Serum Calcium Concentration in Ethylene Glycol Poisoning

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Abstract

Introduction The diagnosis of ethylene glycol intoxication can be challenging. Definitive testing for ethylene glycol is not readily available and clinical decisions are often based on clinical suspicion and the results of more readily available tests. One of these findings is hypocalcemia, presumable through complexation with the ethylene glycol metabolite oxalate.

Methods We performed a retrospective review of all patients admitted to a tertiary care hospital between 2005 and 2013 with laboratory confirmed ethylene glycol intoxication. Serum calcium on presentation was compared to blood gas pH on presentation as well as presentation serum bicarbonate.

Results We did not find any relationship between calcium and serum pH either by linear regression or when dichotomized by pH $\geq$ or <7.3 . We did observe an inverse relationship between serum calcium and bicarbonate.

Conclusions Hypocalcemia is not commonly observed following ethylene glycol poisoning, even in acidotic patients.

Keywords Ethylene glycol · Toxic alcohol · Anion gap metabolic acidosis · Hypocalcemia

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Introduction

The diagnosis of ethylene glycol (EG) intoxication can be challenging. Ethylene glycol assays are not routinely available and treatment for suspected EG intoxication is often commenced based on clinical suspicion and the use of routine, readily available tests including serum electrolytes for anion gap, renal function, measured serum osmolality to calculate an osmol gap, the presence of a lactic acid gap, urinary calcium oxalate crystals, and urine fluorescence [1–4].

Ethylene glycol metabolism ultimately results in the production of oxalic acid. Calcium readily binds to oxalic acid, leading to the characteristic urine oxalate crystals. Consumption of calcium by the complexing with oxalate may result in systemic hypocalcemia. Hypocalcemia has been suggested as one clue to suspected EG intoxication in the setting of a high anion gap metabolic acidosis [5–9]. Besides case reports, there is scant evidence supporting this observation. If EG poisoning causes hypocalcemia, we would expect this finding in patients who are acidotic, that is, patients who have generated sufficient oxalic acid to complex calcium. In patients presenting early following ingestion, or who had co-ingested ethanol and are without metabolic acidosis, we would not expect any perturbation of serum calcium.

The objective of this study was to evaluate serum calcium in relationship to the acid base status of patients presenting with laboratory confirmed EG poisoning and address the question: Is hypocalcemia a common observation with EG poisoning?

Methods

This was a retrospective study of all patients with ICD-9 codes indicating EG/toxic alcohol poisoning admitted to a tertiary

care hospital between January 1, 2005 and December 31, 2013. Toxicall® was simultaneously searched as a cross reference to ensure that all patients were captured. Inclusion criteria included EG or antifreeze exposure. We excluded those cases without a measured EG serum concentration. Data collected included the first set of electrolytes obtained on presentation, including calcium and if performed, ionized calcium, as well as albumin and blood gas.

We examined the relationship between serum calcium concentration and EG poisoning with the first set of chemistries obtained on presentation, since these would be the laboratory investigations a clinician will have at hand when first making clinical decisions. For patients transferred to our institution, we used the first chemistries obtained at the transferring facility. For patients presenting to our hospital, we used the first lab studies obtained in the Emergency Department. We looked at the relationship between serum calcium concentration and EG poisoning several ways. We compared serum calcium concentration to blood pH as a continuous variable. We also compared serum calcium concentration of patients with a pH ≥ 7.3 to those with a pH < 7.3 . We performed these comparisons between pH and calcium in three ways: first with total serum calcium concentration, then with ionized calcium concentration in those cases where this was performed, and finally with corrected serum calcium concentration in cases where both a total serum calcium and an albumin concentration were available.

To calculate a corrected calcium concentration we used the formula $\text{Corrected Calcium} = (0.8 \times (\text{Normal Albumin} - \text{Patient's Albumin})) + \text{Serum calcium}$ [10]. We considered a serum albumin concentration of 4 mg/dL (1 mmol/L) as normal.

Data were analyzed by simple linear regression for the relationship between calcium concentration and pH as well as calcium concentration and HCO_3^- . In addition, one-way ANOVA was used to determine if patients grouped by pH had any difference in their calcium concentration. All analysis was conducted using IBM SPSS Statistics 22.

The study was submitted to the institution's Institutional Review Board and determined to be exempt.

Results

A single reviewer (MJH) abstracted data from hospital charts. Twenty percent of the charts were then randomly reviewed by one of the co-authors (JMM) and no discrepancies in data extraction were noted.

A total of 72 cases were identified through initial search for ICD-9 codes indicating EG/toxic alcohol poisoning and cross reference with Toxicall®. Upon review, 57 were diagnosed with EG intoxication. Cases were excluded based on a negative EG assay ($n = 4$), miscoding ($n = 10$), including one case of brake fluid ingestion, and one case of a young child with

possible EG exposure who remained well and did not have an EG assay performed. Of the 57 cases with EG intoxication, nine more were excluded. Three cases with documented EG exposure lacked a blood gas on presentation and six additional cases had a clinical diagnosis and clinical course suggestive of EG poisoning but lacked an EG assay.

This left 48 cases for analysis. Seventeen of these cases also had an ionized calcium measured and 44 cases had an albumin concentration, allowing for calculation of a corrected calcium. The mean age ($n = 45$) was 40 years (± 17); 58.3% were male; 75% received hemodialysis and 97.9% received fomepizole. The median EG level was 98 mg/dL (IQR 45–195 mg/dL; 15.8 mmol/L, IQR 7.3–31.5 mmol/L). The EG concentrations ranged from 5 to 1320 mg/dL (0.8 to 212.9 mmol/L).

None of the patients in the study group were known to have chronic kidney disease. The mean and median creatinine on presentation in the study group were 1.15 and 1.1 mg/dL (101.7 and 97.3 mmol/L, $n = 48$), respectively. The three patients excluded because they lacked a blood gas had creatinine concentrations of 0.9, 0.9, and 1.7 mg/dL (79.6, 79.6, and 150.3 mmol/L). All three had a normal total serum calcium. Of the other six cases excluded because they lacked an EG assay, five presented with kidney injury. Two of these six had a low total serum calcium, either as measured or corrected (Table 1). No patients died.

Linear regression analysis was not statistically significant for any change of serum calcium to change in serum pH [total $\text{Ca-}R^2 = 0.03$, $F(1, 46) = 1.36$, $p = .25$; ionized $\text{Ca-}R^2 = 0.05$, $F(1, 15) = .74$, $p = .41$; corrected $\text{Ca-}R^2 = 0.01$, $F(1, 42) = .36$, $p = .55$]. Likewise, we did not find a significant difference in serum calcium to pH when patients were dichotomized by pH $\geq$ or < 7.3 . (Fig. 1, Table 2). Total serum calcium was however predictive of measured bicarbonate [$R^2 = 0.17$, $F(1, 46) = 9.26$, $p = .004$] (Fig. 1). This was an inverse relationship with increasing total calcium observed with decreasing serum bicarbonate concentration.

Discussion

The evaluation of a patient with undifferentiated metabolic acidosis can be challenging. Assays for measurement of toxic alcohol concentrations are not readily available. Among the routine tests available that can assist in the evaluation of a toxic alcohol exposure are osmol gap and, in the case of EG intoxication, a lactic acid gap. Despite its limitations, the osmol gap is a readily available calculation commonly used in the evaluation of suspected toxic alcohol ingestion [11]. The lactic acid gap takes advantage of cross reactivity between glycolic acid, a metabolite of EG, and lactic acid using the lactate oxidase method for measuring lactic acid. The lactate oxidase method is more commonly found in point of care

Table 1 Excluded cases

Excluded cases	History, reason excluded	pH	BUN mg/dL (mmol/L)	Creatinine mg/dL (mmol/L)	Total calcium mg/dL (mmol/L)	Albumin g/dL	Corrected calcium	treatment
1. ^a	High clinical suspicion, late presentation, no EG assay performed	7.18	30 (10.7)	3.4 (300.6)	8.2 (2.05)	5.5	7.0	Multiple sessions HD
2.	Prior EG ingestion, presented AKI, high clinical suspicion. No EG assay performed	ND	56 (20.0)	5.4 (477.5)	9.2 (2.3)	4.4	8.9	4MP, multiple sessions HD
3.	Presentation with AKI and hyperkalemia. High clinical suspicion late presentation EG ingestion	7.08	261 (93.2)	33.1 (2926.7)	7.7 (1.93)	4.4	7.4	Multiple sessions HD
4.	History EG ingestion. EG assay reported negative, unable to confirm.	7.46	9 (3.2)	1.3 (115.0)	9.9 (2.48)	5.0	9.1	4MP
5.	History EG ingestion. No assay performed.	ND	20 (7.1)	2.6 (229.9)	9.7 (2.43)	5.0	8.9	4MP, HD
6.	History EG ingestion, late presentation. EG assay negative.	7.25	91 (32.5)	8.3 (733.9)	9.0 (2.25)	3.7	9.2	HD

HD hemodialysis, 4MP fomepizole, ND not performed

^a Renal biopsy during hospitalization revealed calcium oxalate packed renal tubules

instruments while clinical laboratories may use either lactate dehydrogenase or lactate oxidase to measure lactic acid. If both methods are available to the clinician, this cross reactivity may be helpful in the evaluation of an acidotic individual with suspected EG ingestion [1]. Various commercial lactate oxidase reagents react differently with glycolic acid, limiting the utility of this test [12].

Hypocalcemia might be expected from the complexing of calcium with oxalate produced during the metabolism of EG and serve as another indirect marker of ethylene glycol intoxication. Our results suggest that this is not a universal finding and in fact we could find no significant relationship between serum calcium and acidosis in patients with EG poisoning. When dichotomized by pH more acidotic patients tended to have a higher serum calcium, although this did not reach statistical significance. Case reports in the literature include cases with both hypocalcemia on presentation and as well hypercalcemia [5, 8]. The inverse relationship we found between serum bicarbonate and total serum calcium is also contrary of what might be expected if serum calcium were to decrease with worsening acidosis.

Di-sodium ethylene tetra-acetic acid (EDTA) is a potent chelator of calcium. The rapid infusion of di-sodium EDTA leads to hypocalcemia, tetany, and death in rabbits, while a more slow infusion does not [13]. A subsequent study in human volunteers (some with bone disease due to metastatic cancer or multiple myeloma) infused either 2 or 4 g of di-sodium EDTA over 6 h. This led to a dramatic increase in renal excretion of calcium but did not result in a change in the serum calcium measured by oxalate precipitation (EDTA bound calcium is not precipitated by oxalate) [14]. Although hypocalcemia, cardiac arrest, and death from the infusion of di-sodium EDTA have been reported in young children and

adults, these older studies suggest that in adults at slower infusion rates of di-sodium EDTA mobilization of calcium from other body stores, such as skeletal depots, are able to maintain a normal serum calcium concentration in most instances [15]. The rate limiting step in the metabolism of EG is the oxidation of glycolic acid to glyoxylic acid [16]. Jacobsen et al. found that the concentration of glycolic acid is 50- to 100-fold greater than that of either glyoxylate or oxalic acid in a series of poisoned adults: 17–29, <0.2, and ≤0.33 mM, respectively [16]. We hypothesize that the metabolism of glycolic acid to glyoxylate and ultimately oxalic acid proceeds at a rate that allows homeostatic mechanisms to usually maintain a normal serum calcium concentration. Although our data do not address this question directly, our results support this supposition. (Similar to our results, in Jacobsen's study five of six patients had a serum calcium performed on admission and these five all had a serum calcium within the normal range. The blood pH ranged from 6.72 to 7.11 in these five patients.)

Our results suggest that deviations in serum calcium are not a reliable marker of ethylene glycol intoxication. The use of a normal serum calcium, be it total, ionized or corrected, to rule out possible ethylene glycol poisoning is fraught with the same limitations as the use of any other indirect marker used in the evaluation of suspected ethylene glycol poisoning or undifferentiated metabolic acidosis.

Limitations

The retrospective nature of this study limited our evaluation to those EG intoxicated patients who had documentation of the study variables we were interested in. Our sample size was small, particularly the group of patients who had an ionized calcium measured ($n = 17$). The number of patients with

Fig. 1 Graphs of regression analysis with 95% CI lines for relationship of total serum calcium, ionized calcium and corrected calcium with pH and serum calcium with HCO_3

profound acidemia, $\text{pH} < 7.10$, was also small ($n = 10$), further limiting our conclusion regarding the sensitivity of hypocalcemia as a finding with severe EG poisoning. Of the nine cases with a clinical diagnosis and course consistent with

Table 2 Differences in mean calcium concentration between pH groups

	$\text{pH} < 7.3$ (n)	$\text{pH} \geq 7.3$ (n)	p value
Serum calcium	10.2 (33)	8.7 (15)	.05
Ionized calcium	1.1 (12)	1.0 (5)	.37
Corrected calcium	9.1 (31)	8.5 (13)	.33

EG poisoning that we excluded because of lacking either an EG assay or pH two had a low total serum calcium (Table 1).

Another limitation of this study is that we did not take into account the effect of pH on ionized calcium. Acidemia decreases calcium protein binding and increases the ionized calcium fraction [17]. Since we did not observe a change in total calcium over the pH range studied and the impact of acidemia, if any, would be to increase the ionized calcium fraction we do not feel this adversely impacts our conclusions. We also acknowledge that acidosis may be an inadequate or improper surrogate for the production or accumulation of oxalate. We do not however feel this adversely impacts our conclusions.

We did not differentiate between arterial and venous specimens for blood gas analysis. We do not believe that the small difference in pH between these specimens would impact our results to any meaningful extent [18, 19].

Our decision to dichotomize patients with pH ≥ 7.3 from those < 7.3 was arbitrary. We felt that a pH < 7.3 suggested that EG metabolism had progressed with the generation of toxic metabolites. We have no data to support this arbitrary division point. The results using this pH to dichotomize are, however, in agreement with our results by linear regression analysis.

We elected to use a serum albumin of 4.0 mg/dL (1 mmol/L) as our standard albumin for purposes of calculating a corrected serum calcium. If we had chosen a different albumin concentration as our standard, it would have had no impact on our calculation as the relationship between the pH and the output of the calculated serum calcium will remain constant, regardless of what albumin is input as normal [10].

Conclusion

Although hypocalcemia may be seen in select cases of EG intoxication with profound metabolic acidosis, our results suggest that this is not a common finding, even in those patients who present with an anion gap metabolic acidosis. Although hypocalcemia may increase the clinician's concern for EG intoxication, a normal or high serum calcium should not deter from inclusion of EG in the differential diagnosis of the individual with an unexplained high anion gap metabolic acidosis.

Compliance with Ethical Standards

Sources of Funding No outside funding was used in support of this study.

Conflict of Interest The authors have no conflicts to declare.

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