Use of a Rapid Ethylene Glycol Assay: a 4-Year Retrospective Study at an Academic Medical Center

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Abstract Ethylene glycol (EG) is a common cause of toxic ingestions. Gas chromatography (GC)-based laboratory assays are the gold standard for diagnosing EG intoxication. However, GC requires specialized instrumentation and technical expertise that limits feasibility for many clinical laboratories. The objective of this retrospective study was to determine the utility of incorporating a rapid EG assay for management of cases with suspected EG poisoning. The University of Iowa Hospitals and Clinics core clinical laboratory adapted a veterinary EG assay (Catachem, Inc.) for the Roche Diagnostics cobas 8000 c502 analyzer and incorporated this assay in an osmolal gap-based algorithm for potential toxic alcohol/glycol ingestions. The main limitation is that high concentrations of propylene glycol (PG), while readily identifiable by reaction rate kinetics, can interfere with EG measurement. The clinical laboratory had the ability to perform GC for EG and PG, if needed. A total of 222 rapid EG and 24 EG/PG GC analyses were documented in 106 patient encounters. Of ten confirmed EG ingestions, eight cases were managed entirely with the rapid EG assay. PG interference was evident in 25 samples, leading to 8 GC analyses to rule out the presence of EG. Chart review of cases with negative rapid EG assay results showed no evidence of false negatives. The results of this study highlight the use of incorporating a rapid EG assay for the diagnosis and management of suspected EG toxicity by

decreasing the reliance on GC. Future improvements would involve rapid EG assays that completely avoid interference by PG.

Keywords Enzymatic assay · Ethylene glycol · Glycols · Gas chromatography · Propylene glycol

Introduction

Ingestions of toxic alcohols and glycols other than ethanol remain a public health issue. In 2012, US poison control call centers reported over 5000 cases of ethylene glycol (EG) exposures, many of which resulted in major clinical outcomes or death [1]. EG is commonly found in automobile antifreeze and on its own can produce profound central nervous system depression. However, much of the toxicity of EG is caused by its metabolites, glycolic acid and oxalate. Glycolic acid is directly cytotoxic and can cause metabolic acidosis along with neurologic and cardiopulmonary manifestations. Oxalate crystals precipitate in the renal tubules 24–72 h after EG ingestion and can result in acute and potentially permanent renal injury [2–4]. The main therapeutic options for managing EG poisonings are competitive inhibition of alcohol dehydrogenase by fomepizole or ethanol (preventing conversion of EG to toxic metabolites) and/or renal dialysis [2, 5, 6].

The diagnosis of EG ingestion can be clinically challenging. An inebriated or somnolent patient often cannot provide a reliable history, and the differential diagnosis of non-specific symptoms and signs such as altered mental status, elevated anion gap, or elevated osmolal gap is extensive [3, 4]. Gas chromatography (GC), with or without mass spectrometry (GC/MS), can be used for accurate and specific quantitative measurement of EG in serum/plasma and is the current gold standard diagnostic method [3, 4, 7–9]. Although GC is

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widely used for measurement of EG in clinical samples, GC/MS has greater specificity and can avoid interference of EG measurement by 2,3-butanediol (found in serum of some alcoholics) [10] or analytes present at high concentrations in rare inborn errors of metabolism (e.g., propionic acid in methylmalonic acidemia) [11]. However, the expertise and specialized instrumentation required to operate GC or GC/MS limits use in many clinical laboratories. Even in clinical laboratories that routinely operate GC-based methods for EG, the reported ideal turnaround time of 1 h may be difficult to achieve [3, 12].

Rapid EG assays have been reported for use with human samples [13–19], although none have been approved to date by the Food and Drug Administration (FDA) in the USA. Rapid EG assays find application in veterinary medicine, given the potential of animals such as dogs and cats to ingest antifreeze or other EG-containing products [20]. A major limitation of rapid EG assays has been interferences with structurally related compounds that may also be found in patient specimens, notably 2,3-butanediol and propylene glycol (PG) [15, 17, 18].

PG is found in many everyday products, but the most relevant sources for human clinical toxicology are activated charcoal (which may contain PG as an excipient) and a variety of injectable medications, including lorazepam and etomidate [21, 22]. There is an extensive literature on PG toxicity caused by long-term use of PG-containing intravenous medications, mainly in the intensive care unit setting [21–25]. Less commonly, patients may exhibit toxicity from ingestion of PG-based antifreezes [21, 26].

2,3-Butanediol is a compound that can be elevated in people with chronic alcohol use [27–30]. The structural similarity of 2,3-butanediol to EG can also interfere with resolution of EG by some GC methods [10]. There is much less literature on 2,3-butanediol in human specimens, and measurement of this analyte is not commonly performed for clinical purposes.

In 2011, Juenke et al. published data on a modification of a veterinary rapid EG assay (Catachem, Bridgeport, CT) for two automated clinical chemistry analyzers (Beckman Coulter Olympus AU400 and Roche Diagnostics Hitachi 917) that mitigated interferences by altering the original assay kinetics [18]. Juenke et al. reported that the original assay parameters for the Catachem EG assay resulted in significant interference of the assay even by low concentrations of PG. Modification of parameters eliminated interference by low concentrations of PG and allowed for clear recognition of high concentrations of PG by a rate error flag.

Using this published method as a starting point, the University of Iowa Hospitals and Clinics (UIHC) core clinical laboratory adapted the Catachem EG assay for the Roche Diagnostics cobas 8000 c502 analyzer and incorporated it into an existing toxic alcohol/glycol exposure algorithm based on osmolal gap [31]. The laboratory had the ability to perform GC for EG/PG, if needed. The objective of this retrospective study was to determine the utility of incorporating a rapid EG

assay for management of cases with possible EG poisoning. We describe utility of the rapid EG assay for the diagnosis and exclusion of EG ingestion as well as discuss its limitations.

Methods

Institutional Setting and Retrospective Study Design

This retrospective study was performed using an Institutional Review Board (IRB)-approved protocol (University of Iowa IRB protocol no. 20149788) covering the time period from 1 May 2009 to 29 September 2014. UIHC is a 734-bed state academic medical center that serves as a tertiary and quaternary care center. The medical center includes cardiovascular, medical, surgical-neurologic, pediatric, and neonatal intensive care units, along with a Level One Trauma Center. UIHC currently has the only clinical laboratory in the State of Iowa with the capability to perform specific analysis for toxic alcohols and glycols (including EG, PG, isopropanol, methanol, and ethanol) 24 h a day, 7 days a week.

During the time period of study, the electronic health record (EHR) for UIHC was Epic (Epic Systems, Inc., Madison, WI, USA). Epic Reporting Workbench, a tool within Epic for conducting structured searches of historical EHR data, was used to retrieve all instances within the retrospective time period in which the rapid EG assay was ordered for clinical purposes [32, 33]. The search was performed by the last author of this study. Retrospective analysis was conducted of the medical, pharmacy, and laboratory records of patients who had the rapid EG assay performed as part of medical care at UIHC. A previous publication contained data on EG and PG analysis at UIHC [31]. This prior publication provided data on rates and results of GC analysis for EG and PG at UIHC prior to 1 May 2009 and back to 2006.

Analytical Methods—Rapid Ethylene Glycol Assay

EG serum/plasma concentrations were originally determined using a laboratory-developed assay on Roche Diagnostics (Indianapolis, IN, USA) modular P analyzer using the Catachem Ethylene Glycol Reagent. These settings were then transferred to cobas 8000 c502 analyzer when the core clinical laboratory at UIHC switched to the cobas 8000 system in 2013. The original package insert settings were modified to determine the reaction rate at a later time point to minimize PG interference. The cobas c502 settings were as follows: assay type, 2-point end; reaction time/assay points, 10/37–68; primary wavelength, 340 nm; secondary wavelength, 415 nm; absorbance limit, 32,000; reaction direction, increase; sample volume, 1.7 μ L; R1 reagent volume, 17 μ L; R3 reagent volume, 5 μ L; calibration type, 2 points. Negative rapid EG results could automatically verify and transmit to the EHR if no

instrument errors or flags were present [34]. Positive rapid EG results were all reviewed manually by clinical laboratory staff prior to release of results to the EHR. The presence of EG was considered a critical value and required immediate phone call to the clinical service for the patient.

In this adapted rapid EG assay, EG produces a linear reaction rate (Fig. 1a). PG produces a non-linear reaction rate with a plateau within a short span of time (Fig. 1b). The maximum absolute raw signal on the instrument is higher with PG than with comparable concentrations of EG (e.g., 50 mg/dL of PG produces a higher maximal signal than 100 mg/dL of EG in Fig. 1).

Analytical Methods—Gas Chromatography

The GC method for quantitative determination of EG and PG has been previously described in detail [35]. Briefly, the GC system consisted of a PerkinElmer (Waltham, MA, USA) Clarus 580 GC with a PerkinElmer TurboMatrix 40 headspace sample and equipped with a flame ionization detector and an Elite 200 capillary column (PerkinElmer). To 50 μ L of sample, 50 μ L of the 1,3-propanediol internal standard solution,

and 200 μ L of the phenylboronic acid in acetone solution were added. The samples were vortexed for 5 s and centrifuged at 13,200 RPM for 1 min; 10 μ L of the supernatant was transferred to a headspace vial, sealed, and placed on the headspace unit. Vials were thermostatted for 9 min in a 140 $^{\circ}$ C oven before injecting for 0.02 min onto the GC for analysis. The headspace needle and transfer line were at 180 and 205 $^{\circ}$ C, respectively, with the transfer line pressure set at 40 psi. The GC oven was temperature programmed with an initial temperature of 80 $^{\circ}$ C, increasing to 120 $^{\circ}$ C at a rate of 20 $^{\circ}$ C/min, followed by an increase to 300 $^{\circ}$ C at a rate of 45 $^{\circ}$ C/min with a hold at 300 $^{\circ}$ C for 0.5 min. GC injector and detector temperatures were both set at 250 $^{\circ}$ C. 2,3-Butanediol produces peaks on the GC spectra but does not interfere with the peaks for EG, PG, or the internal standard.

Clinical Protocol for Toxic Alcohols and Glycols Testing

The rapid EG assay can be ordered reflexively as part of a toxic alcohol/glycol screening algorithm (Fig. 2a) or by direct standalone order by licensed independent provider by manual

Fig. 1 Reaction kinetics of ethylene glycol and propylene glycol for the rapid ethylene glycol assay. **a** Ethylene glycol produces a linear reaction (evident after 300 s). **b** Propylene glycol produces a non-linear reaction followed by a plateau

Fig. 2 **a** Decision tree for possible toxic alcohol and glycol ingestions. **b** Flow diagram of the retrospective study. The numbers capture all the testing that was performed following the osmolal gap-based algorithm, with the rapid EG assay performed when osmolal gap was greater than 15. There were an additional 27 rapid EG assays ordered by provider independently of the algorithm (described in “Review of Patients with Negative Rapid EG Assay Results”)

requisition or using the EHR computerized provider order entry system. The toxic alcohol/glycol screening algorithm has been described in a previous publication and starts with osmolal gap calculation and ethanol quantitation [31]. After correcting for the estimated osmolal contribution of ethanol [36], an elevated osmolal gap (>15) is reflexed to the rapid EG assay. If the osmolal gap cannot be explained by the results of the rapid EG assay, the pathology resident or attending pathologist is contacted and he or she determines if GC is indicated.

There are two separate GC assays that can be run: one for ethanol/methanol/isopropanol/acetone [31] and the other for EG/PG [35]. Running either or both GC assays requires pathology resident or attending pathologist approval. If PG interference prevents determination of EG by the rapid assay, the clinical service is contacted and read the following script by the clinical laboratory staff: *“An ethylene glycol screen was run and shows the presence of propylene glycol. Propylene glycol is found in activated charcoal and some intravenous medications (e.g., Ativan/lorazepam). Is there a clinical suspicion the patient ingested ethylene glycol, which is most commonly found in antifreeze?”*. In some cases, the clinical service elects not to pursue any further testing (e.g., if additional patient history or laboratory data is available since initial laboratory orders) and the pathology resident or attending pathologist does not need to be involved.

In some cases, the clinical service contacts the pathology resident or attending pathologist earlier in the process when there is a strong clinical suspicion of toxic alcohol or glycol ingestion (including later presenting ingestions where there may not be an osmolal gap but instead other signs such as anion gap and/or metabolic acidosis). The availability of the rapid EG assay as a standalone order allows for fast turnaround screening for EG independent of the osmolal gap protocol. A flow diagram of the patients analyzed in the study is presented in Fig. 2b.

Results

Analytical Characteristics of the Assay

As noted in the “Methods,” the presence of EG in serum/plasma produces a linear reaction rate in the rapid EG assay (Fig. 1a), while PG produces a non-linear reaction rate with a plateau within a short span of time (Fig. 1b). The rapid EG method is linear to 150 mg/dL (Fig. 3a) and correlated well with GC for EG (Fig. 3b). The rapid EG method produced comparable results on both the Roche Diagnostics modular P (older instrument platform) and the newer cobas 8000 c502 analyzers (Fig. 3c).

Fig. 3 Linearity and comparison studies of the rapid ethylene glycol assay. **a** The rapid ethylene glycol assay has linearity up to 150 mg/dL. **b** The rapid ethylene glycol assay on the cobas 8000 analyzer compares well with gas chromatography measurement up to 175 mg/dL. **c** The rapid ethylene glycol method shows similar results when run on Roche Diagnostics modular P and cobas 8000 c502 analyzers

Four-Year Retrospective Review Using the Rapid EG Assay

In a nearly 4-year period in which the rapid EG assay was incorporated into a toxic alcohol/glycol ingestion algorithm (20 Oct 2010–29 Sept 2014), a total of 222 rapid EG assays

and 24 GC runs for EG/PG were performed under 106 patient encounters (Fig. 2b). There were ten confirmed cases of EG ingestion. Eight of these ten cases were diagnosed and managed with the rapid EG assay alone. The remaining two confirmed cases represented 7 of the 24 GC runs for EG/PG. There was one fatality in a 49-year-old male who presented to the emergency department with EG plasma concentration of 1282 mg/dL following ingestion of an unknown but presumably large volume of automobile antifreeze. Despite renal dialysis and antidotal therapy with fomepizole, the patient expired on hospital day 4 of complications of the ingestion.

The rate of glycol GC for EG/PG went from 30 times/year (1 Jan 2006–19 Oct 2010) [31] to 6 times/year (current retrospective analysis). Of the 24 GC runs during the time period where the rapid EG assay was available, only 8 were attributable to additional testing following the discovery of PG interference on the rapid EG assay. Not every PG interference required GC; following discussion with the clinical service, EG toxicity can sometimes be excluded by additional patient history or other clinical or laboratory findings.

One instance of GC analysis was due to unavailability of the rapid EG assay due to malfunction of the automated chemistry analyzer. The remaining GC runs were performed either despite a negative rapid EG result ($n=9$) or in cases where the rapid EG assay had not been performed reflexively (because osmolal gap was not greater than 15) but the clinical service wished GC analysis for EG/PG anyway ($n=6$). In some cases, discussions with the clinical service highlighted that there was unfamiliarity with the availability of the rapid EG assay by the clinical teams (especially when the assay was newly introduced). In no case did GC reveal the presence of EG in a specimen where the rapid EG result was negative for EG and also did not show evidence of PG interference.

Review of Patients with Negative Rapid EG Assay Results

We performed detailed chart review on all cases where the rapid EG assay was negative (Table 1). This included 96 patient encounters (93 unique patients) where the rapid EG assay was performed as reflex for an osmolal gap greater than 15 following the algorithm defined in Fig. 2a. Additionally, the rapid EG assay was negative in 27 patient encounters (all unique patients) where osmolal gap was 15 or less, but the rapid EG assay was ordered directly by provider.

For the 96 patient encounters with osmolal gap greater than 15 but with rapid EG assay negative, a suspected primary cause of the elevated osmolal gap was identified in 78 encounters, using the common causes of elevated osmolal gap defined in a previous retrospective study (Table 1) [31]. There were six cases of isopropanol ingestion and one case of methanol ingestion. In these seven cases of toxic alcohol ingestion, GC was performed immediately after the rapid EG assay was negative following discussion between pathology and the

clinical service. The methanol poisoning presented with serum level of 273 mg/dL and arterial pH of 6.93 and was ultimately fatal despite hemodialysis and aggressive supportive care. Twelve cases of renal failure identified in the 96 encounters were either acute on chronic renal failure or acute renal failure ultimately assigned to a cause other than toxic ingestion. Eighteen cases did not have a clear cause of elevated osmolal gap. Within this group were six cases of overdose of drugs other than toxic alcohols or glycols and seven cases of liver failure. Overall, there was no evidence that an EG or toxic alcohol ingestion was missed by application of the testing algorithm defined in Fig. 2a.

In the 27 patient encounters with osmolal gap of 15 or less and a negative rapid EG assay, there were two cases related to EG. One was a 35-year-old male with accidental spray of large volume (approximately 4 L) of EG to face. The main symptoms were nausea and mucus membrane irritation. These symptoms resolved, and the patient was released from the emergency department without complications. The second case involving EG was a 55-year-old male with a previous history of severe mental illness who was found semi-conscious with altered mental status. There was suspected multi-drug overdose that included possible EG ingestion. Given unknown time of ingestions (hours to possibly days before presentation for emergency medical care), the patient was managed empirically for toxic alcohol/glycol overdose with hemodialysis even with negative rapid EG assay results. The patient was unable to provide complete ingestion history even after recovery. Laboratory abnormalities at time of admission included serum anion gap of 29 (reference range, 8–18) and whole blood lactic acid of 25 mEq/L (reference range, 0.5–2.2). Examination of urine did not reveal oxalate crystals. The patient was ultimately discharged with no evidence of permanent renal or other end-organ damage. In the group of 27 patients, there were a single case of renal failure which was attributed to warfarin overdose-induced hemorrhage and systemic hypotension. This was a 59-year-old male with very complicated previous medical history and hospital course that included intraparenchymal cerebral hemorrhage and pseudomembranous colitis. Overall, there was no evidence of false negatives from the rapid EG assay in this group.

Propylene Glycol Interference

PG interference was flagged by analysis of reaction rate kinetics in 25 (11.3 %) of the rapid EG assays performed on patient samples. Retrospective chart review categorized these interferences into three categories summarized in Table 2, with lorazepam (12 interferences, 48 %) and activated charcoal (7 interferences, 28 %) as the likely source of PG in the majority of instances. The presumptive source PG was not identified in six cases (24 %).

Table 1 Summary of cases testing negative by the rapid EG assay

Chart review information	Rapid EG ordered as reflex (osmolal gap >15)		Rapid EG ordered by provider independent of algorithm and with osmolal gap <15	
	Number of patient encounters ^a	Osmolal gap (mean±standard deviation)	Number of patient encounters	Osmolal gap (mean±standard deviation)
Ethylene glycol ingestion/exposure	0	N/A	2	−1±4
Methanol ingestion	1	111	0	N/A
Isopropanol ingestion	6	43±9	0	N/A
Ethanol-related (including alcoholic ketoacidosis)	35	25±20	12	1±7
Renal failure	12	19±4	1	2
Shock	4	18±2	1	0
Diabetic ketoacidosis	20	24±7	0	N/A
Other	18	18±2	11	−3±7
Total	96	26±22	27	−1±6

N/A not applicable (no patient encounters)

^a For the 96 patient encounters where rapid EG assay was ordered as part of the osmolal gap protocol, there were 93 unique patients (three patients presented twice each within time period of retrospective study)

There were six instances in two patients of EG and PG both detected in the same plasma sample. Of these, there were five samples with PG and EG both present and with PG of 39 mg/dL or higher: (a) PG, 151.3 mg/dL; EG, 553.9 mg/dL; (b) PG, 105.3 mg/dL; EG, 132.9 mg/dL; (c) PG, 53.2 mg/dL; EG, 770 mg/dL; (d) PG, 43.4 mg/dL; EG, 90.3 mg/dL; (e) PG, 39 mg/dL; EG, 1282 mg/dL. There were two samples with PG greater than 50 mg/dL but with EG absent (53 mg/dL and 88.1 mg/dL, respectively).

Costs and Turnaround Time of the Rapid EG Assay

During the time period of retrospective study, the estimated cost of reagents, calibrators, and controls for the rapid EG assay was approximately \$8000/year. This cost was nearly the same as the operational costs (including service and repair contracts) for the GC instrument that could perform EG and PG analysis. The rapid EG assay ran on existing instrumentation in the UIHC core laboratory (Roche Diagnostics cobas 8000 series c502 analyzer) and required no additional technical staff labor. Maintenance of the assay was similar to the

approximately 140 other assays run on the cobas 8000 platform at the UIHC core laboratory. Average turnaround time upon receipt of specimen in the clinical laboratory was 31 min (analytic time of 10 min; remaining time was pre-analytical steps such as sample accessioning, centrifugation, and aliquoting). In contrast, the very fastest turnaround time for GC analysis upon receipt in laboratory would be slightly over 1 hr, factoring in sample preparation and analysis of blanks, standards, and controls. More typically, turnaround time for GC is closer to 90 min or even longer when personnel need to be called in from home to do the analysis.

Discussion

Although relatively uncommon in clinical practice, EG overdoses occur thousands of times per year in the USA [1]. EG ingestions can occur accidentally (e.g., young children or as misguided substitute for ethanol) or as part of intentional self-harm attempts. The gold standard for diagnosis of EG ingestion, GC or GC/MS, is unavailable in many clinical laboratories. However, without proper laboratory diagnosis, patients can be misdiagnosed, resulting in under- and/or over-treatment [3, 12]. Antidote therapy with fomepizole is highly effective but is expensive. Renal dialysis is also effective but also expensive and invasive [2, 5, 6].

The institution in this study (UIHC) has the only clinical laboratory in the state of Iowa with the ability to confirm and quantitate serum EG 7 days a week, 24 h a day. After the implementation of a rapid EG assay in 2010, the use of GC for EG decreased from 30 times/year (2006–2010) [31] to 6 times/year. The current UIHC algorithm was set up to err on

Table 2 Suspected sources of propylene glycol (PG) in cases where rapid ethylene glycol assay showed PG interference

Suspected source of PG	Number of suspected interferences	Number of GC runs performed on these specimens	Confirmed cases of EG toxicity
Lorazepam	12	1	1
Activated charcoal	7	4	2
Not identified	6	2	0

the side of safety in allowing for GC analysis for EG/PG even when the rapid EG reaction rate looked to be affected purely by PG. Ascertaining the presence of PG in the rapid EG assay requires examination of the reaction rate on the instrumentation computer, involving a number of manual steps not needed for any other assays on the automated chemistry instrumentation system at UIHC. One major challenge is maintaining competency in these steps, especially with the infrequency of the PG interference. Suspected toxic alcohol/glycol ingestions often occur in the evening and early morning hours, and laboratory staff working on evenings, nights, weekends, and holidays are often covering multiple benches during a shift due to lighter staffing.

Over a 4-year period, there were ten confirmed cases of EG toxicity. Eight of these were managed by the rapid EG assay alone. Perhaps the biggest advantage of the rapid EG assay is its ability to quickly exclude the presence of EG. The major limitation of the assay was a positive interference by PG, although the presence of PG was easily recognizable by the reaction kinetics. PG interference led to GC analysis in only eight instances over a nearly 4-year time period. Discussion between the laboratory and the clinical team often led to the discussion to not pursue GC analysis. Through detailed chart review of all cases, we did not find any evidence of false negative results using the rapid EG assay.

We estimated costs of the rapid EG assay to be approximately \$8000/year, including expenses for reagents, calibrators, controls, and other supplies. These operational costs were similar to GC (supplies and service/maintenance contracts). The rapid EG assay ran on existing automated clinical chemistry instrumentation and did not require additional technical staff labor. Typical turnaround time for the rapid EG assay at UIHC was approximately 30 min upon receipt in the clinical laboratory, compared with 1–2 h for GC.

The Catachem EG reagent can run on other instrument platforms commonly found in hospital or reference clinical laboratories [17, 18]. In comparison, the cost and technical complexity associated with GC or GC/MS limits availability of this testing to a small number of centralized laboratories [3, 12]. When EG levels are needed relatively infrequently (e.g., a few times per week or less), maintaining competency in GC or GC/MS techniques can be challenging, especially for clinical laboratory personnel spread across day, night, weekend, and holiday shifts.

A recent study at a San Diego, California medical center reported a cost comparison of fomepizole and hemodialysis for treatment of EG (note: these were actual costs, not hospital charges) [37]. At this medical center, a treatment course of fomepizole cost approximately \$2100 (of which about half was medication costs), while hemodialysis cost approximately \$1400. Although we did not undertake a detailed cost comparison of EG poisoning treatment at UIHC, the costs of

fomepizole and hemodialysis treatments are similar to the 2013 California study.

We propose that one of the main benefits of the rapid EG assay is to quickly rule out the presence of EG. Avoiding unnecessary treatment of suspected EG poisonings avoids the costs of fomepizole and/or hemodialysis, along with the resultant risks and inconvenience to patients of unneeded therapy. As mentioned above, the main limitation of the rapid EG assay in this study was primarily interference by PG, which produces a positive interference that is readily recognizable by the reaction kinetics and signal magnitude. A negative result on the rapid EG assay indicates the absence of EG and PG. In our retrospective study, a good example of the benefit of the rapid EG assay was the patient who received splash exposure of large volume of EG to the face. Without the availability of a quantitative EG assay with reasonable turnaround time, the clinical team would have to seriously consider empiric therapy with antidote. At UIHC, avoiding empiric fomepizole or hemodialysis therapy in just five or six patients/year would equal the operational costs of the rapid EG assay.

The main limitations of our study are that the analysis is retrospective and confined to a single academic medical center. The results may not generalize to other hospital or clinic settings. Nevertheless, it is hoped that the results described here provide useful information to other institutions attempting to manage the challenges of EG testing.

Conclusions

The results of this study highlight the use of incorporating a rapid EG assay for the diagnosis and management of suspected EG toxicity by decreasing the reliance on GC. Future improvements would involve rapid EG assays that completely avoid interference by PG. Optimization of the rapid EG assay to completely eliminate PG interferences would further decrease the reliance on GC, decrease turnaround time, and ultimately provide better patient care. The availability of well-validated rapid EG assay protocols for a variety of common clinical chemistry analyzers would be beneficial, as would the development of rapid, specific assays for methanol.

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Compliance with Ethical Standards

Conflicts of Interest The authors all declare no conflicts of interest.

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References

- Mowry JB, Spyker DA, Cantilena Jr LR, Bailey JE, Ford M. 2012 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 30th Annual Report. *Clin Toxicol (Phila)*. 2013;51(10):949–1229.
- Jammalamadaka D, Raissi S. Ethylene glycol, methanol and isopropyl alcohol intoxication. *Am J Med Sci*. 2010;339(3):276–81.
- McQuade DJ, Dargan PI, Wood DM. Challenges in the diagnosis of ethylene glycol poisoning. *Ann Clin Biochem*. 2014;51(Pt 2):167–78.
- Porter WH. Ethylene glycol poisoning: quintessential clinical toxicology; analytical conundrum. *Clin Chim Acta*. 2012;413(3–4):365–77.
- Barceloux DG, Krenzelok EP, Olson K, Watson W. American Academy of Clinical Toxicology Practice Guidelines on the Treatment of Ethylene Glycol Poisoning. Ad Hoc Committee. *J Toxicol Clin Toxicol*. 1999;37(5):537–60.
- Brent J, McMartin K, Phillips S, Burkhardt KK, Donovan JW, Wells M, et al. Fomepizole for the treatment of ethylene glycol poisoning. Methylpyrazole for Toxic Alcohols Study Group. *N Engl J Med*. 1999;340(11):832–8.
- Dasgupta A, Blackwell W, Griego J, Malik S. Gas chromatographic-mass spectrometric identification and quantitation of ethylene glycol in serum after derivatization with perfluorooctanoyl chloride: a novel derivative. *J Chromatogr B Biomed Appl*. 1995;666(1):63–70.
- Porter WH, Rutter PW. Improved GC-MS procedure for simultaneous measurement of ethylene glycol and glycolic acid. *Clin Chem*. 2010;56(12):1900–2.
- Yao HH, Porter WH. Simultaneous determination of ethylene glycol and its major toxic metabolite, glycolic acid, in serum by gas chromatography. *Clin Chem*. 1996;42(2):292–7.
- Jones AW, Nilsson L, Gladh SA, Karlsson K, Beck-Friis J. 2,3-Butanediol in plasma from an alcoholic mistakenly identified as ethylene glycol by gas-chromatographic analysis. *Clin Chem*. 1991;37(8):1453–5.
- Shoemaker JD, Lynch RE, Hoffmann JW, Sly WS. Misidentification of propionic acid as ethylene glycol in a patient with methylmalonic acidemia. *J Pediatr*. 1992;120(3):417–21.
- Wu AH, McKay C, Broussard LA, Hoffman RS, Kwong TC, Moyer TP, et al. National academy of clinical biochemistry laboratory medicine practice guidelines: recommendations for the use of laboratory tests to support poisoned patients who present to the emergency department. *Clin Chem*. 2003;49(3):357–79.
- Eckfeldt JH, Light RT. Kinetic ethylene glycol assay with use of yeast alcohol dehydrogenase. *Clin Chem*. 1980;26(9):1278–80.
- Hansson P, Masson P. Simple enzymatic screening assay for ethylene glycol (ethane-1,2-diol) in serum. *Clin Chim Acta*. 1989;182(1):95–101.
- Blandford DE, Desjardins PR. A rapid method for measurement of ethylene glycol. *Clin Biochem*. 1994;27(1):25–30.
- Long H, Nelson LS, Hoffman RS. A rapid qualitative test for suspected ethylene glycol poisoning. *Acad Emerg Med*. 2008;15(7):688–90.
- Jialal I, Devaraj S. Laboratory diagnosis of ethylene glycol poisoning: the cup is half full? *Am J Clin Pathol*. 2011;136(2):165–6.
- Juenke JM, Hardy L, McMillin GA, Horowitz GL. Rapid and specific quantification of ethylene glycol levels: adaptation of a commercial enzymatic assay to automated chemistry analyzers. *Am J Clin Pathol*. 2011;136(2):318–24.
- Standefor J, Blackwell W. Enzymatic method for measuring ethylene glycol with a centrifugal analyzer. *Clin Chem*. 1991;37(10 Pt 1):1734–6.
- Scherk JR, Brainard BM, Collicutt NB, Bush SE, Almy FS, Koenig A. Preliminary evaluation of a quantitative ethylene glycol test in dogs and cats. *J Vet Diagn Invest*. 2013;25(2):219–25.
- Fowles JR, Banton MI, Pottenger LH. A toxicological review of the propylene glycols. *Crit Rev Toxicol*. 2013;43(4):363–90.
- Zar T, Graeber C, Perazella MA. Recognition, treatment, and prevention of propylene glycol toxicity. *Semin Dial*. 2007;20(3):217–9.
- Chicella M, Jansen P, Parthiban A, Marlowe KF, Bencsath FA, Krueger KP, et al. Propylene glycol accumulation associated with continuous infusion of lorazepam in pediatric intensive care patients. *Crit Care Med*. 2002;30(12):2752–6.
- Lim TY, Poole RL, Pageler NM. Propylene glycol toxicity in children. *J Pediatr Pharmacol Ther*. 2014;19(4):277–82.
- Wilson KC, Reardon C, Theodore AC, Farber HW. Propylene glycol toxicity: a severe iatrogenic illness in ICU patients receiving IV benzodiazepines: a case series and prospective, observational pilot study. *Chest*. 2005;128(3):1674–81.
- Brooks DE, Wallace KL. Acute propylene glycol ingestion. *J Toxicol Clin Toxicol*. 2002;40(4):513–6.
- Casazza JP, Freitas J, Stambuk D, Morgan MY, Veech RL. The measurement of D,L-2,3-butanediol in controls and patients with alcoholic cirrhosis. *Adv Alcohol Subst Abuse*. 1988;7(3–4):33–5.
- Felver ME, Lakshmanan MR, Wolf S, Veech RL. The presence of 2,3-butanediol in the blood of chronic alcoholics admitted to an alcohol treatment center. *Adv Exp Med Biol*. 1980;132(1):229–35.
- Kuehnle J, Holzbaur J. 2,3-Butanediol in serum of alcoholics. *Lancet*. 1983;2(8363):1369–70.
- Rutstein DD, Veech RL, Nickerson RJ, Felver ME, Vernon AA, Needham LL, et al. 2,3-Butanediol: an unusual metabolite in the serum of severely alcoholic men during acute intoxication. *Lancet*. 1983;2(8349):534–7.
- Krasowski MD, Wilcoxon RM, Miron J. A retrospective analysis of glycol and toxic alcohol ingestion: utility of anion and osmolal gaps. *BMC Clin Pathol*. 2012;12:1.
- Krasowski MD, Chudzick D, Dolezal A, Steussy B, Gailey MP, Koch B, et al. Promoting improved utilization of laboratory testing through changes in an electronic medical record: experience at an academic medical center. *BMC Med Inform Decis Mak*. 2015;15(1):11.
- Krasowski MD, Schriever A, Mathur G, Blau JL, Stauffer SL, Ford BA. Use of a data warehouse at an academic medical center for clinical pathology quality improvement, education, and research. *J Pathol Inform*. 2015;6:45.
- Krasowski MD, Davis SR, Drees D, Morris C, Kulhavy J, Crone C, et al. Autoverification in a core clinical chemistry laboratory at an academic medical center. *J Pathol Inform*. 2014;5(1):13.
- Ehlers A, Morris C, Krasowski MD. A rapid analysis of plasma/serum ethylene and propylene glycol by headspace gas chromatography. *Springerplus*. 2013;2(1):203.
- Khajuria A, Krahn J. Osmolality revisited—deriving and validating the best formula for calculated osmolality. *Clin Biochem*. 2005;38(6):514–9.
- Darracq MA, Rentmeester LL, Clark RF, Tomaszewski CA, Schneir AB, Cantrell FL. Cost of hemodialysis versus fomepizole-only for treatment of ethylene glycol intoxication. *Clin Toxicol (Phila)*. 2013;51(3):188.