Basic sciences review

Strong Ion Difference: A New Paradigm or New Clothes for the Acid-Base Emperor

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ABSTRACT

Objective: *To review and compare the 'metabolic' component of an acid-base abnormality by assessing the arterial blood bicarbonate and the 'strong ion difference'*

Data sources: *A review of published peer-review articles and studies reported from 1983 to 1999 and identified through a MEDLINE search on 'strong ion difference'*

Summary of review: *The Henderson-Hasselbalch equation describes the simple relationship between the arterial pH, $PaCO_2$ and bicarbonate concentration (HCO_3^-), and has been used by clinicians to classify acid-base abnormalities as either respiratory or a non-respiratory (i.e. metabolic). However, as the HCO_3^- concentration cannot be measured directly and as it can also be altered by an alteration in the $PaCO_2$, derived values such as the standard bicarbonate, buffer base, base excess and standard base excess have been proposed to assess the true 'metabolic' acid-base component.*

Recently, an analysis of acid-base has been reported based on the law of electroneutrality in aqueous solutions, in which it is proposed that the independent variables of 'strong ions' (e.g. sodium, potassium, calcium, magnesium, chloride and organic anions), CO_2 and non volatile weak acids (i.e. A_{TOT}) alter the dependent variables of pH and HCO_3^-. The concept of 'strong ion difference' (SID) is used to help explain 'metabolic' acid base abnormalities, particularly those associated with saline infusions.

The relationship between the HCO_3^- ion and the SID can be represented as $HCO_3^- = (SID - A^-)$ and the Henderson Hasselbalch equation can be written as $pH \propto (SID - A^-)/PaCO_2$ although, the body regulates pH by regulating the $PaCO_2$ and HCO_3^-, rather than by regulating the SID or A_{TOT}

Conclusions: *In man the renal and respiratory systems regulate acid-base homeostasis by modifying the bicarbonate buffer pair (i.e. PCO_2 and HCO_3^-), with all other body buffer systems adjusting to alterations in this pair. To maintain electrical neutrality there is a change in cation concentration commensurate with the change in bicarbonate concentration.* (**Critical Care and Resuscitation 1999; 1: 211-214**)

Key words: Acid-base, Stewart analysis, standard base excess, strong ion difference, infusion acidosis

An acid-base defect is commonly assessed by considering the arterial blood values of pH as a measure of the intensity of acidity or alkalinity, $PaCO_2$ as a measure of the respiratory component, and HCO_3^- as a measure of the non-respiratory (i.e. metabolic) component.[1]

However, the assessment of the metabolic component using the bicarbonate concentration, has some limitations. While arterial blood pH and $PaCO_2$ may be measured directly, there is no direct method to measure the HCO_3^- concentration. During blood gas analysis it is calculated from the Henderson-Hasselbalch equation

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(i.e. HCO_3^- = 0.0306 x $PaCO_2$ x $10^{(pH - pKa)}$) with the assumptions that the dissociation constant of carbonic acid (i.e. pKa) is 6.10, there is chemical equilibrium and 0.0306 mmol of carbon dioxide dissolves in plasma per mmHg.

While the pKa varies with plasma pH, temperature and ionic strength,[2] in normal subjects and in the acutely ill patient[3] the range is narrow and varies little from 6.10,[2] chemical equilibrium occurs within seconds,[4] and the variation in dissolved carbon dioxide (due largely to changes with temperature) is small. The calculated HCO_3^- concentration can also be checked with the plasma biochemical analysis of 'total CO_2', with 95% of the 'total CO_2' value being due to HCO_3^- (the remaining 5% is due to dissolved CO_2 and carbamino compounds) and is almost never more than 3 mmol/L greater than the calculated value, for blood taken from the same vascular compartment.[5]

Although the problems of measurement may be small, there are problems relating to the validity of a change in HCO_3^- as an index of the metabolic acid-base abnormality, as its concentration will also change with a change in $PaCO_2$. For example, in the absence of a metabolic acid-base defect, for each 10 mmHg acute rise in $PaCO_2$ above 40 mmHg, the arterial blood HCO_3^- increases by approximately 1 mmol/L, and for each 10 mmHg decrease below 40 mmHg the arterial blood HCO_3^- falls by approximately 2.5 mmol/L.[6]

Using these rules of thumb one may correct the calculated arterial plasma HCO_3^- to a $PaCO_2$ of 40 mmHg, with the difference between the corrected HCO_3^- and 24 (i.e. the normal level of calculated HCO_3^- at a pH of 7.4 and $PaCO_2$ 40 mmHg) being due to (in the absence of chronic hypocapnia or chronic hypercapnia) a metabolic acidosis or alkalosis (within $\pm$ 3 mmol/L).[6]

This metabolic acid-base component may also be assessed by deriving the 'standard base excess' using an equation with correction factors that approximate the buffering effect of the extracellular fluid.[7,8] If the standard base excess is negative (in the absence of chronic hypocapnia) a metabolic acidosis exists, when positive (in the absence of chronic hypercapnia) a metabolic alkalosis exists, and if zero any change in the calculated arterial plasma HCO_3^- is caused by an increase or decrease in the $PaCO_2$ (within $\pm$ 3 mmol/L). While other derived indices have also been used to separate the respiratory from metabolic changes of the HCO_3^- (e.g. standard bicarbonate and buffer base) these are no longer used, as they have no greater value compared with standard base excess.

With these considerations in mind the Henderson-Hasselbalch equation is useful, as it illustrates the simple relationship between the variables (e.g. pH $\propto$ HCO_3^- /$PaCO_2$) and how a change in ether $PaCO_2$ or HCO_3^- can alter the pH. The clinical defect is divided into a respiratory or metabolic acidosis or alkalosis (with or without compensation), with the additional calculation of the anion gap allowing one to determine whether there is an obvious anion or non-anion gap acidosis.[6] For the clinician the disorder can be easily typified and appropriately managed.

While this approach to acid-base had remained unchanged and unchallenged for many years, interest has re-emerged in acid-base physiology due largely to the sporadic clinical reports of an increase in plasma chloride and reduction in bicarbonate concentration (and pH) in a patient who has been resuscitated using a large volume of saline.[9,10] The proposal that saline reduces the pH by altering the 'strong ion concentration', is defended by those who use the relatively recent Stewart analysis to explain acid base.[11]

Stewart analysis

The Stewart analysis is based on the law of electroneutrality in aqueous solutions, where the total number of cations must equal the total number of anions.[12,13] The central tenet to the analysis is that only the independent variables, which are strong ions (e.g. sodium, potassium, calcium, magnesium, chloride and organic anions), PCO_2 and the non-volatile weak acids (A_{TOT} which are predominantly the albuminate ions), can change acid-base status, as they change the dependent variables of H^+ and HCO_3^- to maintain electrical neutrality.

The metabolic acid-base abnormality is characterised by calculating the strong-ion difference (or SID = $[Na^+ + K^+ + Ca^{2+} + Mg^{2+}] - [Cl^- + lactate]$); a value which is essentially equal to the sum of the bicarbonate and albuminate ions[14] and similar to the buffer base described by Singer and Hastings 50 years ago.[14-16]

Physical chemistry considerations

However the idea that the post perfusion change in pH is caused by an alteration in a chloride ion concentration has caused some confusion, as it implies that the chloride ion is an acid, an issue that was resolved more than 75 years ago by Brønsted[17] and Lowry,[18] who redefined an acid as a proton (or H^+) donor, and a base as a proton (or H^+) acceptor.

To put it simply, if one starts from the fact that pure H_2O dissociates to form H^+ and OH^-, a dissociation which is temperature dependent (e.g. at 25°C the pH is 7 and at 37°C the pH is 6.8), water is neutral (i.e. H^+ = OH^-) at all temperatures.[19] The addition of 0.9% NaCl will not change its pH. If carbon dioxide is added to pure water to a PCO_2 of 40 mmHg, 1.2 mmol/L of H_2CO_3 forms which (as a weak acid) partially dissociates to yield 0.025 mmol/L of HCO_3^- and H^+ (i.e.

the pH decreases to 4.6).[20] The addition of 0.9% NaCl to this will not change its pH. The addition of sodium bicarbonate to increase the concentration of bicarbonate to 24 mmol/L increases the pH to 7.4 (the solution now contains sodium bicarbonate, which acts as a buffer).

In a closed system, increasing or decreasing the concentration of HCO_3^- by the addition or removal of water (whether it contains saline or not) will also increase or decrease the concentration of PCO_2. The pH will not change.[21] However, reducing the HCO_3^- concentration by the addition of a neutral solution (e.g. water, with or without saline, mannitol, glucose, urea, etc) and keeping the PCO_2 at 40 mmHg will change the pH, as only one half of the buffer pair are altered.

Acidosis due to extracellular volume expansion

In vivo, the situation appears to be a little more complex. Experimental work with isotonic expansion (keeping the $PaCO_2$ at 40 mmHg) has demonstrated that the degree of decrease in plasma bicarbonate concentration is less than that predicted on the basis of the degree of volume expansion,[22,23] indicating that some 'new' extracellular HCO_3^- has been generated from intracellular or bone sources.[24,25] To maintain electoneutrality, sodium and potassium move from the intracellular fluid (ICF) to the extracellular fluid (ECF) and chloride moves from ECF to ICF.

It would appear that using these data, in normal man an acute expansion of the ECF with 0.9% saline by 6.5 litres would be associated with a reduction in the bicarbonate from 24 to 22 mmol/L.[21]

However, while the change in ECF bicarbonate by infusing an isotonic saline solution is limited by generation of 'new' ECF bicarbonate, any associated change in tonicity will influence this bicarbonate change. For example, infusing hypotonic solutions is accompanied by enhanced ECF bicarbonate generation,[26] whereas infusing hypertonic solutions is associated with a reduction in ECF bicarbonate generation, due to an alteration of cellular membrane H^+ ion permeability[27] or change in intracellular H^+ metabolism.[28]

Problems associated with the Stewart approach

In clinical practice, the Stewart analysis focuses the clinician away from considering the HCO_3^- ion as an important component of acid-base disturbance and introduces concepts that may be questioned. For example, hypoproteinaemic alkalosis and hyperproteinaemic acidosis are proposed as acid-base entities,[29] despite there being no respiratory compensation (and thus no perceived pH abnormality by the human organism)[30] and no study to demonstrate a regulation of albumin metabolism for the purpose of pH regulation. Moreover, sodium bicarbonate is believed to correct a metabolic acidosis by altering sodium rather than by altering bicarbonate concentrations[31] (because if PCO_2 and A_{TOT} are held constant, H^+ and HCO_3^- can only be changed by changing the concentration of strong ions[32]). However, this does not affirm the regulation of plasma pH, it just affirms the law of electrical neutrality, where in a solution there can be no change in any anion (or cation) unless there is an equal change in a cation or (anion) respectively.

The analysis also proposes that a metabolic alkalosis due to pyloric stenosis is due to loss of chloride not hydrogen ion because "the amount of total body free H^+ is only about 1.6×10^{-7} mol. If physiology were just simple accounting, a patient with pyloric stenosis would rapidly run out of H^+",[33] a notion that gives no consideration to the vast movement of H^+ between buffers.

Finally, in a low anion gap acidosis when the sodium concentration is elevated and therapy other than $NaHCO_3$ is being considered, the suggestion that "removal of $Cl^- > Na^+$ perhaps by use of renal replacement therapy (such as haemofiltration)"[33] without considering potassium citrate, acetate or lactate (with HCO_3^- generated by anion metabolism), which have been used successfully for years for these disturbances, particularly when hypokalaemia exists, further underscores the problems associated with this approach.

The relationship between HCO_3^- and SID

While the arterial pH is determined by the SID, $PaCO_2$ and A_{TOT} (where $A_{TOT} = HA + A^-$) this is not surprising, as it is determined by the bicarbonate buffer pair (i.e. HCO_3^- and $PaCO_2$), the bicarbonate element of which may be written as $SID - A^-$. In other words the Henderson-Hasselbalch equation may be written as $pH \propto (SID - A^-)/PaCO_2$.

However, it is the regulation and maintenance of acid-base that is important. The Henderson-Hasselbalch approach focuses on the HCO_3^- ion whereas the Stewart approach focuses on the antithesis of the HCO_3^- ion (i.e. 'strong ions' and A^-). In man acid-base balance has long been shown to be regulated by the renal and respiratory system regulation of the bicarbonate pair, with all other body buffer systems adjusting to the alterations in this pair,[1,34] rather than by regulation of the 'strong ions' and A_{TOT}.

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REFERENCES

1. Filley GF. Acid base and blood gas regulation. Lea & Febiger, Philadelphia. 1972

2. Hood I, Campbell EJM. IS pK OK? N Engl J Med 1982;306:864-865.
3. Kruse JA, Hukku P, Carlson RW. Constancy of blood carbonic acid pK' in patients during cardiopulmonary resuscitation. Chest 1988;93:1221-1224.
4. Gennari FJ. IS pK OK? N Engl J Med 1982;307:683.
5. Ryan DH, Holt J. IS pK OK? N Engl J Med 1982;307:683-684.
6. Worthley LIG. CH 45 Hydrogen ion metabolism and disorders. In Synopsis of Intensive Care Medicine. London: Churchill Livingstone, 1994: 451-466.
7. Prys-Roberts C, Kelman GR, Nunn JF. Determination of the in vivo carbon dioxide titration curve in anaesthetized man. Brit J Anaesth 1966;38:500-509.
8. Severinghaus JW. Acid-base balance nomogram- a Boston-Copenhagen detente. Anesthesiology 1976;45:539-541.
9. Goodkin DA, Raja RM, Saven A. Dilutional acidosis. South Med J 1990;83:354-355.
10. Mathes DD, Morell RC, Rohr MS. Dilutional acidosis: is it a real clinical entity? Anesthesiology 1997;86:501-503.
11. Miller LR, Waters JH. Mechanism of hyperchloremic nonanion gap acidosis. Anesthesiology 1997;87:1009-1010.
12. Stewart PA. Modern quantitative acid-base chemistry. Can J Physiol Pharmacol 1983;61:1444-1461.
13. Fencl V, Leith DE. Stewart's quantitative acid-base chemistry: applications in biology and medicine. Respir Physiol 1993;91:1-16.
14. Siggaard-Andersen O, Fogh-Andersen N. Base excess or buffer base (strong ion difference) as measure of a non-respiratory acid-base disturbance. Acta Anaesthesiol Scand Suppl 1995;107:123-128.
15. Singer RB, Hastings AB. An improved clinical method for the estimation of disturbances of the acid-base balance of human blood. Medicine (Baltimore) 1948;27:223-242.
16. Wooten EW. Analytic calculation of physiological acid-base parameters in plasma. J Appl Physiol 1999;86:326-334.
17. Brønsted JN. Einige Bemerkungen über den Begriff der Säuren und Basen. Rec Trav Chim Pays-Bas 1923;42:718-728.
18. Lowry TM. The electronic theory of valency. VI. The origin of acidity. Trans Faraday Soc 1924;20:13-15.
19. Rahn H, Reeves RB, Howell BJ. Hydrogen ion regulation, temperature, and evolution. Am Rev Respir Dis 1975;112:165-172.
20. Filley GF. Acid base and blood gas regulation. Lea & Febiger, Philadelphia. 1972, p 20-25.
21. Garella S, Chang BS, Kahn SI. Dilution acidosis and contraction alkalosis: review of a concept. Kidney Int 1975;8:279-282.
22. Rosenbaum BJ, Makoff DL, Maxwell MH Acid-base and electrolyte changes induced by acute isotonic saline infusion in the nephrectomized dog. J Lab Clin Med 1969;74:427-435.
23. Garella S, Tzamaloukas AH, Chazan JA Effect of isotonic volume expansion on extracellular bicarbonate stores in normal dogs. Am J Physiol 1973;225:628-636.
24. Swan RC, Pitts RF. Neutralization of infused acid by nephrectomized dogs. J Clin Invest 1955;34:205-212.
25. Garella S, Dana CL, Chazan JA Severity of metabolic acidosis as a determinant of bicarbonate requirements. N Engl J Med 1973;289:121-126.
26. Chang BS, Kahn SI, Garella S. Influence of tonicity on bicarbonate generation in volume expansion. Clin Res 1975;23:357A.
27. Dusing R, Leibhammer S, Hoffmann G, Vetter H, Siffert W. Hypertonic saline infusion induces activation of the lymphocyte Na+/H+ antiport and cytosolic alkalinization in healthy human subjects. Clin Investig 1994;72:817-821.
28. Makoff DL, Silva JA da, Rosenbaum BJ, Levy SE, Maxwell MH. Hypertonic expansion: acid-base and electrolyte changes. Am J Physiol 1970;218:1201-1207.
29. Jabor A, Kazda A. Modelling of acid-base equilibria. Acta Anaesth Scand 1995;39 (Suppl 107):119-122.
30. Wilkes P. Hypoproteinemia, strong-ion difference, and acid-base status in critically ill patients. J Appl Physiol 1998;84:1740-1748.
31. Dorje P, Adhikary G, McLaren ID. Dilutional acidosis or altered strong ion difference. Anesthesiology 1997;87:1011-1012.
32. Kellum JA. Strong ion difference theory: more lessons from physical chemistry. Kidney Int 1998;54:1769-1770.
33. Kellum JA. Metabolic acidosis in the critically ill: lessons from physical chemistry. Kidney Int 1998;53(Suppl 66):S81-S86.
34. Pitts RF. Physiology of the kidney and body fluids. 2nd Ed. Year Book Medical Publishers. Chicago 1968.