The Osmolal Gap: What Has Changed?

To the Editor:

The osmolal gap (OG) 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 using serum glucose, potassium, 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 using 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 (Tables 1 and 2). The OG log-transformed parametric reference intervals (central95%) were −8–11 mOsm/kg and 3–22 mOsm/kg using Eqs. 1 and 2, respectively.

General equation (2,4)

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

(1)

Glaser et al. & Dorwart (3–4)

\[
Osm = 1.86(Na^+)
\]

\[
+ \frac{Glucose}{18} + \frac{BUN}{2.8}
\]

\[
+ \frac{EtOH}{4.6} + 9
\]  

(2)

Rasouli et al. (5)

\[
Osm = 1.897(Na^+)
\]

\[
+ \frac{Glucose}{18} + \frac{BUN}{2.8}
\]

\[
+ \frac{EtOH}{4.6} + 13.5
\]  

(3)

Krahn et al. (4)

\[
Osm = 1.86(Na^+ + K^+)
\]

\[
+ 1.15\left(\frac{Glucose}{18}\right) + \frac{BUN}{2.8}
\]

\[
+ 1.2\left(\frac{EtOH}{4.6}\right) + 14
\]  

(4)

\[
Osm = 2(Na^+)
\]

\[
+ 1.15\left(\frac{Glucose}{18}\right) + \frac{BUN}{2.8}
\]

\[
+ 1.2\left(\frac{EtOH}{4.6}\right)
\]  

(5)

ED records identified 157 patients in 1998 and 117 patients in 2007–2009 for whom a serum osmolality measurement was ordered. 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 using 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 using the Modification of Diet in Renal Disease equation to estimate the glomerular filtration rate (eGFR).

Renal insufficiency (eGFR < 60 mL/min/1.73 m²) was present in 14% and 35% of the 1998 and 2007–09 ED patients, respectively. Median OGs, calculated using Eq. 1, were 0 mOsm/kg (central95% −11–19 mOsm/kg) and 16 mOsm/kg (central95% 2–36 mOsm/kg) for 1998 and 2007–09 patients with renal insufficiency. When eGFR was >60 mL/min/1.73 m², the median OGs were −2 mOsm/kg (central95% −12–22 mOsm/kg) and 11 mOsm/kg (central95% −3–39 mOsm/kg) for 1998 and 2007–09. Renal insufficiency did not appear to affect the OG.

Using Eq. 1, in 1998 the median OGs were −2 mOsm/kg (central95% −12–20 mOsm/kg) and −2 mOsm/kg (central95% −14–17 mOsm/kg) for positive and negative ethanol screens, respectively. Using Eq. 1, in 2007–09 the median OGs were 17 mOsm/kg (central95% 1–44 mOsm/kg; 90% CI of the 97.5th percentile upper reference limit 36–54 mOsm/kg) and 11 mOsm/kg (central95% −3–36 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 34% 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 1998 (n = 43) and 2007–09 (n = 28). The clinical sensitivities of the
OGs, calculated using Eqs. 1–5, with respect to detecting volatile substances, were 92%, 100%, 92%, 92%, and 85%, respectively. Eq. 5 showed less clinical sensitivity to the presence of volatiles. Acetone, a metabolite of isopropyl alcohol and a metabolic product that is increased in patients with ketoacidosis, did not affect OG. In 1998, there was only 1 positive acetone. Using Eq. 1, in 2007–09 the median OGs were 16 mOsm/kg (central 95% 1–15 to 66 mOsm/kg; 90% CI of the 97.5th percentile upper reference limit 31–40 mOsm/kg) and 11 mOsm/kg (central 95% 1–36 mOsm/kg; 90% CI of the upper reference limit 31–40 mOsm/kg) for samples with positive and negative acetone results, respectively. Therefore, acetone did not affect the OG.

Hyperglycemia (>200 mg/dL) affected 9% and 17% of the 1998 and 2007–09 ED patients, respectively. In 1998, hyperglycemia had a minimal affect on the OG (median 11 mOsm/kg, central 95% 14–21 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 −8–11 mOsm/kg calculated using Eq. 1 is consistent with the general rule of −10–10 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 3–22 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>
</tr>
<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>
</table>


<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>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</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>
</tr>
<tr>
<td>ED</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>

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.

References
