AJKD
Original Investigation

Formulas for Calculated Osmolarity and Osmolal Gap: A Study of Diagnostic Accuracy

Fanny Lepeytre, MD,[1,] Marc Ghannoum, MD,[2,*] Hélène Ammann, PhD,[3] François Madore, MD, MSc,[1] Stéphan Troyanov, MD,[1] Rémi Goupil, MD, MSc,[1] and Josée Bouchard, MD[1]*

Background: The osmolal gap has been used for decades to screen for exposure to toxic alcohols. However, several issues may affect its reliability. We aimed to develop equations to calculate osmolarity with improved performance when used to screen for intoxication to toxic alcohols.

Study Design: Retrospective cohort study.

Setting & Participants: 7,525 patients undergoing simultaneous measurements of osmolality, sodium, potassium, urea, glucose, and ethanol or undergoing similar measurements performed within 30 minutes of a measurement of toxic alcohol levels at a single tertiary-care center from April 2001 to June 2016. Patients with detectable toxic alcohols were excluded.

Index Test: Equations to calculate osmolarity using multiple linear regression.

Outcomes: The performance of new equations compared with published equations developed to calculate osmolarity, and to diagnose toxic alcohol intoxications more accurately.

Results: We obtained 7,525 measurements, including 100 with undetectable toxic alcohols. Among them, 3,875 had undetectable and 3,650 had detectable ethanol levels. In the entire cohort, the best equation to calculate osmolarity was 2.006×Na + 1.228×Urea + 1.387×Glucose + 1.207×Ethanol (values in mmol/L, $R^2 = 0.96$). A simplified equation, 2.0×Na + 1.2×Urea + 1.4×Glucose + 1.2×Ethanol, had a similar R^2 with 95% of osmolal gap values between −10.9 and 13.8. In patients with undetectable ethanol concentrations, the range of 95% of osmolal gap values was narrower than previous published formulas, and in patients with detectable ethanol concentrations, the range was narrower or similar. We performed a subanalysis of 138 cases for which both the toxic alcohol concentration could be measured and the osmolal gap could be calculated. Our simplified equation had superior diagnostic accuracy for toxic alcohol exposure.

Limitations: Single center, no external validation, limited number of cases with detectable toxic alcohols.

Conclusions: In a large cohort, coefficients from regression analyses estimating the contribution of glucose, urea, and ethanol were higher than 1.0. Our simplified formula to precisely calculate osmolarity yielded improved diagnostic accuracy for suspected toxic alcohol exposures than previously published formulas.

Am J Kidney Dis. 70(3):347-356.

INDEX WORDS: Equation; formula; osmolal gap (OG); osmolality; osmolarity; toxic alcohol; sodium; urea; glucose; ethanol; diagnostic accuracy.

Ingestion of toxic alcohols represents diagnostic challenges because most emergency departments do not have prompt access to laboratory quantification of these substances. The osmolal gap, or the difference between measured osmolality and calculated osmolarity, is often used as a surrogate marker for toxic alcohol exposure. An elevated osmolal gap (typically more than 10-15) is often cited as suggestive of the presence of methanol,[1] ethylene glycol, or isopropanol,[2] although an osmolal gap < 10 does not exclude toxic alcohol exposure.[3]

Unfortunately, calculation of the osmolal gap has limitations.[4] First, it represents a subtraction from 2 entities with different units. Accurate calculation of the osmolal gap would require the conversion of molar to molal concentrations, by adjusting for the concentration of water in plasma (91%-95%).[5-8] Most equations used to calculate osmolarity were obtained decades ago, based on relatively small cohorts with equipment that may not have the same standards as those used today. Furthermore, the extent of the contribution of ethanol to the osmolal gap is controversial.[8,9] Finally, some conditions may increase the osmolal gap, such as diabetic or alcohol ketoacidosis[10-13] and chronic kidney disease.[14-16] Despite these limitations, and until

From the [1]Division of Nephrology, Department of Medicine, Hôpital du Sacré-Cœur de Montréal, Faculty of Medicine, and [2]Division of Nephrology, Department of Medicine, Verdun Hospital, Faculty of Medicine, Université de Montréal; and [3]Department of Medical Biology, Hôpital du Sacré-Cœur de Montréal, Montréal, Québec, Canada.

[*]F.L. and M.G. contributed equally to this work.

Received November 4, 2016. Accepted in revised form March 27, 2017. Originally published online May 31, 2017.

Address correspondence to Josée Bouchard, MD, 5400 Blvd Gouin West, Montréal, Qc, Canada, H4J 1C5. E-mail: josee.bouchard.1@umontreal.ca

0272-6386
http://dx.doi.org/10.1053/j.ajkd.2017.03.023

quantification of toxic alcohols becomes readily and widely available, better computation of the osmolal gap will likely improve the screening and management of patients with suspected toxic alcohol intoxications.

In this study, we aimed to find a more precise equation to compute the osmolal gap in a large cohort of patients using modern automated laboratory equipment, compare this equation with previously published formulas, and assess its diagnostic accuracy for toxic alcohol intoxications.

METHODS

Study Design and Population

We performed a retrospective single-center study at a tertiary-care center aiming to obtain a better equation from multiple linear regression analysis to calculate osmolarity using measurements from a large population. More specifically, we included all samples with simultaneous measurements of serum osmolality, sodium, potassium, urea, glucose, and ethanol from April 2001 through June 2016. We also included the same measurements performed within 30 minutes of each other in patients in whom toxic alcohols were subsequently measured. This step was performed to avoid missing cases for which measurements were not performed at the exact time, but the findings warranted the measurement of toxic alcohols. When multiple measurements were performed for a single patient, we included only the first results. We excluded cases for which sodium, urea, glucose, or ethanol were not measured, and rare cases with aberrant results, defined as any result that was reviewed by the biochemist to be mathematically highly improbable when computing osmolarity.

We determined new equations to calculate osmolarity excluding cases with detectable toxic alcohol levels. We compared the performance of these new equations with commonly used formulas[6,17] and those obtained from regression analysis (Table 1).[2,7,8,18-21] To simplify interpretation of the results, we refer to previously published formulas using numbers and to newly obtained equations using letters. Each equation is identified with the same letter or number throughout the article.

Using samples with detectable toxic alcohol levels, we calculated the sensitivity, specificity, positive and negative predictive values, and accuracy of calculated osmolal gap ≥ 5 (to optimize sensitivity when the pretest probability is high) or osmolal gap ≥ 10 (to optimize specificity when the pretest probability is low) to predict toxic alcohol concentrations ≥ 5 mmol/L. The toxic alcohol threshold of 5 mmol/L was used because it is often considered a level over which alcohol dehydrogenase blockade should be initiated.[22,23] We followed the Standards for Reporting Diagnostic Accuracy Studies (STARD) guidelines for diagnostic accuracy studies[24] and conducted this project according to principles from the Declaration of Helsinki. Our ethics committee approved the study (2017-1370). Written consent was waived because of the retrospective observational nature of the study.

Laboratory Analyses

All specimens were centrifuged within 60 minutes after collection. Sodium and potassium levels were determined by indirect potentiometry (Modular S; Roche Diagnostics). Urea was assessed by enzymatic urease method, and glucose, by enzymatic hexokinase method (Modular P; Roche Diagnostics). Osmolality was measured by the freezing point depression (Fiske 210; Advanced Instruments), and ethanol, by enzymatic alcohol dehydrogenase (Integra 400 plus; Roche Diagnostics). Toxic alcohols were measured by gas chromatography (Agilent 6890N; Agilent Technologies). Coefficients of variation of each of these measurements were as follows: sodium, 0.5% to 0.7%; potassium, 1.0% to 2.2%; urea, 1.9% to 3.6%, glucose, 2.3% to 3.0%; osmolality, 0.8% to 2.4%; ethanol, 2.9% to 4.3%; and toxic alcohols, 5% to 10%.

Prespecified Statistical Analyses

Newly Obtained Equations From Regression Analyses

All equations excluded cases with detectable toxic alcohols. We first performed linear regression models with measured osmolality as the dependent variable and solute concentrations as independent variables to determine the best equation for calculated osmolarity. More specifically, we performed linear regression models in 3 steps. First, we included all patients with undetectable ethanol concentrations ($<$2.2 mmol/L [$<$10 mg/dL]) using sodium, urea,

Table 1. Previously Published Equations for Calculating Osmolarity

Equation Type and No.[a]	No. of Observations	Equation	Reference
Common equations			
1	Not listed	2×Na + Urea + Glucose	Gennari[6] (1984)
2	Not listed	(1.86×Na + Urea + Glucose)/0.93	Aabakken[17] (1994)
Equations obtained from regression analysis			
Those excluding ethanol			
3	98 patients	1.75×Na + Urea + Glucose + 10.1	Edelman[21] (1958)
4	715 patients	1.86×Na + Urea + Glucose + 9	Dorwart[7] (1975)
5	100 patients	1.89×Na + 1.38×K + 1.03×Urea + 1.08×Glucose + 7.45	Bhagat[2] (1984)
6	305 patients	1.85×Na + 1.28×Urea + 1.03×Glucose	Hoffman[18] (1993)
7	162 patients	1.82×Na + 0.97×Urea + 0.75×Glucose + 24	McQuillen[19] (1999)
8	210 samples	1.89×Na + Urea + Glucose + 13.5	Rasouli[20] (2005)
Those with ethanol			
9	37 patients	2×Na + Urea + 1.15×Glucose + 1.0×Ethanol	Khajuria[8] (2005)
10	37 patients	1:86× (Na +K) + Urea + 1:15×Glucose + 1.2×Ethanol + 14	Khajuria[8] (2005)

Note: All values are in mmol/L. For use with conventional units, multiply urea by 2.8, glucose by 18, and ethanol by 4.6.
[a]Numbers correspond to labels used in the text to identify these previously published equations.