Journal of Medical Toxicology (2023) 19:368–373
https://doi.org/10.1007/s13181-023-00958-y

ORIGINAL ARTICLE

Assessing the Role of Initial Serum Calcium Concentration in Patients with Ethylene Glycol Poisoning

Michael J. Hodgman[1,2] · Jeanna M. Marraffa[1,2] · Brian G. Wiener[3] · Mary Ann Howland[4,5,6,7] · Christine Stork[1,2] · Maria Mercurio-Zappala[7] · Mark Su[3,7]

Received: 27 February 2023 / Revised: 6 July 2023 / Accepted: 13 July 2023 / Published online: 26 July 2023

Abstract

Introduction Assays for ethylene glycol (EG) with a rapid turn-around time are not routinely available. Clinicians must rely on historical features and readily available clinical tests, combined with clinical acumen, to guide the initial management of suspected EG poisoning. Hypocalcemia has been suggested as a clue supporting the diagnosis of EG poisoning in patients presenting with an unexplained high anion gap metabolic acidosis (HAGMA). A previous small study challenged this assumption.

Methods This was a retrospective case series of one state's poison control system of confirmed EG-poisoned patients between September 2017 and April 2021. The definition of EG poisoning was based on suspected EG ingestion and a serum EG concentration > 5 mg/dL. Patients who were suspected to have EG toxicity but did not have a confirmed EG concentration or the EG concentration was less than 5 mg/dL were excluded. Routine laboratory studies were recorded for all patients. Comparisons between serum calcium on presentation to presenting blood pH, bicarbonate, anion gap, and creatinine were assessed for correlation.

Results There was no correlation between the presenting calcium and either pH or creatinine. There was a weak positive correlation between the initial serum calcium and anion gap, a weak negative correlation between the initial serum calcium and bicarbonate.

Conclusion On hospital presentation, hypocalcemia was not associated with EG poisoning, even in patients with a HAGMA. A normal serum calcium on presentation does not exclude the diagnosis of EG poisoning.

Keywords Ethylene glycol poisoning · Hypocalcemia · Toxic alcohol · High anion gap metabolic acidosis

Introduction

Assays for ethylene glycol (EG) with a rapid turn-around time to assist in clinical decision-making are not routinely available. Clinicians must make use of historical features, routine laboratory tests and clinical acumen for the early management of suspected EG poisoning. Hypocalcemia has

Data in this manuscript were previously presented at the North American Congress of Clinical Toxicology (NACCT) Annual Meeting (Virtual), September 2021.

Supervising Editor: Howard Greller, MD

✉ Michael J. Hodgman
hodgmanm@upstate.edu

[1] Upstate New York Poison Center, 750 E. Adams St, Syracuse, NY, USA

[2] Department of Emergency Medicine, Upstate Medical University, Syracuse, NY, USA

[3] Division of Medical Toxicology, Ronald O. Perelman Department of Emergency Medicine, New York University Grossman School of Medicine, New York, USA

[4] St. John's University College of Pharmacy and Health Sciences, New York, NY, USA

[5] New York University School of Medicine, New York, NY, USA

[6] Bellevue Hospital Emergency Department, New York, NY, USA

[7] Department of Health and Mental Hygiene, New York City Poison Control Center, New York, NY, USA

been suggested as a clinical finding supportive of the diagnosis of EG poisoning in a patient with a high anion gap metabolic acidosis (HAGMA) [1–4]. The proposed mechanism is the consumption of free calcium by complexation with oxalic acid, the ultimate organic acid in the metabolism of EG, forming the nearly insoluble calcium oxalate salt. Given this proposed mechanism, patients already with a HAGMA would more likely be expected to be hypocalcemic, whereas those presenting early after EG ingestion and with trivial metabolism of the parent compound would be less likely to have an abnormal serum calcium.

A previous single institution retrospective review found no correlation between serum pH and total serum calcium, ionized calcium (iCa) or albumin-corrected serum calcium in patients with documented ethylene glycol poisoning [5]. This small study had several limitations, including missing data that resulted in the exclusion of some EG positive cases as well as a small number of patients with severe acidemia (pH < 7.10).

To address some of the limitations of this previous study, particularly the small number of severely acidotic patients (pH < 7.10, $n = 10$), we performed a larger multicenter study to further investigate the association between serum calcium and acid base status in EG poisoned patients on initial presentation to a healthcare facility. This was a retrospective case series of ethylene glycol poisoning reported to either the Upstate New York Poison Center (UNYPC) or the New York City Poison Control Center (NYCPCC). These are the only two poison centers in New York, with yearly call volumes of about 42 and 80,000, respectively (UNYPC and NYCPCC). The primary study question was, is hypocalcemia a useful diagnostic tool for EG poisoning? A secondary objective was to look for other possible associations between serum calcium and other important laboratory tests in EG-poisoned patients.

Methods

From September 2017 through April 2021, all cases of laboratory confirmed ethylene glycol poisoning were identified. Candidate cases were identified by review of Toxicall on a daily basis for either verbatim entry of ethylene glycol in the substance description or the entry of either product code for ethylene glycol in the product description. Weekend and holiday cases might not have been identified until the following business day. Case collection was aided by an anomaly alert sent to several of the study investigators at the UNYPC. A later review of Toxicall was performed to ensure there were no missed cases. Cases were not limited to single substance exposure. An EG concentration above the laboratory detection limit, typically ≥ 5 mg/dL, was used to define ethylene glycol poisoning. This study was non-interventional beyond requesting that poison information specialists recommend that an EG concentration be performed for all suspected cases of EG poisoning. Baseline demographic information as well as first reported laboratory test results by the healthcare facility were recorded. We extracted the following laboratory data directly from the poison center chart: serum electrolytes, creatinine, total and ionized serum calcium, albumin, anion gap, blood gas, lactate, ethanol, measured osmolality, and osmol gap. We limited ourselves to the initial lab results for all cases as these would most likely reflect those tests clinicians use to make decisions in real time and without the aid of a blood EG concentration. Since an EG concentration was used merely for confirmation purposes, this test may have been performed on blood obtained at a subsequent blood draw. For laboratory results that were reported as less than the reporting limit for the test (serum bicarbonate or pH), an imputed value of [lower limit – 1 or lower limit – 0.1, respectively] was assigned. Patients suspected of EG toxicity but without a confirmed EG concentration or an EG concentration less than 5 mg/dL were excluded. Data were entered into an anonymized, identical data collection sheet at each poison center. The two data collection forms were merged at study completion prior to analysis.

Statistical Analysis

Continuous data were analyzed with descriptive statistics (i.e., mean, range, standard deviation). Associations between the initial total (or ionized) calcium as a potential predictor of EG toxicity were compared to serum pH, serum bicarbonate, and anion gap by correlation testing. Correlation between the presenting serum creatinine was also compared to calcium. The data were assessed for normality using both the Shapiro-Wilk and Kolmogrov-Smirnov test. Correlation analysis was performed using the non-parametric Spearman's rank correlation for non-normally distributed data and Pearson's correlation coefficient for normally distributed data; a p-value < 0.05 was considered a statistically significant correlation. All analyses were performed using Prism 9 for macOS (GraphPad Software, San Diego, CA, USA).

This study was deemed IRB exempt by the sponsoring institution of each poison center (Upstate Medical University, Syracuse and New York City Department of Health).

Results

There were a total of 81 subjects with confirmed EG poisoning during the study period, 34 from the NYCPCC, and 47 from the UNYPC. Of these, 26 did not have a presenting serum calcium documented in the poison center chart (20 from NYCPC and 6 from UNYPC), leaving 55 cases that met inclusion criteria, 41 from UNYPC (75%) and 14 from NYCPCC (25%). Thirty-five subjects were male (64%). The mean and median age of included subjects was 46 and 48

years, respectively. Of the 55 cases, 19 were coded as intentional ingestions and 1 as an unintentional ingestion, and in 35, no reason for the exposure was documented. Forty-one of 52 (79%) had a serum bicarbonate ≤ 15 mmol/L, 43 of 54 (79%) had an anion gap > 15, 14/55 (25%) had a total serum calcium < 8.5 mg/dL, and 22/52 (42%) had a serum creatinine > 1.2 mg/dL (see Table 1).

Fifty-two of the 55 subjects (95%) had sufficient data to allow for comparison of total serum calcium to pH, bicarbonate and creatinine. In two cases with the pH reported as < 7.0 an imputed value of 6.9 was used. In 54 cases, comparison to the anion gap was possible (Fig. 1). Six cases had a serum bicarbonate reported as less than the lower limit of quantification, < 5 mEq/L in 2, < 6 mEq/L in 3, and < 8 mEq/L in one. After imputation of a bicarbonate for these 6 cases, there were 54 cases for comparison of calcium to the anion gap. The data were not normally distributed by either the Shapiro-Wilk or Kolmogrov-Smirnov test; correlation testing was assessed using Spearman's ρ. Results are presented graphically in Fig. 2.

There was no correlation between the presenting serum calcium and pH ($n = 52$, rho $= -0.093$, $p = 0.511$). There was a weak positive correlation between the initial serum calcium and anion gap ($n = 54$, rho $= 0.382$, $p = 0.004$) and a weak negative correlation between the initial serum calcium and bicarbonate ($n = 52$, rho $= -0.283$, $p = 0.042$). There was no correlation between the total serum calcium on presentation and serum creatinine ($n = 52$, rho < -0.002, $p = 0.987$). Ionized calcium was recorded in only 7 cases and albumin in only 20; comparisons using these variables were not performed. A measurable ethanol concentration was reported in 8 cases, ethanol was absent in 33, and was not reported or not performed in 14 cases. Comparison of calcium to osmol gap was not performed either due to missing data, such as an ethanol, measured osmolality, or calculated osmolarity in 21 of the 55 cases. Additionally, in some cases, it was not clear from the poison center documentation if the reported calculated osmolarity already included an ethanol correction or not.

Discussion

The evaluation of patients with suspected EG poisoning continues to be a challenge. Few hospitals have a readily available, rapid turnaround assay for EG. This can result

Table 1 Laboratory results. Values are initial values reported to poison center.

	Total calcium (mg/dl) [nl 8.5–10.3]	pH	Bicarbonate(mmol/L) [nl 22–32 mmoI/L]	Anion gap [nl 4–12]	Creatinine (mg/dL) [nl 0.5–1.3]	Ethylene glycol (mg/dL)
# subjects	55	52	52	54	52	55
Mean	9.07	7.115	11.33	23.91	1.56	142.9
Median	9.4	7.115	11	23.5	1.2	96
IQR 25–75	8.3–9.9	6.995–7.285	5.5–14	19–31	0.895–1.86	36–159
Range	4.3–11.4	6.68–7.42	2–28	8–40	0.6–8.3	11.5–1394

(Reference ranges provided merely for perspective and may differ institution to institution. Reference ranges from:urmc.rochester.edu/encyclopedia.aspx)

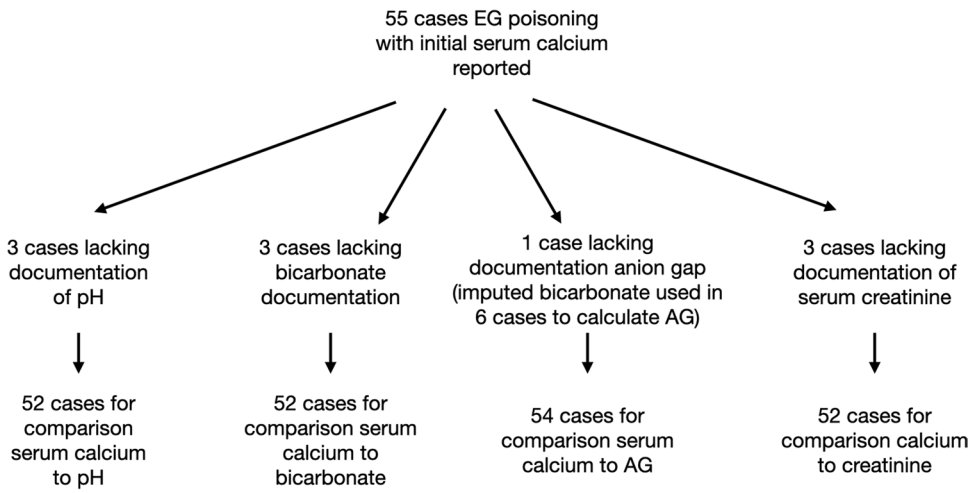

Fig. 1 Summary of cases available for correlation calculation with each variable.

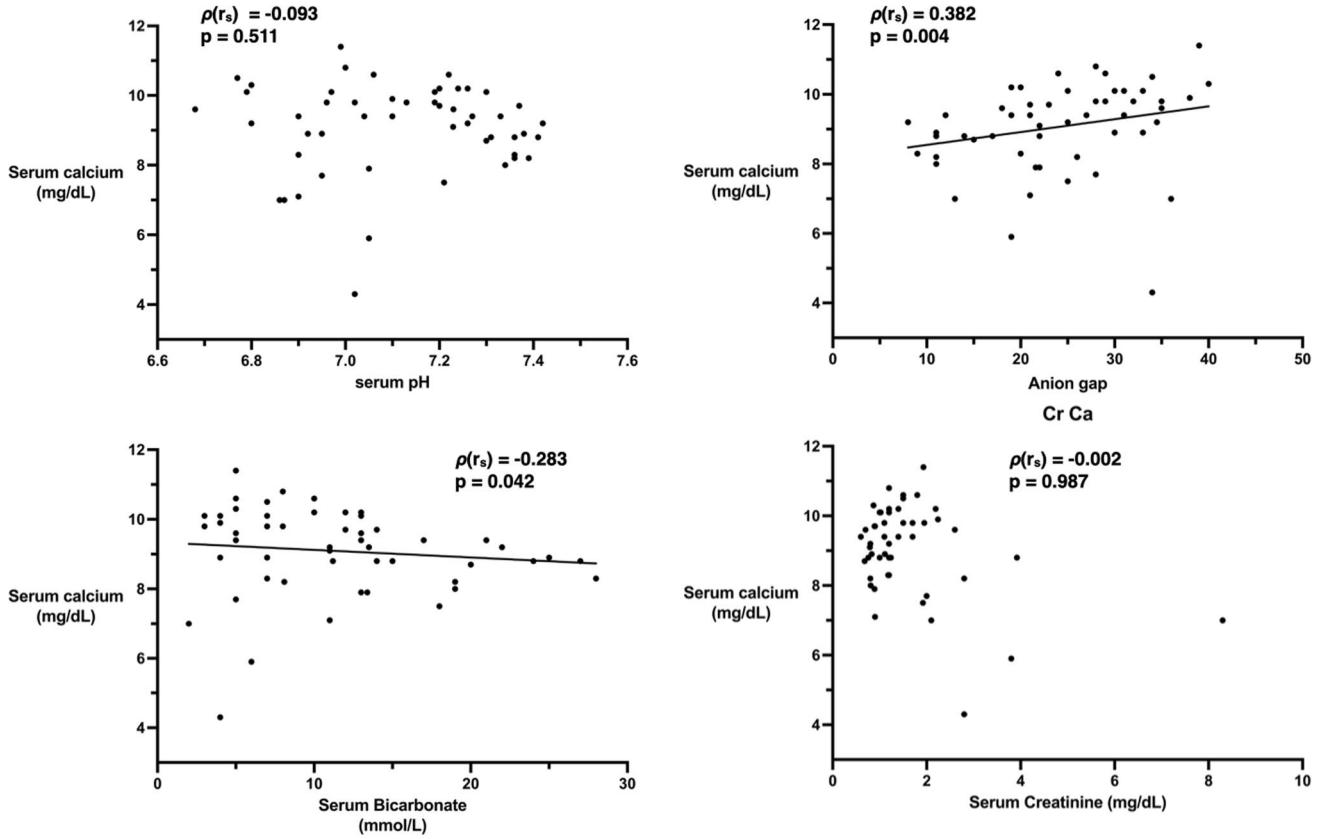

Fig. 2 Correlation of initial serum calcium to pH, bicarbonate, anion gap and creatinine

in a significant delay before a definitive diagnosis can be made. Prompt treatment however may prevent complications such as acute kidney injury (AKI) and neurologic toxicity. Clinicians must use their clinical acumen, aided by readily available tests, such as an otherwise unexplained anion gap metabolic acidosis or elevated osmol gap to facilitate decision-making. Hypocalcemia has also been posited as a clue to the diagnosis of EG poisoning [1–4], although in addition to our previous study, a study by Sutter et al. also questioned that. In their study of 45 patients with confirmed EG poisoning, using a model of multiply imputed data sets, a higher serum calcium on hospital presentation was predictive of EG poisoning [6].

Glycolic acid, glyoxylic acid, and oxalic acid are all byproducts of EG metabolism [1]. Hypocalcemia may result from the complexation of calcium with oxalate to form the essentially insoluble salt calcium oxalate monohydrate, which has a room temperature solubility product constant (K_{sp}) of 2.32×10^{-9} [7]. Despite this, and similar to a previous study, we did not find evidence of a significant relationship between serum calcium and metabolic acidosis in EG-poisoned patients [5]. In fact, we observed a weak negative correlation between serum calcium on presentation to serum bicarbonate and a positive correlation between serum calcium and anion gap (i.e., calcium concentration tended to be higher with a lower bicarbonate and higher with a larger anion gap). The finding of a weak negative correlation between serum calcium and bicarbonate was observed previously as well [5].

One explanation for the lack of any significant correlation between serum calcium and EG-related metabolic acidosis is that homeostatic mechanisms are able to keep pace with oxalate production as EG is metabolized. Typically, the concentration of glycolic acid is 50 to 100-fold higher than that of either glyoxylic acid or oxalic acid [8]. This suggests that the rate-limiting step in the complete metabolism of EG to oxalic acid is the oxidation of glycolic acid to glyoxylic acid. If the subsequent metabolism of glyoxylic acid to oxalic acid occurs at a rate that allows normal homeostatic mechanisms to compensate for calcium complexation with oxalic acid, serum calcium concentrations would not be expected to be dramatically impacted.

Several studies suggest that this may indeed be the case. Ethylenediamine acetate (EDTA) is a potent calcium chelator, forming essentially insoluble Ca_2EDTA [K_{sp} of 4.07×10^{-16}] [9]. A study in rabbits demonstrated the

dependence of the rate of infusion of ethylenediamine tetra-acetic acid on the development of hypocalcemia. Rapid infusion of 100 mg/kg led to rapid demise due to hypocalcemia while a slower infusion of 2000 mg/kg over 3 hours was tolerated before ultimate demise [10]. In dogs, a 50 mg/kg infusion of trisodium EDTA administered over 1 hour resulted in a transient decrease in serum calcium, with concentrations returning to above 90% baseline value within 1 hour of infusion completion [11]. A study of human volunteers infused with either 2 or 4 g di-sodium EDTA over 6 hours did not result in any appreciable change in serum calcium [12]. The results of this study suggest that, at least in adults, rapidly mobilizable calcium stores are able to compensate for the consumption of free and albumin-bound calcium during infusion of di-sodium EDTA at these rates. Whether this is also true in children poisoned by EG is unknown. Fatalities associated with the inadvertent infusion of di-sodium EDTA instead of the intended calcium di-sodium EDTA have been reported in children. In one case, a 2-year-old child died with hypocalcemia about 3 hours after initiation of an infusion at 75 mg/h; in a second case, a 5-year-old child died but neither the dose nor infusion rate were reported [13].

We had few subjects in our study with significant kidney injury and observed no correlation between a lower serum calcium concentration and elevated serum creatinine. Although our data are limited to test this question, one possible explanation for the hypocalcemia sometimes observed in EG-poisoned patients is concomitant acute kidney injury (AKI). Like chronic kidney failure, hypocalcemia is often a feature of AKI. Proposed mechanisms include impaired conversion of 25-hydroxyvitamin D3 to 1,25-dihydroxyvitamin D3, decreased gut and kidney responsiveness to 1,25 D3, and skeletal resistance to parathyroid hormone [14]. These same mechanisms may have a role in the development of hypocalcemia when it is observed in patients with AKI from EG ingestion.

A small case series by Jacobsen et al. supports AKI as a possible contributing factor [8]. In this case series, 6 critically ill patients presenting with EG poisoning had profound metabolic acidosis with anion gaps greater than 30. In 5 of the 6 in whom it was reported, the serum calcium on admission was normal (2.23–2.52 mmol/L or 9.28 to 10.08 mg/dL). All 6 patients went on to develop AKI. In the four patients with both a presenting serum calcium and a follow-up calcium 6–12 hours later, hypocalcemia was present on the repeat testing (1.82–1.94 mmol/L or 7.28–7.76 mg/dL).

Hypocalcemia has also been described in EG-poisoned patients without AKI. A 33-year-old female presented with intoxication and a history of EG ingestion. She had normal electrolytes and serum creatinine with an anion gap of 18 on presentation. She was promptly treated with intravenous ethanol and received hemodialysis. Four hours later, during HD, her serum calcium was 10.2 mg/dL with a bicarbonate of 20 mEq/L and an AG of 13. Twelve hours post presentation and completion of 4 hours of HD, she had a bicarbonate of 29 mEq/L, AG of 7, creatinine of 0.8 mg/dL, and calcium of 7.5 mg/dL. Her calcium remained low for at least the next 12 hours [15]. In this particular case, it is difficult to attribute hypocalcemia to EG metabolites as she never manifested a significant acidemia and was promptly and appropriately treated.

Stašinskis R et al. recently reported their findings from a retrospective cohort of 47 adults with EG poisoning admitted to a single referral center [4]. They described the change in iCa over time following admission. They reported that hypocalcemia was a common finding, with 60% having hypocalcemia on admission and over 90% at some point during their hospitalization. They defined hypocalcemia as an iCa < 1.18 mmol/L. (A reference range for iCa at their institution was not provided. A standard laboratory reference text lists a normal ionized calcium in adults as 1.05–1.3 mmol/L [16].) Although they observed that a low iCa was a common finding at some point after hospital admission, their data showed no correlation between pH and iCa at the time of hospital admission. An important difference between their study and ours is that we were looking specifically for any correlation between the serum calcium on presentation and markers of more severe poisoning, such as a low pH or bicarbonate, elevated AG, and creatinine, rather than changes in calcium over time after admission.

Limitations This study addresses one of the limitations of our previous study, the number of patients with severe acidosis (pH < 7.10, $n = 26$ compared to $n = 10$ in the previous [5]). However, there are a number of other important limitations to this study. Most importantly, we did not have an a priori estimation of the degree of correlation between the variables investigated and serum calcium and therefore did not perform an a priori power calculation and cannot exclude a type II error for those comparisons where no correlation was found. Three-fourths of the cases were from the UNYPC; this lack of a more balanced distribution of cases between the 2 poison centers also limits the generalizability of our results. Data extraction was performed by the study authors, and we did not perform any measure of inter-rater reliability between abstractors or the two poison centers. The lack of consistent documentation in the poison center chart also impacted the total number of cases we were able to study and as well limited our comparisons. Twenty-six of 81 cases of EG poisoning were excluded solely due to lack of a serum calcium. Of the 55 we report on, iCa and albumin were uncommonly documented in the poison center chart, and we did not investigate these further. We assumed that

the first chemistries reported in the poison center chart represented the intake results at hospital. Although we can assume with confidence that the results for calcium, bicarbonate, anion gap, and creatinine were from a single contemporaneous blood sample, it is possible that blood gas pH may have been performed on a specimen obtained at a different time. Confounders include an inability to account for any impact that time from exposure to ED presentation or that ethanol co-ingestion may have had on serum calcium. We do not know if any of our subjects had pre-existing kidney disease or other medical conditions that could potentially impact baseline calcium concentration (e.g., hyper-parathyroidism, hypo- or hyper-albuminemia). Some of these factors may also be unknown to the clinician at the time of presentation. We also acknowledge that the cut-off values we use in the results section are arbitrary and intended only to highlight the number of patients in this study who most would agree were sicker.

Despite these many limitations, our results demonstrate that even in patients suspected of being late presenters of EG poisoning based on either a low bicarbonate or an elevated AG, the weak correlations we observed between the first reported serum calcium and either the bicarbonate or AG occurred in the "opposite" direction as to what might be expected from the complexation of serum calcium by oxalate.

Our conclusions are limited to adults, and we would not presume that these findings are also true in children. During the study period, one of the reference labs used to confirm EG exposure transitioned to an enzymatic EG assay. This assay is not specific for EG and false positives may occur [17]. However, since these cases were all clinically suspected EG exposures, we do not feel that this affects our results.

Conclusion On hospital presentation, hypocalcemia was not associated with EG poisoning, even in patients with a HAGMA. A normal serum calcium on presentation does not exclude the diagnosis of EG poisoning. In adults presenting with an unexplained anion gap metabolic acidosis, serum calcium concentration should not influence a clinician's decision to either pursue or discard EG poisoning as part of them differential diagnosis.

Source of Funding None.

Declarations

Conflict of Interest None.

References

1. Wiener S. Toxic Alcohols. In: Nelson L, Howland MA, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS, editors. Goldfrank's toxicologic emergencies. Eleventh edition. ed. New York: McGraw-Hill Education; 2019. p. 1421–34.
2. Mégarbane BBS, Baud FJ. Methanol, ethylene glycol and other toxic alcohols. In: Shannon M, Borron SW, Burns MJ, Haddad LM, Winchester JF, editors. Clinical management of poisoning and drug overdose. 4th ed. Philadelphia: Saunders/Elsevier; 2007. p. 611–22.
3. Scalley RD, Ferguson DR, Piccaro JC, Smart ML, Archie TE. Treatment of ethylene glycol poisoning. Am Fam Physician. 2002;66(5):807–12.
4. Stasinskis R, Stasinska K, Mukans M, Graudins A, Liguts V, Lejnieks A. Changes in ionized calcium in ethylene glycol poisoning. Proc (Bayl Univ Med Cent). 2022;35(4):460–5.
5. Hodgman M, Marraffa JM, Wojcik S, Grant W. Serum calcium concentration in ethylene glycol poisoning. J Med Toxicol. 2017;13(2):153–7.
6. Sutter ME, Al-Khameess WA, Abramson JL, Morgan BW. Predictors of ethylene glycol ingestion cases called into a regional poison center. J Med Toxicol. 2012;8(2):130–4.
7. Solubility Product Constants. https://www.periodni.com/solubility_product_constants.html. accessed 29 Dec 2021.
8. Jacobsen D, Ovrebø S, Ostborg J, Sejersted OM. Glycolate causes the acidosis in ethylene glycol poisoning and is effectively removed by hemodialysis. Acta Med Scand. 1984;216(4):409–16.
9. Xiong Y, Kirkes L, Westfall T. Experimental determination of solubilities of di-calcium ethylenediaminetetraacetic acid hydrate [Ca2C10H12N2O8·7H2O(s)] in NaCl and MgCl2 solutions to high ionic strengths and its Pitzer model: applications to geological disposal of nuclear waste and other low temperature environments. Chem Geol 2017;454:15–24.
10. Popovici A, Geschickter CF, Reinovsky A, Rubin M. Experimental control of serum calcium levels in vivo. Proc Soc Exp Biol Med. 1950;74(2):415–7.
11. Sanderson PH, Marshall F 2nd, Wilson RE. Calcium and phosphorus homeostasis in the parathyroidectomized dog; evaluation by means of ethylenediamine tetraacetate and calcium tolerance tests. J Clin Invest. 1960;39(4):662–70.
12. Spencer H, Vankinscott V, Lewin I, Laszlo D. Removal of calcium in man by ethylenediamine tetra-acetic acid A metabolic study. J Clin Invest. 1952;31(12):1023–7.
13. Centers for Disease C, Prevention. Deaths associated with hypocalcemia from chelation therapy--Texas, Pennsylvania, and Oregon, 2003-2005. MMWR Morb Mortal Wkly Rep. 2006;55(8):204–7.
14. Leaf DE, Christov M. Dysregulated mineral metabolism in AKI. Semin Nephrol. 2019;39(1):41–56.
15. Stokes JB 3rd, Aueron F. Prevention of organ damage in massive ethylene glycol ingestion. JAMA. 1980;243(20):2065–6.
16. Pagana KD, Pagana TJ, Pagana TN. Mosby's diagnostic and laboratory test reference. 15th edition. ed. St. ed. Louis: Mosby; 2021.
17. Vo KT, Wu AH, Smollin C, Benowitz NL. A falsely elevated ethylene glycol level using laboratory enzymatic assay. Abstracts from the 2016 American College of Medical Toxicology (ACMT) Annual Scientific Meeting. J Med Toxicol. 2016;12:10.