3.5: Osmolar Gap

Note

'Osmolar gap' has several alternative names: 'osmol gap', 'osmole gap', 'osmolarity gap' & 'osmolal gap'; these all refer to the same thing. For consistency, the term "osmolar gap" is used exclusively through this book.

3.5.1: What is the 'osmolar gap'?

Definitions

- An **osmole** is the amount of a substance that yields, in ideal solution, that number of particles (Avogadro's number) that would depress the freezing point of the solvent by 1.86K
- **Osmalality** of a solution is the number of osmoles of solute per kilogram of solvent.
- **Osmolarity** of a solution is the number of osmoles of solute per litre of solution.

So osmalality is a measure of the number of particles present in a unit weight of solvent. It is independent of the size, shape or weight of the particles. It can only be measured by use of a property of the solution that is dependent on the particle concentration. These properties are collectively referred to as **Colligative Properties**. Osmalality is measured in the laboratory by machines called osmometers. The units of osmalality are mOsm/kg of solute

Osmalality is calculated from a formula which represents the solutes which under ordinary circumstances contribute nearly all of the osmalality of the sample. There are many such formulae which have been used. One widely used formula for plasma which is used at my hospital is:

\[
\text{Calculated osmolarity} = (1.86 \times [Na^+]^+) + [text (glucose)] + [text (urea)] + 9 \text{label(osmolarity)}
\]
Regarding units

For the Equation \ref{osmolarity}, all concentrations are in mmol/l, and not mg/100mls. The result will then be in mOsm/l of solution. This equation is often expressed differently in North America where glucose & blood urea nitrogen (BUN) are reported in mg/dl. This version is essentially identical as it just includes conversion factors to convert mg/dl to mmol/l:

\[
\text{Calculated osmolarity} = (1.86 \times [Na^+]) + \frac{\text{glucose}}{18} + \frac{\text{BUN}}{2.8} + 9
\]

This formula become popular after a study (by Dorwart & Chambers) comparing 13 different formulae found this one to yield the most accurate results.

What level of osmolar gap is "abnormal"?

An osmolar gap > 10 mOsm/l is often stated to be abnormal. The support for this contention is poor. One study (Hoffman RS et al, 1993) suggested the use of this formula:

\[
\text{Calculated osmolarity} = (2 \times [Na^+]) + \frac{\text{glucose}}{18} + \frac{\text{BUN}}{18} + \frac{\text{ethanol}}{4.6}
\]

They found a mean osmolar gap of 2.2 with SD 5.5 mOsm/l. The 95% range (mean +/- 2SD) was -14 to +10. This study is probably the basis for the >10 value as being abnormal. The range for normal values is very dependent on the particular formula that is used.

Osmolarity is easy to calculate because it only requires the measurement of 3 substances and these are routinely measured in every hospital biochemistry laboratory. Its calculation is usually programmed into the biochemistry autoanalyser and is routinely printed on the standard result sheet and is available to you even without having to ask.

The osmolar gap is the difference between the 2 values: the osmolality (which is measured) and the osmolarity (which is calculated from measured solute concentrations).

\[
\text{Osmolar gap} = \text{Osmolality} - \text{Osmolarity}
\]

In healthy persons, the osmolar gap is small as the osmolarity (calculated using the formula above) is a fairly good estimate of the osmolality. But in some conditions, there are significant amounts of abnormal substances present which contribute to the total osmolality and then the osmolarity will underestimate the osmolality. Consequently the osmolar gap will necessarily be increased. A given concentration of abnormal other solutes (in mg/dl) will contribute more particles (mOsm/kg) if they have a low molecular weight. It follows then that if the osmolar gap is significantly elevated, this provides indirect evidence that there must be a significant concentration of one or more low molecular substances present. It does not identify these abnormal solutes but alerts you to their presence.

A minor point for completeness: The units of osmolality (mOsm/kg) and osmolarity (mOsm/litre) are different so strictly they cannot be subtracted from one another. That said though, the value of the difference is clinically useful so this problem will be ignored.
3.5.2: Type of Osmometer

You MUST check the type of osmometer used by your hospital

The osmolality is measured in the pathology laboratory using an instrument called an osmometer which uses one of the colligative properties as the basis for its measurement.

Currently available osmometers fall into 2 groups:

- Those using the colligative property of freezing point depression
- Those using the colligative property of vapour pressure depression.

Only osmometers using freezing point depression method should be used

Why? Because they are the only type of osmometer that can detect all the volatile alcohols which can abnormally increase the osmolar gap. The other type of osmometer cannot do this. An explanation for this difference is:

"Vapor pressure osmometry, in contrast to osmometry using the freezing point depression method, requires an equilibrium between vapor and liquid phases and is unreliable when volatile chemicals such as ethanol and methanol are present because these chemicals tend to remain in the vapor phase" (from Glaser, 1996)

You must check what type your pathology laboratory is using otherwise you will be misled by spuriously normal osmolar gap results.

3.5.3: What is the meaning & usefulness of a high osmolar gap?

An elevated osmolar gap provides indirect evidence for the presence of an abnormal solute which is present in significant amounts. To have much effect on the osmolar gap, the substance needs to have a low molecular weight and be uncharged so it can be present in a concentration (measured in mmol/l) sufficient to elevate the osmolar gap.

Ethanol, methanol, ethylene glycol (used in anti-freeze solutions), isopropanol, and propylene glycol (used as a vehicle with some drugs e.g. lorazepam) are solutes that cause an elevated osmolar gap. If you suspect that your patient may have ingested one of these substances than, as a screening tool, you should determine the osmolar gap. (See Lynd et al, and Krasowski et al.) This testing is readily available in hospitals. Apart from ethanol levels, determination of the levels of other toxic glycols and alcohols is much less commonly available in pathology laboratories.

Main Use of Osmolar gap: Screening test for detecting abnormal low MW solutes

Ethylene glycol is used as an anti-freeze in car radiators.

Osmolar Gap: Use with Caution

Important reservations need to be made about the clinical utility of the osmolar gap, in particular:
- Its calculation depends on measurement of three substances and an osmolality measurement, so the error is the sum of the errors of all these measurements
- Many formulae are available to calculate osmolarity and the calculated value varies significantly depending on which one is used
- The osmolar gap has a wide normal range in the population
- The osmolar gap may be normal with ethylene glycol ingestion because of its higher MW (in comparison to methanol). The sensitivity of the test in detecting toxic ingestion of ethylene glycol is not high
- As ethylene glycol and methanol are metabolised, the osmolar gap decreases (and the anion gap increases) so a 'normal' value is more likely if the patient presents late.

**Ethanol Cloaking: A Practical Problem**

An elevated osmolar gap indicates an unknown solute but does not identify it. It is important to follow-up and determine what substance (or substances) is responsible. As an example, consider the following situation:

Consider a patient who has ingested ethanol as well as ethylene glycol or methanol. The ethanol will increase the osmolar gap and you can miss the presence of the more toxic substances if you make the assumption that the gap is due to the ethanol alone. This mistake could have serious adverse consequences for the patient.

**Solution 1:** For this reason, it is advisable to request an ethanol level whenever you request a measured osmolality. You can then correct the osmolar gap for any ethanol present and determine a 'corrected' osmolar gap. This approach is generally readily available in hospitals and has the advantage of indirectly detecting the presence of ANY other such low molecular weight toxin and not just ethanol. You won't know what this other solute is yet but your suspicions are raised and you can proceed to more specific analyses.

**Note**

To convert ethanol levels in mg/dl to mmol/l divide by 4.6. For example, an ethanol level of 0.05% is 50mg/dl. Divide by 4.6 gives 10.9mmols/l

**Solution 2:** Another way to sort this out is if there is clinical suspicion AND your laboratory has the facilities, is to request specific assays for methanol or ethylene glycol. However, depending on the technique your laboratory uses, you may or may not detect other rare ingestions. You can miss the specific toxins that you are trying to measure if time has passed and they have already been extensively metabolised to their toxic products. In this latter case, you would be misled as to the toxic potential lurking in your patient.

The problem with this solution is that many laboratories do not measure these levels so your specimen may need to be sent to a distant large laboratory. The method used in our referring lab is a gas chromatographic separation followed by a mass spectroscopic detection. This is labour intensive and time consuming so the laboratory adds an additional layer of the need to discuss the case with a chemical pathologist before the analysis is agreed to. Only about 15% of requests get through this step in our local experience.
References


