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ORIGINAL ARTICLE

Accuracy of a Glycerol Dehydrogenase Assay for Ethylene Glycol Detection

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Abstract

Introduction Ethylene glycol (EG) is a frequently considered toxicant in poisoned patients. Definitive diagnosis relies on gas chromatography (GC), but this is unavailable at most hospitals. A glycerol dehydrogenase (GDH)-based assay rapidly detects EG. A rapid turnaround time and wide availability of necessary instrumentation suggest this method could facilitate the rapid detection of EG.

Methods This is a prospective, observational analysis of banked, remnant serum samples submitted to the laboratory of a large, multi-hospital healthcare system. Samples were submitted over a 12-month period for the explicit purpose of testing for suspected EG ingestion. All samples underwent GC and the GDH-based assay.

Results Of the 118 analyzed samples, 88 had no EG detected by GC, and 30 were "positive." At the manufacturer's threshold of 6 mg/dL EG, there was 100% (95%CI; 88.7–100) positive percent agreement (PPA) and 98% (92.1-99.6) negative percent agreement (NPA). Adjusted to a threshold of 9 mg/dL, both the PPA and NPA were 100%. Deming regression of the observed concentrations revealed a slope of 1.16 (1.01 to 1.32) and intercept of −5.3 (−8.9 to −1.7).

Conclusions The GDH assay provides a sensitive and specific method for the detection and quantification of EG that is comparable to a GC-based method. More widespread use of this rapid, inexpensive assay could improve the care of patients with suspected toxic alcohol exposure. Further study is needed to evaluate the test performance in real-time patient treatment decisions.

Keywords Ethylene glycol · Glycerol dehydrogenase · Screening · Gas chromatography · Toxic alcohols

Introduction

Poisoning by ethylene glycol (EG), the principal component of automotive antifreeze, is an often-considered and high-stakes diagnostic challenge. Left untreated, the endogenous metabolism of EG to its metabolites, glycolic acid and oxalate, leads to metabolic acidosis, acute kidney failure, and death [1]. While EG accounted for only 0.32% of single-substance exposure calls to poison centers, it was the fifth most common measured analyte in decedents after excluding recreational and illegal substances [2].

Definitive diagnosis of ethylene glycol exposure is made by gas chromatography (GC) [3]. Unfortunately, GC is not readily available in most hospitals. In the minority that have GC available, the test is time-consuming. Without rapidly available and definitive results, clinicians depend on nonspecific and imperfect proxy markers [4] to make this tentative diagnosis. Elevated anion gap metabolic acidosis may suggest this poisoning, but this acid–base disturbance occurs

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later [1, 5], when the patient may already be at significant risk without appropriate treatment [6]. Further, this finding is nonspecific, carrying broad diagnostic considerations [7] and may even be absent early on or in rare cases [8–10]. As an osmotically active toxicant, high serum osmolal gap may be present, but this finding is also nonspecific [11, 12]. Elevated osmolal gap may still be absent in poisoned patients [13–16] and cannot be used to exclude this poisoning.

Other approaches exploit laboratory artifact in measurement of lactate as a proxy for toxic metabolites [17–20], though this hinges on availability of multiple methods for testing lactate and will occur only after toxic metabolism has occurred. Some may consider urinary fluorescence as suggestive of fluorescein, an additive to many antifreeze formulations, though this finding is nonspecific [21, 22]. Oxalate crystalluria may also occur, though a broad differential for this finding exists [23]. Even the constellation of multiple suggestive markers may mislead the ultimate diagnosis [24].

To obviate these challenges, enzyme-based assays provide an alternative means of arriving at detection and rapid quantification of EG. One such assay, a veterinary product manufactured by Catachem Inc. (Oxford, Conn), uses glycerol dehydrogenase (GDH) to detect EG (Fig. 1). The assay shows good sensitivity for EG and is adaptable to both qualitative [25] and quantitative [26, 27] analytical tests. A few hospitals have already adopted this GDH-coupled test with good results [28, 29]. In the present study, we examined in-house implementation of a GDH-based assay on a commercially available automated chemistry analyzer for EG and compared these results to the gold-standard GC-based method.

Methods

We performed an observational analysis of banked, remnant serum samples prospectively collected over a 12-month period. We collected samples from the core clinical chemistry laboratory of a large, multi-hospital healthcare system. All samples were submitted for the explicit purpose of testing for suspected EG exposure. After initial testing by GC, the laboratory stored samples at minus 20 °C for up to 1 year prior to analysis by the enzyme-based assay. Stored samples were retested with GC to confirm ethylene glycol levels were consistent with original results obtained on fresh specimens. A priori power calculation was not performed owing to the historical rarity of positive samples.

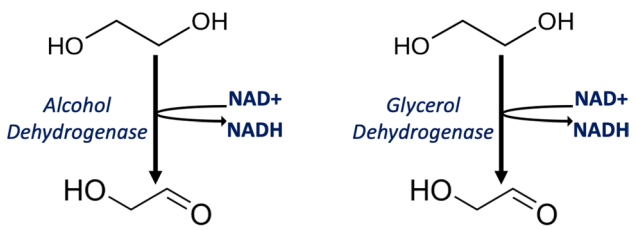

Fig. 1 Ethylene glycol undergoes endogenous metabolism to glycolaldehyde by alcohol dehydrogenase (ADH). Glycerol dehydrogenase (GDH) similarly oxidizes EG to glycolaldehyde while reducing NAD to NADH.

We used a GDH-based assay manufactured by Catachem Inc. (product code: C405-0A) to perform enzymatic determination of EG concentrations on a Roche Diagnostics (Indianapolis, IN, USA) Cobas c502 analyzer according to Catachem's instructions for use. The instrument settings were as follows: assay type, 2-point end; reaction time/assay points, 10/55–60; primary wavelength, 415 nm; secondary wavelength, 340 nm; absorbance limit, 32,000; sample volume, 1.7 µL; R1 reagent volume, 140 µL; R3 reagent volume, 28 µL; and calibration type, linear, 2 points. We used the manufacturer-established EG limit of detection of 6 mg/dL for the GDH-based assay during initial validation.

All samples also underwent GC, which was used for the initial real-time clinical decision-making. We performed GC on an Agilent 7890A with a flame ionization detector (Agilent Technologies, Santa Clara, CA) coupled to a 7693A autoinjector and Rtx-BAC plus fused silica capillary column (Restek, Centre County, PA). For sample preparation, to 100 µL of serum, 200 µL of 1.3 propanediol internal standard solution is added, followed by a 10 second vortex, and a 5-minute centrifugation. A 100 µL aliquot of supernatant is transferred to a clean vial, and 100 µL of 40 millimolar phenylboronic acid solution (in acetonitrile) is immediately added. The tubes are capped and vortexed for 10 s, left to rest for 60 s. A 100 µL aliquot of the top layer is transferred to an autosampler, and 1 µL of prepared sample is injected for analysis. The helium gas flow rate is set to a constant 5.4 mL/minute. The oven temperature is initially 60°C and ramped to 240°C at a rate of 20°C per minute. The detector temperature is also set to 240°C with the following flow setpoints: H2, 30 mL/minute; air, 400 mL/minute; and makeup (helium), 30 mL/minute. The total runtime is 14 minutes. The analytical measurement range is 4 to 300 mg/dL. Samples above this range are diluted with bovine serum to within the measuring range of the assay. The laboratory established EG limit of detection for the GC method is 4 mg/dL.

We first validated the EG GDH assay in accordance with guidelines from the Clinical and Laboratory Standards Institute (CLSI) including CLSI EP07 [30], CLSI EP35 [31], and CLSI EP15-A3 [32]. Using plasma specimens confirmed negative for EG, the limit of the blank (LOB) was 2 mg/dL, and the limit of detection (LOD) was 8 mg/dL. This LOD is similar to the manufacturer's reported LOD of 6 mg/dL. At a selected clinically relevant EG concentration of 27 mg/dL, the coefficient of variation (CV) was 6.92%. The analytical

measuring range was 10–155 mg/dL (manufacturer claim of 5–310 mg/dL).

Specificity and interferences were evaluated by both spiking of potential interfering substances and by testing patient samples with high concentrations of analytes associated with potential interfering substances. Specimens with known concentrations of ethylene glycol were spiked with intralipid, bilirubin, hemolysate, or propylene glycol, and recovery of ethylene glycol was calculated. Individual remnant samples containing high concentrations of lactate (> 10 mmol/L), lactate dehydrogenase (> 2000 mg/dL), bilirubin (> 30 mg/dL), blood urea nitrogen (> 100 mg/dL), ethanol (> 300 mg/dL), or glucose (> 400 mg/dL) from patients without ethylene glycol as indicated by GC testing were assessed for false-positive results. We did not assess for diethylene glycol (DEG) interference in this study as we confirmed all first-time positive results by the GDH assay with GC testing.

We used descriptive statistics and confidence intervals to report key test characteristics. We used GraphPad Prism v9 for statistical analysis of agreement and Deming regression. Deming regression was chosen to evaluate systematic error as it assumes bias with both analytical methods [33]. The Washington University Institutional Review Board determined the study to be non-human subjects research and approved the study with waiver of written informed consent.

Results

We received a total of 121 samples submitted for EG testing. From these samples, we evaluated 118 samples by both GC and the GDH-based assays. We excluded three samples not analyzed by GDH testing by the end of the study period. Among the 118 analyzed samples, GC detected EG at or above 4 mg/dL in 30 samples. Of these 30 samples, 17 were derived from serial collection of three EG-positive patients, and the remaining 13 were isolated collections from individual patients. Eighty-eight samples had no detectable EG by GC.

At the GDH assay manufacturer's discriminatory threshold of 6 mg/dL, the positive percent agreement (PPA) was 100% (95% CI: 88.7–100), and the negative agreement (NPA) was 98% (92.1-99.6, kappa = 0.89, 95% CI: 0.80–0.99) between the GDH assay and the GC method (Fig. 2). However, when adjusted to the lab defined LOD of 8 mg/dL, the PPA was 100% (95% CI: 88.7–100), and NPA was 98.9% (93.8–99.9). We set a threshold of 9 mg/dL to provide ideal agreement (PPA 100%, NPA 100%, kappa = 1.0). Further, we observed some positive interference in moderately to grossly hemolyzed specimens and validated a limit of detection of 10 mg/mL, which permits use of specimens with mild hemolysis, up to 200 mg/dL.

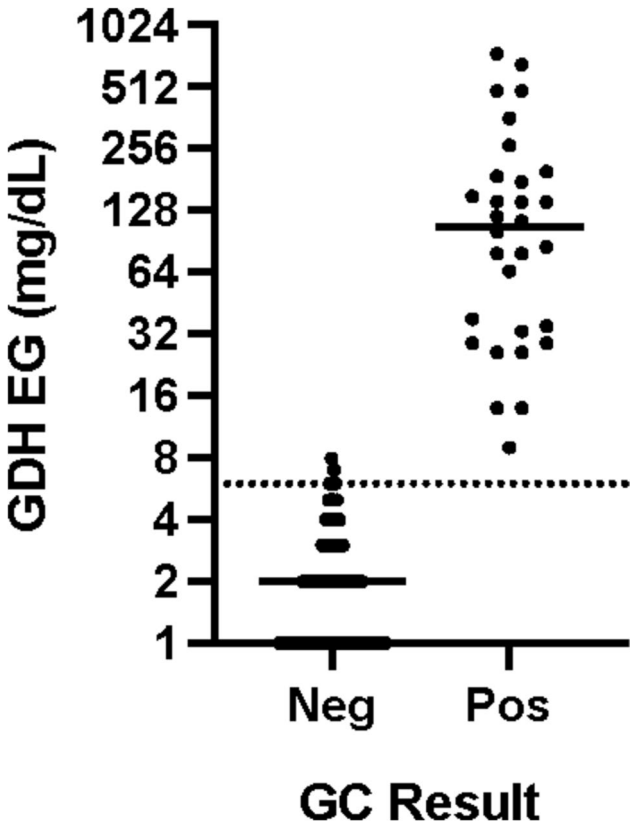

Fig. 2 Ethylene glycol concentration by GDH method is plotted in samples determined to be "negative" versus "positive" by GC. The manufacturer's discriminatory threshold of 6 mg/dL was used to judge the presence of EG by GC. GDH, glycerol dehydrogenase. GC, gas chromatography. EG, ethylene glycol.

To evaluate the quantitative accuracy, we plotted EG concentrations measured from the GC and GDH methods (Fig. 3) which demonstrated a Pearson correlation of 0.98 (0.98–0.99) between the two methods. The Deming regression demonstrated a slope 1.16 (1.01 to 1.32) and intercept of −5.3 (−8.9 to −1.7). In our analytical measurement range studies, we determined the upper limit of linearity to be approximately 155 mg/dL. All specimens above this value are diluted up to 10-fold in saline, a dilution scheme validated according to Clinical Laboratory Standards Institute guideline EP34 [34].

Testing for interference found a positive bias of 30 mg/dL at 50 mg/dL of propylene glycol in specimens with no EG present. There was no interference with lactate concentration up to 15 mmol/L, lactate dehydrogenase activity of 590 U/L, or ethanol concentration of 300 mg/dL. There was no interference in hemolyzed, icteric, or lipemic specimens up to a hemolysis index of 200 (0.2 g/dL hemoglobin), icteric index of 30 (total bilirubin 30 mg/dL), or a lipemic index of 1000 (triglyceride 1000 mg/dL). No relevant interferences were observed in the cohort of clinical patient specimens tested.

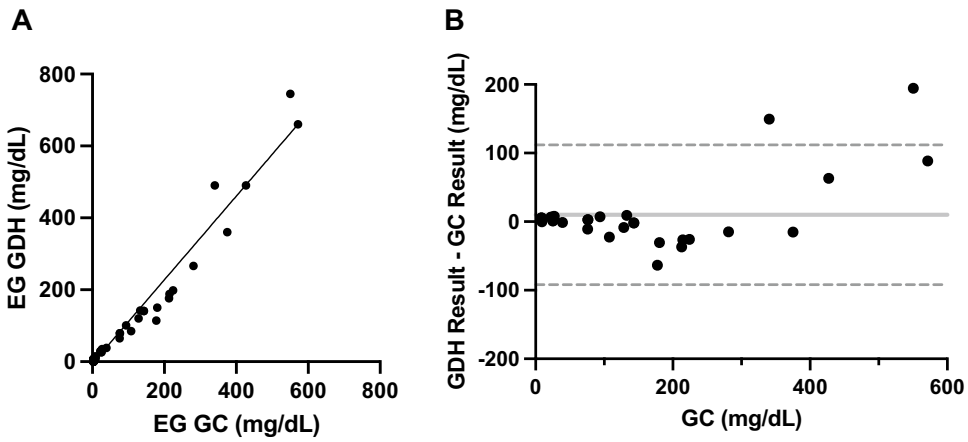

Fig. 3 **A** Deming regression of the GDH- and GC-derived EG values plotted with slope 1.16 (1.01 to 1.32). The intercept of the plot was −5.3 (−8.9 to −1.7). **B** Bland–Altman plot of the difference in measured EG concentrations plotted against the GC-derived result. GDH, glycerol dehydrogenase. GC, gas chromatography. EG, ethylene glycol.

Discussion

While other studies have examined this assay qualitatively [25], retrospectively [28], or on prepared samples [26, 27], our study validates this method on prospectively collected human samples. Further, this study provides quantitative analysis of the method, including test performance characteristics. Our analysis is consistent with other studies [26–29] and supports its readiness for clinical application using a large number of non-construed patient specimens submitted for GC testing. Applying these methods, we would expect in-house validation of this assay to be generalizable to clinical laboratories capable of performing high-complexity testing.

The results of this study demonstrate the GDH-based EG assay is sensitive and accurate compared to gas chromatography-based methods for EG detection. While the thresholds for perfect sensitivity and specificity vary slightly, both fall well below an actionable threshold of 20 mg/dL necessitating treatment with alcohol dehydrogenase blockade [35]. Although other studies have reported interference from propylene glycol and 2,3 butanediol [27–29, 36], β-hydroxybutyrate [37], and lactate [38], these potential confounders either were not present or did not generate false-positive or false-negative results in our samples. However, we did not perform sensitivity analysis, as the study was designed solely to look for diagnostic test performance and not to look for confounders. We did observe positive interference with propylene glycol through spiking studies, and laboratories that adopt the assay must be aware of this potential interference.

The principal advantages of the GDH method over the GC method are the ability to perform it using widely available automated analyzers and to rule out ethylene glycol exposure and quantitate EG during treatment. Although reagent costs are introduced by this method, it does not require manual extraction of specimens and recalibration for each run. Juenke et al. estimated an 85% labor reduction [27] in switching to the GDH-based assay from GC. Most importantly, most facilities lack GC, and definitive testing may then take several days to obtain a result. Without this testing, most facilities are unable to adhere to the Extracorporeal Treatments in Poisoning (EXTRIP) workgroup recommendation for widespread availability of rapid EG testing within 2 to 4 hours [39].

This method presents opportunity for cost-savings by providing early diagnostic clarity. For patients in whom EG poisoning is suspected, first-line empiric treatment requires administration of fomepizole [40], an alcohol dehydrogenase inhibitor. While EG-negative patients will undergo treatment that is altogether unnecessary, even EG-positive patients may receive treatment beyond the point of benefit from fomepizole.

Unlike GC, this assay neither detects nor excludes methanol ingestion or other toxic alcohols. However, other enzymatic point-of-care methods are effective in identifying formate, the immediate metabolite of methanol [41–43]. Formate appears to be the clinically significant metabolite in the context of these poisonings [44], with toxicity correlating more closely with this metabolite than with methanol concentrations [45]. Tandem application of both enzyme-based tests might further mitigate the risk of missing these diagnoses.

Nearly 80% of the specimens had no detectable EG, but some of these patients likely received fomepizole empirically for up to a day while awaiting GC results. The faster anticipated turnaround time and the ability to deploy this in more hospitals may reduce the unnecessary use of fomepizole or critical care resources.

Our study has limitations that need to be acknowledged. Most importantly, this study represents a single-site application of this enzymatic method. Although other studies have validated this method, prior studies were single-site studies limited by small numbers of true positive patient specimens. The present study includes a larger number of true positive patient specimens including several serial

samples collected from patients during treatment. A priori determination of in-house interference patterns might identify potential confounders and refine the interpretation of the results. Finally, this study was not designed to assess how decision-making by clinicians is impacted by this assay.

The lack of pre-existing Food and Drug Administration (FDA) approval for this assay does present an additional barrier to rapid and broad implementation, thus limiting the generalizability of our findings. Despite previous studies reporting successful use of this method, this test is labeled as a veterinary use assay which is not FDA approved for clinical testing. There is no current FDA-approved laboratory test for assessing the presence of ethylene glycol.

Non-FDA-approved assays can be used in clinical laboratories under Clinical Laboratories Improvement Amendment (CLIA) regulations but require extensive validation by the performing laboratory and are considered high-complexity laboratory developed tests. This dictates that laboratories must both establish and validate assay performance characteristics. The increased technical and time burden associated with this may constrain broad implementation of the assay. Laboratories that are not licensed to perform high-complexity testing are also not authorized to use non-FDA approved assays. In addition, instrument manufacturers are typically unable to provide any assistance in the development, validation, maintenance, or troubleshooting of non-FDA-approved assays.

Conclusions

This enzymatic assay using GDH is accurate and efficient for the detection and quantification of ethylene glycol in serum. It can be performed using conventional laboratory equipment and may be reliably used to rapidly rule out ethylene glycol exposure. This assay offers the prospect of potential savings toward direct testing costs and hospital-associated costs. Future research should assess its effect on antidote and critical care resource use.

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Declarations

Conflict of Interest David Templeton, MS, and Catachem Inc. (Oxford, CT) provided the glycerol dehydrogenase reagents. Neither Mr. Templeton nor any other agents or employees of Catachem Inc. had any role in the study design or the data analysis.

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