Unusual Causes of Elevation in the Osmolal Gap

How to be circumspect with serum and solvents

Daniel T Holmes, MD FRCPC
Division Head, Clinical Chemistry
Department of Pathology and Laboratory Medicine
St. Paul’s Hospital
Review the definition of osmolality, the osmolal gap.
Review challenges in determining the osmolal gap.
Review the common causes of elevated osmolal gap.
Introduce more recently described causes of elevation and the appropriate clinical response.
Molality is defined as the amount of solute per mass of solvent (units mol/kg).

Compare: Molarity is the amount of solute per volume of solution (units mol/L).

If the solvent is water and the solution is dilute, molality and molarity are very close to one another.
Definition

- Osmolality is defined as the number of osmotically active particles per mass of solvent.
- Osmolarity is defined as the number of osmotically active particles per volume of solution.
- These are approximately equal in dilute aqueous solutions because 1kg solvent ~1L solution.
Osmolality is determined by freezing point depression – that is, the extent to which the freezing point is decreased is proportional to the osmolality.

This can be used to infer the presence and concentration of osmotically active compounds.
OK – that was the second-last basic chemistry slide

\[ T_f = \text{molality} \times K_f \times i \]

\[
\text{oosmol/L} = \sum_{i} \varphi_i n_i C_i
\]
What is the practical application of this?

- In real solutions, the concentration of an osmotically active compound will not necessarily contribute to the osmolal gap on a one:one basis.
- This concept is seen real-world application in our clinical lab calculation for the osmolal gap.
Osm = 2[Na\(^+\)] + [glucose] + [urea] + 1.25[EtOH]

Because EtOH contributes more to the osmolality than simply its molarity.

But in fact this phenomenon has been found to extend to glucose\(^1\), methanol and number of other compounds\(^2\).

Theorem: Only neutrally charge compounds can contribute to the osmolar gap.

- This can be uncharged organic compounds
  - endogenous compound, solvents, volatiles, metabolites.

- Can also be “zwitterions” – that is, compounds having both a positive and negative ion on the same molecule.
  - quintessentially the neutral amino acids
Examples of Zwitterions

Glycine

Alanine

Proline

Valine

Leucine

Isoleucine

Methionine
There are at least 5 sources of error in the formula for calculated osmolality (in addition to the fact that molality is being estimated from molarity).

1. The factor of 2
2. The measurement of Na
3. The measurement of glucose
4. The measurement of urea
5. The measurement of EtOH
The combined random analytical error when multiple results are summed in this manner increases the error by the sum of the squares of the respective errors\(^1\).

Practically speaking, for typical results, this would amount to +/-10 mOsm/kg uncertainty in the OGAP.

Case 1

- 19 yo Male, Type I DM
- Poorly compliant with insulin
  - Previous admissions for DKA
- Found down, brought to ER by EHS
# Case I: Labs

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na (whole blood)</td>
<td>131</td>
<td>135-145 mmol/L</td>
</tr>
<tr>
<td>K (whole blood)</td>
<td>6.3</td>
<td>3.5-5.0 mmol/L</td>
</tr>
<tr>
<td>Cl</td>
<td>86</td>
<td>95-107 mmol/L</td>
</tr>
<tr>
<td>CO₂</td>
<td>4</td>
<td>21-29 mmol/L</td>
</tr>
<tr>
<td>Urea</td>
<td>11.1</td>
<td>2.0-8.2 mmol/L</td>
</tr>
<tr>
<td>Cre (Jaffe)</td>
<td>237</td>
<td>45-115 umol/L</td>
</tr>
<tr>
<td>Cre (whole blood)</td>
<td>192</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>99</td>
<td>3.3-11.0 mmol/L</td>
</tr>
<tr>
<td>Osm</td>
<td>411</td>
<td>275-295 mmol/kg</td>
</tr>
<tr>
<td>EtOH</td>
<td>&lt;2</td>
<td>&lt;2 mmol/L</td>
</tr>
<tr>
<td>OGap</td>
<td>39</td>
<td>&lt;10 mmol/kg</td>
</tr>
<tr>
<td>Agap</td>
<td>41</td>
<td>&lt;10 mmol/L</td>
</tr>
<tr>
<td>pH</td>
<td>6.92</td>
<td>7.35-7.45</td>
</tr>
</tbody>
</table>

"Life's full of questions, isn't it, Batman? Though, naturally, I prefer to think of them as riddles."
Can we account for the gap?

What are the potential contributors?

- Toxic alcohols?
  - none detected

- Ketones?
  - Yes, but only acetone contributes
  - acetone=9 mmol/L, BHB=11.9 mmol/L

- Lactate?
  - No, not in and of itself – make buzzer sounds
  - lactate=8.7 mmol/L [0.5-1.6]
Case 1: Missing Osmoles

- We still have a gap of 31 mmol/kg
- Any other contributors?
  - Free fatty acids?
    - No, fully ionized.
  - Glycerol?
    - Yes, in principle but when measured tends to be below 1 mmol/L
  - Zwitterions?
    - Yes, in these cases, results come in around 4-5 mmol/L

What about the Na?

- The Na is low in the context of hyperglycemia?
- Perhaps the problem is pseudohyponatremia leading to a spuriously low Na and supriously low calculated osmolality and elevated Ogap?
FALSELY ELEVATED OSMOL GAP DUE TO HYPERTONIC HYponATREMIA

*Department of Emergency Medicine, Mayo Clinic, Rochester, Minnesota and †Drug and Poison Information Center, Cincinnati, Ohio
Reprint Address: Matthew D. Sztajnkrycer, MD, PhD, Department of Emergency Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN, 55905

Elevated serum glucose results in movement of free water into the extracellular space, and subsequent apparent hyponatremia despite normal or elevated serum osmolality. The serum sodium value is reduced by approximately 1.6 mEq/L for every 100 mg/dL increase in serum glucose above 100 mg/dL. This condition, referred to as hypertonic hyponatremia, also may be seen with the therapeutic use of glycerol or mannitol. It has no physiological significance, and will correct as euglycemia is reestablished. However, if not accounted for when calculating the osmol gap, it will result in an erroneous elevation of the gap by 3.2 mOsm per 100 mg/dL increase in serum glucose.
Hyperglycemia causes true hyponatremia and “correction formula” answers a physiological question, “What do we expect the Na to be after the glucose has been corrected?”

Suppose the glycerol and amino acids take care of another 5 mmol/kg.
  > We still have 25 mmol/kg.

But is glucose’s contribution 1:1?
Case 1: Missing Osmoles

Fig. 1. Passing Bablok regression analysis of plasma glucose and various OGs from in vitro experimental data. $N = 100$.

Case 1: Missing Osmoles

- If the glucose concentration is 99 mmol/L then the “excess osmoles” that this contributes has become very substantial and accounts for another 15 mmol/kg.
- We therefore now only have 10 mol/kg unaccounted for.
- And the rest?
The Sick Cell Syndrome?

Osmolar gap hyponatremia in critically ill patients: Evidence for the sick cell syndrome?

Jean Guglielminotti, MD; Pascal Pernet, MD, PhD; Eric Maury, MD; Marc Alzieu, MD; Michel Vaubourdolle, PharmD, PhD; Bertrand Guidet, MD; Georges Offenstadt, MD

**Conclusion:** Hyponatremia with increased osmolar gap related to endogenous solutes accumulation is observed frequently in hyponatremic intensive care patients, especially in patients with the most severe organ dysfunctions. The nature of the endogenous solutes accounting for the increased osmolar gap remains to be determined. Simultaneous correction of sodium and osmolar gap suggests a causal link between increased osmolar gap and hyponatremia and may support the concept of sick cell syndrome.

Sick Cell Syndrome?

Figure 1. Evolution of the plasma osmolar gap (open circle) during the correction of hyponatremia (filled circle) in 26 patients with an initial osmolar gap >10 mosm/kg (left) and in 21 patients with an initial osmolar gap <10 mosm/kg (right); data are presented as mean ± 1 sd. *p < .05 and **p < .0001 for comparison with initial values.
Table 2. Biological characteristics

<table>
<thead>
<tr>
<th></th>
<th>OG Patients (n = 30)</th>
<th>Non-OG Patients (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma sodium concentration, mmol/L</td>
<td>126 ± 6</td>
<td>125 ± 5</td>
</tr>
<tr>
<td>Plasma water content, %</td>
<td>93.8 ± 0.6</td>
<td>93.5 ± 0.5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Plasma potassium concentration, mmol/L</td>
<td>4.1 ± 0.8</td>
<td>3.9 ± 0.8</td>
</tr>
<tr>
<td>Plasma glucose concentration, mmol/L</td>
<td>7.6 ± 1.6</td>
<td>6.9 ± 1.7</td>
</tr>
<tr>
<td>Plasma urea concentration, mmol/L</td>
<td>10.7 ± 13.2</td>
<td>10.0 ± 8.9</td>
</tr>
<tr>
<td>Plasma creatinin concentration, µmol/L</td>
<td>110 ± 107</td>
<td>139 ± 165</td>
</tr>
<tr>
<td>Creatinin clearance, mL/min</td>
<td>71 ± 30</td>
<td>65 ± 52</td>
</tr>
<tr>
<td>Calculated plasma osmolality, mosm/kg</td>
<td>269 ± 20</td>
<td>267 ± 14</td>
</tr>
<tr>
<td>Measured plasma osmolality, mosm/kg</td>
<td>286 ± 20</td>
<td>271 ± 15&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Plasma osmolar gap, mosm/kg</td>
<td>17.2 ± 7.1</td>
<td>4.2 ± 3.7&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

OG, osmolar gap; ICU, intensive care unit.
<sup>a</sup>p = .05; <sup>b</sup>p < .01; <sup>c</sup>p < .0001. Results are expressed as mean ± SD.
Case 1 Conclusions

- Glucose “overcontributes” to the osmolality by 15%.
- Hyperglycemic Hyponatremia is a true hyponatremia and “corrections” should not be applied to the sodium for gap calculations.
- Amino acids and glycerol can contribute to Ogap in ketoacidosis.
- “Excess” Ogap in the critically ill may go to 30 mmol/kg.
Case 2

- 53 yo construction worker is drinking on the job.
- Drank 150-200 mL of unknown liquid contained in Gatorade bottle thinking that it was ethanol.
- Within 20 mins he had vomited and become unexpectedly drowsy.
- EHS called and arrives 30 mins after ingestion.
- GCS=5 - Intubation attempted on scene.
  - Failed.
Case 2

- GCS declines to 3 on scene.
- Arrives at ER 75 mins post-ingestion.
- HR 80; RR 16; BP= 94/67
- ++airway edema, organic solvent smell
  - combitube intubation
- BP dropped to 74/61 – inotrope infusion
- Coworker calls and identifies the substance as “ethylene glycol”.
- Fomepizole loading dose of 15 mg/kg given.
# Case 2 - Labs

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>140</td>
<td>135-145 mmol/L</td>
</tr>
<tr>
<td>K</td>
<td>3.7</td>
<td>3.5-5.0 mmol/L</td>
</tr>
<tr>
<td>Cl</td>
<td>110</td>
<td>95-107 mmol/L</td>
</tr>
<tr>
<td>CO₂</td>
<td>22</td>
<td>21-29 mmol/L</td>
</tr>
<tr>
<td>Glu</td>
<td>10.0</td>
<td>3.3-11.0 mmol/L</td>
</tr>
<tr>
<td>Cre</td>
<td>57</td>
<td>45-115 umol/L</td>
</tr>
<tr>
<td>Urea</td>
<td>3.8</td>
<td>2.0-8.2 mmol/L</td>
</tr>
<tr>
<td>EtOH</td>
<td>30</td>
<td>&lt;2 mmol/L</td>
</tr>
<tr>
<td>Lactate</td>
<td>2.8</td>
<td>0.5-1.6 mmol/L</td>
</tr>
</tbody>
</table>
## Case 2 – Labs on Admission

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agap</td>
<td>8</td>
<td>&lt;10 mmol/L</td>
</tr>
<tr>
<td>Osm</td>
<td>337</td>
<td>275-295 mmol/kg</td>
</tr>
<tr>
<td>OGap</td>
<td>7</td>
<td>&lt;10 mmol/kg</td>
</tr>
<tr>
<td>pH</td>
<td>7.31</td>
<td>7.35-7.45</td>
</tr>
<tr>
<td>pCO₂</td>
<td>43</td>
<td>35-45</td>
</tr>
<tr>
<td>pO₂</td>
<td>239</td>
<td>&gt;75</td>
</tr>
<tr>
<td>cHCO₃</td>
<td>21</td>
<td>21-25</td>
</tr>
</tbody>
</table>
Case 2 – Labs on Admission

- Ketones, MeOH, ethylene glycol, isopropanol, acetone all undetectable
- ASA/APAP undetectable
- MSDS Sheet was provided by coworker.
- Ingestion was 2-butoxyethanol also known as ethylene glycol monobutyl ether.
## Case 2: Labs – 10 hrs post admission

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGap</td>
<td>16</td>
<td>&lt;10 mmol/L</td>
</tr>
<tr>
<td>Osm</td>
<td>319</td>
<td>275-295 mmol/kg</td>
</tr>
<tr>
<td>OGap</td>
<td>15</td>
<td>&lt;10 mmol/kg</td>
</tr>
<tr>
<td>pH</td>
<td>7.20</td>
<td>7.35-7.45</td>
</tr>
<tr>
<td>pCO₂</td>
<td>27</td>
<td>35-45</td>
</tr>
<tr>
<td>pO₂</td>
<td>138</td>
<td>&gt;75</td>
</tr>
<tr>
<td>cHCO₃</td>
<td>10</td>
<td>21-25</td>
</tr>
</tbody>
</table>
Case 2

- Patient transferred to ICU
- pH hit a nadir of 7.16 and lactate climbed to 7.3 mmol/L, whereupon CVVHD was initiated.
- Dialysis led to rapid metabolic improvement – D/C after 24 h
- Patient extubated.
- Discharged with no sequelae.
2-butoxyethanol

- 2BE is a common additive to commercial cleaning fluids
- Ingestion is characterized by:
  - Hypotension
  - CNS depression
  - Metabolic acidosis
  - Elevation in transaminases
  - Renal injury and hematuria
  - DIC
  - ARDS
  - Hemolytic anemia – most often in animal models
2-butoxyethanol

- Under the action of alcohol dehydrogenase, 2BE is oxidized to 2-butoxyacetic acid which is renally excreted.
- Like other toxic alcohols this leads to metabolic acidosis.
2-butoxyethanol

- Reported management strategies for 2BE ingestion include:
  - EtOH infusion
  - Combination Ethanol/HD
  - Fomepizole
  - HD
- In this case pre-existing EtOH intoxication and fomepizole administration failed to prevent acidosis.
- GC-MS analysis of pt serum confirmed the presence of 2BE and the 2-butoxyacetic acid metabolite.

Case 2 Conclusions

- Features of the clinical presentation were inconsistent with the consumption of ethylene glycol:
  - Rapid obtundation/hypotension
  - Organic solvent smell
- Osmolar gap with toxic levels of 2BE may not lead to Ogap > 10 mmol/kg
- Immediate dialysis should lead to favourable outcome
Case 3

- 53 yo M
- Found down/seizing
- Known epileptic and alcoholic
  - non-compliant with Rx phenytoin
- 3 witnesses seizures by EHS
- Awake but confused
  - Transferred to ER
- In ER, 5 more seizures, ~15 s duration
  - 2 mg midazolam given
  - 1 g loading dose phenytoin given
Case 3

Numerous meds required to control seizures:

- From 2153h to 2218h given 9 mg lorazepam IV
- At 2223h given 1000 mg dilantin IV
- At 2310h given 2 gm MgSO$_4$ IV
- At 0130h given 15 mg diazepam IV
## Case 3 Labs at 2230h

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>146</td>
<td>135-145 mmol/L</td>
</tr>
<tr>
<td>K</td>
<td>3.4</td>
<td>3.6-4.7 mmol/L</td>
</tr>
<tr>
<td>Cl</td>
<td>121</td>
<td>110-112 mmol/L</td>
</tr>
<tr>
<td>TCO₂</td>
<td>19</td>
<td>22-31 mmol/L</td>
</tr>
<tr>
<td>Urea</td>
<td>2.4</td>
<td>2.5-8.0 mmol/L</td>
</tr>
<tr>
<td>Cre</td>
<td>53</td>
<td>60-100 umol/L</td>
</tr>
<tr>
<td>Glu</td>
<td>5.5</td>
<td>3.6-11.0 mmol/L</td>
</tr>
<tr>
<td>EtOH</td>
<td>54</td>
<td>&lt;2 mmol/L</td>
</tr>
<tr>
<td>Osm</td>
<td>434</td>
<td>281-297 mmol/kg</td>
</tr>
<tr>
<td>Ogap (EtOH accounted)</td>
<td>67</td>
<td>&lt;10 mmol/kg</td>
</tr>
<tr>
<td>Lactate/Ketones</td>
<td>Not Performed</td>
<td></td>
</tr>
<tr>
<td>ASA/APAP</td>
<td>Not Detected</td>
<td></td>
</tr>
</tbody>
</table>
Case 3

- Lab on-call is paged ~3:00 am
- Toxic alcohol coingestion?
- Repeat labs performed STAT
<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>145</td>
<td>135-145 mmol/L</td>
</tr>
<tr>
<td>K</td>
<td>4.3</td>
<td>3.6-4.7 mmol/L</td>
</tr>
<tr>
<td>Cl</td>
<td>114</td>
<td>110-112 mmol/L</td>
</tr>
<tr>
<td>TCO₂</td>
<td>21</td>
<td>22-31 mmol/L</td>
</tr>
<tr>
<td>Urea</td>
<td>2.6</td>
<td>2.5-8.0 mmol/L</td>
</tr>
<tr>
<td>Cre</td>
<td>67</td>
<td>60-100 umol/L</td>
</tr>
<tr>
<td>Glu</td>
<td>6.4</td>
<td>3.6-11.0 mmol/L</td>
</tr>
<tr>
<td>EtOH</td>
<td>16</td>
<td>&lt;2 mmol/L</td>
</tr>
<tr>
<td>Osm</td>
<td>320</td>
<td>281-297 mmol/kg</td>
</tr>
<tr>
<td>Ogap (EtOH accounted)</td>
<td>1</td>
<td>&lt;10 mmol/kg</td>
</tr>
</tbody>
</table>

I knew I shoulda taken that left turn at Albuquerque!
## Case 3

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.33</td>
<td>7.35-7.45</td>
</tr>
<tr>
<td>pCO$_2$</td>
<td>41 mm Hg</td>
<td>36-44 mmHg</td>
</tr>
<tr>
<td>pO$_2$</td>
<td>87 mm Hg</td>
<td>75 mm Hg</td>
</tr>
<tr>
<td>Lactate</td>
<td><strong>2.2</strong></td>
<td>0.5-2.1 mmol/L</td>
</tr>
</tbody>
</table>
Case 3

- Both sets of osmolality results repeated and both repeat correctly.
- What osmotically active substance has the ability to vanish so rapidly?
### Table 2
Commonly used intravenous drugs that contain propylene glycol.

<table>
<thead>
<tr>
<th>Drug and concentration</th>
<th>Amount of propylene glycol (% v/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lorazepam, 2 mg/ml</strong></td>
<td>80</td>
</tr>
<tr>
<td>Phenobarbital, 30–130 mg/ml</td>
<td>67.8–75.0</td>
</tr>
<tr>
<td><strong>Diazepam, 5 mg/ml</strong></td>
<td>40</td>
</tr>
<tr>
<td>Pentobarbital, 50 mg/ml</td>
<td>20–40</td>
</tr>
<tr>
<td><strong>Phenytoin, 50 mg/ml</strong></td>
<td>40</td>
</tr>
<tr>
<td>Trimethoprim–sulfamethoxazole, 16 mg/ml:80 mg/ml</td>
<td>40</td>
</tr>
<tr>
<td>Etomidate, 2 mg/ml</td>
<td>35</td>
</tr>
<tr>
<td>Nitroglycerin, 5 mg/ml</td>
<td>30</td>
</tr>
<tr>
<td>Esmolol, 250 mg/ml</td>
<td>25</td>
</tr>
</tbody>
</table>

Adapted with permission from Lippincott Williams & Wilkins © Arroliga AC et al. (2004) Relationship of continuous infusion lorazepam to serum propylene glycol concentration in critically ill adults. *Crit Care Med* **32**: 1709–1714.²

Abbreviation: v/v, volume/volume.
Case 3 - Chromatography

Propylene Glycol = 72 mmol/L

---

Internal Standard Report

Sorted By: Retention Time
Calib. Data Modified: 17/02/2010 1:57:09 PM
Multiplier: 1.0000
Dilution: 1.0000

Use Multiplier & Dilution Factor with ISTDs

Sample ISTD Information:

<table>
<thead>
<tr>
<th>ISTD</th>
<th>ISTD Amount</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.00000</td>
<td>ISTD</td>
</tr>
</tbody>
</table>

Signal 1: FID1 A,

<table>
<thead>
<tr>
<th>RetTime</th>
<th>Sig Type</th>
<th>Height</th>
<th>Amt/Height ratio</th>
<th>Amount [MMOL/L]</th>
<th>Grp</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.726</td>
<td>1 BB+</td>
<td>347.48480</td>
<td>3.30397</td>
<td>71.57531</td>
<td></td>
<td>PROPGLY</td>
</tr>
<tr>
<td>1.945</td>
<td>1 BP+I</td>
<td>16.04016</td>
<td>1.00000</td>
<td>1.00000</td>
<td>ISTD</td>
<td>ISTD</td>
</tr>
</tbody>
</table>

Totals without ISTD(s): 71.57531

Results obtained with enhanced integrator!
Propylene Glycol

- Common Drug adjuvant in benzodiazepines, barbiturates, phenytoin, trimethoprim-sulfamethoxazole, and Etomidate
- Metabolized by ADH to D and L Lactate
- $t_{1/2} = 1.4-3.3 \text{h}$
Propylene Glycol

- Oil dispersant
- Emulsification agent
- Moisturizer
  - cosmetics, massage oil, shampoo
- Low-toxicity antifreeze
- Coolant
- Artificial fog solution
Propylene Glycol

- Generally considered a safe compound but there are multiple reports of iatrogenic toxicity by
  - Lorazepam infusion
    - Even with concomitant CVVHD
  - Diazepam infusion
  - Etomidate infusion
  - Trimethoprim/Sulfamethoxazole
  - Ingestion
- Toxicity possible at levels > 100 mg/dL = 13 mmol/L.
Toxicity

- Reported morbidity
  - D-lactic acidosis\(^1\)
  - L-lactic acidosis\(^2,3\)
    - Usually mild: 2-6 mmol/L
  - Acute kidney injury requiring HD\(^4\)
    - Renal function will not necessarily recover\(^5\)
  - Chronic polyneuropathy/myopathy\(^5\)
  - Seizures\(^6\)
  - Hemolysis
  - Cardiorespiratory arrest (topical!)\(^7\)

Management

- Treatment is usually simply to withdraw the causative medication.
  - Can be avoided by ensuring the PG infusion is less than 0.29-2.9 g/h\(^1\).
- In cases of: renal failure, very high serum propylene glycol levels, or severe metabolic acidosis, dialysis is warranted.

Something does not make sense.

- Level of OGap=67 mmol/kg and PG=72 mmol/L at midnight and OGap=1 mmol/kg at 3 am.
  - But the half life is 1.4-3.3h.
  - And the half-life is extended in the presence of EtOH.
  - Further, the patient did not develop lactic acidosis or any other metabolic abn.

What gives?
The midnight specimen was actually contaminated with propylene glycol.

In fact, the phenytoin level on the midnight specimen required multiple dilutions to obtain a meaningful result:

- Phenytoin: 1380 [40-80] umol/L

This suggests that the phenytoin infusion was the cause of the whole debacle:

- Phentoin levels > 200 umol/L lead to coma and seizures.
Case 3 Conclusions

- Propylene glycol is a common carrier agent for a number of drugs with low toxicity.
- In cases of continuous infusion of high doses of these drugs, toxicity is reported:
  - L and D lactic acidosis
  - Acute kidney injury
  - Seizures/Neuropathy/Myopathy (rare)
Conclusion

- It’s not all ethylene glycol and methanol.
- You have to be circumspect with serum and solvents.
Questions?