also, the experimental measurement of serum protein concentrations by the assays used here will not be adversely compromised. If the biuret assay is used, centrifugation and (or) a short incubation time are adequate to prevent dextran-induced interference, and eliminate the need to modify the color reagent.

References

Michael A. Dubick
James J. Summary
Jacqueline Y. Greene
Charles E. Wade

Excess Serum Osmolality after Ingestion of Methanol: the Exception, Not the Rule

To the Editor:

Drs. Meatherall and Krahn (1) recently presented three cases of excess osmolality gap (EOG) in serum after ingestion of methanol alone or in combination with ethylene glycol. Unfortunately, no other cases of methanol ingestion alone were presented or mentioned, and one is left with the impression that EOG occurs after most, if not all, ingestions of methanol. In our experience, the majority of methanol ingestions do not present with EOG and, in the few that do, the EOG can be rationalized.

Table 1 summarizes data from eight patients presenting with methanol ingestion without concurrent ingestion of ethanol or any other alcohol-related compounds. Methanol, ethanol, isopropanol, and acetone were measured by headspace gas chromatography (2) with a Model F45 headspace gas chromatograph (Perkin-Elmer Corp., Analytical Instruments, Norwalk, CT), equipped with a 2.4 m x 2 mm (i.d.) Tightsep® glass column packed with GP 60/80 mesh Carbopack B/5% Carbonwax 20 M (Supelco Inc., Bellefonte, PA). Ethylene glycol and propylene glycol were determined by direct-injection gas chromatography (3), with 1,3-propanediol as the internal standard. A Model 5720 gas chromatograph (Hewlett-Packard Co., Palo Alto, CA), equipped with a column similar to that for the previous analyses, was used. Serum specimens were not analysed for minor osmotically active compounds such as glycerol, sorbitol, inositol, ether, trichloroethanes, and paraldehyde (4). Osmolality was measured by freezing-point depression with a Model 3MO Micro-Osmometer (Advanced Instruments Inc., Needham, MA). Calculated osmolality was determined from 2 (Na+) + glucose + urea (4, 5), with all values expressed as mmol/L.

For six patients with widely differing serum methanol concentrations (10-166 mmol/L), the EOG is not excessive, ranging from 0 to 13 mmol/L. Patient 7, with an EOG of 36 mmol/L, received an intravenous solution of mannitol, 200 g/L for 1.5 h before blood collection. Mannitol, which can induce serum osmolality abnormalities (4), is probably the causative factor of the EOG in this patient. For patient 8, who also had an EOG of 36 mmol/L, methanol was the only osmotically active compound detected.
This patient, however, was profoundly acidic (pH 6.68), with an above-normal concentration of serum creatinine (152 μmol/L; normal 50–115 μmol/L) implying organ failure and (or) shock. As demonstrated by Inaba et al. (6), such patients can exhibit EOG, which is postulated to occur from abnormal escape of intracellular solutes (e.g., amino acids) or intermediate compounds of body metabolism. Cases 2 and 3 presented by Drs. Meatherall and Krahn (pH 6.77 and 7.15) could fit this category. Furthermore, large osmolal gaps have been found in anion gap metabolic acidosis, e.g., lactic acidosis (7). Although lactate was not analyzed in our patient 8 and Meatherall and Krahn’s patient 2, both presented with an increased anion gap. The mechanism for EOG in anion gap metabolic acidosis is not known, but is theorized to result from the release of organic substances from ischemic tissues (6).

Drs. Meatherall and Krahn used the Dorwart–Chalmers formula for calculation of osmolality (5). Applying this equation to our patient’s values calculated osmolality values significantly less (P < 0.05: two-tailed, paired t-test) than those obtained by using the formula of 2Na+ + glucose + urea, and the corresponding EOG values were significantly greater (P < 0.05: two-tailed, paired t-test).

We concur with Drs. Meatherall and Krahn that a nonionized methanol metabolite(s) would probably not account for EOG after methanol ingestion. Contributory factors to the EOG observed in their patients could include underestimation of calculated osmolality by the Dorwart–Chalmers formula (6), total combined analytical errors, the undetected presence of an osmotically active exogenous compound (e.g., mannitol), organ failure, and (or) anion gap metabolic acidosis.

Drs. Meatherall and Krahn have documented the interesting phenomenon of excessive osmolar gap after methanol ingestion. The cause remains purely speculative. However, from our experience, EOG after methanol ingestion is not common, and can usually be explained by reasons previously outlined.

References

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The authors of the article in question respond:

To the Editor:

It is our impression that LeGatt et al. have come to the wrong conclusions when they read our paper, perhaps because we had attempted to be very concise and clear. To clarify the misunderstandings pointed out in their letter, we address the following points:

1. Nobody should be "left with the impression that EOG occurs after most, if not all, ingestions of methanol." We clearly stated in our introduction (7) that "we draw particular attention to the fact that the osmolar gap in some cases grossly overestimates the amount of alcohol present" (emphasis added).

Table 1. Laboratory Results from Eight Patients Presenting with Methanol Ingestion

<table>
<thead>
<tr>
<th>Reference Interval</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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<tbody>
<tr>
<td>Na, mmol/L</td>
<td>135–150</td>
<td>143</td>
<td>144</td>
<td>138</td>
<td>152</td>
<td>150</td>
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<td>Urea, mmol/L</td>
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<td>10.6</td>
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<tr>
<td>Glucose, mmol/L</td>
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<td>8.4</td>
<td>6.2</td>
<td>18.4</td>
<td>5.4</td>
<td>6.3</td>
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<td>pH</td>
<td>7.35–7.45</td>
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<td>7.0</td>
<td>7.4</td>
<td>6.5</td>
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<td>tCO₂, mmol/L</td>
<td>23–31</td>
<td>18</td>
<td>&lt;5</td>
<td>25</td>
<td>5</td>
<td>5</td>
<td>&lt;5</td>
<td>5</td>
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<td>Anion gap, a mmol/L</td>
<td>12–14</td>
<td>19</td>
<td>32</td>
<td>12</td>
<td>38</td>
<td>31</td>
<td>21</td>
<td>40</td>
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<td>Osmolality, mmol/kg</td>
<td>280–295</td>
<td>346</td>
<td>422</td>
<td>302</td>
<td>439</td>
<td>490</td>
<td>350</td>
<td>453</td>
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<td>Calc. b</td>
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<td>333</td>
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<td>288</td>
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<tr>
<td>Calc. c</td>
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<td>287</td>
<td>277</td>
<td>321</td>
<td>299</td>
<td>277</td>
<td>287</td>
<td>290</td>
</tr>
<tr>
<td>Methanol, mmol/L</td>
<td>± 10</td>
<td>± 10</td>
<td>± 10</td>
<td>± 10</td>
<td>± 10</td>
<td>± 10</td>
<td>± 10</td>
<td>± 10</td>
</tr>
</tbody>
</table>

* Anion gap = (Na⁺) – (Cl⁻ + tCO₂).
* Calculated osmolality = 2Na⁺ + glucose + urea.
* Calculated osmolality (Dorwart–Chalmers formula) = 1.86Na⁺ + glucose + urea + 9.
* Excess osmolality gap = osmolality – (calc. osmol + total alcohol concentration).
* Excess osmolality gap = osmolality – (calc. osmol + total alcohol concentration).

Urinalysis screens for ketones were negative for all patients.

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