3.2: The Anion Gap

The anion gap (AG) represents the concentration of all the unmeasured anions in the plasma. The negatively charged proteins account for about 10% of plasma anions and make up the majority of the unmeasured anion represented by the anion gap under normal circumstances. The acid anions (e.g., lactate, acetoacetate, sulfate) produced during a metabolic acidosis are not measured as part of the usual laboratory biochemical profile. The $H^+$ produced reacts with bicarbonate anions (buffering) and the $\ce{CO2}$ produced is excreted via the lungs (respiratory compensation). The net effect is a decrease in the concentration of measured anions (i.e., $\ce{HCO3^-}$) and an increase in the concentration of unmeasured anions (the acid anions) so the anion gap increases.

AG is calculated from the following formula:

$$\text{Anion Gap} = [\ce{Na^{+}}] - [\ce{Cl^{-}}] - [\ce{HCO_{3}^{-}}]$$

Reference range is 8 to 16 mmol/l. An alternative formula which includes $[\ce{K^+}]$ is sometimes used particularly by Nephrologists. In Renal Units, $[\ce{K^+}]$ can vary over a wider range and have more effect on the measured Anion Gap. This alternative formula is:

$$\text{AG} = [\ce{Na^{+}}] + [\ce{K^{+}}] - [\ce{Cl^{-}}] - [\ce{HCO_{3}^{-}}]$$

The reference range is slightly higher with this alternative formula. The $[\ce{K^{+}}]$ is low relative to the other three ions and it typically does not change much so omitting it from the equation does not have much clinical significance.

Major Clinical Uses of the Anion Gap

- To signal the presence of a metabolic acidosis and confirm other findings
• Help differentiate between causes of a metabolic acidosis: high anion gap versus normal anion gap metabolic acidosis. In an inorganic metabolic acidosis (eg due to HCl infusion), the infused Cl\(^-\) replaces HCO\(_3\)\(^-\) and the anion gap remains normal. In an organic acidosis, the lost bicarbonate is replaced by the acid anion which is not normally measured. This means that the AG is increased.

• To assist in assessing the biochemical severity of the acidosis and follow the response to treatment

It is determined from a calculation involving three other measured ions, so the error with an AG is much higher than that of a single electrolyte determination. The commonest cause of a low anion gap is laboratory error in the electrolyte determinations. The 95% error range for the AG is about +/− 5 mmol/l (i.e., a 10 mmols/l range!)

• If the AG is greater than 30 mmol/l, than it invariably means that a metabolic acidosis is present.

• If the AG is in the range 20 to 29 mmol/l, then about one third of these patients will not have a metabolic acidosis.

Other clinical guides should also be used in deciding on the presence and severity of a metabolic acidosis. Significant lactic acidosis may be associated with an anion gap which remains in the reference range. Lactate levels of 5 to 10 mmols/litre are associated with a high mortality if associated with sepsis, but the AG may be reported as within the reference range in as many as 50% of these cases! (Dorwart & Chalmers 1975) (See also discussion in Section 8.4 regarding lactate-chloride antiport.)

The anion gap is useful especially if very elevated or used to confirm other findings. Causes of a high anion gap acidosis can be sorted out more specifically by using other investigations in addition to the history and examination of the patient. Investigations which may be very useful are:

• Lactate
• Creatinine
• Plasma glucose
• Urine ketone test

Key Fact: Hypoalbuminaemia causes a low anion gap

Albumin is the major unmeasured anion and contributes almost the whole of the value of the anion gap. Every one gram decrease in albumin will decrease anion gap by 2.5 to 3 mmoles. A normally high anion gap acidosis in a patient with hypoalbuminaemia may appear as a normal anion gap acidosis. This is particularly relevant in Intensive Care patients where lower albumin levels are common. A lactic acidosis in a hypoalbuminaemic ICU patient will commonly be associated with a normal anion gap.


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