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원 저

급성 중독환자에서 삼투압 계산식으로 추정된 에탄올 농도의 유효성 검증

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Discrepancies and Validation of Ethanol Level Determination with Osmolar Gap Formula in Patients with Suspected Acute Poisoning

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Purpose: Osmolar gap (OG) has been used for decades to screen for toxic alcohol levels. However, its reliability may vary due to several reasons. We validated the estimated ethanol concentration formula for patients with suspected poisoning and who visited the emergency department. We examined discrepancies in the ethanol level and patient characteristics by applying this formula when it was used to screen for intoxication due to toxic levels of alcohol.

Methods: We retrospectively reviewed 153 emergency department cases to determine the measured levels of toxic ethanol ingestion and we calculated alcohol ingestion using a formula based on serum osmolality. Those patients who were subjected to simultaneous measurements of osmolality, sodium, urea, glucose, and ethanol were included in this study. Patients with exposure to other toxic alcohols (methanol, ethylene glycol, or isopropanol) or poisons that affect osmolality were excluded. OG (the measured-calculated serum osmolality) was used to determine the calculated ethanol concentration.

Results: Among the 153 included cases, 114 had normal OGs (OG≤14 mOsm/kg), and 39 cases had elevated OGs (OG>14). The mean difference between the measured and estimated (calculated ethanol using OG) ethanol concentration was -9.8 mg/dL. The 95% limits of agreement were -121.1 and 101.5 mg/dL, and the correlation coefficient R was 0.7037. For the four subgroups stratified by comorbidities and poisoning, the correlation coefficients R were 0.692, 0.588, 0.835, and 0.412, respectively, and the mean differences in measurement between the measured and calculated ethanol levels were -2.4 mg/dL, -48.8 mg/dL, 9.4 mg/dL, and -4.7 mg/dL, respectively. The equation plots had wide limits of agreement.

Conclusion: We found that there were some discrepancies between OGs and the calculated ethanol concentrations. Addition of a correction factor for unmeasured osmoles to the equation of the calculated serum osmolality would help mitigate these discrepancies.

Key Words: Formula, Osmolar gap, Osmolarity, Toxic alcohol, Predictive value of tests

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INTRODUCTION

Ingestion of toxic alcohols causes diagnostic challenges because most emergency departments do not have prompt access to laboratory modalities for quantification of such substances[1,2]. Serum level measure-

ments methods are labor-intensive and not available at most clinical laboratories affiliated with hospitals and medical centers, except at some larger medical center laboratories. Osmolar gap (OG) or the difference between measured and calculated osmolality, is often used as a surrogate marker for toxic alcohol exposure[1]. An elevated OG (typically more than 10-15) is often suggestive of the presence of ethanol, methanol, ethylene glycol, or isopropanol[2]. The primary use of OG determination at present is to screen for the possible presence of exogenous toxic substances in emergency or intensive care patients[3].

Unfortunately, OG calculation has several limitations. Most equations used to calculate osmolality were derived decades ago, based on in vitro studies, by including healthy volunteers or small cohorts and using equipment that may not have had the same standards as those used currently. Furthermore, the extent of the contribution of ethanol to OG remains controversial[4-6].

Finally, some conditions, including diabetic or alcohol ketoacidosis and chronic kidney disease, may lead to an increase in OG, therefore, physicians must be cautious with interpretation of toxicological tests[7]. Despite these limitations, and until quantification of toxic alcohols becomes readily and widely available, better computation of OG will likely improve the screening and management of patients with suspected toxic alcohol levels.

We aimed to validate the formula for estimated ethanol concentration that incorporates OG and elucidate its usefulness or improved performance in screening for intoxication to toxic alcohols. We also investigated several conditions associated with wide discrepancies between the estimated and measured ethanol concentrations by analyzing serum samples from patients with suspected intoxication who visited our emergency department.

METHODS

1. Population

We conducted a retrospective analysis of laboratory and medical records of patients who represented with clinical history or signs and symptoms consistent

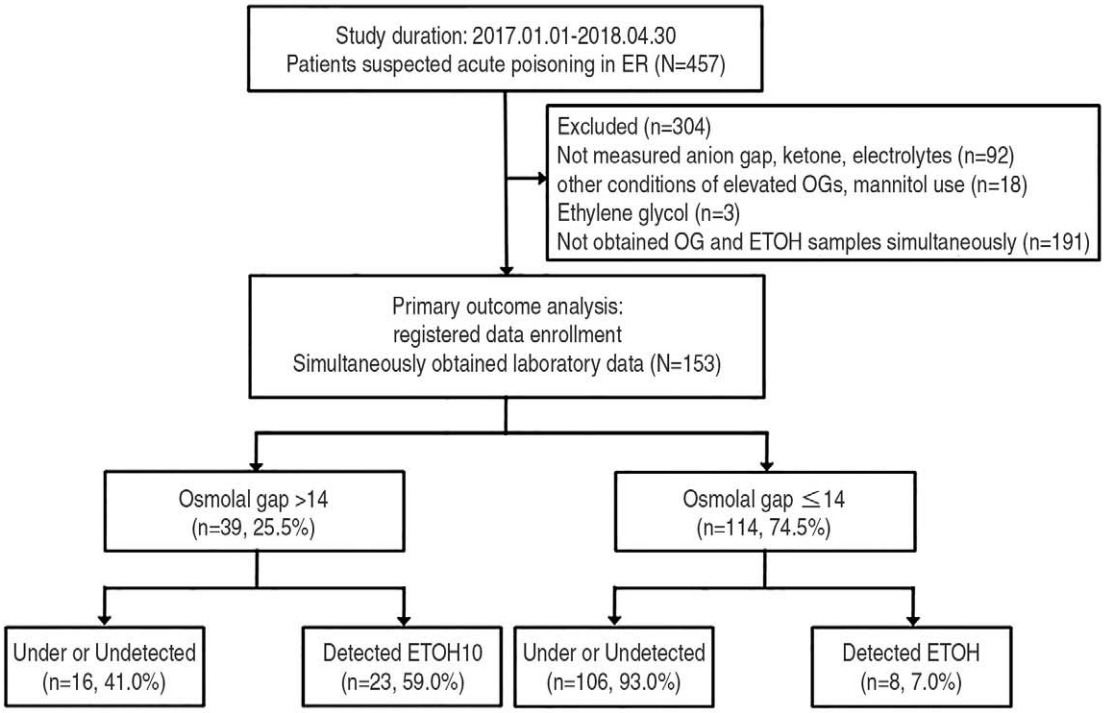

Fig. 1. Flow chart of patient enrollment and primary outcomes.
ER: emergency room, OG: osmolar gap, ETOH: blood ethanol level.

with suspected acute poisoning (e.g., altered mental status with negative findings on imaging, or suicide attempt) and visited a regional emergency medical center from January 2017 to April 2018 (Fig. 1). We included 153 cases undergoing simultaneous measurements of osmolality, sodium, potassium, urea, creatinine, glucose, ketone, lactate, and ethanol. When multiple measurements were performed for a single patient, we only included the first results. Patients with documented evidence of exposure to other toxic alcohols (methanol, ethylene glycol, or isopropanol) as well as those in whom the required tests had not been simultaneously performed were excluded from the study[5]. We excluded all subsequent measurements taken after the first measurement for individuals included in the analysis; we also excluded patients with missing values required for OG calculation.

2. Laboratory analyses and data collection

We collected blood samples of patients admitted to the emergency department who were subjected to tests for determining the levels of serum ethanol, sodium, urea, and glucose levels as well as osmolality and subsequently recorded these values. Predicted osmolality was calculated by excluding ethanol level using the following formula with conventional units[1,6,8]: 2 Na [mEq/L]+(Urea [mg/dL])/2.8+(Glucose [mg/dL])/18. Ethanol level was measured using a chemical analyzer (Dimension Vista 1500® Intelligent Lab System; Siemens, Germany) with the linear by loci method from 0 to 1000 mg/dL. Serum osmolality was determined via freezing point depression on an osmometer (Model 2020, Advanced Instruments, Norwood, MA). OG was calculated by subtracting the measured serum osmolality from the calculated serum osmolarity[5]. We subsequently conducted linear regression analysis of the data to ascertain the relationship between plasma ethanol concentration and OG[1].

Here, the correction factor was 4, and the formula used was OG=[Ethanol level]/4[1]. Owing to differences in study subjects and research methods, correction factors are derived differently (3.68, 4.0, 4.6)[1,8,9]. Moreover, correction factor depends on molecular weight of the exposed material.

3. Outcomes and definition

For validating the pre-existing formulas that determine contribution of ethanol to OG, we divided all patients with elevated OGs based on the suspicion of having toxic ethanol ingestion (OG〉14 mOsm/kg). An elevated OG (defined by an OG value exceeding the threshold range of 10-15) suggests the presence of osmotically active substances other than sodium, blood urea nitrogen, glucose, and ethanol[8]. The charts of patients whose initial laboratory test results showed an OG value of 〉14 but an ethanol concentration 〈 10 mg/dL, were reviewed to identify the likely cause for elevated OGs (unexplained OGs)[8]. Figure 1 shows the patient samples and subsets that were subjected to a more detailed analysis.

The primary endpoints were elevated OG (OG〉14) and ingestion of ethanol at toxic levels (ethanol≥10 mg/dL)[8]. Secondary endpoints were consequent comorbidities (acute kidney injury, chronic renal disease, shock, ketosis, or metabolic acidosis) and acute poisoning. We classified cases into four subgroups: intoxication with comorbidities, intoxication without comorbidities, non-intoxication with comorbidities, and non-intoxication without comorbidities. In each group, we compared the correlation between calculated ethanol levels using OG and the measured ethanol concentration.

4. Statistical analyses

Demographic data are presented as raw numbers and percentages. All continuous data with a normal distribution were analyzed using Student's t-test, whereas, non-normal data were evaluated using Mann-Whitney test. Pearson's chi-square or Fisher's exact test was used to compare all categorical data.

Relationship between OG and measured ethanol concentration was established via linear regression analysis[1]. Bland-Altman method was used to evaluate the agreement of absolute and relative (%) differential biases between measured ethanol concentrations

and calculated levels[10,11]. Diagnostic characteristics of OGs were evaluated using receiver operating characteristic (ROC) curves. ROC curves were constructed to determine the optimal thresholds (using Youden's index or OG value of 〉14), including likelihood ratios, sensitivities, and specificities, which are associated with the rate of change in OG for predicting toxic ethanol ingestion (measured ethanol level〉10 mg/dL)[8,12].

All p values are two tailed, and p〈0.05 was considered statistically significant. Data were analyzed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA) and MedCalc (MedCalc Software, Mariakerke, Belgium).

5. Ethical approval

The study was reviewed and approved by the Institutional Review Board of our hospital (00-2019-05-032).

RESULTS

We calculated contribution of ethanol to OG using 153 observations obtained from 152 patients. One patient was observed on two separate occasions. There were 122 cases with undetectable ethanol levels (〈10 mg/dL) and 31 cases with detectable ethanol levels (≥10 mg/dL). Thirty (23.1%) cases had ethanol levels nearly equal to zero (〈3 mg/dL). Thirty-nine cases had elevated OGs at 〉14 (Table 1 and Fig. 1).

1. Correlation of measured ethanol levels OG

Among the 31 cases with detectable ethanol levels,

Table 1. Clinical and demographic characteristics of enrolled patients based on the increment in osmolar gaps

	Overall N=153	OG > 14 N=39	OG ≤ 14 N=114	*p*-value
Male, n (%)	73 (47.7)	25 (64.1)	48 (42.1)	0.018
Age, years, median (IQR)	57 (37-70)	57 (49-61)	55 (32-70)	0.522
Clinical comorbidities, n (%)				
Acute poisoning	118 (77.1)	29 (74.4)	89 (78.1)	0.634
Renal failure, AKI	30 (19.6)	12 (30.8)	18 (15.8)	0.042
Shock	38 (24.8)	20 (51.3)	18 (15.8)	<0.001
Ketosis	28 (18.3)	14 (35.9)	14 (12.3)	0.001
Metabolic acidosis	14 (9.2)	11 (28.2)	3 (2.6)	<0.001
Acute hepatic failure	9 (5.9)	3 (7.7)	6 (5.3)	0.694
Sepsis	9 (5.9)	3 (7.7)	6 (5.3)	0.694
Laboratory findings, median (IQR)				
BUN [mg/dL, NR 6-20]	14.4 (9.4-26.1)	18.0 (12.4-42.1)	13.3 (8.7-22.1)	0.003
Creatinine [mg/dL, NR 0.5-1.2]	0.9 (0.6-1.7)	1.3 (0.8-2.6)	0.8 (0.6-1.6)	0.010
Glucose [mg/dL, NR 70-110]	124 (105-177)	134 (113-260)	122 (104-151)	0.010
Sodium [mmol/L, NR 136-146]	140 (137-142)	140 (135-142)	140 (137-142)	0.906
pH	7.41 (7.34-7.44)	7.33 (7.19-7.39)	7.42 (7.38-7.44)	<0.001
HCO_3 [mmol/L, NR 22-26]	19.7 (15.6-22.5)	16.8 (11.5-21.0)	20.0 (16.8-22.7)	0.002
Anion gap	14.0 (10.6-17.7)	17.7 (14.7-20.5)	12.9 (10.1-15.7)	<0.001
Lactate [mmol/L, NR 0.7-2.1]	2.2 (1.2-4.0)	4.0 (2.4-5.2)	1.6 (1.2-2.9)	<0.001
Ketone body [mmol/L, NR <0.6]	0.2 (0.1-0.5)	0.3 (0.2-3.8)	0.3 (0.1-0.5)	0.027
Osmole [mOsm/kg, NR 289-302]	298 (286-319)	332 (322-350)	293 (283-302)	<0.001
Ethanol levels [mg/dL, NR <10]	3.0 (1.0-3.0)	96.6 (3.0-154.0)	3.0 (1.0-3.0)	<0.001
Toxic ethanol detection, n (%)				
Ethanol level <10 mg/dL	122 (79.7)	16 (41.0)	106 (93.0)	<0.001
Ethanol level, 10-100 mg/dL	11 (7.2)	4 (10.3)	7 (6.1)	
Ethanol level, 101-200 mg/dL	13 (8.5)	12 (30.8)	1 (0.9)	
Ethanol level >200 mg/dL	7 (4.6)	7 (17.9)	0 (0.0)	

OG: osmolar gap, IQR: interquartile range, AKI: acute kidney injury, BUN: blood urea nitrogen

the median ethanol concentration was 132.2 mg/dL while the range was 10.6-357.3 mg/dL. The mean serum osmolality was 327.0 mOsm/kg and the range was 270-372 mOsm/kg.

Among 153 cases, 39 (25.5%) had elevated OGs. The median patient age was 57 years [interquartile range (IQR), 49-61 years), and there were 25 (64.1%) male patients. Univariate analysis revealed that elevated OGs were more likely among patients with acute kidney injury, hemodynamic shock, ketosis, metabolic acidosis, or increased anion gap than among those without such comorbidities (median, 17.7 vs.12.9, $p<0.001$). Additionally, levels of glucose (median, 134 mg/dL vs. 122 mg/dL, $p=0.010$), lactate (median, 4.0 mmol/L vs. 1.6 mmol/L, $p<0.001$), and creatinine (median, 1.3 mg/dL vs. 0.8 mg/dL, $p=0.010$) were significantly higher in the elevated OG group (Table 1).

Figure 2 demonstrates a linear relationship between the ethanol level and OG. There was a significantly proportional relationship between ethanol concentration and OG (r=0.7037, $p<0.001$, Fig. 2). Moreover, the correlation of measured ethanol levels with OG among patients with undetectable or detectable ethanol concentrations is shown as a scatter plot in Figure 2.

2. Analysis of misinterpreted cases

Among 114 cases without elevated OGs, 8 cases (7.0%, underestimated group) had toxic ethanol levels (ethanol〉10 mg/dL). Among the 39 patients with elevated OGs (OG〉14), 16 (41.0%, overestimated group) had undetectable (ethanol〈3.0 mg/dL) or non-toxic ethanol levels (ethanol〈10 mg/dL). The clinical characteristics of the aforementioned patients are summarized in Appendix 1 and 2.

3. Validation of OGs for toxic ethanol ingestion prediction

An ROC curve of OGs showed that for the prediction of toxic ethanol ingestion, optimal specificity and sensitivity at a cutoff value of 14 mOsm/kg were 86.9% and 74.2% respectively. With regard to the maximal Youden index, the sensitivity and specificity of OGs were 71.0% and 92.6% (AUC, 0.869; cutoff, 20 mOsm/kg), respectively (Fig. 3).

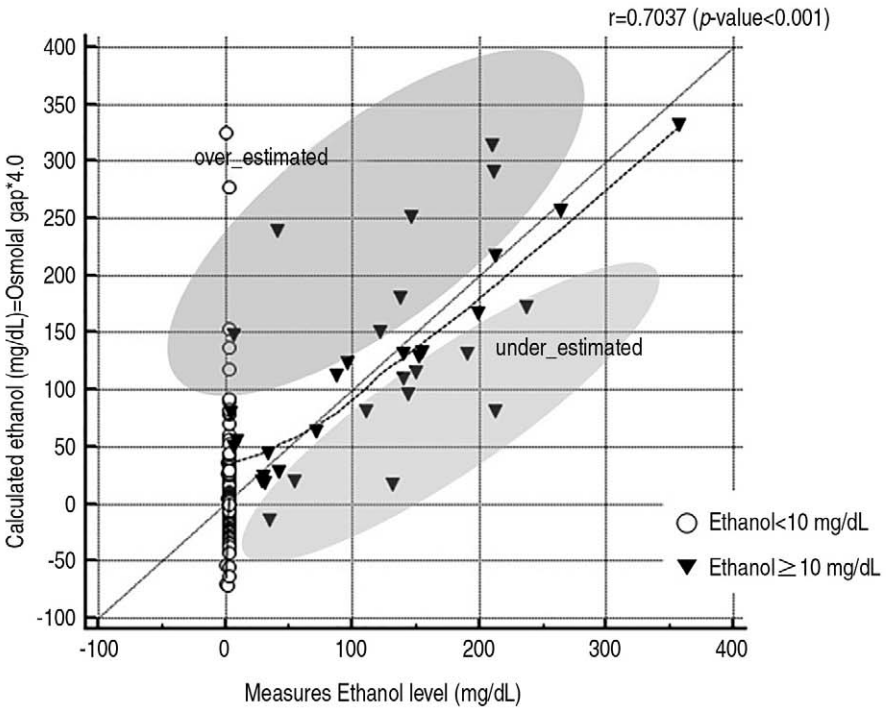

Fig. 2. Linear regression model of 153 samples, which compares calculated ethanol levels using osmolar gap and measured ethanol concentration. The solid line denotes regression slope and other dotted lines show 95% prediction limits.

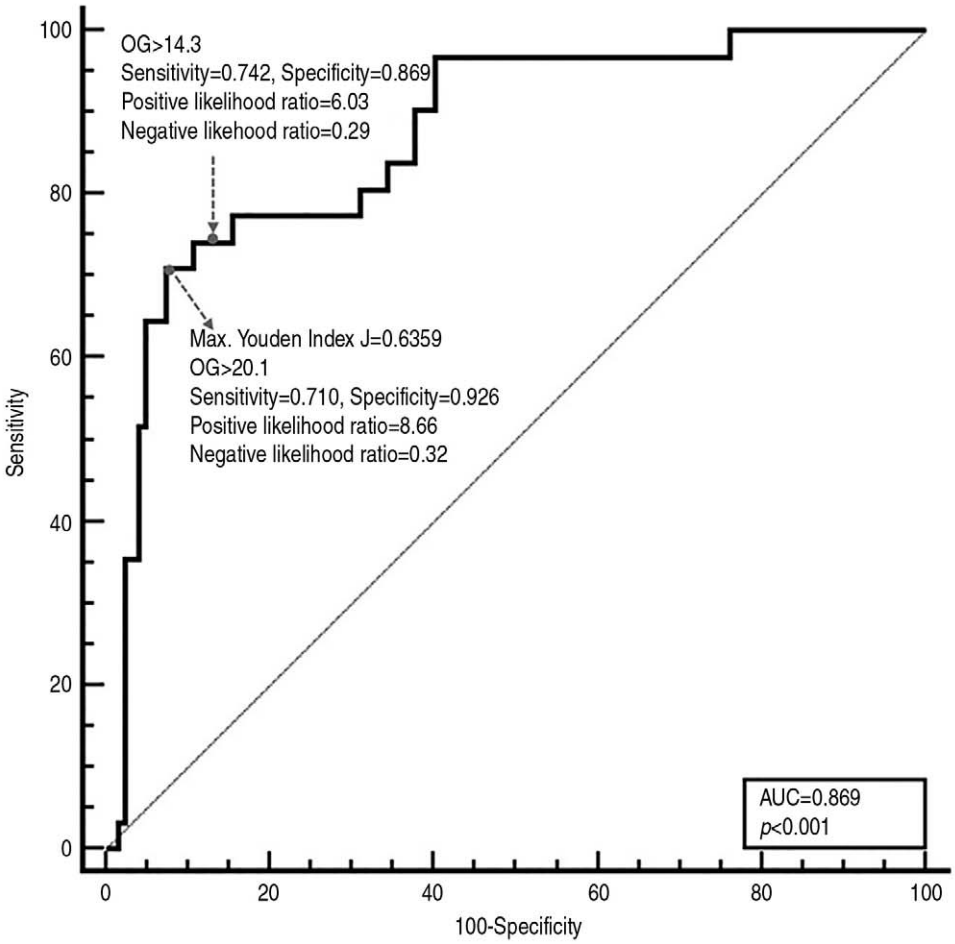

Fig. 3. ROC curve of osmolar gaps for the diagnosis of toxic ethanol ingestion. In relation to the prediction of toxic ethanol ingestion, the sensitivity and specificity of OGs were 74.2% and 86.9% (AUC: 0.869; cutoff: 14 mOsm/kg) and 71.0% and 92.6% (cutoff: 20), respectively. OG: osmolar gap, ethanol: blood ethanol level.

4. Assessing agreement between two ethanol levels in subclinical groups

Table 2 shows the clinical and laboratory parameters for the four subgroups stratified by comorbidities and poisoning status. The accuracy of equations was evaluated using Bland-Altman analysis. In subgroup analysis, the correlation coefficients r for the four aforementioned groups were 0.692, 0.588, 0.835, and 0.412 (Table 2), the mean differences between the measured and calculated ethanol levels were -21.3 mg/dL, -48.8 mg/dL, 9.4 mg/dL, and -4.7 mg/dL (Fig. 4A-D), and the 95% limits of agreement were -168.7 to 126.1 mg/dL, -162.1 to 64.5 mg/dL, -57.6 to 76.3 mg/dL, and -69.4 to 60.0 mg/dL, respectively. The equation plots had wide limits of agreement.

On comparing the difference between the percentages of two measurements, the bias was -110.5% and 2s agreement range was ±225.5% (from -336.0% to 115.0%) in intoxicated patients with comorbidities. In intoxication patients without comorbidities, the bias was -181.3% and 2s agreement range was ±2050.2% (from -2231.5% to 1868.8%). The measurement differences seemed to change with ethanol concentrations and became higher when the ethanol levels were higher in patients with acute poisoning, regardless of them having disease complications.

DISCUSSION

We performed a comprehensive reassessment of estimated ethanol concentrations using OG among patients with suspected poisoning admitted to an emergency department. We also stratified our results to ensure

that their precision and accuracy would be preserved with increased measured osmolality. Seven percent of cases with toxic ethanol ingestion had normal OGs, but ethanol levels were overestimated in 41.0% cases with elevated OGs. Therefore, we found some discrepancies in OGs and calculated ethanol concentrations. The measurement differences seemed to change with ethanol concentrations and became higher when the ethanol levels were higher in patients with acute poisoning, regardless of them having disease complications. Furthermore, the subgroup analysis revealed that the difference in patients with acute poisoning increased regardless of disease.

The differing results reported by various investigators may be related to the varying characteristics of study samples (e.g., presence and absence of ethanol intake, or healthy volunteers) or data manipulation (compared with ethanol and osmolality which diminished ethanol contribution)[6,13,14]. The present study was conducted to validate the formula derived by Purssell et al.[5,15] that linked ethanol concentration with OG. OG is often used to help diagnose toxic alcohol poisoning when direct measurements are unavailable. However, the accuracy of estimated ethanol concentration varies in emergency settings and is affected by clinical conditions, such as ketosis and renal disease. In our emergency department, we found that 13 of 16 patients had chronic kidney disease, and 10 of them had ketosis with or without metabolic acidosis at emergency department admission. Several patients had elevated OGs owing to uremia or ketoacidosis; therefore, they had non-toxic ethanol levels[8].

Accurate estimation of ethanol to OG can limit the number of patients who are unnecessarily treated for toxic alcohol ingestion with antidotal therapy or hemodialysis[1,16]. Additionally, physicians need to act judiciously, given that there is a possibility of misinterpreting serially estimated ethanol concentrations for targeted monitoring of antidote level during alcohol detoxification. Our results suggest that calculation of OG and its use to guide therapeutic decisions remain problematic[1]. OG is useful for establishing the presence of toxic alcohol and ethanol levels in

Table 2. The clinical findings and correlation coefficients of the subgroups

	AKI Ketoacidosis Shock (+)		AKI Ketoacidosis Shock (-)	
	Intoxication (+) N=45	Intoxication (-) N=24	Intoxication (+) N=73	Intoxication (-) N=11
Age (years)	60.0 (47.5-70.0)	62.5 (55.3-75.8)	47.0 (25.0-62.5)	70.0 (62.0-83.4)
Gender, male, n (%)	29 (64.4)	17 (70.8)	21 (28.8)	6 (54.5)
Sodium [mEq/L]	139 (133-142)	138 (130-142)	141 (139-143)	134 (108-139)
BUN [mg/dL]	16.9 (9.0-36.9)	47.2 (32.6-76.3)	11.3 (8.9-15.5)	11.7 (7.4-20.2)
Glucose [mg/dL]	137 (115-226)	212 (121-286)	112 (99-131)	141 (119-154)
Creatinine [mg/dL]	1.4 (0.75-2.05)	3.25 (1.65-4.55)	0.70 (0.60-0.90)	0.70 (0.55-1.35)
Ketone [mmol/L]	0.50 (0.20-1.60)	0.30 (0.20-3.90)	0.20 (0.10-0.25)	0.10 (0.10-0.25)
pH	7.38 (7.24-7.42)	7.34 (7.24-7.42)	7.42 (7.39-7.44)	7.44 (7.40-7.46)
Base deficit [mEq]	8.30 (3.90-15.45)	11.35 (7.95-15.55)	3.60 (1.40-2.90)	3.30 (1.25-4.75)
Lactate [mmol/L]	4.30 (2.35-6.40)	3.05 (2.28-6.78)	1.40 (1.0-5.90)	2.20 (1.55-3.40)
Anion gap	17.1 (13.2-19.5)	15.5 (9.6-20.2)	12.9 (10.3-15.1)	7.2 (5.2-13.2)
Calculated Osm	293 (285-303)	304 (201-320)	291 (288-296)	283 (229-296)
Measured Osm [mOsm/kg]	305 (288-337)	318 (300-339)	294 (286-296)	288 (267-298)
Measured ethanol [mg/dL]	3.0 (3.0-57.0)	3.0 (3.0-3.0)	3.0 (3.0-3.0)	3.0 (3.0-3.0)
Range of ethanol [mg/dL]	0.8 to 357.3	3.0 to 146.9	0.1 to 237.2	3.0 to 7.0
OG >14	17 (37.8)	9 (37.5)	12 (16.4)	1 (9.1)
Ethanol ≥10	15 (33.3)	1 (4.2)	15 (20.5)	0 (0.0)
Pearson correlation[a]	0.692	0.588	0.835	0.412
p-value	<0.001	0.002	<0.001	0.208

AKI: acute kidney injury, Osm: Osmolality, OG: Osmolar gap.

[a] Coefficiency r by linear regression analysis between OG and measured ethanol levels

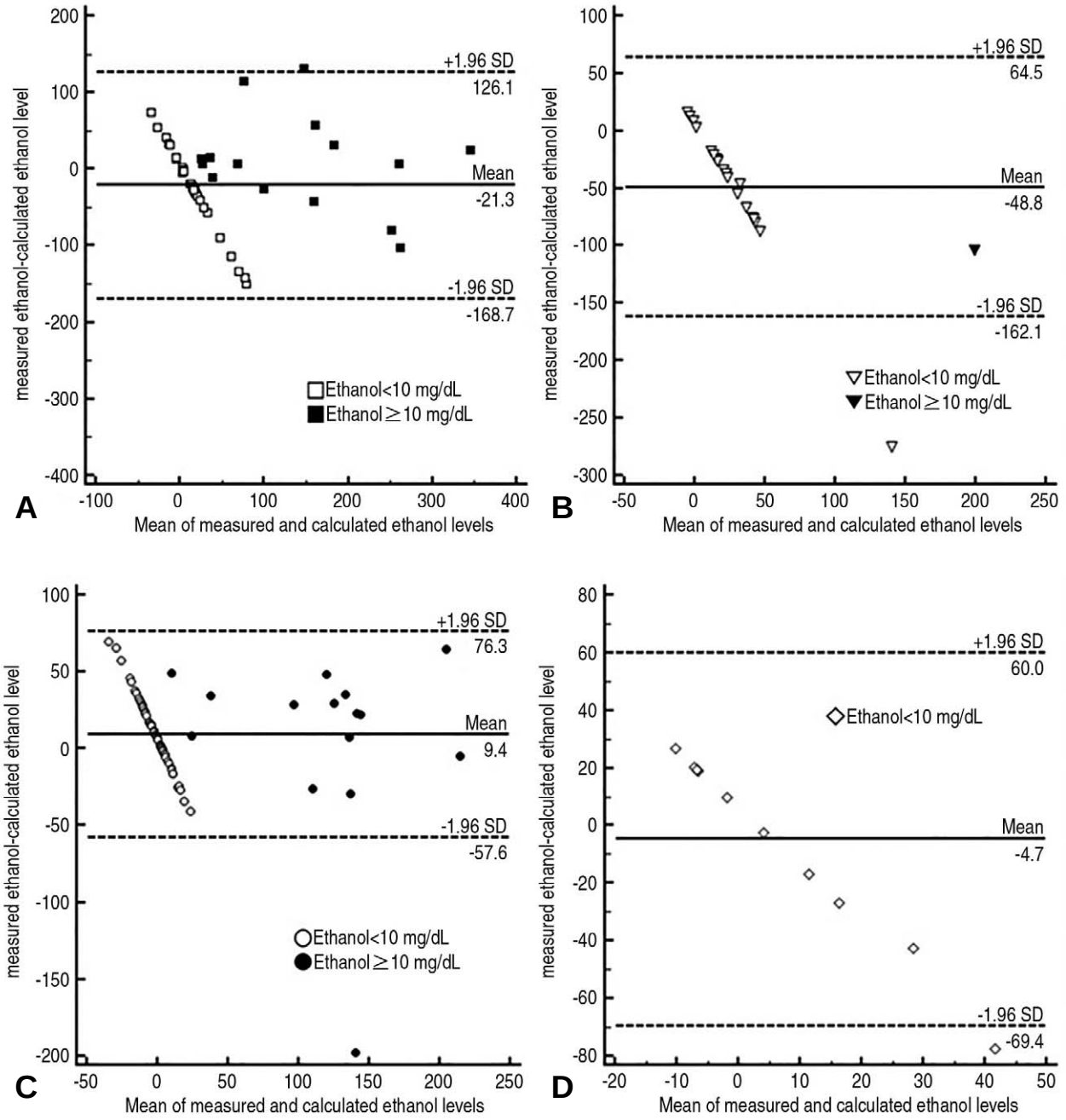

Fig. 4. Bland-Altman plots describing the agreement between measured ethanol level and calculated ethanol concentration using osmolar gap. Scatter plots have been stratified by patient condition and ethanol concentration status. (**A**) Bland Altman plot for patients with comorbidities and acute poisoning. (**B**) plot for patients with comorbidities, but without acute poisoning. (**C**) plot without affecting comorbidities, but with acute poisoning, and (**D**) plot for patients without affecting comorbidities and acute poisoning. Dotted lines denote limits of agreement (±1.96 standard deviations). Solid line shows average differences between measured and predicted values. Scatter plots have been stratified by patient condition and ethanol concentration status.

plasma, but it lacks the precision and sensitivity to be a reliable tool for ruling out this type of exposure.

Discrepancies and overestimations between measured and estimated ethanol concentrations have been reported, and our study corroborated such observations. Snyder et al.[17] reported that the mean difference between calculated and measured blood ethanol levels was 49.2 mg/dL. Calculated ethanol was greater than measured blood ethanol level in 83% patients[17]. Here, the measured ethanol levels were overestimat-

ed in 41.0% patients with elevated OG. Addition of a correction factor for unmeasured osmoles to the equation of calculated serum osmolality could reduce this error[17]. Ketone formation and a decreased water fraction during hyperglycemia may also explain some of these findings[18].

In case of known or suspected exposure to a toxic alcohol, OG alone is an unreliable screening variable[16]. Our study concurs with other studies that demonstrated OG to be a useful diagnostic tool in conjunction with clinical history and physical examination. Krasowski et al.[8] reported that, among 341 patients with an OG of 〉14 mOsm/kg (including correction for estimated ethanol contribution) on initial presentation to the medical center, 77 were tested positive for one or more toxic alcohols by gas chromatography, while all patients had elevated anion gaps, OGs, or both. This suggests that OG may have a fairly poor specificity (even with a relatively high cutoff of 〉14 mOsm/kg). Other than toxic alcohols, the most common causes for an elevated OG were recent consumption of a large quantity of ethanol accompanied with suspected alcoholic ketoacidosis, renal failure, shock, and recent administration of mannitol.

OG may be increased by numerous factors, including renal failure, ketoacidosis, shock, electrolyte abnormalities, and contrast dye administration[8]. Such selectivity could affect test performance (e.g., if clinicians avoided testing patients with uremia, this would eliminate false-positives from the study and increase specificity)[9].

We found that the correlation between the calculated ethanol level using OG and the measured ethanol level in patients with suspected acute poisoning was 0.704 (range in subgroups, 0.412-0.835). In previous studies, Pearson correlation coefficients were ranged from 0.93 to 0.994 for healthy volunteers or patients poisoned with known toxic alcohols[1,4,5,13,14,17]. Chang et al.[19] reported that the correlation between OG and measured ethanol level was 0.916 in all non-trauma and trauma patients; 0.939 non-trauma without shock patients; 0.917 in trauma without shock patients; and 0.844 trauma patients with shock. The accuracy of estimated ethanol level was found to be lower in poisoning patients than that in trauma patients or patients poisoned with known toxic alcohols. The bias (measurement differences) seemed to change with ethanol concentrations, becoming higher with increasing ethanol concentrations among patients with acute poisoning, regardless of them having disease complications. These results suggest the direct cellular toxic effects of poisoning and increase in unmeasured osmotic substances in plasma.

It cannot be confirmed whether these alcohols or their metabolites are absent when OG is "normal". The gap itself is not well defined, has a wide range of variability in the normal population, and does not increase consistently with toxic alcohol ingestion. A "normal" OG does not exclude toxic alcohol exposure, and extreme caution is required while interpreting a "normal" OG (even 〈5) when there are indications of such an exposure, including a history of ingestion, classic symptoms, or an elevated anion gap[7].

Despite our important findings, this study has several limitations. First, the study had a small sample size; because we had a small number of cases with detectable ethanol concentrations, we could not conduct subgroup validations according to intoxicants, age groups, and combined shock or chronic renal diseases. Second, the toxins were determined by emergency physicians who transcribed bottle labels and prescriptions; therefore, our poisoning-related data may have been incomplete, and we may have missed poisons or toxic alcohols that affected OGs. Third, OG is calculated as osmolarity. There should be the assumption that there is no difference between osmolality and osmolarity as the units are differently calculating values. Moreover, we were unable to perform any statistical power analyses (either a priori or post hoc test) or external validation. Therefore, future large-scale prospective studies that overcome our shortcomings should be conducted to validate our findings.

In the setting of known or suspected exposure to a toxic alcohol, OG alone is an unreliable screening tool. It cannot be confirmed whether these alcohols or their metabolites are absent when the OG is "normal".

CONCLUSION

We found that some discrepancies exist between real ethanol levels and calculated ethanol concentrations using OGs. Addition of a correction factor for unmeasured osmoles to the equation for calculated serum osmolality would reduce such an error. The gap itself is not well defined, has a wide range of variability in the normal population, and does not increase consistently with toxic alcohol ingestion. The emergency practitioner must be aware of these limitations to avoid unnecessary morbidity or even mortality in such situations.

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Appendix 1. Summary of toxic ethanol ingestion without elevated osmolar gap (n=8)

Age	Gender	Ethanol (mg/dL)	AG	OG	Clinical history and remarks
20	Female	34.6	14.7	-3.60	DI (acetaminophen), AKI (-), acidosis (-), shock (-)
70	Male	132.2	15.7	4.38	DI (pyrethroid), AKI (-), acidosis (-), shock (+)
26	Female	31.3	19.2	4.46	DI (doxylamine+diphenhydramine), AKI (-), shock (+)
23	Female	54.2	16.2	4.96	DI (caustics), AKI (-), acidosis (-), shock (-)
85	Female	68.5	15.2	5.04	DI (ethanol+multidrug), AKI (-), acidosis (-), shock (-)
72	Male	30.3	21.3	6.00	DI (pyrethroid), AKI(-), acidosis (-), shock (+)
64	Male	42.7	19.8	6.87	DI (organophosphate), AKI (+), acidosis (+), shock (+)
65	Male	33.8	20.4	11.03	DI (multidrug), AKI (-), acidosis (-), shock (+)

AG: anion gap, OG: osmolar gap, DI: drug intoxication, AKI: acute kidney injury

Appendix 2. Summary of non-toxic ethanol ingestion with elevated osmolar gap (n=16)

Age	Gender	Ethanol mg/dL	OG	BUN g/dL	Glucose mg/dL	Sodium mmol/L	Clinical history and remarks
76	Male	<3.0	14.32	35.5	216	140	Mental change, metabolic acidosis (+)
84	Female	<3.0	14.43	78.9	259	140	Meningitis, AKI (+), ketoacidosis (+)
50	Male	<3.0	15.10	42.2	177	138	Non-traumatic rhabdomyolysis, AKI (-). shock (+)
59	Male	<3.0	17.48	146.6	579	170	Hepatorenal syndrome, AKI (+), sepsis (+), shock (+)
64	Male	<3.0	19.60	45.6	380	132	Hepatic failure, AKI (+), shock (+)
77	Female	<3.0	20.11	9.8	133	97	Mental change, hyponatremia, AKI (-), shock (-)
81	Female	3.6	20.13	48.8	260	138	Cardiac arrest, hyperkalemia, AKI (+), acidosis (+)
23	Male	<3.0	20.79	18.0	626	126	Mental change, ketosis (+), shock (+)
61	Male	<3.0	22.48	36.0	120	142	Sepsis, disorientation, AKI (+), ketosis (+)
61	Female	<3.0	23.09	68.5	188	140	Epilepsy, AKI (+), ketosis (+)
62	Male	<3.0	29.37	40.8	793	127	Confusion, ketoacidosis (+), shock (+)
53	Male	<3.0	34.07	51.3	515	141	DI (unknown), AKI (+), acidosis (+), shock (+)
47	Male	6.7	37.12	14.6	102	142	DI (antipsychotics), ketosis (+), shock (+)
81	Female	<3.0	81.22	36.1	286	140	DI (unknown), AKI (+), ketoacidosis (+), shock (+)
60	Female	<3.0	88.32	108.3	198	168	Confusion, Cushing disease, AKI (+), ketosis (+)
42	Female	<3.0	169.44	68.6	235	125	Heart failure, AKI (+), ketoacidosis (+), shock (+)

OG: osmolar gap, BUN: blood urea nitrogen, AKI: acute kidney injury, DI: drug intoxication