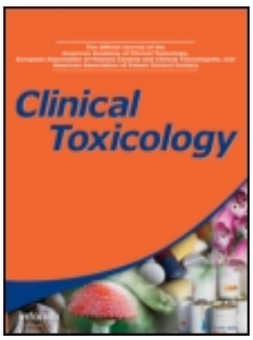

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CRITICAL CARE

Validation of a pre-existing formula to calculate the contribution of ethanol to the osmolar gap

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Purpose. The aim of this study was to validate the formula derived by Purssell et al. that relates blood ethanol concentration to the osmolar gap and determine the best coefficient for use in the formula. The osmolar gap is often used to help diagnose toxic alcohol poisoning when direct measurements are not available. *Methodology.* Part I of the study consisted of a retrospective review of 603 emergency department patients who had a concurrent ethanol, basic metabolic panel and a serum osmolality results available. Estimated osmolarity (excluding ethanol) was calculated using a standard formula. The osmolar gap was determined by subtracting estimated osmolarity from the actual osmolality measured by freezing point depression. The relationship between the osmolar gap and the measured ethanol concentration was assessed by linear regression analysis. In Part II of this study, predetermined amounts of ethanol were added to aliquots of plasma and the estimated and calculated osmolarities were subjected to linear regression analysis. *Results.* In the cases of 603 patients included in Part I of the study, the median ethanol concentration in these patients was 166 mg/dL (Q1: 90, Q3: 254) and the range ethanol concentrations was 10–644 mg/dL. The mean serum osmolality was 338 mOsm/kg (SD: 30) and a range of 244–450 mOsm/kg. The mean osmolar gap was 47 (SD: 29) and a range of − 15 to 55. There was a significant proportional relationship between ethanol concentration and osmolar gap ($r^2 = 0.9882$). The slope of the linear regression line was 0.2498 (95% CI: 0.2472–0.2524). The slope of the linear regression line derived from the data in Part II of the study was 0.2445 (95% CI: 0.2410–0.2480). *Conclusions.* The results of our study are in fairly close agreement with previous studies that used smaller samples and suggest that an accurate conversion factor for estimating the contribution of ethanol to the osmolar gap is [Ethanol (mg/dL)]/4.0.

Keywords Toxic alcohols; Laboratory; Osmolar gap

Introduction

Ingestion of non-ethanol alcohols, such as ethylene glycol, isopropanol, and methanol are diagnostic challenges when presenting to the emergency department. Since many healthcare facilities do not have the capability to measure these specific alcohols in a clinically relevant timeframe, there is a potential for missed diagnoses that could result in significant morbidity and mortality. A time-honored method for detecting and quantifying toxic alcohol ingestion is the osmolar gap, which is the measured osmolality minus the osmolarity estimated by the equation below:[1]

$$2 \times \text{Na (mEq/L)} + (\text{BUN [mg/dL]})/2.8 + (\text{glucose [mg/dL]})/18.$$

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While the osmolar gap calculation cannot definitively rule in/out the presence of non-ethanol alcohols, an osmolar gap > 10 mOsm/L, may suggest the presence of osmotically active substances, such as the toxic alcohols methanol or ethylene glycol, and may prompt further investigation.

Exposure to ethanol is common in emergency department patients and has significant contributions to the osmolar gap.[2] Since ethanol measurements are widely available in hospital laboratories, clinicians may take the osmotic influence of ethanol into account by adding its contribution to the calculated osmolarity. Traditionally, this is done by dividing the patient's ethanol level, when reported as mg/dL, by 4.6.[3,4] Purssell et al. and others have noted that with high ethanol concentrations, this conversion factor produces inaccurate estimates of the osmolarity.[5]

Purssell and colleagues published data showing that 3.7, rather than 4.6, may be a better factor to use when calculating the contribution of ethanol to serum osmolarity. To our knowledge, their findings have not been experimentally reproduced and validated. The principal aim of our study

was to determine the most accurate conversion factor for calculating the contribution of ethanol to serum osmolarity by retrospectively evaluating laboratory data from patients visiting our emergency department and by measurements made on plasma samples to which ethanol was added.

Toxic alcohols, such as methanol and ethylene glycol, are associated with significant morbidity and mortality when patients using these intoxicants are not treated. These products can be found in household items, such as antifreeze, windshield wiper fluid, varnish remover, and lacquers. In the body, methanol and ethylene glycol are ultimately metabolized to formic acid and oxalic acid, respectively. These metabolites can contribute to ocular toxicity from methanol and renal toxicity from ethylene glycol.[6–8] In hospitals with laboratories capable of measuring these toxic alcohols, antidotal therapy with alcohol dehydrogenase inhibitors, such as fomepizole or ethanol, can be initiated to prevent further end organ damage. However, most clinical laboratories are unable to measure these alcohols within their facility and the osmolar gap is used as a surrogate for non-ethanol alcohol concentration. Being able to more accurately assess the osmolar gap may help guide clinicians towards more directed management of patients including appropriate laboratory workup and the application or avoidance of therapies, such as fomepizole (Antizol®) or hemodialysis.

Materials and methods

This study compromised both an *in vivo* and an *in vitro* part to mirror that of Purssell's study. Part I of this study was a retrospective review of laboratory results for patients seen in the emergency department over a 2-year period from 2006 through 2007. Only patients that had simultaneous laboratory results for a basic metabolic panel (sodium, potassium, chloride, bicarbonate, calcium, glucose, BUN, and creatinine), measured serum osmolality, and serum ethanol were selected for review. If patients had all of the laboratory results above but they were not drawn at the same time, these patients were excluded. The basic metabolic panel was performed on a Roche Modular Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN); ethanol was measured on the Modular system by an enzymatic method (Roche Diagnostics). The ethanol method was linear from 0 to 1000 mg/dL; specimens with an ethanol concentration greater than 1000 mg/dL were manually diluted 1:5. Serum osmolality was determined via freezing point depression on an osmometer (Model 3320, Advanced Instruments, Norwood, MA). The database query did not exclude cases with possible confounders, such as a severe lactic acidosis, dysproteinemia, lipemia, ketosis, or non-ethanol alcohol ingestion. The estimated osmolarity was calculated using the formula:

$$2 \times \text{Na (mEq/L)} + (\text{BUN [mg/dL]})/2.8 + (\text{glucose [mg/dL]})/18.$$

The osmolar gap was calculated by subtracting between the measured serum osmolality and calculated serum osmolarity. We then applied linear regression analysis to the data to ascertain the relationship between plasma ethanol concentration (in mg/dL) and osmolar gap.

Part II of this study was an *in vitro* experiment using expired plasma obtained from the blood bank to establish the relationship between known ethanol concentrations and the osmolar gap in plasma presumably devoid of significant biochemical abnormalities. One unit of ethanol-free plasma was divided into 32 equal aliquots of 2 mL each. These specimens were fortified with 0, 5, 15, and 25 μL of 99% pure ethanol. The resulting ethanol concentrations in the four aliquots in each set were approximately 0, 50, 150, and 250 mmol/L (0, 230, 690, and 1150 mg/dL, respectively). As in Part I of the study, a basic metabolic profile, plasma osmolality, and plasma ethanol concentrations were measured on each of the 32 specimens. The osmolar gap was calculated and linear regression analysis was applied as in Part I of the study.

Finally, we divided the ethanol concentrations in Part I into ranges 0–200, 201–300, 301–400, 401–500, and >500 mg/dL. Linear regression analysis was applied to each subset to determine whether the conversion factor between ethanol concentration and osmolarity varied according to ethanol concentration.

This study was approved by the University of Florida Health Science Center/Jacksonville Institutional Review Board.

Statistical analysis

To fully examine the relationship between osmolar gap and ethanol, several levels of statistical analysis were used. All p values were set at 0.05 for statistical significance. Pearson's correlation coefficient was calculated to identify the presence and magnitude of correlation. Linear regression was conducted to identify the predictive magnitude of ethanol levels on osmolar gap; these models are compared using R^2 as a goodness of fit. Our linear regression analysis was done using robust regression with LTS estimation controlling of outliers.[9] Parameter coefficients were estimated using weighted least squares. For the *in vitro* experiments, we conducted linear regression at each concentration level. This allowed us to isolate the magnitude of effect for each level. All statistical analysis was conducted using SAS 9.22 (Cary, NC).

Results

Part I of the study was a retrospective review of the laboratory results on 603 patients who presented to the ED over a 2-year period with concomitant ethanol, osmolality, and basic metabolic profile measurements. One patient was excluded due to an erroneous laboratory value. The median ethanol concentration in these patients was 166 mg/dL (Q1: 90, Q3: 254) and the range ethanol concentrations was 10–644 mg/dL. The mean serum osmolality was 338 mOsm/kg (SD: 30) and a range of 244–450 mOsm/kg. The mean osmolar gap was 47 (SD: 29) and a range of -15 to 55. Osmolar gap and ethanol were found to have a high linear correlation with $r = 0.943$ ($p < 0.0001$). The slope of the linear regression

line was 0.2498 (95% CI: 0.2472–0.2524). The linear regression for this data is seen in Fig. 1. The R^2 value for the regression was 0.9882. The regression line was fit without an intercept as the y-intercept was felt to be irrelevant and the slope of the line of clinical significance. The best-fit equation to predict the change in osmolar gap per unit of ethanol concentration was:

$$\Delta \text{ Osmolar gap (mOsm/L)} = \text{Ethanol (mg/dL)}/4.00.$$

These data would suggest that the best formula to account for the contribution of ethanol to the osmolar gap would be as follows:

$$2\,\text{Na (mEq/L)} + (\text{BUN [mg/dL]})/2.8 + (\text{Glucose [mg/dL]})/18 + (\text{Ethanol [mg/dL]})/4.$$

The use of the LTS method for estimation, which allows for the controlling of outliers and through the use of weighted least squares estimation of parameters, allowed us to gauge the effect of outliers on the data. There were 13 data points, approximately 2.5% of the data set, determined to be outliers and eliminated from the statistical analysis. The outliers had a significant influence on the correlation between ethanol concentration and the change osmolar gap by reducing the value of the correlation coefficient ($r^2 = 0.7824$). However, by using the aforementioned modeling approach, we were able to control for the effect of the outliers on the linear model and calculate a parameter estimation that is robust from this influence.

In the *post-hoc* analysis, data from Part I was grouped according to ethanol concentrations (see Table 1) and linear regression was performed on each subset to determine whether the ethanol coefficient would vary with increasing ethanol concentration. The cases were not evenly divided between groups. There were 362 cases in the range of <200 mg/dL, whereas 91 cases were in the category of >300 mg/dL. The ethanol coefficients among these concentration ranges varied from 3.81 to 4.15. As before, robust linear regression analyses were applied to these data, and outliers were controlled for.

Part II of this study was an *in vitro* experiment in which ethanol-free plasma was fortified with predetermined amounts of ethanol. There were 32 specimens in this experiment. Fig. 2 displays the robust linear regression plot of these data. The data demonstrated a linear relationship with an R^2 of 0.9988. The slope of the linear regression line was 0.2445 (95% CI: 0.2410–0.2480). The confidence interval ethanol coefficient was 4.03–4.15, and the best-fit equation was:

$$\text{Osmolar gap (mOsm/L)} = \text{Ethanol (mg/dL)}/4.09.$$

Discussion

In an ideal solution, solutes contribute to the osmolarity in direct proportion to their molar concentration, based on Raoult's Law. Plasma osmolarity, therefore, can be estimated by adding together the concentrations of the most prevalent solutes—sodium and its corresponding anions, glucose, and urea—giving rise to the commonly used equation for calculated osmolarity: $(2 \times [Na^+]) + ([Glu]/18) + ([BUN]/2.8)$. The denominators for glucose and BUN convert their concentrations from mg/dL to mmol/L. Experimental data subjected to linear regression have refined the coefficient in the first term to approximately 1.86, which is used in some osmolarity estimates.[10] The estimated osmolarity differs from the measured osmolality due to the presence of other solutes in plasma, the cumulative concentrations of which represent the "osmolar gap." Under normal circumstances, the osmolar gap is 5–10 mOsm/L, and some osmolarity estimates include that factor in the calculation. A study by

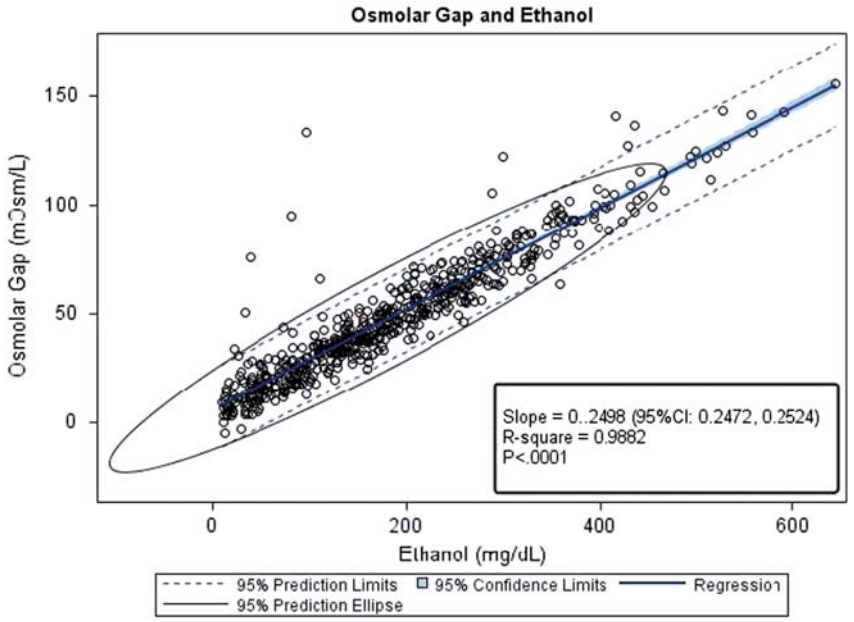

Fig. 1. Part 1 data consisting of retrospective review of 603 data points comparing osmolar gap and ethanol concentrations (mg/dL) (See colour version of this figure in the online version www.informahealthcare/ctx).

Table 1. Post-hoc analysis.

Ethanol (mREg/dl)	N	Robust linear factor	R^2	*p*-Value
0–200	362	3.81	0.9770	<0.0001
201–300	150	4.01	0.9944	<0.0001
301–400	60	4.02	0.9967	<0.0001
401–500	22	4.15	0.9974	<0.0001
>500	9	4.14	0.9996	<0.0001

Hoffman and colleagues found that the osmolar gap can range from −14 to 10.[11] When the osmolar gap is larger than expected, it suggests the presence in plasma of a solute other than glucose or urea that is in high enough concentration to significantly influence the osmolarity. Solutes that can reach osmotically influential concentrations include alcohols, and the osmotic diuretics mannitol and sorbitol. Among these, ethanol is by far the most common.

Ethanol has a molecular weight of 46 and infinite solubility in water. Therefore, each mg of ethanol per deciliter of plasma should contribute approximately 0.22 mOsm/kg to the osmolality. However, this and previous studies have demonstrated that linear regression analysis of osmolar gap versus ethanol concentration generates a slope that is greater than 1/4.6, the predicted slope based on the molecular weight of ethanol.[5,10] The deviation suggests that the ethanol concentration underestimates its contribution to the osmolarity. The reason for this deviation from predicted behavior is not known, but may be related to ethanol partitioning between aqueous and non-aqueous phases in plasma. Addition of pure ethanol to plasma in Part II of this study produced a coefficient that also differed from the predicted 4.6, perhaps due to the same partitioning phenomenon.

The osmolar gap can be unreliable because it is influenced by many disease states, toxins, and medications. Examples include sepsis, severe lactic acidosis, toxic alcohols, acetone, and mannitol. The problems associated with sole use of the osmolar gap to rule out toxic alcohol ingestion have been discussed in the literature.[12–14] Hoffman and colleagues mentioned in their 1993 study that osmolar gaps can vary considerably, and an osmolar gap of 10 may be regarded as normal when in fact the gap can be grossly elevated if the patient's baseline osmolar gap is − 10 due to one or more of the influences noted above.[11] For example, an osmolar gap of 6 mOsm/L in a patient with a baseline gap of − 10 mOsm/L theoretically represents an ethylene glycol level of 99 mg/dL, well above treatment levels. Osmolar gaps in excess of 50 mOsm/L are most likely the result of alcohols since very few medical conditions or drugs can elevate a gap to that extent.

The limitations of this study include the difficulty establishing temporal relationships between alcohol use and osmolar gap, the inability to assess the management of the patients included, and the possibility of subject bias and confounding variables, such as the presence of non-ethanol alcohols. Even with these limitations, our study represents an actual patient population and with the characteristics typical of intoxicated patients presenting in emergency departments. There was a difference noted in the ethanol coefficients derived in Parts I and II of this study. This difference in ethanol coefficients is likely due to unmeasured ethanol or non-ethanol alcohol metabolites. The *in vitro* part of the study was pure unmetabolized ethanol. Although the plasma used in Part II did not contain citrate as a preservative, it is possible that the added constituents in the donor plasma had unpredictable influences on the osmolality. Finally, this select patient population may limit the generalizability of these results to other situations and institutions.

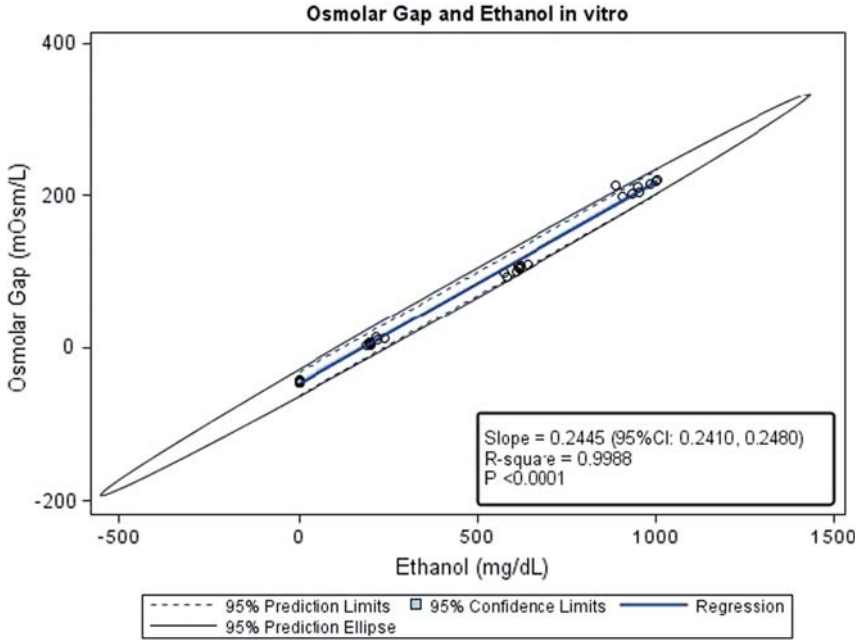

Fig. 2. Part 2 data consisting of in vitro experiment whereby ethanol-free plasma was fortified with predetermined amounts of ethanol. Linear regression was performed to determine the relationship between ethanol concentration (mg/dL) and osmolar gap (See colour version of this figure in the online version www.informahealthcare/ctx).

Our study sought to verify the factor derived by Purssell and colleagues in 2001, or derive a new factor that more accurately represents the contribution of ethanol to the osmolar gap calculation. The results of this study were similar to those reported by Purssell and colleagues. Both studies determined that the relationship between ethanol concentration and the osmolar gap deviates from theoretical predictions. Moreover, the osmolar gap calculation relies on a number of variables, each of which also has a degree of error associated with its measurement. Therefore, the osmolar gap is an inherently imprecise estimate, the errors in which can be quite large. Of note, during the 2-year time frame of the study, there were 180 cases of toxic alcohol exposures reported to the regional poison center. Of these 180 cases, 16 cases were at the healthcare facility where this study took place. We suspect that the outliers included those 16 cases.

The osmolar gap can be used as a surrogate marker for clinically important osmotically active solutes, including non-ethanol alcohols. Accurately accounting for the contribution of ethanol to the osmolar gap can limit the number of patients who are unnecessarily treated for toxic alcohol ingestions with expensive antidotal therapies or hemodialysis. However, our results suggest that calculation of the osmolar gap, and its use to guide therapeutic decisions, is problematic. The osmolar gap is useful to establish the presence of a non-ethanol alcohol or some other substance in plasma, but lacks the precision and sensitivity to be a reliable tool for ruling out this type of exposure. The surprising variability in the relationship between ethanol concentration and osmolar gap across a range of ethanol concentrations, as demonstrated by our *post-hoc* analysis of the data in Part I of our study, suggests the need for additional studies to characterize the chemical behavior of ethanol in biological matrices.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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