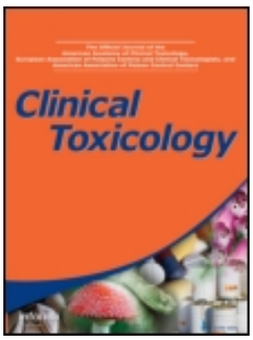

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RESEARCH ARTICLE

Contribution of serum ethanol concentration to the osmol gap: a prospective volunteer study

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Background. The contribution of ethanol ([EtOH]) to the osmol gap (OG) is commonly described by the formula [EtOH (mg/dL)]/*k*, where *k* is assumed to be 4.6 (one-tenth of its molecular weight) if ethanol behaves ideally in solution. However, several studies on convenience samples of patients suggest that ethanol does not behave ideally and that *k* may be significantly different from this ideal constant. *Objectives*. To determine prospectively the relationship between serum ethanol concentration and total serum osmolality in a group of healthy volunteers. *Methods.* Experimental subjects ingested 20 mL of 100% ethanol diluted in sugar-free soda at a rate of one drink every 10 min, up to a maximum of seven drinks. Control subjects ingested 20 mL of water diluted in sugar-free soda at the same rate. Blood samples were obtained at baseline and then at every 20 min for 180 min to measure serum [EtOH] concentration, electrolytes, glucose, and osmolality (via freezing-point depression). The OG was calculated by subtracting predicted osmolality from measured osmolality. The OG was then divided by [EtOH] to determine the coefficient of ethanol's contribution to total serum osmolality. *Results*. A total of 10 volunteers (five men and five women; mean age, 38.8 years, and range, 28–49 years) participated in and completed the study. Eight (four male and four female) were in the experimental group, and two (one male and one female) were in the control group. Mean peak [EtOH] was 229 mg/dL (median, 223.5 mg/dL; IQR, 171–273 mg/dL) and a linear relationship between [EtOH] and OG (Pearson coefficient of 0.98) was found. Using covariate correction for each subject's baseline OG, *k* was calculated to be 4.25 (95% CI, 4.13–4.38) averaged over all participants. *Conclusions*. In this volunteer study, the coefficient describing the contribution of ethanol to serum osmolality (*k*) was found to be 4.25. This indicates that ethanol contributes more to total serum osmolality than would be predicted for an ideal solute.

Keywords Osmol gap; Ethanol; Intoxication

Introduction

Patients with intentional ingestion of toxic alcohols such as methanol or ethylene glycol present frequently to the emergency department.[1] The same patients occasionally drink ethanol with the toxic alcohol; such a combination can confuse the clinical picture, since both ethanol and non-ethanol alcohols are intoxicating and are osmotically active. Although specialized laboratories exist that can test for toxic alcohols, such tests are typically send-out laboratories at most hospitals and the results are often not available for hours to days. Because the toxicity of these alcohols results from their metabolism, time is of the essence in order to make a determination of whether or not to treat.

Since all alcohols are osmotically active, physicians often rely on the calculation of an "osmol gap (OG)" to determine the presence of a possible toxic alcohol ingestion. This simple method is based on a calculation of the serum's primary osmotically active components: sodium, blood urea nitrogen (BUN), glucose, and ethanol (when present), where the calculated osmolality is subtracted from the measured osmolality. The resulting OG can then be used to estimate the presence of a toxic alcohol such as methanol or ethylene glycol. This calculation depends on theoretical coefficients based on ideal solutions to determine the contributions of the BUN, glucose, and ethanol to the calculated osmolality equation. Previous studies examining the contribution of ethanol to the osmolality equation, performed on convenience samples of intoxicated patients in a hospital setting, have shown variations around its theoretical values.[2–6] We proposed to determine the contribution of ethanol to the OG in a controlled setting using volunteers ingesting a standardized ethanol mixture.

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Materials and methods

This was a human volunteer study designed to determine the true osmolar contribution of ethanol to the measured serum OG. The study was approved by the local Institutional

Review Board and took place in the emergency department of a tertiary care academic hospital. Ten volunteers were recruited and completed a written informed consent. Subject exclusion criteria included the following: age < 21 years; pregnancy; known intolerance or allergy to alcohol ingestion; and ingestion of ethanol-containing beverages or medications or other osmotically active substances within the preceding 24 h.

Volunteers had a peripheral intravenous catheter placed and 5 cc of whole blood was obtained at baseline and at every 20 min for a total of 180 min for the measurement of serum ethanol concentration ([EtOH]), sodium (Na), blood urea nitrogen (BUN), glucose (Glu), and osmolality (measured via freezing-point depression). Predicted osmolality was calculated using the most commonly used formula for calculation of serum osmolality[7]:

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

The OG was determined by subtracting the calculated osmolality from the measured osmolality. [EtOH] was then divided by the OG to determine the coefficient (k) of ethanol's contribution to total serum osmolality at each time interval for each subject. Prior to starting ethanol ingestion, each subject's baseline OG was calculated, and this baseline value was subtracted from subsequent values in order to obtain a more accurate measurement of k.

At time zero, experimental subjects began ingesting 20 mL of 100% ethanol diluted in sugar-free soda (sugar-free soda was used to minimize any effect on serum osmolality due to exogenous sugar) at a rate of 1 drink every 10 min, up to a maximum of 7 drinks. Control subjects ingested 20 mL of water diluted in sugar-free soda at the same rate. A portable Breathalyzer device was employed at 20-min intervals to obtain a noninvasive estimate of blood alcohol concentration (BAC). Participants were allowed to opt out of ingesting further alcohol at any time and for any reason. Medical monitors continuously assessed the subjects and asked them to stop further ethanol consumption based upon their physical responses or whether the monitor assessed that the BAC obtained through the portable Breathalyzer precluded safe ingestion of further ethanol.

Statistical analysis

The derived coefficient from each subject was averaged within individual subjects and across all subjects over time. A Kruskal–Wallis test was used to test for differences within subjects over time and differences between subjects over time. A Pearson correlation coefficient was calculated to determine the association between [EtOH] and serum osmolality. Means, medians, and interquartile ranges (IQR) were calculated for measured variables.

Without any previously reported controlled data, group size analysis could not be performed. For this volunteer study, eight subjects and 2 controls were chosen based on the assumption of 15% variability of the coefficient within and between subjects. Statistical analysis was performed using Stata 12.1 software (StataCorp LP, College Station, TX).

Table 1. Mean, minimum, and maximum blood ethanol levels by time among the eight subjects drinking ethanol.

Time (min)	Mean [EtOH] ± SD (mg/dL)	Min–Max [EtOH] (mg/dL)
t = 20	36.8 ± 17.7	15–69
t = 40	92.8 ± 25.5	55–125
t = 60	166.5 ± 36.6	111–213
t = 80	216.5 ± 69.4	149–353
t = 100	219.4 ± 67.9	154–350
t = 120	216.9 ± 65.4	153–343
t = 140	213.9 ± 65.0	148–344
t = 160	207.4 ± 62.5	142–333
t = 180	202.9 ± 64.8	134–337

SD = standard deviation.

Results

Ten healthy subjects were recruited and completed the study: five men and five women (mean age, 38.8 years; range, 28–49 years). Eight were recruited into the experimental portion, and two into the control group. Both groups consisted of an equal number of men and women. Seven participants ingested the maximum of seven drinks; one participant voluntarily stopped after having ingested five drinks.

In the experimental group, BACs increased over time with the consumption of ethanol. The mean peak [EtOH] was 229 mg/dL (median, 223.5 mg/dL; IQR, 171–273 mg/dL). Ethanol levels by time are shown in the Table 1. The OG increased linearly with the [EtOH] concentration (correlation coefficient of 0.98).

At $t = 20$, the ethanol coefficient (k) was highly variable among participants (n = 8, Fig. 1). Starting at $t = 40$ min and thereafter until the conclusion of the study, k was similar across time points averaged among all subjects (n = 64, Figs. 1 and 2). However, there was significant variability in k when comparing average k over all time points between individual subjects (n = 72, $p < 0.001$, Fig. 3).

Mean baseline OG among all subjects was 2.84 (median, 4.71; IQR, 0.47–5.38). Excluding the first 20 min of ethanol ingestion and accounting for each individual's baseline OG, the ethanol coefficient (k) was calculated to be 4.25 (95% CI, 4.13–4.38) averaged over all participants and all time periods.

Serum osmolality in the two control subjects remained similar over time, indicating that the sugar-free soda vehicle used did not contribute appreciably to serum osmolality.

Discussion

Toxic alcohol ingestion is a frequent occurrence; based on data obtained from the American Association of Poison Centers for 2010, 7656 exposures were reported to US poison control centers with 738 resulting in moderate to major outcomes and 22 deaths occurring.[8] The availability of laboratories that can measure serum levels of ethylene glycol and methanol is severely limited; results typically can only be obtained by sending the serum to another facility, often delaying the confirmation by hours to days.

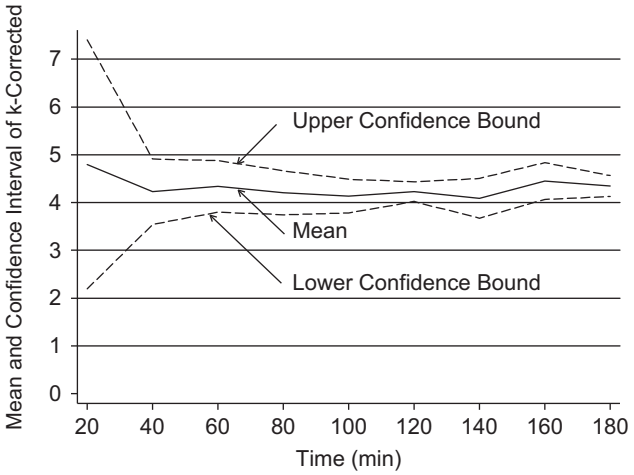

Fig. 1. Ethanol coefficient averaged among all experimental subjects over time. Solid line represents the mean; dotted lines represent 95% confidence intervals.

At present, most physicians utilize the calculated serum osmolality to help determine the OG in order to ascertain whether a toxic alcohol may be present. This equation, as noted above, relies on the assumption that ethanol acts as ideal solute, where the contribution of an osmotically active substance to serum osmolality is determined by dividing the serum concentration (in mg/dL) by a conversion factor of one-tenth the molecular weight of the compound in order to yield a result measured in mmol/L. Ethanol, which has a molecular weight of 46, would theoretically have a conversion factor of 4.6 (1/10th of 46).

In our study of healthy human volunteers, we found the coefficient or conversion factor to be 4.25 both over time and over varying serum ethanol levels. This is similar to other previously reported uncontrolled studies of intoxicated patients that derived ethanol coefficients ranging 3.7–4.3.[2–6] These data suggest that ethanol does not behave ideally in its contribution to serum osmolality and that 4.25 may be a better estimate than 4.6 given the design of our study. This is likely due to multiple factors, most notably the fact that serum is only 93% water and does not take into account the volume of plasma when determining the coefficient.

Limitations

Our study has several limitations. This was a relatively small study; our data are based upon observations recorded in eight experimental patients. All of our subjects were healthy volunteers, which helped to eliminate confounding variables; however, our results may not necessarily apply to patients with lactic acidosis, ketosis, dysproteinemia, or other conditions that can affect the OG. Additionally, given the prospective nature of our study, we were able to factor in each subject's baseline OG which theoretically resulted in a more accurate determination of the contribution of ethanol to the OG. The baseline OG varies from person to person and even within single individuals over time.[9] In most real-world clinical scenarios, however, this baseline value is not known and therefore the calculation of OG is made using the assumption of a zero baseline OG. Our data also showed that measurement of *k* could vary depending upon the individual, which suggests that the use of a specific coefficient, while relatively consistent on a population basis, is not necessarily applicable to an individual patient.

Another limitation is the fact that our calculations were based upon a fairly narrow range of serum ethanol levels; Garrard et al. did a post-hoc analysis of their retrospective data that suggested that the coefficient is not linear and rises with increasing ethanol levels, from 3.81 at moderate concentrations to 4.15 at levels $>$ 500 mg/dL.[6] We did not feel that we could ethically allow our participants to obtain levels higher than those that were achieved in our study. Nevertheless, it is possible that had higher levels been achieved in our participants, the coefficient would be different.

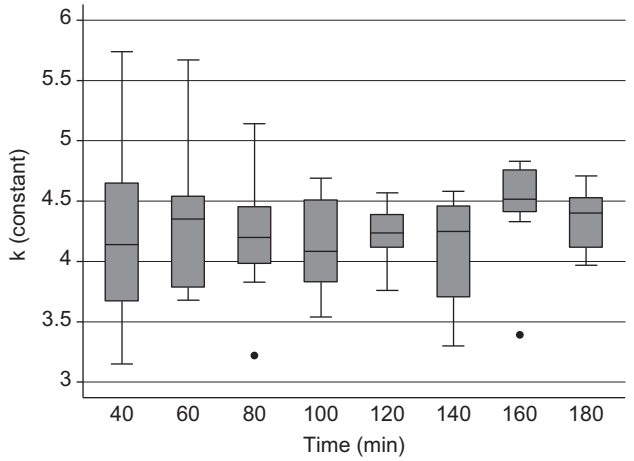

Fig. 2. Box and whisker plot of ethanol constant (*k*) over time. Boxes represent IQR; horizontal lines in boxes represent medians; whiskers represent the lowest and highest data still within 1.5 IQR. Outlier values are represented in solid circles.

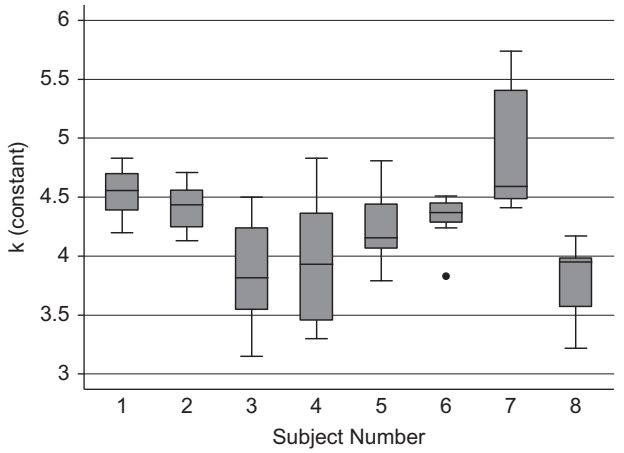

Fig. 3. Box and whisker plot of ethanol constant (*k*) by subject. Boxes represent IQR; horizontal lines in boxes represent medians; whiskers represent the lowest and highest data still within 1.5 IQR. Outlier values are represented with solid circles.

Perhaps, most importantly, one must remember that the method of using OGs as a tool to rule out toxic alcohol ingestion is fraught with peril. A "normal" OG can range from −14 to 10,[4] and it is this variability that can mask toxic levels of methanol or ethylene glycol, even without the confounding issue of ethanol co-ingestion. Indeed, previous authors have cautioned against the use of the OG as a primary determinant to rule out poisoning with toxic alcohols.[10] The OG should be used with caution and only as an adjunct to good clinical decision-making.

Conclusion

In this volunteer study, the coefficient describing the contribution of ethanol to serum osmolality (k) was found to be 4.25. This indicates that ethanol contributes more to total serum osmolality that would be predicted for an ideal solute, and it may be useful in determining the OG during the presentation of potential toxic alcohol ingestion.

Declaration of interest

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

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