Correlation of osmolal gap with measured concentrations of acetone, ethylene glycol, isopropanol, methanol, and propylene glycol in patients at an academic medical center

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A B S T R A C T

The ingestion of toxic alcohols including methanol, ethylene glycol, and isopropanol remains a significant public health problem. These compounds can cause central nervous system depression and, for methanol and ethylene glycol, organ damage from toxic metabolites. The presence of these compounds in serum/plasma can often be determined and monitored by measuring the osmolal gap (OG). However, other compounds originating from endogenous or exogenous sources, such as propylene glycol and acetone, can also increase the OG. Conversion factors can be used to estimate specific concentrations of acetone and toxic alcohols from OG. In this retrospective study, data were analyzed for 260 samples originating from 158 unique patients that had determination of both OG and concentrations for toxic alcohols at an academic medical center central laboratory. Specific analysis included gas chromatography (acetone, isopropanol, methanol, ethylene glycol, propylene glycol) and/or enzymatic assay (ethylene glycol). Many samples also contained ethanol. The data was grouped by type of ingestion. The present study analyzed the relationship between the OG calculated from measured plasma/serum osmolality and the OG estimated by applying conversion factors to measured concentrations of the different compounds. The correlations tend to be linear and vary by compound, with methanol and ethylene glycol having the highest R^2 values of 0.93 and 0.95, respectively, consistent with other published studies. Higher variability was seen for the data for isopropanol and acetone. For each of the data subsets, the estimated toxic alcohol concentration calculated using conversion factors from OG tends to overestimate the actual concentration of the compound. Overall, the present study demonstrates the generally linear relationship between OG determined by osmolality and the OG estimated using measured concentrations of acetone and toxic alcohols.

1. Introduction

Although not as commonly ingested as ethanol, ingestion of other toxic alcohols remains a significant public health problem [1–6]. The toxic alcohols include methanol, isopropanol, and ethylene glycol. When ingested, each compound and its metabolites may cause organ damage and central nervous system (CNS) depression; thus, such ingestions are treated as medical emergencies. These compounds are found in common household and industrial products which are easy to obtain. Ethylene glycol is the primary component of automobile antifreeze, methanol is present in windshield washing fluid, and isopropanol is found in 'rubbing alcohol'. Like ethanol, all three of these compounds can cause fatal CNS depression at high enough concentrations, especially when combined with other CNS depressants such as benzodiazepines or opioids. Ethylene glycol and methanol are

particularly harmful because they also form dangerous metabolites that can cause severe organ damage [1,4,5,7]. Isopropanol is less harmful because it is metabolized to acetone, which is a normal component of human metabolism [6]. The metabolites of ethylene glycol include glycolic acids and oxalic acid. Oxalic acid reacts with calcium in the kidneys to produce calcium oxalate stones, potentially causing acute renal failure. Likewise, methanol is metabolized to formaldehyde and then formic acid, which damages the optic nerve and may lead to permanent blindness.

Gas chromatography (GC), with or without mass spectrometry, is the gold standard for detecting toxic alcohols in plasma or serum samples [1,2,6,8,9]. It is also useful in the management of such ingestions, because it can provide quantitative data that guides further treatment decisions. However, GC is time and labor-intensive. As a result, many facilities do not have access to GC analysis, and the

turnaround time to have it performed at a remote clinical laboratory precludes timely, life-saving treatment [4,5,10]. It is critical to diagnose toxic alcohol ingestions quickly, particularly when they involve methanol or ethylene glycol, because the efficacy of treatment depends on how much time has elapsed. One alternative method that has emerged for analysis of ethylene glycol are ethylene glycol enzymatic assays that can run on standard clinical chemistry analyzers with rapid turnaround time to determine quantitative ethylene glycol concentrations [11–14]. It is important to note that standard drug of abuse screening panels, commonly used in emergency medicine [15], will not detect the toxic alcohols.

Fomepizole, an alcohol dehydrogenase inhibitor, has emerged as a specific treatment for methanol and ethylene glycol poisoning, because it prevents the formation of the more toxic metabolites [16,17]. An alternative choice is to use ethanol to inhibit alcohol dehydrogenase. However, once metabolites have been generated, fomepizole or ethanol have less benefit, and organ damage from metabolites may occur. If too much time has passed, hemodialysis, an invasive procedure, is required to remove these other compounds.

Due to the time-sensitive nature of toxic alcohol ingestion cases, clinical decisions are often made using clinical signs, symptoms, and history provided by the patient or other witnesses [1,2,4–7]. Basic blood chemistry tests and arterial blood gas analysis can be performed quickly to provide information that can guide a patient's treatment. The anion gap may also provide valuable clinical information. Ethylene glycol and methanol ingestions are known causes of anion gap due to the production of metabolites such as glycolic acid, oxalic acid, and formic acid.

The osmolal gap (OG) is an important tool for diagnosing and managing patients with suspected toxic alcohol ingestions [8,9,18–27]. The OG is determined using common laboratory tests, which permits treatment decisions to be made more quickly than GC. The OG is determined by first measuring serum/plasma osmolality ('measured osmolality') on an osmometer, ideally using freezing point depression. A 'calculated osmolality' is then determined using common laboratory tests such as blood urea nitrogen (BUN), glucose, and sodium to estimate the osmolality from major endogenous components of serum/plasma. The difference between measured and calculated osmolality is referred to as the OG. If ethanol is present, its estimated contribution to osmolality can also be included in the calculated osmolality. There is debate over the use of OG to diagnose toxic alcohol ingestions and also myriad formulae proposed for estimating serum/plasma osmolality [19,20,24,27–32].

An elevated OG suggests the presence of osmotically active substances in addition to typical endogenous contributors [8,9,19,29,30]. This may occur with toxic alcohol ingestions or with a variety of conditions. These include diabetic ketoacidosis, alcoholic ketoacidosis, renal failure, or shock. The infusion of mannitol for conditions such as increased intracranial pressure may also increase the OG. Thus, when used in combination with physical examination and history, the OG is an important tool for determining the presence and severity of a toxic alcohol ingestion. The reduction of an elevated OG during treatment can also serve as a surrogate marker for clearance of toxic alcohols from the body.

Propylene glycol is another compound that can cause an elevated OG [22,33–38]. Although similar in name and molecular structure to ethylene glycol, propylene glycol is considered much less toxic. Its similar chemical properties make it suitable as a less toxic alternative to ethylene glycol-based antifreeze products. Propylene glycol is also used in many other applications including foods, cosmetics, tobacco products (including e-cigarette solutions), and pharmaceuticals. It is commonly present in activated charcoal preparations and poorly water-soluble intravenous medications because it can dissolve hydrophobic substances, even in the presence of water [34,37,39]. Common intravenous preparations that contain propylene glycol as a diluent are lorazepam, diazepam, and etomidate. Several studies have examined propylene

glycol toxicity in the context of repeated exposure to these preparations, especially for patients that require extended sedation for intubation or other reason [22,25,33,35,36]. The other source of propylene glycol toxicity is the ingestion of propylene glycol-based antifreeze products [34,37].

There are commonly used conversion factors for interconverting between OG and toxic alcohol plasma/serum concentrations. These can be used, for example, in estimating ethylene glycol concentrations once the OG is determined [4]. These conversion factors assume minimal or no contribution to OG by metabolites. This assumption holds fairly well for ethylene glycol, methanol, and propylene glycol due to their conversion to metabolites that dissociate in the blood. The metabolites can contribute to metabolic acidosis and elevated anion gap; however, while they may increase serum osmolality, the impact of these anions on OG is nullified by the inclusion of Na^+ concentration multiplied by a factor of 2 in calculated osmolality equations [1,2,21]. Isopropanol is more complicated given that both isopropanol and its metabolite acetone can contribute significantly to osmolality [6]. The contribution of ethanol to osmolality in actual ingestions is complicated due to unmeasured metabolites of ethanol or pathophysiologic complications such as alcoholic ketoacidosis that may also impact OG [2,21,29].

The current study utilizes retrospective data from an academic medical center that serves as an emergency and toxicology treatment center and that has the only clinical laboratory in a wide geographic region that specifically determines toxic alcohol concentrations. The purpose of the study was to ascertain how well standard determination of OG compared to OG estimated from serum/plasma concentrations of ethylene glycol, isopropanol, methanol, acetone, and propylene glycol.

2. Methods

2.1. Analytical methods

Serum/plasma electrolytes, BUN, glucose, and ethanol were determined on Roche Diagnostics (Indianapolis, IN, USA) chemistry analyzers. The basic analytical methodology did not change during the retrospective study period. Serum/plasma osmolality was determined by freezing point depression analysis on an osmometer. Serum/plasma concentrations of acetone, methanol, isopropanol, ethylene glycol, and propylene glycol were measured by GC, with a lower concentration limit for clinical reporting of 10 mg/dL [9,38]. Beginning in October 2010, the clinical laboratory introduced an enzymatic assay for ethylene glycol (Catachem, Oxford, CT), the analytical characteristics of which have been described previously [12,14].

2.2. Study design

A retrospective analysis approved by the University of Iowa Institutional Review Board (protocol #201906709) was conducted. The institution uses Epic (Epic, Inc.) as the electronic health record (EHR). As described in previous studies [40,41], Epic Reporting Workbench (RWB) is a reporting tool within the EHR that can retrieve data based on specified query parameters [40]. The RWB report captured all cases in which OG had been determined and specific analysis for toxic alcohols and/or glycols had been performed. All cases were chart reviewed for clinical history, ingestion details, and treatment.

During the entire retrospective time period, the institution had a panel of laboratory tests known as the "Ethanol Volatile Panel" which included serum/plasma sodium, BUN, glucose, and ethanol (by enzymatic assay), and measured osmolality [9]. The panel included two OG results, either with or without estimated contribution of ethanol. If the OG that also included contribution of ethanol exceeded 15, the covering pathology resident or faculty was notified. The pathology resident or faculty then contacted the clinical service to determine clinical need for further testing by GC. Starting in October 2010, Ethanol Volatile Panel orders that resulted in an elevated OG automatically reflexed to the

enzymatic ethylene glycol assay [14]. If the results of this enzymatic assay did not explain the elevated OG, the cross-covering pathology or resident or faculty was notified. The ethylene glycol enzymatic assay could also be ordered by clinicians as a standalone test without any restriction. All laboratory analyses reported in the present study were performed by clinical laboratory staff as part of patient care, i.e., no laboratory analyses were performed for research purposes only.

2.3. Retrospective dataset

The retrospective time period was from November 1, 1996 through May 31, 2019. There were a total of 260 measurements and 158 unique patients. The first measurements during a clinical encounter were considered as "Initial" measurements; the remainder during that encounter were considered as "Follow-up" measurements. Some measurements were repeat follow-up measurements obtained during one hospital stay, while others were due to later readmissions. One patient in particular had four separate admissions involving elevated acetone levels and seven admissions involving isopropanol ingestions. One other patient had two encounters involving isopropanol ingestion, and three patients had two encounters related to ingesting ethylene glycol.

The ingestions were then divided into groups based on which toxic alcohols or glycols were present. One patient is included in both the propylene glycol and acetone groups, because she had both present at different times over the course of one admission. Both of these measurements are listed as "Initial" since they represent the initial elevations for each compound. If two glycols or alcohols were detected in one sample, the data were categorized into the group of the more clinically serious ingestion, with ethylene glycol, methanol, and isopropanol in descending order as clinically serious. For example, if there was detection of both ethylene glycol and propylene glycol, the data would be included with the ethylene glycol measurements. Five data points were from a single patient with methanol and ethylene glycol both detected. Since this patient's initial serum ethylene glycol concentration was nearly 18-times his initial methanol concentration (605 mg/dL and 34 mg/dL, respectively), these measurements were categorized with the ethylene glycol data described below.

The estimated timing from ingestion to each measurement was determined from chart review. The approximate time of ingestion was ascertained either from the patient or witnesses, allowing us to calculate the time elapsed from ingestion to each blood draw. "Early" indicates less than a 12 h delay before laboratory measurement, and "late" indicates a delay of greater than or equal to 12 h. If a range was given, the value at the center of the range was used. The timing was listed as "unknown" if the clinical history was determined to be too unreliable, either due to lack of information or multiple, widely different estimates listed in the chart. Many of these timing values are likely greater than 12 h, but this is not always representative of when the patient initially sought care. This is due to the fact that many of these patients were transferred from other hospitals.

There is no timing data listed for acetone resulting for cause other than isopropanol because of the biology of the compound. It is the only one of the five compounds in this study that can be produced endogenously, and only two of the measurements in this category are thought to be related to ingestions other than ethanol. Therefore, timing since ingestion data for acetone is largely unavailable and would not be of value.

2.4. Statistical analyses and calculations

OG of serum/plasma specimens was calculated using a formula by Khajuria and Krahn [28]: OG = (Measured Osmolality) – {2 x [Sodium] + (1.15 *[Glucose]/18) + ([BUN]/2.8) + (1.2 *[Ethanol]/4.6)}, with serum/plasma sodium concentration in mEq/L and the remaining serum/plasma analyte concentrations in mg/dL. Anion gap was equal to the serum/plasma sodium concentration minus the sum of the serum/

plasma bicarbonate and chloride concentrations, with all analytes measured in mEq/L. Standard conversion factors for estimating toxic alcohol and acetone concentrations in mg/dL by multiplying OG by the conversion factor are: ethylene glycol, 6.2; isopropanol, 6.0; methanol, 3.2; acetone, 5.8; and propylene glycol, 7.6 [4–6,25].

Deming regression analysis was used to determine the correlations between OG and toxic alcohol serum/plasma concentrations and also OG calculated by different mechanisms (EP Evaluator (Data Innovations, Burlington, VT)). Paired t-test was performed on method comparison plots, with P < 0.05 considered significant.

3. Results

3.1. Overall demographics

Data were analyzed for for 158 patients (67 females, 91 males) who had GC analysis for alcohols (acetone/isopropanol/methanol), glycols (ethylene glycol/propylene glycol), and/or enzymatic ethylene glycol analysis performed on the same specimen as one in which OG was determined. There is a male predominance in the acetone, ethylene glycol, and methanol groups, while the isopropanol and propylene glycol groups have more females (Table 1). The average age was 40.3 years and the median age was 40.8 years (range: 0.9–77.1; Table 1).

3.2. Overall correlation between osmolal gap estimates

Fig. 1 demonstrates the relationship between the OG derived from measured serum/plasma osmolality (x-axis) and the OG estimated from conversion factors applied to alcohol/glycol concentrations (y-axis) There is a linear relationship between the two values when all the data is combined, with an R^2 value of 0.919 and the y-intercept close to 0 (Fig. 1A; in this figure, as with all the figures in Fig. 1, the solid line equals linear regression and the dashed line is the line of unity). This plot has a slope of 0.868, which implies that the estimated OG converted from alcohol/glycol concentrations slightly underestimates the OG calculated from measured osmolality. The next sections describe the subgroups in detail.

3.3. Methanol group

The methanol group (19 samples; 12 unique patients, 9 males and 3 females) has the lowest average patient age of 32 years (Table 1) with three of the twelve patients being young children under the age of 3 years. Ten of the samples that contained methanol contained no other toxic alcohols or acetone, while 9 had ethanol present. Of the 19 samples, chart review revealed that 4 were collected "early" (within 12 h of ingestion), 4 were collected "late" (more than 12 h after ingestion), and no timing information could be obtained for 11 of the samples. There was a single patient with a combined methanol and ethylene glycol that is discussed in the ethylene glycol subgroup below. One methanol-containing sample also had isopropanol, acetone, propylene glycol, and ethanol present. This patient was a 52-year-old male who had a history of heavy, chronic ethanol use and alcoholic hepatitis. He was given intravenous lorazepam at an outside hospital, and this is the probable source of the propylene glycol. There is no mention of ingestion of isopropanol or methanol in his chart. Of the methanol-containing samples, excluding the one with the high ethylene glycol concentration, 47.4% of them had an anion gap. In Fig. 1B, where only the methanol ingestion data is included, the relationship between different estimates of OG is distinctly linear despite having relatively few data points. The R^2 value for these data is 0.934.

3.4. Ethylene glycol

The ethylene glycol group (133 samples; 53 unique patients, 33 males and 20 females) has an average patient age of 40.3 years

Table 1
Patient Demographics.

	N Unique Patients (females/males)	N with Anion Gap[a]	Average Age ± SD	Median Age	Age Range	Total Measurements[b] (initial/follow-up)	Number of Measurements with Anion Gaps (≥16) (yes/no/unknown)	Timing of Measurements[c] (early/late/unknown)
Acetone	36 (11/25)	24	43.6 ± 18.3	46.4	1.4 - 69.9	42 (41/1)	(28/5/9)	–
Ethylene Glycol	53 (20/33)	24	40.3 ± 14.8	39.8	17.6 - 72.1	133 (57/76)	(31/50/52)	(39/55/39)
Isopropanol	30 (18/12)	8	44.3 ± 17.8	41.4	0.9 - 77.1	39 (36/3)	(15/17/7)	(15/4/20)
Methanol	12 (3/9)	8	32 ± 24.0	31	1.7 - 64.6	19 (12/7)	(9/1/9)	(4/4/11)
Propylene Glycol	27 (15/12)	13	34.8 ± 13.6	32.7	8.5 - 60.9	27 (27/0)	(13/12/2)	(9/0/18)
Total	158 (67/91)	77	40.3 ± 17.1	40.8	0.9-77.1	260 (172/88)	(96/85/79)	(67/63/88)

[a] Number of patients who had an anion gap at any point during his or her encounter which co-occurred with an elevated toxicology measurement (ethylene glycol, acetone, isopropanol, propylene glycol, or methanol).

[b] Number of samples from the 158 patients. "Initial" measurements represent the first sample with an elevated level of one of the compounds, while "follow-up" are follow-up measurements during the encounter. Patients with multiple encounters have one "initial" measurement per encounter.

[c] Number of samples which are determined to have been collected "early," less than 12 h or "late," more than 12 h, after introduction of the compound into the body based on chart review. Timing is "unknown" if chart review is unavailable or inconclusive. No timing data is available for acetone because acetone was produced endogenously in most of these cases.

(Table 1). Two of these patients are less than 18 years old, but both were less than 6 months from turning 18 at the time of clinical presentation. Twenty-five of the 133 samples containing ethylene glycol also had ethanol present, 13 contained propylene glycol, and 3 contained propylene glycol and ethanol. Five of the ethylene glycol samples were unique in that they also contained methanol, a less common ingestion. These five measurements are data from one admission of one patient who consumed an antifreeze product that contained both compounds. In 22.3% of the samples that included ethylene glycol, an anion gap was also detected. Of the 133 samples, 39 were collected "early" after ingestion. Fifty-five of the samples were collected "late." No timing information could be acquired by chart review for 39 of the samples

Fig. 1C displays the association between the two OG calculations for the ethylene glycol data. This graph has the highest R^2 value of any of the six displayed plots in Fig. 1 (0.949) and has a similar slope to the combined data graph at 0.851. The relationship appears to be linear, even at very high OG measurements, and has no apparent outliers.

3.5. Propylene glycol

The propylene glycol group (27 samples; 27 unique patients, 12 males and 15 females) has an average patient age of 34.8 years, with two patients under the age of 18 years. 17 samples revealed no other compounds and 10 contained ethanol. Of these 27 samples, 48.1% had an anion gap. Chart review was performed to identify likely source of propylene glycol, which can come from a variety of iatrogenic sources, with two of the most common being lorazepam (tradename: Ativan) intravenous formulations and activated charcoal. Ten cases were likely due to the use of activated charcoal and 2 were related to intravenous lorazepam. Five other cases were ingestions of over-the-counter drugs. Two of these five involved cough suppressant liquids and/or mucous relief solutions, both known sources of propylene glycol. The other three may have directly ingested propylene glycol in the drugs they consumed, or they may have received activated charcoal from an outside hospital before transfer. Another case of direct propylene glycol ingestion involved the consumption of antifreeze that contained propylene glycol instead of ethylene glycol. In nine cases, no source of propylene glycol could be identified through chart review. Fig. 1D, which only displays data from propylene glycol measurements where no toxic alcohols were present, appears to be less linear at low OG levels (at around 20 and below), but becomes more linear at higher OG values. The relationship is still relatively well explained by a linear model with an R^2 value of 0.821.

3.6. Isopropanol

The isopropanol group (39 samples; 30 unique patients, 12 males and 18 females) includes one young child who was less than one year old. All 39 measurements containing isopropanol also contained acetone. Ethanol was also detected in two of the samples, propylene glycol was detected in 2 of the samples, and one sample included ethanol and propylene glycol. An anion gap was detected in 38.5% of these samples. In Fig. 1E, which demonstrates the isopropanol ingestion data, the relationship between the two OG calculations is less linear than Figs. 1A-D, with an R^2 value of 0.731 and abundant variation above and below the best-fit line. This data is unique from the other single-compound graphs in that each measurement of isopropanol also contained some level of acetone, its metabolite, which was accounted for in the estimated OG.

3.7. Acetone

The acetone group (42 samples; 36 unique patients, 25 males and 11 females) comprises samples containing acetone but without isopropanol, ethylene glycol, or methanol. Of the 42 measurements that
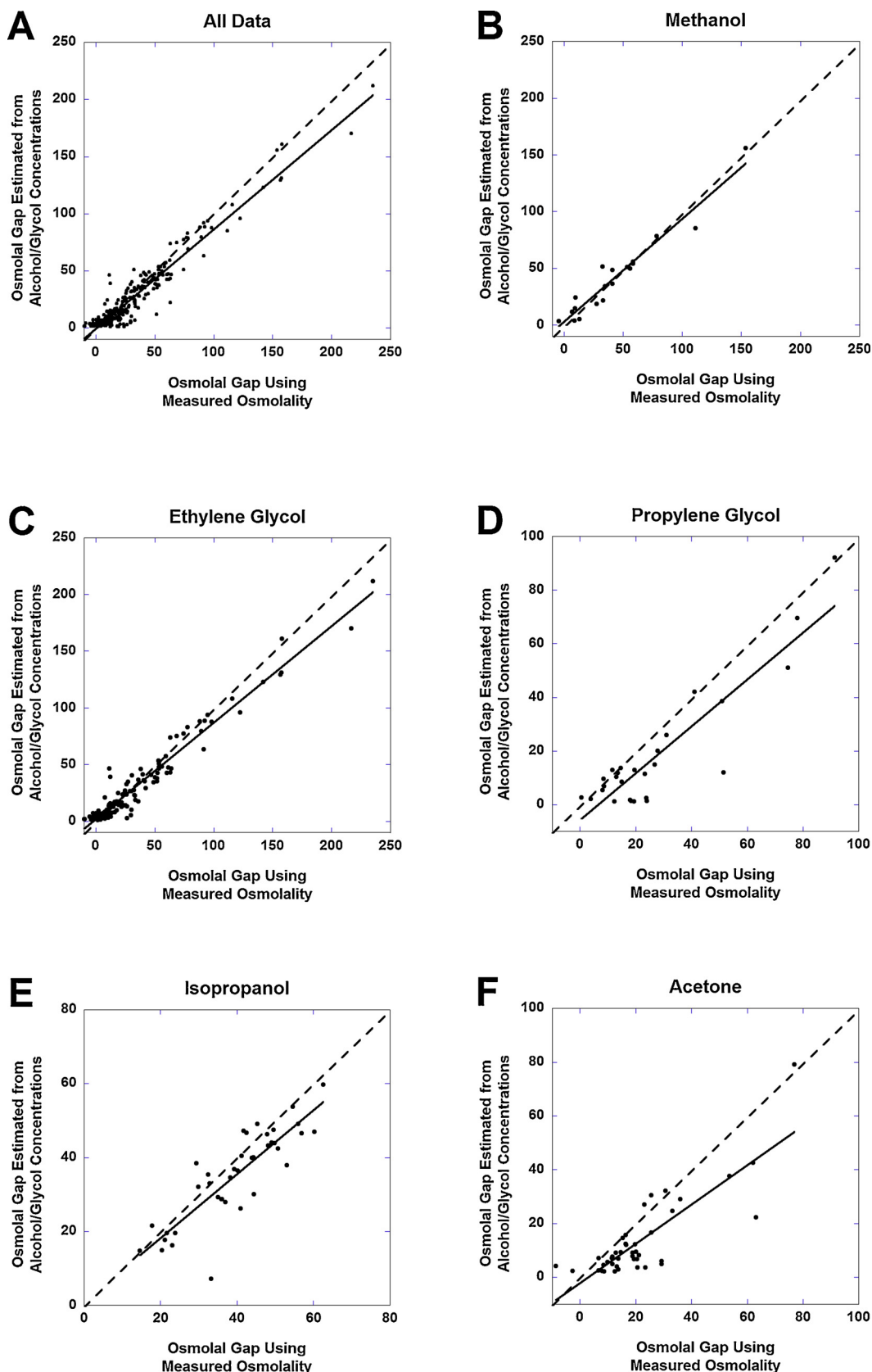
Fig. 1. Osmolal gap calculated by traditional route using measured osmolality vs. osmolal gap estimated from measured values of toxic alcohols and glycols using conversion factors. Figs. 1A combines all 260 measurements, while Fig. 1B–F divide the data by primary ingestion. The solid lines indicate the best-fit line for each data set and the dotted lines represent the line of unity. The linear regression equations are as follows: (A) All data: y-intercept, -0.053; slope, 0.868; R^2, 0.919; (B) Methanol: y-intercept, 3.243; slope, 0.908; R^2, 0.934; (C) Ethylene glycol: y-intercept, 2.114, slope, 0.851, R^2, 0.949; (D) Propylene glycol: y-intercept, -5.568; slope, 0.874; R^2, 0.821; (E) Isopropanol: y-intercept, 1.103; slope, 0.863; R^2, 0.731; (F) Acetone: y-intercept, -2.034; slope, 0.732; R^2, 0.694. The slope was significantly different from 1.0 for propylene glycol ($p < 0.05$) and acetone ($p < 0.05$).

met these criteria, 1 also contained ethanol, 8 contained propylene glycol, and 1 contained both ethanol and propylene glycol. Sixty-seven percent of these measurements were associated with an anion gap. Ethanol-related conditions (alcoholic ketoacidosis, ethanol withdrawal) were the most common diagnoses among patients with elevated acetone in the absence of isopropanol ingestion, accounting for 12 patients. Diabetic ketoacidosis was the next most common likely cause and was found in 9 of the patients. Four were attributed to starvation ketoacidosis and five to ketoacidosis of an unspecified etiology. Two had liver and kidney failure, and three cases were related to a drug overdose or toxic ingestion. Finally, chart review was unavailable for one patient who had elevated acetone levels.

Fig. 1F displays the association between the two OG calculations. These demonstrate the weakest linear relationship of the six graphs in Fig. 1, with an R^2 of 0.694. This graph also had the lowest slope of only 0.731, while each of the other 5 graphs had a slope that ranged from 0.851 to 0.908. This may be because the OG estimation cannot take into account other compounds present (e.g., additional endogenous compounds or unmeasured metabolites of ethanol), especially in complicated cases that include ketoacidoses and multi-organ failure.

### 3.8. Estimation of toxic alcohol concentrations from osmolal gap

Figs. 2 and 3 demonstrate the relationship between the measured toxic alcohol concentration by GC or enzymatic assay of each compound and the estimated concentration of each compound derived from the OG using conversion factors. In each of the compounds, the best-fit line is situated above the line of unity. This indicates that the estimated concentration derived from the OG tends to overestimate the concentration of each compound. This effect is most noticeable in the acetone and propylene glycol groups (Fig. 2C, B). These groups have comparatively low R^2 values of 0.49 and 0.22, respectively. The graphs for the methanol and ethylene glycol data follow the line of unity much more closely. The methanol data has an R^2 value of 0.93 and the ethylene glycol has an R^2 value of 0.95 (Figs. 2A, B). Both have slopes close to one, 1.11 and 1.19, respectively, and low y-intercepts, 1.47 and 1.88. The isopropanol group falls somewhere in the middle of the groups in terms of R^2 value and slope with values of 0.70 and 0.84, respectively (Fig. 3A).

4. Discussion

Toxic alcohol/glycol ingestions are difficult to diagnose because of the nonspecific signs and symptoms [1,2,4–7]. This study demonstrates the linear relationship between the OG determined from measured osmolality and the OG estimated from actual alcohol/glycol concentrations determined by GC or the enzymatic assay for ethylene glycol in patients treated at an academic medical center. This is demonstrated by the R^2 value of 0.919 for the combined data from all five substance categories. The data for the ethylene glycol and methanol group follow a clear linear relationship. The relationship remains linear even for the mixed ingestion data, which includes all the isopropanol data and a portion of the data for each of the other compounds. While acetone, the metabolite of isopropanol, contributes significantly to the OG, metabolites of ethylene glycol and methanol contribute less due to their dissociation in serum [1,2,4,5,18].

For all the compound groups, the OG determined by measured osmolality tends to be higher than the OG that is estimated from concentrations. This yields a slope of 0.868 for the combined data when the OG determined from measured osmolality is on the x-axis. Importantly, the y-intercept is close to 0 in all the groups, with a value of -0.053 in the combined data set. The relationship holds even at low OG values.

The present study also evaluated the relationship between the measured concentration of each compound (by GC or ethylene glycol enzymatic assay) and the estimated concentration of each compound derived from the OG using common conversion factors. Like the OG

Methanol

Ethylene Glycol
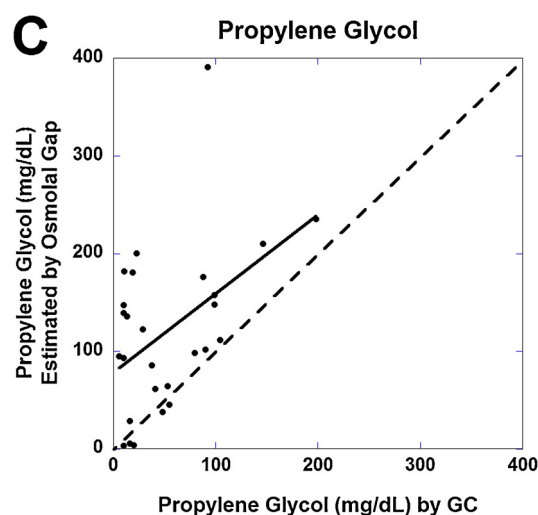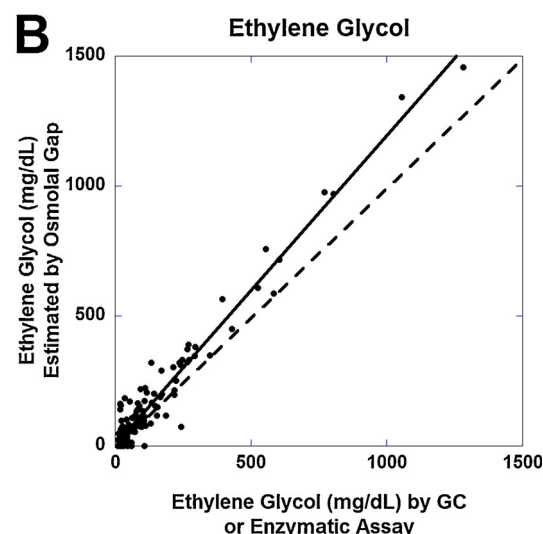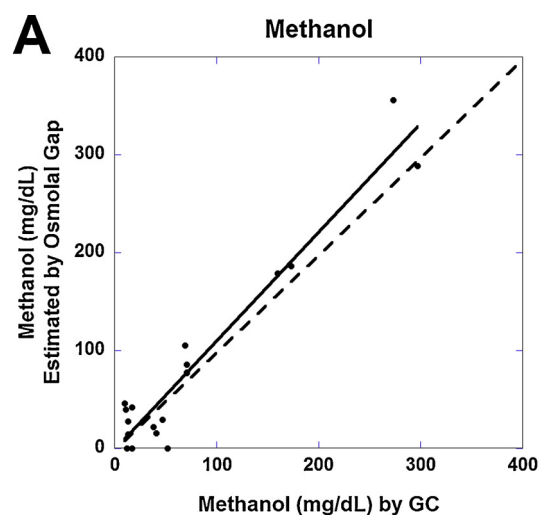
Propylene Glycol

(caption on next page)

versus OG data described above, the relationship was linear with high R^2 values for the methanol and ethylene glycol data of 0.93 and 0.95, respectively. These two groups also had y-intercepts close to 0 and

Fig. 2. Concentration (mg/dL) of methanol or glycol measured by enzymatic assay (ethylene glycol) or gas chromatography (methanol, ethylene glycol, propylene glycol) vs. concentration (mg/dL) estimated by osmolal gap using compound-specific conversion factors. The solid lines indicate the best-fit line for each data set and the dotted lines represent the line of unity. The linear regression equations are as follows: (A) Methanol: y-intercept, -1.465; slope, 1.113; R^2, 0.925; (B) Ethylene glycol: y-intercept, 1.883; slope, 1.191; R^2, 0.950; (C) Propylene glycol: y-intercept, 78.185; slope, 0.808; R^2, 0.215. The slope was significantly different from 1.0 for propylene glycol ($p < 0.05$).
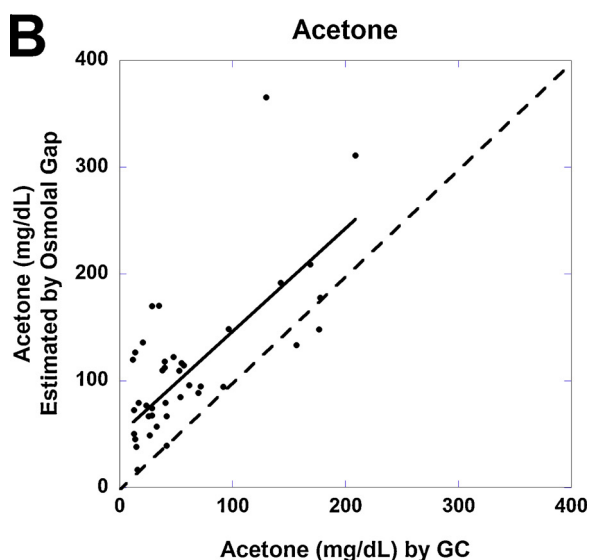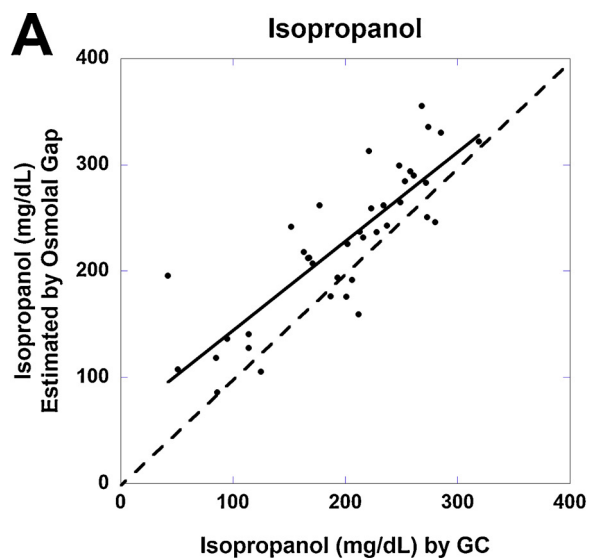

Fig. 3. Concentration (mg/dL) of isopropanol and acetone measured by gas chromatography vs. concentration (mg/dL) estimated by osmolal gap using compound-specific conversion factors. The solid lines indicate the best-fit line for each data set and the dotted lines represent the line of unity. The linear regression equations are as follows: (A) Isopropanol: y-intercept, 59.989; slope, 0.840; R^2, 0.696; (B) Acetone: y-intercept, 49.698; slope, 0.965; R^2, 0.485. The slope was significantly different from 1.0 for acetone ($p < 0.05$).

slopes slightly greater than 1, possibly reflecting the presence of other metabolites that subtly impact OG. The isopropanol data had an intermediate R^2 value of 0.7, and the acetone and propylene glycol groups had relatively low R^2 values of 0.49 and 0.22, respectively. These correlations are consistent with other findings; in particular, the acetone and propylene glycol groups often represent complicated cases

with unmeasured compounds affecting OG. Interestingly, the isopropanol, propylene glycol, and acetone data all demonstrate slope values of less than 1. This appears to be occurring in these cases because our calculation overestimates the concentrations more significantly at lower actual concentrations.

Previous studies have examined the relationship between OG and methanol or ethylene glycol and found these are best represented by a linear model [18,26,42] Other studies have looked at propylene glycol concentration and toxicity in the context of lorazepam infusion [22,33,35]. In general, these studies tend to demonstrate more widely distributed data for the relationship between propylene glycol concentration and OG. The present study included propylene glycol concentration data from many sources including infusion and ingestion.

The present study includes data on isopropanol and acetone, which has been sparse in the literature. The isopropanol ingestion data in the present study fits a linear model well when comparing the OG from measured osmolality and the OG estimated from the isopropanol plus acetone concentrations. It also appears that the isopropanol plus acetone concentration estimated from the OG is generally a good approximation of the actual combined concentration of these species. This implies that the conversion factor of 5.9, the average of the individual conversion factors for acetone and isopropanol, is a reasonable approximation.

This study has some limitations. One limitation is that all data included in the analysis were collected at a single academic medical center. Another limitation is that the data were collected over a period of two decades. The analytical measurements did not change fundamentally during this time, but instrumentation varied over the years. A final limitation is that this study utilized clinical data, so not all GC analysis was performed for every sample.

5. Conclusion

Overall, a linear relationship was found between the OG calculated from measured plasma/serum osmolality and the OG estimated by applying conversion factors to measured concentrations of the different compounds. The OG estimated from measured concentrations tends to underestimate the OG calculated from measured osmolality. The analysis of the relationship between the measured serum/plasma concentration of each compound and the estimated concentration of the compound derived from the OG also revealed linear relationships, although to varying degrees depending on the compound. These data suggest that, in combination with an adequate history, the OG and compound-specific conversion factors are helpful for estimating the concentration of a compound in a patient's blood to guide clinical management.

Authors' contributors

HRG and MDK conceived the study, performed the analysis, and wrote the manuscript. HRG prepared the manuscript. MDK obtained the necessary regulatory approval. Both authors read and approved the final manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.toxrep.2019.12.005.

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