Importance of Glycolic Acid Analysis in Ethylene Glycol Poisoning

To the Editor:

The case conference entitled “Ethylene glycol poisoning: toxicokinetics and analytical factors affecting laboratory diagnosis” (1) provided a thorough review of many toxicological aspects involved in the diagnosis and monitoring of ethylene glycol (EG) poisoning. The authors stated that “the most serious clinical features observed in EG poisoning are due not to the parent compound but to the metabolites”. It was disappointing, therefore, that the authors did not include glycolic acid (GA) analysis in their investigations. Toxicologists first reported the importance of GA analysis in EG poisonings over 10 years ago (2, 3). The third case in this case conference was a diagnostic challenge to the authors because of repeated negative serum EG measurements. Based on our experience with GA analysis in many EG poisonings (4), the diagnosis of EG poisoning could have been made with serum GA analysis in case 3 without a renal biopsy. As stated in the conference, GA accounts for >90% of the anion gap in EG-poisoned patients (the anion gap in case 3 was 20 mmol/L).

It was also mentioned that initial serum EG concentrations in EG poisonings can be very high (127 mmol/L in case 2), whereas death has been reported with virtually undetectable serum EG concentrations. The authors consider this a discrepancy. In our experience, however, an alcoholic who drinks EG typically presents very late for medical attention after EG ingestion. Due to the rapid metabolism of EG to GA, one can anticipate having EG poisoning cases where the diagnosis can only be made by a renal biopsy or at autopsy (if GA analysis is unavailable). Our impetus to develop a serum GA method 8 years ago was based on a similar EG case (undetectable EG in serum) where the ingestion of EG was established by the presence of characteristic oxalate crystals in a renal biopsy several days later. We have had two cases since 1993 with negative EG measurements and GA concentrations >10 mmol/L on admission.

The authors of this conference noted that analysis of GA is unavailable at most medical centers and reference laboratories. In 1996, a report in this journal (5) described a robust gas chromatographic method for the simultaneous quantitation of EG and GA. Clinical laboratories with access to a gas chromatograph (equipped with a capillary column and a flame ionization detector) could easily develop a reliable method for GA quantitation in serum.

Further justification for GA analysis in the management of EG poisoning cases includes the following: Individuals (such as children) with low but measurable EG concentrations in the absence of GA may not require hemodialysis because toxic metabolite formation can be blocked efficiently by ethanol treatment. In addition, treatment of EG poisoning by hemodialysis in adults and children is still based on specific EG serum concentrations (6), not on the concentration of GA present. Because unmetabolized EG is relatively nontoxic (compared with GA), the availability of GA quantitation provides important laboratory support to clinicians treating EG poisoning cases. Continuing hemodialysis after all GA has been removed may not be required if the patient remains on ethanol treatment until the EG has lowered to <5 mmol/L.

Despite the low incidence of EG poisoning cases seen by most clinical toxicology laboratories, clinical chemists should provide analysis of GA and EG. In this laboratory, the presence of EG and GA are both screened for whenever a request for EG is received. The same rationale made for the availability of GA analysis in EG cases applies to methanol poisoning cases (7). Laboratories serving regional poison control centers should provide analysis of the toxic methanol metabolite (formate) in addition to GA analysis.

Albert D. Fraser
Dalhousie University
Queen Elizabeth II Health Sciences Centre
1278 Tower Rd.
Halifax, Nova Scotia
B3H 2Y9 Canada
Fax 902-473-7042
E-mail adfraser@is.dal.ca

References
be well prepared for these relatively infrequent cases of ethylene glycol poisoning. We believe that glycolic acid measurements can be useful as a supplement, but not as a substitute, to serum ethylene glycol determination, although in most cases the latter will be sufficient. Furthermore, serum ethylene glycol determined enzymatically should be confirmed by another method such as gas chromatography–mass spectrometry (6). However, in the acute setting of managing the intoxicated patient, the use of serum ethylene glycol (determined enzymatically on an automated analyzer (7, 8), anion and osmolar gaps coupled with arterial blood gases measurements will provide the greatest diagnostic yield at lowest cost. This approach is of particular utility in many medical centers that do not have access to a sophisticated reference toxicology laboratory. Thus, a recent survey of 95 teaching hospitals has shown that ethylene glycol determination was performed in only 25% of the polled hospitals (with a median turnaround time of 1.5 h), whereas if the test was sent out, the turnaround time was 42 h (9).


Bryan A. Wolf
Les Shaw
University of Pennsylvania
School of Medicine
Department of Pathology and Laboratory Medicine
3620 Hamilton Walk
Philadelphia, PA 19104-6082

*Author for correspondence. E-mail wolfb@mail.med.upenn.edu.

The Nonlinearity Seen for LDL-Cholesterol with Lyophilized Material Is a Matrix Effect

To the Editor:

Recently, Genzyme Corporation (Cambridge, MA) developed and patented a direct method for LDL-cholesterol (LDL-C) determination. The method uses an antibody to separate LDL from VLDL and HDL. Because the method is analogous to that for HDL-cholesterol (HDL-C) in that it requires a separation step and that matrix effects have been documented to interfere with the assessment for linearity for that analyte, we investigated the effect matrix has on the evaluation of linearity for the direct measurement of LDL-C (1).

We determined LDL-C on the Cobas FARA (Roche Diagnostic Systems), using cholesterol reagents: cholesterol esterase and oxidase (Boehringer Mannheim Diagnostics) and an LDL-C kit (Sigma Diagnostics). We tested linearity, using the following materials: CAP Linearity Survey material LN2-21 (College of American Pathologists, Northfield, IL); reconstituted according to instructions, mixed high- and low-concentration vials to make five, equally-spaced in concentration solutions; HDL-C and LDL-C control material (Sigma Diagnostics); and Enzyme diluent (DuPont Clinical Diagnostic Systems). In addition, we used Centriprep 100 concentration tubes (Amicon) to concentrate serum and a Sorvall RT 6000 Centrifuge with H1000B swinging bucket rotors to separate the phases in the LDL-C method.

Serum was added to the LDL-C separation tubes, each tube containing latex beads coated with affinity-purified goat polyclonal antibody against specific apolipoproteins. HDL and VLDL adhere to the latex beads, allowing one to centrifuge the samples in the Sorvall centrifuge and pour off the filtrate solution containing the remaining LDL. We then determined cholesterol with the Cobas FARA.

We followed a previously published method of preparing samples for linearity studies, producing nine concentrations (1). In addition, we concentrated serum, centrifuging it in the Centriprep 100 for 20 min at 3000 rpm at a 12-cm radius (1000g) in the Sorvall centrifuge. We reconstituted HDL-C and LDL-C control materials following the manufacturers’ directions, and diluted them as above. In addition, we reconstituted LDL-C controls, separating the LDL-C. We made nine dilution concentrations (1) and determined cholesterol to measure the LDL-C fraction.

We evaluated all data using the polynomial evaluation method for linearity, as described by Kroll and co-workers (1, 2). In the polynomial method for linearity, the nonlinear beta coefficients are statistically analyzed by use of the t-test. If the nonlinear beta coefficients are statistically significant, the method is nonlinear; if not, the method is linear.

The lyophilized materials, CAP Linearity Survey material, and the LDL and HDL controls all had statistically significant nonlinear coefficients (P <0.02) and were nonlinear. The routine serum and concentrated, postprecipitator pools did not have statistically significant beta coefficients and therefore were linear. The nonlinearity of the HDL-C and LDL-C controls and the CAP samples was sigmoid in shape, whereas the serum, concentrated serum, and LDL-C control material precipitated before dilution, all appeared linear (Fig. 1).