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Ethanol and the Limitations of the Osmol Gap

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Study objective: The osmol gap can help detect and manage those with toxic alcohol exposure, and it is altered by all alcohols including ethanol. The optimal correction for ethanol that would allow accurate detection of an alternative alcohol is unclear.

Methods: We conducted a prospective cohort study to assess baseline variations in osmol gap, and then to assess the validity of 2 commonly used coefficients (correction factors) for ethanol. Twenty-two healthy volunteers received a body mass–based dose of oral ethanol that targeted an estimated peak blood ethanol concentration >200 mg/dL. We measured laboratory values prior to ethanol administration and at 2, 4, and 6 hours after ingestion. We considered an osmol gap >10 or <−10 abnormal and an osmol gap of >10 after correction as a false positive.

Results: Four of the 22 subjects (18%) had an osmol gap >10 at baseline. Following ethanol ingestion and across 66 timepoints (N=66), there were 14 abnormal osmol gap tests (21%) when corrected with an ethanol coefficient of 4.6, and 31 (47%) abnormal tests when corrected using the Purssell ethanol coefficient of 3.7. The mean difference between the baseline and the post-ethanol corrected osmol gap was lower with the molecular weight correction factor of 4.6 compared with the Purssell correction factor of 3.7 (0.2 versus 11.0; $P<.001$).

Conclusion: Our data show that the osmol gap is occasionally elevated absent ingestion of any alcohol, and using an ethanol correction coefficient of 4.6 produced a better clinical osmol gap input albeit still with some variation. [Ann Emerg Med. 2025;■:1-5.]

Please see page XX for the Editor's Capsule Summary of this article.

Keywords: Ethanol, Osmol gap, Toxic alcohol exposure.

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SEE EDITORIAL, P. XXX.

INTRODUCTION

Background

Toxic alcohol ingestions cause harm and require prompt identification and treatment. The calculated osmol gap is a common tool to help detect the presence of ingested alcohols. Ethanol is the most common cause of osmolality elevations in emergency department patients and is easily measured independently.[1,2] Toxic alcohol ingestions, namely ethylene glycol and methanol, are the trigger for less than 1% of all poison center calls but have high morbidity and mortality.[3,4] Many try to accurately correct osmol gap calculations for ethanol to better use this tool in care.[3] Direct measures of these toxic alcohols are much less readily available, enhancing the need for a useful osmol gap approach to guide early care in possible exposures.[3]

Importance

Because metabolites of toxic alcohol ingestions can rapidly cause end-organ damage, it is important to initiate curative therapies in a timely manner. Therapies and interventions to treat toxic alcohol poisoning are costly and invasive (eg, hemodialysis), which underscores the need to optimize the diagnostic accuracy of the osmol gap.[5,6]

Traditionally, a common way to account for ethanol in the osmol gap calculation was to divide the measured ethanol concentration (mg/dL) by 4.6; this recommendation is because ethanol is completely soluble in water and has a molecular weight of 46 g/mol (adjusted by 1/10 for unit conversion).[7] However, multiple studies have shown that the measured slope of the osmol gap versus ethanol concentration is more than a direct correlation with [ethanol]/4.6.[8-11] Thus, the most accurate coefficient is unclear.

Goals of This Investigation

We sought to determine the range in baseline and postexposure osmol gap calculations after ethanol ingestion over time. We calculated osmol gaps with different formulas (one newly derived) in healthy volunteers prior to the ingestion of ethanol and at set intervals after ethanol ingestion. We hypothesized that some baseline osmol gap calculations will be outside the normal range, and the

Editor's Capsule Summary

What is already known on this topic

The osmol gap can be used to detect unmeasured osmotically active particles but must be adjusted for ethanol when present.

What question this study addressed

What is the range of osmolar gaps at baseline and after ethanol ingestion?

What this study adds to our knowledge

In 22 healthy volunteers the best correction factor was 4.6 though it was imperfect.

How is this relevant to clinical practice

This work informs the use of the osmol gap in detecting atypical alcohols and ethylene glycol.

corrected osmol gap may vary and be incompletely accounted for using a correction factor.

METHODS

Study Design and Setting

We conducted a prospective cohort study of 22 healthy adult (21 years and older) volunteers in a research lab setting.

Participants

We recruited by word of mouth and locally posted advertisements. The sample of size was pragmatic based on the practicality of completing the study within 6 months. All experimentation had a board-certified medical toxicologist (RM) overseeing the care and testing, and our design and study had local institutional review board approval [7030209].

Participant screening included general health questions and Cut, Annoyed, Guilty, and Eye questionnaire to screen for alcohol use disorder; any positive screening responses indicating moderate to severe alcohol use disorder led to exclusion. Additional exclusion criteria are in Appendix E1 (study protocol, available at http://www.annemergmed.com).

Interventions

Volunteers received ethanol by mouth in body mass–based doses calculated to achieve a peak serum concentration >200 mg/dL. Participants had 1 hour to finish the ethanol dose.

Measurements

Serum laboratory testing occurred prior to ethanol ingestion and at 2, 4, and 6 hours after the start of ethanol ingestion. Laboratory testing included serum ethanol (mg/dL), osmolality (mOsm/kg), sodium (mEq/L), blood urea nitrogen (BUN) (mg/dL), and glucose (mg/dL). Measured osmolality was by freezing-point depression analysis (3300 Micro-Osmometer, Advanced Instruments, Norwood, MA). To calculate the osmol gap, we subtracted the calculated osmolarity from the measured osmolality. The calculated osmolarity was determined using the standard formula[8]:

$$(2 * [\text{Na mOsm/L}] + [\text{BUN mg/dL}]/2.8 + [\text{glucose mg/dL}]/18 + [\text{ETOH mg/dL}]/4.6)$$

We considered the normal osmol gap range as –10 to 10.

Outcomes

We treated all calculated osmol gap as accurate if they were in the above range.[7] We defined a false-positive osmol gap as >10.[7] We could not measure false-negative rates as no patient ingested another exogenous osmolality. We performed sensitivity analyses for calculation of false-positive rates using Purssell's formula (coefficient of 3.7 for ethanol) and a tiered formula (coefficient of 2.67 [ethanol 0 to 100 mg/dL], 3.27 [101 to 200 mg/dL], 3.53 [201 to 300 mg/dL], and 3.72 [>300 mg/dL]) derived from a retrospective data set the authors had previously collected.[11] We calculated means and 95% confidence intervals (CI) for parametric data and medians and interquartile ranges (IQRs) for nonparametric data. The mean change from baseline osmol gap to post-ethanol ingestion osmol gap calculation used the Wilcoxon signed rank test and IPM SPSS Statistics Version 29.0.0.0 (IBM Corp., Armonk, NY) was the data analysis tool.

RESULTS

Characteristics of Subjects

Twenty-two participants enrolled and completed the study with none excluded based on health screening or Cut, Annoyed, Guilty, and Eye questionnaire. The study cohort had 13 men and 9 women, and the median age of participants was 29 years (range, 21 to 62 years).

Main Results

The mean peak ethanol concentration achieved was 247 mg/dL (range, 125 to 341) (Table 1). Mean laboratory results (sodium, BUN, and glucose) and osmol gaps across the study timepoints are shown in Table 1.

The mean baseline measured osmolality prior to any ingestion of ethanol was 286 mOsm/kg. The median

Table 1. Laboratory values from the entire data set in the first half and osmal gaps at set intervals after ingestion of oral ethanol.

Variables	Mean/Medians	95% CI/IQR	Range	N
Peak ethanol (mg/dL)	247	218-276	(175-431)	88
Mean sodium (mEq/L)	137	136.5-137.5	(127-146)	88
Mean BUN (mg/dL)	13	12.6-13.4	(7-19)	88
Mean glucose (mg/dL)	99	97-101	(67-132)	88
Measured osmolality at 0 h	286	281-291	(272-320)	22
Osmal gap at 0 h	−0.7	−2.0 to 2.6	(−7.5 to 53.7)	22
Osmal gap (4.6) at 2 h	1.5	−2.9 to 5.4	(−16 to 40.3)	22
Osmal gap (4.6) at 4 h	2.4	−0.3 to 6.6	(−10.9 to 22.5)	22
Osmal gap (4.6) at 6 h	−0.3	−3.1 to 4.6	(−10.6 to 42.0)	22
Osmal gap (3.7) at 2 h	−10.8	−12.8 to −5.1	(−30.1 to 27.8)	22
Osmal gap (3.7) at 4 h	−7.1	−12.1 to −5.0	(−27.3 to 12.3)	22
Osmal gap (3.7) at 6 h	−7.9	−12.6 to 33.7	(−25.7 to 33.7)	22

Data are presented as medians/means and IQRs/95% CIs depending on the spread of the data. The osmol gap after ingestion of ethanol is shown with whichever coefficient was used in parentheses.
CI, Confidence interval; *IQR*, interquartile range.

baseline osmol gap was –0.7 (IQR, –2.0 to 2.6; range, –7.1 to 53.7). There was a false-positive rates of 18% with participants (4/22) having a baseline osmol gap >10. One participant had a baseline osmol gap of 53.7.

The proportion of false-positive osmol gaps following ethanol ingestion varied by correction equation (Figure). A coefficient of 4.6 had a false-positive rate of 15% with an accuracy (values from –10 and +10) of 79%. The Purssell coefficient of 3.7 had a false-positive rate of 5% (3/66), albeit with lower accuracy (53%; 35/66) (Table 1). Our derived tiered coefficient formula had the lowest false-positive rate (3%), but the worst accuracy (29%), with most out-of-range osmol gaps < –10 (Table 2).

We calculated the difference in osmol gap from baseline to osmol gap after ethanol ingestion (osmol $gap_{ethanol}$-osmol $gap_{baseline}$) for each participant. A coefficient of 4.6 had a significantly smaller difference than Purssell's coefficient (–0.2 [95% CI, –2.2 to 1.8] versus –11.0 [–13.3 to –8.7]; $P<.001$). The difference was lower at ethanol concentrations <150 mg/dL(2.2 [0.5 to 3.9] versus –4.3 [–6.1 to –2.5]; $P<.001$).

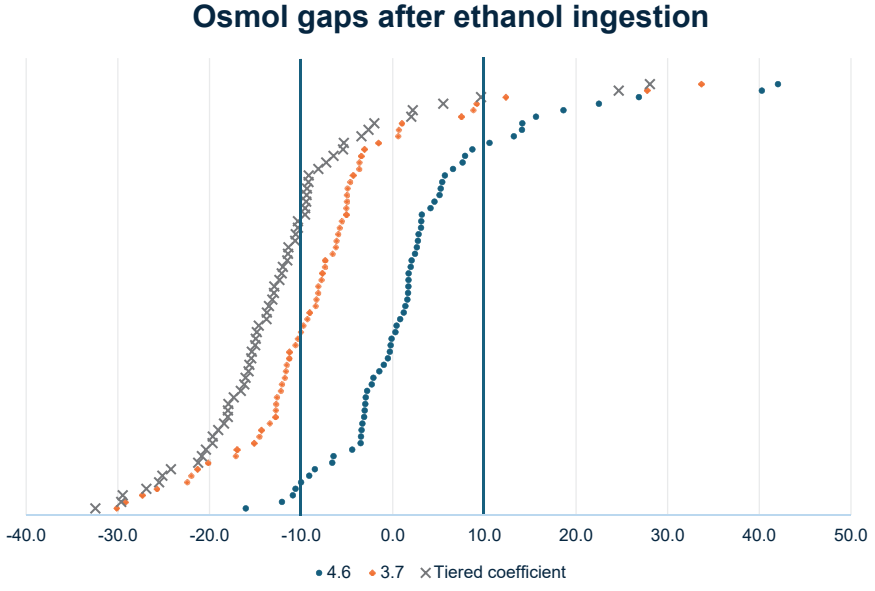

Figure. The calculated osmol gap using 3 different equations (one using 4.6 as the divisor for ethanol, one using 3.7, and one using tiered coefficients based on the ethanol concentration range) for each time the equation was calculated (n=66).

Table 2. The percent of osmol gaps calculated that were falsely positive (>10) and those that were within the bounds of −10 and +10 (defined as accurate).

Category	Overall (4.6)	Overall (3.7)	Ethanol (4.6)	Ethanol (3.7)	Excluding Outlier (4.6)	Excluding Outlier (3.7)
N	88	88	66	66	63	63
False positive	16%	8%	15%	5%	13%	2%
Accuracy	80%	60%	79%	53%	81%	54%

These calculations were performed using the formula for calculated osmolarity using a coefficient of 4.6 and also 3.7 and for all measures of the osmol gap, the osmol gap after ethanol was ingested, and finally after ethanol was ingested, but with the participants with large baseline osmol gaps (>20) excluded.

LIMITATIONS

We had a small sample of only volunteers that limits precision and could introduce generalizability concerns, though the observations are still foundational. Testing outside toxidrome or alcohol use disorder may limit the ability to extrapolate our results to others. Osmol gap calculations for toxic alcohol concerns are frequent in patients with alcohol use disorder in the emergency department, which would suggest the need to confirm these results in that patient population. We saw one large baseline osmol gap, potentially skewing the results. Retesting confirmed that result. This was an outlier though there may be similar results in the general population. Our lab tests occurred in a Clinical Laboratory Improvement Amendment certified and College of American Pathologists accredited laboratory, though measurement error is always possible. Even small changes in a serum sodium measurement can greatly change the calculated osmol gap.

DISCUSSION

We found an abnormal osmol gap in 21% of participants following ethanol ingestion corrected using the standard coefficient of 4.6 for ethanol. The accuracy was lower using the Purssell coefficient of 3.7. These findings were similar to rates found in retrospective studies of suspected toxic alcohol ingestions.[12,13] We also identified an osmol gap >10 prior to the ingestion of alcohol in 18% of participants. These findings of elevated osmol gap at baseline and inaccurate correction for blood ethanol raises concern about the clinical utility of this test.

The inaccuracy of the baseline osmol gap in a population without alcohol use disorder or reported comorbidities suggests potential pitfalls in the diagnostic utility of the test in the management of suspected toxic alcohol ingestions. First, based on guideline recommendations, an osmol gap >10 could prompt treatment with antidotal therapy.[3,5,6] Additionally, without timely quantitative direct measurement of a toxic alcohol, the persistence of the osmol gap could prompt re-exposure to treatments and prolong the overall length of stay. Second, these results also demonstrate that the calculated osmol gap could fall in the normal range when there is a toxic exposure present. For example, an ingestion of ethylene glycol producing a serum concentration of 128 mg/dL, an amount that would lead to renal injury, in a patient whose baseline osmolar gap is –15, would result in an osmol gap of +5. This would be a false-negative result that could lead to a misdiagnosis, a delay in treatment, and added morbidity. Third, in a patient who had a positive baseline osmol gap, an ingestion of ethanol could lead to a very high osmolar gap again triggering misdirected care especially if the clinical picture was concerning for a toxic alcohol (eg, toxic encephalopathy from the ethanol itself, metabolic acidosis from alcoholic ketoacidosis, etc).[12,14]

Despite concerns, now clearer, we see osmol gap measurement as retaining clinical utility. Most patients who present after an unknown overdose with encephalopathy may benefit from an osmol gap calculation; if elevated, it allows timely and appropriate early treatment once integrated into the clinical scenario and while recognizing the test's limits. However, direct measurement of the toxic alcohol concentration remains the best way to assure the correct diagnosis.[15]

If quantitative toxic alcohol testing is not available and an osmol gap calculation must be relied on, our data support that a coefficient of 4.6 is the current best correction for the ethanol contribution to serum osmolality.

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Author contributions: RM and AP conceived of and designed the project. RM, AP, and KF developed the protocol and obtained approval form the university institutional review board. RM and KF managed the clinical study. RM, ASc, and AP were involved in the carrying out the experiment. AS and RM interpreted the data. AS drafted the manuscript and all authors edited and approved the final manuscript. AS takes responsibility for the manuscript as a whole.

Data sharing statement: All data will be available. Contact Dr. Alexander Sidlak at alexander.sidlak@inova.org.

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