Using the Strong Ion Gap to Interpret Acid-Base Status

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Blood gas analysis and assessment of electrolytes and acid-base balance provide a broad view of your patient's metabolic 'landscape', giving you insight into lung function and primary and secondary disturbances of regulation of many substances in the body. The gas pressure of oxygen (pO_2) in the arterial blood tells you about lung function and the pO_2 in venous blood tells you something about oxygen delivery to the tissues served by that vein. The gas pressure of carbon dioxide (pCO_2) defines ventilation. Analysis of electrolyte and hydrogen ion concentration (pH) provide insight into many different primary disorders, and their concentrations have direct effects on metabolic function.

Blood gas analysis gives you quick quantification of problems (hypoxemia, ventilation failure, marked abnormalities of hydrogen ion concentration) that may require intervention to stabilize the animal. With this information we can often do a decent job of symptomatically restoring pO_2, pCO_2, and hydrogen ion concentration back to normal ranges with oxygen, ventilation assistance, and electrolyte administration. Assuming one is capable of providing that symptomatic support, it turns out that the *reason(s)* for those abnormalities often has more bearing on the final outcome for your patient. So for lung function disorders, hypoxemia caused by pneumonia or metastatic cancer has different consequences than hypoxemia caused by acute lung injury from other causes. Similarly, disorders of acid-base balance with abnormal hydrogen ion concentration are quite varied, and the prognosis for people or animals with hyperchloremic acidemia from diarrhea may be quite different from patients with an identical pH abnormality due to accumulation of acetate and citrate during hemorrhagic shock.

In this presentation I am going to completely ignore interpretation of oxygenation of the blood and will mention ventilation only so far as to remind you that blood gas analyzers calculate bicarbonate concentration from pH and pCO2. We will focus on the non-respiratory causes of abnormalities of hydrogen ion concentration and take a look at different methods of quantifying the things that contribute to it.

A bit of history (really, it's relevant!): In 1908 Lawrence J. Henderson was the first to characterize the relationship between hydrogen ion concentration, bicarbonate, and dissolved carbon dioxide in solutions expressed as:

$$[H^+] * [HCO_3^-] = K * [H_2CO_3], \text{ where K is a dissociation constant.}$$

The value of K can be solved for by rearranging to:

$$K = [H^+] * [HCO_3^-]/[H_2CO_3],$$

and since the concentration of carbonic acid $[H_2CO_3]$ is roughly 0.03 mmol per mm Hg of carbon dioxide gas, the formula can be expressed as (*stay with me here!*):

$$K = [H^+] * [HCO_3^-]/(0.03 * pCO_2)$$

The classic approach for characterizing acid-base balance brought us the concept of pH, a unit-less 1909 invention of chemist Søren Peter Lauritz Sørensen and adapted by the Danish physician Karl Albert Hasselbalch to express Henderson's formula as the base 10 logarithm. When solved for the negative log of hydrogen ion concentration (*we're almost there!)* to give us the familiar, if confusing, formula:

$$pH = pK + \log(\text{base}/\text{acid}),$$

and in the case of the carbonic acid-hydrogen+bicarbonate pairing this is expressed as:

$$pH = 6.1 + \log([HCO3]/.03 * pCO_2).$$

Why bother describing this? There are at least a couple of consequences of thinking about acid-base balance in terms of this logarithmic equation. For one, it lets you forget that when we talk about hydrogen ion concentration we are talking about TINY concentrations compared to other electrolytes: for every hydrogen ion in the extracellular fluid of a normal dog there are about 3.5 MILLION sodium ions (which should tell you there is no such thing as a 'direct' cell membrane sodium-hydrogen exchange pump). For another, the formula gives the misleading impression that acid-base balance is "tightly controlled", when in fact a change of 0.3 pH units (for example from 7.5 to 7.2) is equivalent to a *doubling* of hydrogen ion concentration (from 40 to 80 nanomoles/L) – not a very tight control at all. And finally, it gives the impression that acid-base balance – hydrogen ion concentration – is determined by control of PCO_2 and bicarbonate concentrations, when in fact bicarbonate is a dependent factor whose concentration is neither sensed nor manipulated by the body. This last point is where I am heading, because paying attention to the things that DO affect hydrogen ion concentration gives you more insight into what's going on and what to do.

So how do you measure acid base?

Quantifying acid-base disorders has come within reach to emergency, 24-hour, and specialty hospitals as well as primary care clinics that manage significant numbers of sick hospitalized patients. A number of analyzers are available including the VetScan i-STAT 1 Analyzer (Abaxis), the VitalPath Blood Gas & Electrolyte Analyzer (Heska), the epoc Veterinary Portable Blood Gas Electrolyte and Critical Care Analyzer (Epocal), and the VetStat Electrolyte and Blood Gas Analyzer (IDEXX). There are many other machines designed for higher volume users; for example Gem Premiere series, Nova's pHOx Ultra, and Radiometer's ABL800 Flex.

What determines acid-base balance?

Three things

The respiratory system

The concentration of "strong" ions (Na, Cl, K, Ca, Mg, sulfate, lactate, and others)

The concentration of "weak" ions, which in biology are weak acids, and tend not to dissociate as strongly as the "strong" guys. In healthy animals this is mostly protein (and 70% of the activity is from albumin) and phosphate).

Now some details about these 3 actors: Respiratory system function - ventilation - is *defined* by pCO_2. The effect of carbon dioxide gas pressure on acid-base balance is direct, consistent, linear, and straightforward. When dogs have a primary metabolic (nonrespiratory) disturbance in hydrogen ion, they should react by increasing or decreasing their ventilation to adjust hydrogen ion concentration back towards normal, and they do this by a reasonably predictable amount. "Strong ions" are the charged particles that result from dissolving salts in water. These particles are charged AND they aren't reactive – that is, they do not bind with oppositely charged things and exist all alone because at physiological pH they are highly dissociated and they carry about their business hydrated by surrounding water molecules. In biology most of them are also electrolytes, the components of salts that conduct electricity in solution. "Weak ions", are mostly weak acids whose pK (the pH at which the compound is 50% dissociated) is within a single pH unit of 7.4. So, the ability of these compounds to carry or release a proton isn't constant and varies with the pH of the solution (body fluid). Hydrogen ions are provided by the dissociation of water into H+ and OH-, and the concentration of these two is determined by the concentration of all the other charged ions in the solution.

By the law of electroneutrality, the concentration of positively charged ions in solution in water has to equal the concentration of negatively charged ions. Because it is the relative concentration of these that determines hydrogen ion concentration, we can use the readings from chemistry panel to get some insights into the cause of acid-base disturbances! So, in extracellular fluid (sampled as plasma):

[all the cations] = [all the anions]

We commonly measure some of these and the formula can be expanded to:

[Na] + [K] + [all the *other* cations] = [Cl] + [HCO3] + [all the *other* anions]

If you switch things around a bit we get:

[Na] + [K] - [Cl] - [HCO3] = [all the *other* anions] - [all the *other* cations]

And this is the classic formula for the Anion Gap. So when you see a measurement of anion gap, you are looking at an estimate of the result of subtracting the "unmeasured" cation activity from "unmeasured" anion activity, arrived at by subtracting the concentration of chloride and bicarbonate ions from the cations sodium and potassium. The word "unmeasured" is in quotes because some of them are in fact measured on your chemistry profile (calcium, phosphate, magnesium, lactate) or could be measured if specially requested (sulphate, urate, beta-hydroxybutyrate). Some – albumin and total protein- are always measured but we didn't know what to do with them because their ionic activity is complex was unknown until recently.

Why is this gap important? It's because many metabolic disturbances are brought about by the addition or retention of compounds that are anions or (less often) cations, and an accurate accounting of them helps with diagnosis (when the added substances are markers of specific disorders), treatment (when identification of substances leads to specific therapies), or prognosis (when the presence of increased or decreased concentrations of individual substances corresponds to severity of illness.

Have you noticed that laboratories provide a pretty big range of normal values for the anion gap that is pretty wide? The reason for this is that the concentration of chloride relative to sodium is affected by water balance, and also because there is a wide range of normal concentration for protein and phosphorus, two anions with more complex charge behavior that depends on the current pH. Therefore, major changes in the system, like the addition of large amounts of an organic anion can be easily hidden by low or lowish albumin and/or phosphorus, and major deviations in chloride relative to sodium happen secondary to changes in water balance. In the last 20 years several methods have been introduced in an attempt to "tighten up" the anion gap concept to make it a more sensitive instrument for detecting the presence of ions that shouldn't be there.

Quantitative chemistry: Modifications of the anion gap

This brings us to the point of the presentation: we now have some means to factor in these "unmeasured" ions into the anion gap to look for evidence that they are in fact players for individual patients with metabolic acid-base disorders. The anion gap formula can be adjusted for albumin or total protein:

Albumin-adjusted AG: AG + 0.42 X (37.7 - [albumin])

Total protein–adjusted AG: AG + 0.25 X (63.7 - [total protein]),

where albumin or total protein are expressed as grams/liter (multiply the reported gm/dl values by 10).

These can be further refined by adding in phosphate:

Albumin-adjusted AG: AG + 0.42 X (37.7 - [albumin]) + 1.4 X (1.8 – [phosphate])

TP–adjusted AG: AG + .25 X (63.7 - [total protein]) + 1.4 X (1.8 – [phosphate]),

where phosphate is expressed as mmols/liter (to get mmols/liter, multiply the mg/dl value by .3229).

An adjusted anion gap that lies outside of the laboratory reference range for normal dogs provides more specific evidence that unmeasured anions are present when albumin or phosphate is abnormal. However, the modified AG does not take into account the effects of water balance or the effect of pH on the ionic activities of protein and phosphorus; this is partially addressed by the…

Base excess gap

Another approach has been to combine the approaches of Siggaard-Andersen (base excess) with Stewart (quantification of strong ions) by partitioning the base excess measurement into four 'physical chemical' components:

- The contribution of free water
- The effect of plasma [Cl]
- The plasma albumin and phosphate concentrations
- Unmeasured anions.

Although this approach is somewhat limited by the use of a fixed, linear approximation of the activity of albumin it does allow for more sensitive identification of contributors to a base excess or deficit. In the presentation I will give you a link to an Excel based calculator I created that does these calculations for you; patient values are entered on the first worksheet and dog or cat results are summarized on their respective pages.

The strong ion gap (SIG)

McCullough and Constable went a step further than this by using a quantitative chemistry approach to determine the presence of unmeasured anions in cats and dogs, respectively. From their work, simplified formulas to identify the presence of unmeasured ions are based on the concept that the net positive charge derived from strong ions (Na + K + 2Ca + 2Mg – Cl – lactate) is balanced electrically by the anion activity of albumin, total protein, and phosphorus. If phosphorus concentration is not markedly abnormal, convenient (well, convenient if you have a scientific calculator!) formulas to estimate SIG based only on the pH-dependent anion activity of albumin and the results of a standard chemistry profile are, for the dog:

$$SIG = [albumin] \times (0.348 + 0.469/\{1 + 10^{\wedge(7.77-pH)}\}) - AG$$

(suggested normal range = 0 +/- 5) or

$$SIG = [TP] \times (0.206 + 0.273/1 + 10^{\wedge(7.77-pH)}\}) - AG$$

(suggested normal = 0 +/- 6)

and for cats:

$$SIG = [albumin] \times (0.76/\{1 + 10^{\wedge(7.17-pH)}\}) - AG + 9$$

(suggested normal = 0 +/- 5).

For dogs, if you do not have a blood gas machine and assume that pH and $[PO_4]$ are close to normal, the SIG formula may be reduced to:

SIG = [albumin] X 0.49 – AG or SIG = [TP] x 0.29 – AG

For all of these the SIG is expressed in mEq/L, the albumin or TP concentration is in Grams/L, and the AG is in mEq/L. Values that lie below the lower limit of the suggested normal range (- 5 or -6 depending on whether using albumin or TP) suggests the presence of excess unmeasured anions, and values > than the upper limits (+5 or +6) suggest the presence of unmeasured cations, a relatively rare event. The presence of unmeasured anion in the absence of obvious cause (shock, ketoacidosis, uremia) should prompt further investigation into the cause. For the presentation I will demonstrate the use of these tools on several case examples.

References

McCullough SM, Constable PD (2003), Calculation of the total plasma concentration of nonvolatile weak acids and the effective dissociation constant of nonvolatile buffers in plasma for use in the strong ion approach to acid-base balance in cats, American Journal of Veterinary Research 64: 1047-1051

Constable PD, Stampfli HR (2005), Experimental determination of net protein charge and A(tot) and K(a) of nonvolatile buffers in canine plasma, J.Vet.Intern.Med 19: 507-514