The Osmolal Gap: What Has Changed?

To the Editor:

The osmolal gap (OG)\(^1\) is calculated in the emergency department (ED) when ingestion of ethylene glycol, methanol, isopropyl alcohol, acetone, or other osmotically active substances are suspected. Serum osmolality is measured and also calculated with the variables serum glucose, sodium, and blood urea nitrogen (BUN) concentrations. The difference between the measured and calculated osmolality is defined as the OG. Boyle et al. (1) recently cautioned against using the OG as a screening tool for toxic-alcohol poisoning. One reason relates to the debate about what constitutes a normal OG and the variations in the range of osmolal gaps (2). To address what constitutes a normal OG, we determined the OG range for healthy subjects and examined data from hospitalized patients by use of several published equations for calculating serum osmolality.

After obtaining informed consent, we collected blood from 126 self-reported healthy subjects. The serum osmolality glucose, potassium, sodium, and BUN were within respective reference intervals (Table 1 and 2). The OG log-transformed parametric reference intervals (central\(_{5\%}\)) were \(-8\) to 11 mOsm/kg and 3 to 22 mOsm/kg by use of Eqs. 1 and 2, respectively.

General equation (2,4)

\[
\text{Osm} = 2(\text{Na}^+) + \frac{\text{Glucose}}{18} + \frac{\text{BUN}}{2.8} + \frac{\text{EtOH}}{4.6} + 14 \tag{1}
\]

Glaser (3) and Krahn and Khajuria [(4); see Dorwart’s equation]

\[
\text{Osm} = 1.86(\text{Na}^+) + \frac{\text{Glucose}}{18} + \frac{\text{BUN}}{2.8} + \frac{\text{EtOH}}{4.6} + 9 \tag{2}
\]

Rasouli and Kalantari (5)

\[
\text{Osm} = 1.897(\text{Na}^+) + \frac{\text{Glucose}}{18} + \frac{\text{BUN}}{2.8} + \frac{\text{EtOH}}{4.6} + 13.5 \tag{3}
\]

Krahn and Khajuria (4)

\[
\text{Osm} = 1.86(\text{Na}^+) + \frac{1.15(\text{Glucose})}{18} + \frac{\text{BUN}}{2.8} + \frac{1.2(\text{EtOH})}{4.6} + 14 \tag{4}
\]

\[
\text{Osm} = 2(\text{Na}^+) + \frac{1.15(\text{Glucose})}{18} + \frac{\text{BUN}}{2.8} + \frac{1.2(\text{EtOH})}{4.6} \tag{5}
\]

ED records identified 157 patients in 1998 and 117 patients in 2007–2009 for whom a serum osmolality was measured and calculated osmolality were measured simultaneously. Cases were eligible if serum glucose, potassium, sodium, BUN, ethanol, and osmolality were measured simultaneously. Cases were excluded when ethylene glycol, isopropyl alcohol, or methanol was detected. In 1998, there were 45 positive volatile screens (43 ethanol, 1 ethylene glycol, 1 acetone). In 2007–09, 54 positive screens were confirmed (32 ethanol, 6 ethylene glycol, 2 methanol, 5 isopropyl alcohol, 9 acetone). Serum osmolality was calculated by use of several equations (2–5), and a general correction for ethanol was included. Because large OGs have been observed in renal failure (2), we assessed the renal function of each subject by use of the Modification of Diet in Renal Disease equation to estimate the glomerular filtration rate (eGFR).

Renal insufficiency (eGFR <60 mL/min/1.73 m\(^2\)) was present in 14% and 35% of the 1998 and 2007–09 ED patients, respectively. Median OGs, calculated by use of Eq. 1, were 0 mOsm/kg (central\(_{95\%}\)–11 to 19 mOsm/kg) and 16 mOsm/kg (central\(_{95\%}\)–2–36 mOsm/kg) for 1998 and 2007–09 patients with renal insufficiency. When eGFR was >60 mL/min/1.73 m\(^2\), the median OGs were –2 mOsm/kg (central\(_{95\%}\)–12 to 22 mOsm/kg) and 11 mOsm/kg (central\(_{95\%}\)–3 to 39 mOsm/kg) for 1998 and 2007–09, respectively. Renal insufficiency did not appear to affect the OG.

Using Eq. 1, in 1998 the median OGs were –2 mOsm/kg (central\(_{95\%}\)–12 to 20 mOsm/kg) and –2 mOsm/kg (central\(_{95\%}\)–14 to 17 mOsm/kg) for positive and negative ethanol screens, respectively. Using Eq. 1, in 2007–09 the median OGs were 17 mOsm/kg (central\(_{95\%}\)–1–44 mOsm/kg; 90% CI of the 97.5th percentile upper reference limit 36–54 mOsm/kg) and 11 mOsm/kg (central\(_{95\%}\)–3 to 36 mOsm/kg; 90% CI of the upper reference limit 31–41 mOsm/kg) for positive and negative ethanol screens, respectively. In 2007–09, ethanol caused a 54% increase in the median OG despite a correction factor being used for its presence. However, the 95% CIs of the OG upper reference limits overlap. A small number of measured osmolalities were followed up with volatile screens, including ethanol; the clinical sensitivities and specificities of the OG (Eq. 1) for identifying ethanol were (16%, 93%) and (78%, 47%), respectively for

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1 Nonstandard abbreviations: OG, osmolal gap; ED, emergency department; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

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Clinical Chemistry 56:8 (2010) 1353
Acetone, a metabolite of isopropyl alcohol and a metabolic product that is increased in patients with ketoacidosis, did not affect the OG. Thus, acetone did not result in a negative acetone result, respectively. Therefore, acetone did not affect the OG.

In 1998, hyperglycemia had a minimal affect on the OG (median 17 mOsm/kg, central 95% 14 to 21 mOsm/kg), but in 2007–09 hyperglycemia increased the median OG and the 97.5th percentile (median 17 mOsm/kg, central 95% 1–48 mOsm/kg).

Although it has been suggested that the OG has increased over time (4), we found that the reference interval of −8 to 11 mOsm/kg calculated by use of Eq. 1 is consistent with the general rule of −10 to 10 mOsm/kg for healthy subjects (1). We conclude that renal insufficiency, ethanol, and acetone have minimal influence on the observed OG ranges in our ED. The apparent increase observed in ED patients may reflect more selective ordering, as evidenced by the 67% reduction in orders from 1998–2008, and possibly an increase in the number of patients with diabetic ketoacidosis.

Recognizing the limitations of using the OG is important. If a patient’s normal baseline OG is −8 mOsm/kg and the patient presents in the ED with an OG of 10 mOsm/kg, although within the reference interval, this change in OG (18 mOsm/kg) may result from toxic ingestion. Finally, the equation used to calculate serum osmolality must be considered when evaluating the OG. Note that Eq. 2 requires a higher OG reference interval of 3 to 22 mOsm/kg (mean OG 12 mOsm/kg), which is consistent with published mean OGS of 8–15 mOsm/kg (4).

Physicians must have the correct OG reference interval for the equation they use.

Table 1. Reference intervals of measured analytes.

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Central 95%</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mg/dL</td>
<td>87 (16.8)</td>
<td>85</td>
<td>56–137</td>
<td>52–137</td>
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<tr>
<td>Potassium, mmol/L</td>
<td>4.1 (0.3)</td>
<td>4.2</td>
<td>3.5–4.8</td>
<td>3.2–4.9</td>
</tr>
<tr>
<td>Sodium mmol/L</td>
<td>140.8 (1.7)</td>
<td>141</td>
<td>137–144</td>
<td>135–146</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>13.4 (3.4)</td>
<td>13.8</td>
<td>7.6–20.7</td>
<td>5.9–23.2</td>
</tr>
<tr>
<td>Osmolality, mOsm/kg</td>
<td>292.6 (4.8)</td>
<td>292</td>
<td>283–303</td>
<td>282–303</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Osmolal gaps*</th>
<th>n</th>
<th>General (Eq. 1)</th>
<th>Eq. 2</th>
<th>Eq. 3</th>
<th>Eq. 4</th>
<th>Eq. 5</th>
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</thead>
<tbody>
<tr>
<td>Healthy</td>
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<tr>
<td>2008</td>
<td>126</td>
<td>−8 to 11</td>
<td>3 to 22</td>
<td>−7 to 12</td>
<td>−10 to 9</td>
<td>−9 to 11</td>
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<td>ED</td>
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<tr>
<td>1998</td>
<td>156</td>
<td>−11 to 19</td>
<td>−1 to 32</td>
<td>−11 to 21</td>
<td>−20 to 14</td>
<td>−18 to 16</td>
</tr>
<tr>
<td>2007–09</td>
<td>104</td>
<td>−1 to 36</td>
<td>9 to 45</td>
<td>−1 to 37</td>
<td>−6 to 25</td>
<td>−5 to 27</td>
</tr>
</tbody>
</table>

* Central 95% osmolal gaps, log-transformed parametric.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures of Potential Conflicts of Interest: Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:

Employment or Leadership: None declared.

Consultant or Advisory Role: None declared.

Research Funding: W.L. Roberts, ARUP Laboratories.

Expert Testimony: None declared.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

References

Letters to the Editor

First- and Second-Trimester ADAM12s in Down Syndrome Screening

To the Editor:

ADAM12s, a disintegrin and metalloprotease 12s, is a placenta-derived glycoprotein involved in tissue growth and differentiation. It has been shown to be an early screening marker for trisomy 21 before the 10th week of gestation (1) and a potential second-trimester marker. A recent report suggested that measurements of a serum marker in both the first and second trimesters (repeated measures) could provide better performance than single measurements in either trimester (2).

We sought to demonstrate the potential value of such repeated measures of ADAM12s for the screening of Down syndrome.

A cohort of 7194 women underwent integrated biochemical screening before amniocentesis at the Department of Obstetrics and Gynecology, University of Messina, between December 1, 2006, and March 31, 2009. After collection, the maternal serum samples were stored at −80 °C. We selected paired first- and second-trimester samples from 19 Down syndrome pregnancies (cases) from frozen storage for ADAM12s measurement. Of the Down syndrome cases, 14 were identified from amniocentesis results, and 5 were identified at birth. Two of the latter were excluded owing to maternal smoking and the unknown potential effects of smoking on maternal ADAM12s values in serum. ADAM12s also was measured in frozen samples from 562 unaffected pregnancies matched for gestational age (GA).

GAs ranged between 7 and 10 weeks in the first trimester and between 14 and 17 weeks in the second. All the women in the study were Caucasian. Although the patients in the Down syndrome cases had a higher mean maternal age than the unaffected pregnancies (35.3 years vs 30.4 years), previous studies have shown that ADAM12s concentration is unrelated to maternal age (3).

Median maternal weights (cases, 62.6 kg; unaffected pregnancies, 63.4 kg) and GAs in the first trimester (cases, 64 days; unaffected, 65 days) and the second trimester (cases, 112 days; unaffected, 111 days) were comparable.

ADAM12s was measured in 25 μL of serum with a time-resolved fluorescence immunosay DELFIA assay kit (PerkinElmer Life and Analytical Sciences). This method is a solid-phase assay in which 2 monoclonal antibodies (6E6 and 8F8) are directed against 2 separate antigenic determinants on the ADAM12 molecule. Concentrations were expressed as multiples of the median (MoM) for unaffected pregnancies of the same GA by means of 2 regression equations derived from the first- or second-trimester control groups. QC samples derived from pooled serum stored at −80 °C had ADAM12s concentrations of 86.5, 415.8, and 917.5 ng/L and were measured in duplicate at the beginning and at the end of each run. The mean CVs were 4.9%, 2.9%, and 3.5%, respectively.

Analyse-it (Analyse-it Software) and SPSS (version 14; SPSS) software were used for statistical analysis. In particular, the detection rate (DR) at a 5% false-positive rate (FPR) and the likelihood ratio of a positive were computed with the Analyse-it program. The same results were also calculated with the integrated model described by Royston and Thompson (4) with the model parameters (mean and SD) for the first and the second trimesters and taking into account the correlation coefficients between trimesters for ADAM12s in Down syndrome and unaffected pregnancies.

The weighted log-linear regression equations for the first and second trimesters in the unaffected group were, respectively:

\[
\text{ADAM12}_{\text{first}} = 10^{0.0269 \cdot \text{GA} + 0.613}
\]

and

\[
\text{ADAM12}_{\text{second}} = 10^{0.0108 \cdot \text{GA} + 1.721},
\]

where GA is expressed in days. The ADAM12s MoM values were re-