion, and 18/21 presented within 6 h of ingestion representing early presentation to health care facilities.

The final logistic regression model that was applied to all 20 data sets indicated that higher levels of serum calcium (continuous), osmolar gap (continuous), and anion gap (dichotomous, ≥ 13) were each associated with statistically significant or marginally significant increases in the odds of a final diagnosis of EG poisoning (Table 2). In contrast, pH levels were not independently related to the EG poisoning outcome and were not included in the final model. When analyzing the subset of patients with complete data, results were consistent with the final prediction model.

The final model's predictive performance on the multiply imputed data sets is shown in Table 3. The c-index was estimated at 0.81, indicating that the model showed a reasonable ability to discriminate between subjects with confirmed EG poisoning and subjects with potential toxic alcohol poisoning who ultimately did not have EG poisoning. The calibration slope was 0.90, indicating that the model's predicted probabilities may have been somewhat too extreme. Based on a linear predictor cut-point that maximized the sum of sensitivity and specificity, the final model had a sensitivity and specificity of 78% and 89%, respectively, while the positive and negative predictive values were 84% and 83% respectively (Table 4).

Table 4 Sensitivity, specificity, positive predictive value, and negative predictive value of logistic regression model

	Median (range) [%]
Sensitivity	78 (60–90)
Specificity	89 (76–98)
Positive predictive value	84 (72–96)
Negative predictive value	83 (76–94)

Data are summary estimates from 20 multiply imputed data sets

Discussion

The results of this study demonstrate that there was a high prevalence of EG poisoning as the final diagnosis for patients with an unexplained metabolic acidemia or potential toxic alcohol ingestion called into our regional PC. A potential history of toxic alcohol ingestion was found to be correct in 61% of patients with this history. Additionally, our study shows that a higher serum osmolar and anion gap are predictive of EG poisoning, which is congruent with previously accepted knowledge. In addition to these predictors, an elevated serum calcium level is also associated with an increased odds ratio for the diagnosis of EG poisoning. This finding, along with the fact that pH is not predictive of EG poisoning, is unexpected.

A surprising finding in our study was that an elevated serum calcium level is predictive of EG poisoning. This is counterintuitive since the current understanding of the pathophysiology of EG is that it should decrease serum calcium by metabolic byproducts binding to oxalic acid to form calcium oxalate crystals [8]. It is possible that our study subjects presented to a healthcare setting and had their blood collected prior to the point when significant calcium–oxalic acid binding could have occurred. Alternatively, perhaps this unexpected finding may result from electrolyte shifts and/or stress responses. To date, studies of various physiologic stressors, such as diabetic ketoacidosis or cerebrovascular events, have demonstrated differing effects on serum calcium levels. Serum calcium is often unchanged or low in the setting of diabetic ketoacidosis, whereas elevated serum calcium has been found in cerebral infarctions [9, 10]. Finally, this finding may represent a limitation of the study due to the total number of patients. Further investigation is needed to validate this finding.

One of the important findings in our study is that 44% of the enrolled subjects eventually had the diagnosis of EG poisoning as confirmed by detectable EG levels. One reason for this was that a history of toxic alcohol ingestion was a part of the inclusion criteria. However, additional factors likely play a role in this finding. PCs are a passive reporting system that may be biased to increased calls for ill patients of unclear etiology. Additionally, the enrollment in the study coincided with the second trial of convicted killer, Lynn Turner, who was found guilty of murder of her second husband with the cause of death as EG poisoning in Georgia. Previous work has demonstrated intentional EG poisonings increase after media coverage of antifreeze related murders [11]. These findings likely account for the high percentage of EG poisoning.

The fact that pH was not predictive of poisoning likely reflects our inclusion criteria. To qualify for our study, subjects had to have a presenting metabolic acidemia or a reported history of toxic alcohol ingestion. Subjects without a reported history of toxic alcohol ingestion had to be

acidemic in order to be enrolled in the study. In contrast, subjects with a history of a toxic alcohol ingestion could be enrolled in the study even if they were not acidemic. Because of this predetermined inclusion criteria, our numbers likely were not large enough to independently allow serum pH to be statistically significant. However, this does exemplify the difficulties that toxicologists and PCs face in evaluating patients with an undifferentiated metabolic acidemia. Hence, it is important to recognize that serum pH alone may not be predictive of EG poisoning.

The major limitation of our study was missing data which may have affected our model. Every effort was made to obtain all data points in real-time. All subjects who met our inclusion criteria were immediately referred to the on-call toxicologist for evaluation and data collection. Additionally, standard PC follow-up calls and data collection were directly conducted by the medical toxicology fellows. To minimize the effect of missing data points, statistical correction was used. Another major limitation revolved around the inability to obtain an osmolar gap. As a part of our standard PC recommendations for potential toxic alcohol poisoning, this test was suggested, but several hospitals did not have the ability to perform this analysis in their facility. The other piece of missing laboratory information included serum calcium. This test is available and was requested by the PC, but was not often ordered by the provider. Attempts were made to receive this information, but we were required to use a statistical correction to account for this missing data. Finally, PCs require medical providers to call, and therefore a bias may be present to initiate a poison center call.

In summary, the diagnosis of ethylene glycol poisoning in the setting of an undifferentiated metabolic acidemia or an unsubstantiated history of toxic alcohol ingestion can be extremely challenging. Our prediction model identified that the combination of elevated serum calcium, elevated osmolar gap, and elevated anion gap is associated with a high likelihood of EG poisoning. Additional studies are needed to further refine and validate these variables as prediction tools for toxic alcohol poisoning.

Conflict of Interest There are no financial or other conflicts of interest to disclose.

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