Derivation and Validation of a Formula to Calculate the Contribution of Ethanol to the Osmolal Gap

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Study objectives: We sought to evaluate the relationship between osmolal gap and serum ethanol level and derive a formula that can be used clinically to calculate the expected osmolal gap in the presence of ethanol. Some investigators have noted that the residual osmolal gap appears to increase as the ethanol level increases, and thus it is important to determine the exact relationship between these 2 values.

Methods: In part 1, a convenience sample of emergency department patients undergoing serum ethanol determination had sodium, urea, and glucose levels and osmolality determined on the same blood sample, and values were prospectively recorded. Predicted osmolality excluding ethanol was calculated with the following formula:

2 Na (mEq/L) + (Urea [mg/dL])/2.8 + (Glucose [mg/dL])/18.

The osmolal gap was determined by subtracting the calculated serum osmolality excluding ethanol from the measured serum osmolality. Linear regression analysis was then used to derive a formula for the relationship between ethanol and the osmolal gap. This formula was then prospectively validated on a second convenience sample of patients. In part 2, we repeated this experiment in vitro by adding known amounts of ethanol to serum.

Results: We derived the formula to calculate the contribution of ethanol to the osmolal gap by using 98 observations. The mean ethanol level was 197.8 mg/dL (SD 138.5), with a range of 0 to 538.2 mg/dL. The relationship between ethanol and osmolal gap was linear, with a Pearson coefficient of correlation of 0.99. Linear regression analysis generated a model with the following formula:

Osmolal gap=(Ethanol [mg/dL])/3.7 – 0.35

or, in SI units:

Osmolal gap (mOsm/kg)=1.25 (Ethanol [mmol/L]) – 0.35

The 95% confidence interval (CI) for the multiplicative factor was 1/3.58 to 1/3.80 (or, in SI units, 1.21 to 1.28). The 95% CI for the additive constant was –2.19 to 1.50. We prospectively validated our formula on 128 patients. The mean residual osmolal gap for this group of patients was 0.84 mOsm/L (SD 5.65; range, –18.40 to 17.85 mOsm/L). The results of the in vitro experiments were similar.

Conclusion: Our data suggest that the best formula for the calculation of the contribution of ethanol to osmolality is as follows:

Ethanol (mg/dL)/3.7

or, in SI units:

1.25 (Ethanol [mmol/L])

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INTRODUCTION

Serum osmolarity can be measured or it can be estimated by using various formulas that account for the contribution of the common osmotically active constituents of serum. The difference between measured osmolality and calculated osmolarity is referred to as the osmolal gap. The terms "osmolal" and "osmolar" are used interchangeably in the medical literature to describe the gap, but osmolal is now the preferred term.[1] The assessment of osmolal gap can be important in the diagnosis of methanol and ethylene glycol poisoning. An elevated osmolal gap implies the presence of unmeasured osmotically active substances, such as methanol or ethylene glycol.

The terminology used to describe the osmolal gap is confusing. Some authors include the contribution of ethanol in the calculation of osmolarity, whereas others do not. For clarity, we will adhere to the following definitions throughout this article. When ethanol is not included in the calculation of serum osmolarity, we will use "calculated osmolarity excluding ethanol" to refer to the calculated serum osmolarity and "osmolal gap" to refer to the difference between measured osmolality and calculated osmolarity. When ethanol is included, we will use "calculated osmolarity including ethanol" to refer to the calculated serum osmolarity and "residual osmolal gap" to refer to the difference between measured osmolality and calculated osmolarity. Some authors use the term "excess osmolal gap" in place of "residual osmolal gap."

Many formulas are used to calculate the approximate osmolality of serum. If the patient has ingested ethanol, the following formula is often used[2-5]:

Calculated serum osmolarity including ethanol=
2 Na (mEq/L) + (Urea [mg/dL])/2.8 +
(Glucose [mg/dL])/18 + (Ethanol [mg/dL])/4.6 (Equation 1),

or, in SI units:

Calculated serum osmolarity including ethanol=
2 Na (mEq/L) + Urea (mmol/L) + Glucose (mmol/L) +
Ethanol (mmol/L) (Equation 2).

Several investigators have noted that this and other formulas in common use do not adequately reflect the contribution of ethanol to serum osmolarity. It has been noted that the residual osmolal gap calculated with this formula increases with increasing ethanol levels. We investigated this phenomenon by prospectively analyzing serum samples from patients who presented to our emergency department with suspected ethanol intoxication and by using in vitro experimentation.

MATERIALS AND METHODS

In the first part of this study, we prospectively collected blood samples on a convenience sample of patients who presented to the ED of a large urban hospital with a diagnosis of suspected ethanol intoxication. When the treating physician ordered an ethanol level, the following tests were also performed: electrolyte, urea, glucose, and serum osmolality measurements. Electrolyte, urea, glucose, and ethanol levels were determined by using a high-volume analyzer (Beckman CX7-Model 7566, Beckman Instruments Inc., Fullerton, CA), and serum osmolality was measured by means of freezing-point depression with an osmometer (Advanced Micro Osmometer, Advanced Instruments Inc., Norwood, MA). Patients were excluded if laboratory testing had been completed that detected the presence of lipemia, ketosis, dysproteinemia, or hemolysis or if the required tests were not obtained simultaneously. The serum osmolarity excluding ethanol was calculated by using the following formula for calculated osmolarity excluding ethanol:

2 Na (mEq/L) + (Urea [mg/dL])/2.8 +
(Glucose [mg/dL])/18 (Equation 3).

The osmolal gap excluding ethanol was calculated by subtracting the calculated osmolarity excluding ethanol from the measured serum osmolality. We then used linear

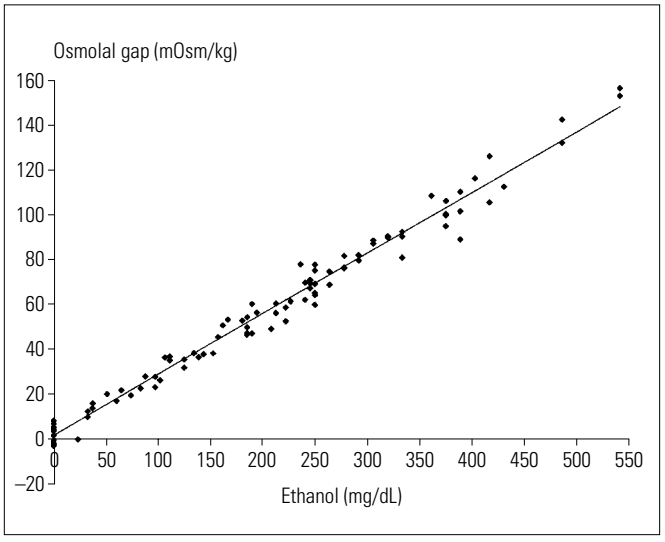
regression analysis to evaluate the relationship between the osmolal gap and the measured ethanol level and to generate a best-fit model (SPSS, version 6.1 for MacIntosh; SPSS Inc., Chicago, IL). This model was then prospectively validated with data from a second convenience sample of patients who presented to the same ED.

For the second part of the study, an in vitro substudy, we obtained 8 specimens of ethanol-free serum. Each specimen was divided into 4 aliquots of 2 mL each, and 0, 5, 15, and 25 μL of 99% pure ethanol was added to arrive at final ethanol concentrations of approximately 0, 50, 150, and 250 mmol/L. For each of the 32 samples, we measured electrolyte, urea, glucose, ethanol, and serum osmolality levels. We then calculated the osmolal gap. Once again, the relationship between the osmolal gap and the ethanol level was determined by means of linear regression (SPSS, version 6.1 for MacIntosh).

Our objective was to evaluate the relationship between the osmolal gap and the serum ethanol level and to derive and validate a formula that can be used in the presence of ethanol.

Both parts of this study were approved by both our hospital and university ethics committees (institutional review boards).

Figure 1.
Relationship between ethanol level and osmolal gap. Osmolal gap is defined as measured osmolality minus calculated osmolarity excluding ethanol (mOsm/kg; y axis) versus measured ethanol (mg/dL; x axis). The line represents the linear regression line y=x/3.69 – 0.3.



RESULTS

In part 1, we calculated the contribution of ethanol to the osmolal gap by using 98 observations obtained from 97 patients. One patient presented on 2 separate occasions. Three patients were excluded because the required tests were not obtained simultaneously. The mean ethanol level was 197.8 mg/dL (44.0 mmol/L), with an SD of 138.5 mg/dL (30.1 mmol/L) and a range of 0 to 538.2 mg/dL (0 to 117 mmol/L). The mean osmolal gap was 54.8 mOsm/kg, with a range of –4.9 to 153.9 mOsm/kg. Figure 1 displays the extremely linear relationship we found between the ethanol level and the osmolal gap. The Pearson coefficient of correlation between these 2 variables was 0.99.

The following best-fit equation relating the ethanol level to the osmolal gap was generated from a linear regression model:

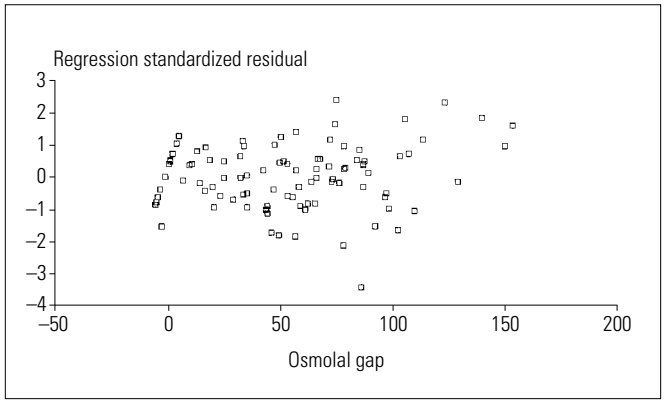
Osmolal gap (mOsm/kg)=
(Ethanol [mg/dL])/3.7 – 0.35 (Equation 4),

or, in SI units:

Osmolal gap (mOsm/kg)=
1.25 Ethanol (mmol/L) – 0.35 (Equation 5).

The 95% confidence interval (CI) for the multiplicative factor for ethanol was 0.26 (1/3.80) to 0.28 (1/3.58) or, in SI units, 1.21 to 1.28. The 95% CI for the additive constant was –2.19 to 1.50. Evaluation of the regression model showed no evidence of violation of model assumptions, and plotting of model residuals (Figure 2) showed no evidence of heteroskedasticity (ie, no evidence that the

Figure 2.
Evaluation of patient-generated model.



accuracy of the model varied with changes in the magnitude of the osmolal gap).

This suggests that the formula for calculation of osmolarity including ethanol should be as follows:

Calculated osmolarity including ethanol (mOsm/kg)= 2 Na (mEq/L) + (Urea [mg/dL])/2.8 + (Glucose [mg/dL])/18 + (Ethanol [mg/dL])/3.7 (Equation 6),

or, in SI units:

Calculated osmolarity including ethanol (mOsm/kg)= 2 Na (mEq/L) + Urea (mmol/L) + Glucose (mmol/L) + 1.25 Ethanol (mmol/L) (Equation 7).

Because of its minor contribution, the intercept was removed to simplify the formula.

We then prospectively validated our results with data from 128 patients. One patient was excluded because of incomplete data. The mean ethanol level in this validation set was 195.5 mg/dL (42.4 mmol/L), with an SD of 124.5 mg/dL (27.0 mmol/L) and a range of 0 to 552.7 mg/dL (0 to 120.0 mmol/L). Thirteen (10.2%) patients had ethanol levels of zero.

Using the new formula (equations 6 and 7), the mean residual osmolal gap was 0.84 mOsm/L, with an SD of 5.65 mOsm/L and a range of –18.40 to 17.85 mOsm/L. Nine (7%) patients had a residual osmolal gap (new) of greater than 10 mOsm/L. These patients had a mean ethanol level of 233.7 mg/dL, with a range of 69.2 to 387.2 mg/dL.

When we calculated the residual osmolal gap for the second group of 128 patients by using the standard formula (equations 1 and 2), the mean residual osmolal gap was 11.45 mOsm/L, with an SD of 8.13 mOsm/L and a range of –5.8 to 36.9 mOsm/L. This time, 67 (52%) patients had a residual osmolal gap of greater than 10 mOsm/L. By using the new formula, 83.6% (56/67; 95% CI, 72.5% to 91.5%) of these patients would have been potentially spared a work up for a concerning osmolal gap.

In part 2, the results of the in vitro experiment were as follows. The pooled mean ethanol level was 451.8 mg/dL (98.1 mmol/L), with an SD of 353.4 mg/dL (76.7 mmol/L). The mean osmolal gap was 113.8 mOsm/kg, with an SD of 90.0 mOsm/kg. The Pearson coefficient of correlation between these variables was 0.99.

The following best-fit equation using the in vitro data was generated from a linear regression model:

Osmolal gap (mOsm/kg)= (Ethanol [mg/dL])/4.0 + 0.46 (Equation 8),

or, in SI units:

Osmolal gap (mOsm/kg)= 1.16 Ethanol (mmol/L) + 0.46 (Equation 9).

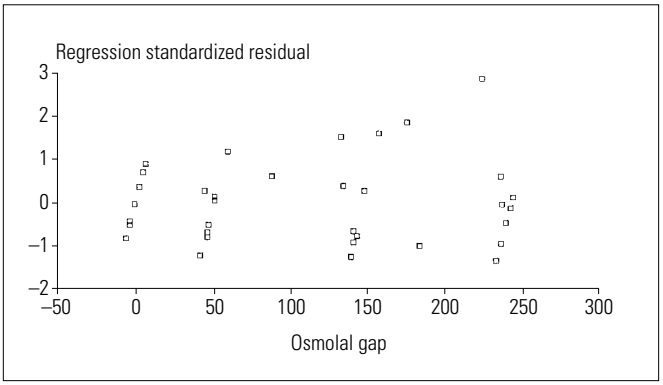
The 95% CI for the multiplicative factor was 0.24 (1/4.12) to 0.28 (1/3.58) or, for SI units, 1.12 to 1.19. The 95% CI for the additive constant was –3.81 to 4.73. Again, evaluation of the regression model showed no evidence of violation of model assumptions, and plotting of model residuals (Figure 3) showed no evidence of heteroskedasticity.

DISCUSSION

Osmolarity is the measure of the total number of particles in 1 L of solution. Osmolality refers to the total number of particles per kilogram. Serum osmolality is measured by means of vapor pressure or freezing-point depression. If the serum contains volatile solvents, vapor-pressure osmometry will yield erroneous results. Serum osmolarity can also be estimated from the concentrations of various osmotically active serum constituents. The most common formula for calculating serum osmolarity including ethanol is equation 1 (see "Introduction").

Methanol and ethylene glycol are both extremely toxic, and physicians must be vigilant not to miss cases of poisoning with these agents. The definitive quantitative test for these substances is gas chromatography. This test is expensive, difficult to perform, and not available in smaller centers. In many centers, staff must be called in during off hours or weekends to perform this test. The patient must be kept in the hospital for several hours until the test is completed or transferred to a major center where the test can be done. Because of these difficulties, physicians who

Figure 3.
Evaluation of in vitro–generated model.



suspect toxic alcohol poisoning often rely on surrogate markers, such as the residual osmolal gap, to influence further therapy, diagnostic evaluation, or both. Patients with suspected toxic alcohol poisoning may receive complicated or expensive treatment with intravenous ethanol or fomepazole while the diagnosis is being established.

Methanol and ethylene glycol are osmotically active substances that contribute to the osmolal gap. If a large, unexplained residual osmolal gap is found, further testing is required to rule out an ingestion of methanol or ethylene glycol. Problems associated with using the residual osmolal gap as a screening test to determine the presence of methanol or ethylene glycol have been well described.[6,7] However, in spite of these limitations, the magnitude of the residual osmolal gap is usually considered when a physician is deciding whether to obtain methanol and ethylene glycol levels.

Hoffman et al[8] calculated the residual osmolal gap using a variety of formulas. When equation 1 was used, the mean residual osmolal gap was –2 mOsm/L, with an SD of 6.1. This means that 95% of the patients in this data set had residual osmolal gaps between –14 and 10 mOsm/L. Given the high toxicity of the toxic alcohols, this wide range means that persons with residual osmolal gaps within the normal range could still have toxic alcohol poisoning. In fact, a case of serious ethylene glycol poisoning has been reported with a residual osmolal gap of less than 10 mOsm/L.[9] Conversely, an increased residual osmolal gap does not necessarily imply that the patient has ingested a toxic alcohol. Lactic acidosis, ketoacidosis, sepsis, and numerous other medical conditions may all contribute to an increased residual osmolal gap. Fortunately, most of these conditions are evident and do not prompt a search for a toxic alcohol. The results of our study and others indicate that equation 1, the standard formula found in most textbooks of emergency medicine and toxicology,[2-5] will overestimate the residual osmolal gap in patients with high ethanol levels. This has major clinical implications.

Using equation 1 in the patients in our validation set yielded a residual osmolal gap of greater than 10 mOsm/kg more than 50% of the time. Our results and the results of other studies[8,10-16] have shown that the residual osmolal gap increases as the ethanol level increases. Therefore, it is more likely that physicians will obtain testing for methanol or ethylene glycol on patients with high ethanol levels. Patients with high ethanol levels are afforded some protection from the toxic effects of methanol or ethylene glycol because ethanol blocks alcohol dehydrogenase, which is necessary for conversion of these substances to toxic metabolites. Obtaining methanol or ethylene glycol levels on all patients with a residual osmolal gap of greater than 10 is costly and results in significant delays in patient disposition. A formula that more accurately reflects the contribution of ethanol to serum osmolality will be helpful both in the detection of patients with ingestion of methanol or ethylene glycol and the expedient disposition of patients with high ethanol levels.

We derived a formula (equations 6 and 7) that more accurately reflects the contribution of ethanol to serum osmolarity. The coefficient of ethanol in our formula is 0.27 (1/3.7) or 1.25 when using SI units. This is larger than the factor of 0.22 (1/4.6), which is used to calculate the contribution of ethanol to the serum osmolality in the standard formula (equation 1). The reason that the factor 0.22 (1/4.6; or 1.0 if using SI units) is generally used is because 1 mg/dL of ethanol equals 0.22 mmol/L ethanol, and it has been assumed that 1 mmol of ethanol will produce 1 mOsm/kg of osmolarity.

Our finding that the multiplicative factor for ethanol should be greater than 0.22 (or greater than 1 when using SI units) is consistent with the results of several other studies (Table).[8,10-16] It is difficult to directly compare these studies because different formulas are used for the calculation of the serum osmolality excluding ethanol. Most authors determined the relationship between the ethanol level and the osmolol gap. Hoffman et al[8] used logistic regression to determine the multiplicative factors for sodium, urea, and glucose, as well as for ethanol. The study by Britten et al[10] includes patients presenting to a trauma center. All other studies were convenience samples of patients presenting to an ED. Despite these methodologic differences, in every study, an increasing residual osmolal gap as the ethanol level increases was found. When the relationship between the residual osmolal gap and the ethanol level was determined in the various studies, the coefficients for ethanol varied from 0.22 (1/4.52) to 0.38 (1/2.65) or 1.1 to 1.74 when using SI units. This is larger than 0.217 (1/4.6), or 1 for SI units, which is the coefficient for ethanol in many formulas in common use. Our data suggest that a coefficient of 0.27 (1/3.7; or 1.25 in SI units) should be used for ethanol. In selecting the best formula for clinical use, the consequences of errors in each direction must be considered. Given the seriousness of toxic alcohol poisoning, a rule that is highly sensitive (thus resulting in false-positive results but few false-negative results) is preferable. In this regard, the proportion of patients we found with a residual osmolal gap of greater than 10 using our new formula (7%) does not appear excessive.

There are possible physical, chemical, analytic, and physiologic explanations for our finding that 1 mmol of ethanol contributes 1.25 mOsm to serum osmolality. We believe the most likely explanation for our results is that ethanol in solution has a nonideal osmotic behavior. An ideal solvent means that 1 mmol/L of the compound would produce 1 mOsm/L of osmolarity. Nonideal behavior would mean that the effect of osmolarity by a given amount of compound would not be unity. Most compounds do not have ideal osmotic behavior because molecules form physiochemical bonds with other molecules, resulting in an effect on osmolarity that is not unity.[17]

We also considered other possibilities for our findings. A proportional analysis error (error with a magnitude that changes with the concentration of analyte) in the measurement of any of the analytes could have produced the results. However, our hospital laboratory participates in a rigorous internal and external quality-assurance program. Also, our study produced results similar to those of several others. This makes a systematic analytic error unlikely.

Some authors have suggested that a factor of 0.93 should be used to reflect the nonaqueous portion of plasma. Osmolarity is a measure of particles in plasma water. However, water accounts for only 93% of the total plasma volume. Inclusion of this factor would not explain the magnitude of the coefficient. If this were the explanation, we would have expected the coefficient of ethanol to be 1.08 and not 1.25.

Patients who have ingested ethanol could have increases in other small organic compounds in serum. These compounds might either be ingested with ethanol or produced by the metabolism of ethanol. However, if this were the explanation, we would not expect the relationship between the serum ethanol level and the osmolar gap to be linear. The fact that the Pearson correlation coefficient exceeded 0.99 makes this explanation very unlikely.

The difference we found between the in vivo study results and the in vitro study results could be caused by physiologic changes that occur with the ingestion of ethanol. Further study is required to answer this question; however, the trend and general magnitude of the in vitro findings support our primary conclusions.

In interpreting the results of this study, the following limitations should be considered. The study population was composed of patients presenting to a single ED. All laboratory testing was done with 2 analyzers in a single laboratory. It would be useful to validate the formula with other patient populations and other laboratories to ensure that the results of this study are generalizable. We did not carry out assays for osmotically active substances other than sodium, urea, glucose, and ethanol unless this was clinically indicated. We also did not complete testing on patients for lipemia, dysproteinemia, or hemolysis unless clinically indicated. However, we would not have expected a linear relationship between the osmolar gap and the ethanol level if unrecognized osmotically active

Table.
Results of previous studies.

Authors	Units	No. of Patients	Coefficient Sodium	Coefficient Urea	Coefficient Glucose	Coefficient Ethanol	Constant
Geller et al[11]	Standard	37	1.86	1/2.8	1/18	1/3.82	11.9
	SI		1.86	1	1	1.2	11.9
Galvan and Watts[12]	Standard	203	2.0	1/2.8	1/18	1/4.04	3.4
	SI		2.0	1	1	1.14	3.4
Snyder et al[13]	Standard	81	2.0	1/3	1/20	1/3.84	24.9
	SI		2.0	0.93	0.9	1.2	24.9
Hoffman et al[8]	Standard	321	1.85	1/2.18	1/17.5	1/4.22	14.8
	SI		1.85	1.28	1.03	1.09	14.8
Pappas et al[14]	Standard	151	2.0	1/2.6	1/16.7	1/4.11	–2.7
	SI		2.0	1.08	1.08	1.12	–2.7
Britten et al[10]	Standard	218	1.86	1/2.8	1/18	1/2.65	3.7
	SI		1.86	1	1	1.74	3.7
Glasser et al[15]	Standard	21	1.86	1/2.8	1/18	1/4.18	0.7
	SI		1.86	1	1	1.1	0.7
Osterloh et al[16]	Standard	79	2.0	1/2.8	1/18	1/4.3	0.85
	SI		2.0	1	1	1.06	0.85

substances other than ethanol had played a major role. Although we do not anticipate that the relationship we found would be altered by the presence of a toxic alcohol, such as methanol or ethylene glycol, a final limitation is that none of the study patients had ingested such compounds, and an evaluation of the performance of our formula in such situations is warranted.

We found there is a linear relationship between the serum ethanol level and the osmolal gap. We were able to derive and prospectively validate a formula that more accurately reflects the contribution of ethanol to serum osmolarity. Our findings suggest that each millimole of ethanol contributes 1.25 mOsm to serum osmolarity and that the multiplicative factor for ethanol in formulas used to calculate serum osmolarity should be 0.27 (1/3.7) or 1.25 if using SI units.

Author contributions: RAP and JB conceived of the study. RAP, MP, and JB designed the study. MP supervised the data collection. RAP and RBA-L managed the data. RBA-L provided advice and the study design and methodology and analyzed the data. RAP drafted the manuscript. JB and RBA-L contributed substantially to its revision. RBA-L takes responsibility for the statistical analysis. RAP takes responsibility for the paper as a whole.

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