Clinical practice review

Hyperchloraemic Acidosis: Another Misnomer?

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ABSTRACT

Objective: *To review the term hyperchloraemic acidosis.*

Data sources: *Articles and reviews from peer reviewed journals on acid-base physiology.*

Summary of review: *The concept of hyperchloraemic acidosis is well established in medicine and regularly taught to medical students. Unfortunately, it is yet another medical misnomer. Hyperchloraemic acidosis is only likely to exist with normal plasma sodium concentrations. This is because the acidosis is due to a decreased strong-ion-difference rather than the hyperchloraemia alone. If hyponatraemia is present, an identical acidosis can exist without hyperchloraemia; or if hypernatraemia is present there may be hyperchloraemia without acidosis. Even those who cling to the bicarbonate centred approach to acid-base physiology should recognise that describing acid-base changes in terms of chloride alone is less meaningful than considering both the strong cations and the strong anions. For those clinicians, using the Stewart approach the value of the terms "strong ion acidosis" and "strong ion alkalosis" should be readily apparent.*

Conclusions: *The use of the term hyperchloraemic acidosis is a misnomer as the chloride ion may be elevated or depressed in the absence of an acid bade abnormality.* (**Critical Care and Resuscitation 2004; 6: 188-192**)

Key words: Acid-base, strong ion difference, hyperchloraemic acidosis, dilutional acidosis

For almost a century physiologists have recognised that chloride and bicarbonate are, quantitatively, the principal anions (negatively charged ions) in plasma (Figure 1).[1] Minor anions, quantitatively, include albumin, phosphate, organic acids such as lactate, and sulphate. The principal cation (positively charged ion), quantitatively, is sodium.[1] Minor cations include potassium, calcium, and magnesium. One requirement of clinical chemistry is that a physiological compartment such as the extracellular space should have electro-neutrality:[2,3] no overall electrical charge, because the sum of the anions equals the sum of the cations. This is the reason the anion and cation columns in the electrolyte diagrams called "Gamblegrams"[3,4] are the same height (Figure 1).

Since the 1920s, clinical chemists have reported that, in many clinical situations, there is a reciprocal relationship between the concentration of plasma bicarbonate and the concentration of plasma chloride.[1,5] During metabolic alkalosis an increase in bicarbonate concentration is often accompanied by a decrease in plasma chloride concentration.[1,6] Conversely, during acidosis, a decrease in bicarbonate may be accompanied by an increase in chloride.[6,7] The reciprocal relationship may be weaker during acidosis because other anions such as lactate may have increased concentrations. For over 50 years, the clinical scenario of acidosis with decreased bicarbonate and increased chloride has been called hyperchloraemic metabolic acidosis.[8]

Diagnosing "hyperchloraemic" acidosis

Hyperchloraemic acidosis has long been associated with several clinical situations: diarrhoea, renal tubule acidosis and renal failure.[6,9] Another situation is hyper-

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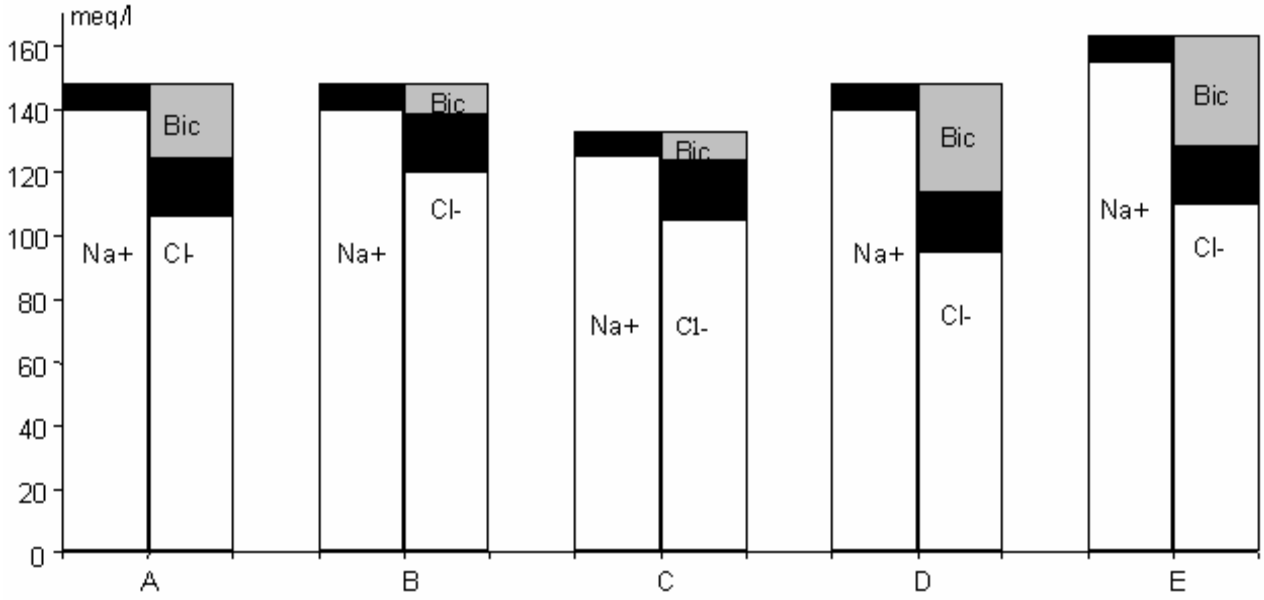

Figure 1. Gamblegrams. These diagrams show different patterns of plasma electrolytes and acid-base status that may be found in patients, particularly those in the intensive care unit (ICU). The five "Gamblegrams" (A to E) have the cations in the left hand column and the anions in the right hand column. The equal height of the cation and anion columns highlights the need for elctroneutrality. The major electrolytes are identified: sodium (Na+), chloride (Cl-), and bicarbonate (Bic). The black parts of the columns are minor cations and anions. The concentrations of the minor ions are constant in examples A to E. Changes in the partial pressure of carbon dioxide are assumed to not be contributing to bicarbonate changes. **(A)** Electrolytes typical of a patient with decreased albumin with a slightly decreased strong-ion-difference to compensate; the bicarbonate is normal. **(B)** A strong ion metabolic acidosis secondary to hyperchloraemia. **(C)** A strong ion metabolic acidosis similar to (B) but without hyperchloraemia due to coexisting hyponatraemia. **(D)** A strong ion metabolic alkalosis with hypochloraemia. **(E)** A strong ion metabolic alkalosis similar to (D) but with hyperchloraemia which is offset by coexisting hypernatraemia

chloraemic acidosis following administration of sodium chloride solutions such as 0.9% saline (Table 1). This phenomenon has recently been examined in the anaesthesia literature.[10-14] Post-saline acidosis was, however, first recognised in 1923.[15]

Several developments in acid-base physiology aid in making the diagnosis of hyperchloraemic acidosis. The first were methods that attempt to determine the metabolic (non-respiratory) acid-base status from the effects of carbon dioxide. These include the "rules of thumb"[6,9] and base-excess.[3] Further developments include methods to determine if unmeasured acids are present,[16-19] the best known being the anion gap.[6,9] An underlying assumption of the anion gap is that the sum of the cations equals the sum of the anions: electro-neutrality. An anion gap less than 16 mmol/L makes large concentrations of unmeasured anions in the plasma sample unlikely.[9]A hyperchloraemic acidosis is likely to be a narrow anion gap acidosis.[9]The anion gap can be corrected for changes in albumin, particularly the hypoalbuminaemia typical of critically ill patients.[19] However, exactly how the corrected anion gap should be interpreted is still being resolved.

Mechanism controversy

The explanation for the acidifying mechanism in hyperchloraemic acidosis has undergone 180 degree changes over the last 60 years. In the 1930s Van Slyke described anions, particularly chloride, as acids; and cations, particularly sodium, as bases.[1] In 1931 Peters and Van Slyke,[1] felt that bicarbonate was a marker of acid-base status and commented "…the most important (facts) concern the roles played by the individual anions other than bicarbonate, and by the cations, in determining the acid-base balance and the bicarbonate content of the blood". Changes in plasma bicarbonate follow, amongst other things, changes in plasma chloride.

Van Slyke's approach contrasts sharply with the bicarbonate-centred approach that emerged in the 1950s.[20-22] The bicarbonate-centred approach to acid-base physiology views bicarbonate as both a marker of acid-base status and an underlying mechanism. It has ongoing and dominant popularity.[2,6,9] Changes in plasma chloride follow, amongst other things, changes in plasma bicarbonate.

More recently, Stewart[2,23,24] has extended Van Slyke's work and directly incorporated elctroneutrality. Stewart focussed on the importance of strong ions (completely dissociated ions), in particular the size of the difference between strong cations and strong anions: the strong-ion-difference. In plasma, the strong-ion-

difference is largely the difference between sodium cations and chloride anions.[25] Stewart returned to an approach similar to Van Slyke: changes in bicarbonate follow, amongst other things, changes in chloride and changes in sodium.

Clinical situations

Hyperchloraemic metabolic acidosis has long been associated with renal impairment[6,8,9,26] and to a lesser extent with the intravenous administration of sodium chloride solutions.[26] Recently there has been renewed interest in hyperchloraemic metabolic acidosis for several reasons. First, several groups have suggested that perioperative hyperchloraemic acidosis, following administration of saline is more frequent than is widely recognised.[10,27-31] Second, in addition to (and possibly secondary to) hyperchloraemic acidosis, saline administration may be associated with clinically important adverse events including abdominal pain, decreased splanchnic perfusion, and diminished renal function when compared to the administration of fluids such as Hartmann's solution.[28,31,32] Animal work has even suggested that, compared to alternatives, saline resuscitation may lead to greater mortality.[33] A third factor adding to the interest in hyperchloraemic acidosis is the growing clinical application of the Stewart approach to acid-base physiology.[2,18,34] Hyperchloraemic acidosis after saline infusion goes to the heart of the differences between the Stewart and bicarbonate-centred approaches to acid-base physiology.[13]

Saline infusion versus Hartmann's and Plasmalyte

Several groups have examined the electrolyte, acid-base, and clinical effects of different intravenous solutions, particularly 0.9% sodium chloride.[10,27-32] All studies have found that the use of sodium chloride is associated with a metabolic acidosis with an increased plasma chloride. In the most widely quoted study, Scheingraber and colleagues found that perioperative infusion of about 5 litre of 0.9% saline during two hours of major gynaecological surgery led to a much greater metabolic acidosis than the use of Ringers lactate solution; a solution similar to Hartmann's solution (Table 1). The mean post fusion pH and base excess were 7.28 and -4.0 mmol/L. for saline and 7.35 and -1.0 mmol/L for Ringer's lactate. This followed on from a similar finding by McFarlane and colleagues[27] who used saline or Plasmalyte (Table 1) at 15 mL/kg/hr for major abdominal surgery. In the Plasmalyte group the base-excess fell by 1.2 mmol/L and by 5.0 mmol/L in the saline group. Both Scheingraber[10] and McFarlane[27] used saline in a manner that would be common in operating rooms around the world. Therefore the post saline acidosis is likely to be a common phenomenon.

Briefly, why is the acid-base effect of Hartmann's and Plasmalyte different from 0.9% saline? The answer lies in the lactate, acetate, and gluconate anions that replace chloride in these solutions (Table 1). From a Stewart perspective, as these strong anions are removed from the plasma by the liver (which is faster than renal elimination of chloride), this widens the plasma strong-ion-difference and is alkalinising.[35] From the bicarbonate-centred view the anions are metabolised to form bicarbonate.[36]

Strong ion acidosis

Constable[13,37] has been an important contributor to the recent debate comparing the bicarbonate-centred and Stewart approaches to acid-base physiology. In an editorial,[13] Constable concluded that post saline hyperchloraemic metabolic acidosis is in fact a "classic" strong ion acidosis. There is a raised plasma chloride concentration and a decreased bicarbonate concentration without hypernatraemia (Figure 1, Gamblegram B). Those who follow the bicarbonate-centred approach would use the rules of thumb or base excess to conclude that this is a metabolic acidosis with hyperchloraemia: a hyperchloraemic metabolic acidosis; the acidosis being due to a decrease in bicarbonate. Those using the Stewart approach would see the increase in plasma

Table 1. Electrolyte content (mmol/L) in crystalloid solutions for intravenous use.

	0.9% saline	Hartmann's	Plasmalyte	Ringer's
Osmolality	300	274	288	274
Sodium	150	129	140	130
Chloride	150	109	98	109
Potassium	0	5	5	4
Calcium	0	2.0	0	3.0
Magnesium	0	0	1.5	0
Other Anions	0	29(lactate)	27(acetate) 23(gluconate)	28(lactate)

chloride concentration as an important component of an underlying decrease in the strong-ion-difference that is acidifying.[13]

Those using a bicarbonate-centred approach sometimes explain this post infusion hyperchloraemic acidosis as a form of "dilutional" acidosis.[38] The mechanism is dilution of plasma bicarbonate by the infused fluid.[39] For sodium chloride solutions, the dilution of bicarbonate by sodium chloride leads to a chloride becoming a larger component of the total plasma anions and bicarbonate contributing less. The increase in chloride is marker for rather than a cause of the acidosis. However, acidosis is also seen with infusions of solutions of uncharged solutes such as mannitol.[39] Bicarbonate-centred clinicians have emphasised that the mechanism is the dilution of bicarbonate irrespective of the eventual effect on other plasma electrolytes. How can this mannitol phenomenon be explained using the Stewart approach? The answer lies in the strong-ion-difference. As mannitol (no ions) is infused the decrease in sodium will be faster than the decrease in chloride. Therefore there will be relative hyponatraemia leading to a decreased strong-ion-difference and acidosis. (Figure 1, Gamblegram C).

We have conducted several studies using a database with 300 blood samples from 300 patients taken when the patients were admitted to our intensive care unit.[18] Among 300 samples we found 18 samples with a base excess more negative than -2 mmol/L, a chloride less than 107 mmol/L and an anion gap less than 16 mmol/L. The mean sodium was 135 mmol/L. That is, we found 18 samples of apparent strong ion acidosis without hyperchloraemia and without significant amounts of other acids. Further, across the 300 samples there was closer agreement between the sodium minus chloride difference and bicarbonate than between bicarbonate and chloride alone.[40]

Strong ion alkalosis?

Although most attention has been paid to acidosis, as said earlier, metabolic alkalosis with increased plasma bicarbonate is often associated with decreased plasma chloride concentration.[1,6] From a Stewart perspective, in the presence of a normal plasma sodium concentration, there will be an increased strong-ion-difference causing the alkalosis[24] (Figure 1, Gamblegram D). For patients in intensive care unit there is often an alkalinising effect from decreased plasma weak acid concentration secondary to decreased plasma albumin concentration. This hypoalbuminaemic alkalosis is one of several areas where the Stewart approach to acid-base physiology provides a straightforward explanation for a common clinical phenomenon while the bicarbonate-centred approach struggles.[41]

Before we assume that this alkalosis can always be seen as a "hypochloraemic metabolic alkalosis" we should consider that it is possible for a patient who has an increased plasma sodium concentration to have both an increased plasma bicarbonate concentration and an increased plasma chloride concentration. In our database of 300 samples we found 13 with base excess greater than 2 mmol/L and a chloride greater than 107 mmol/L. The mean sodium concentration was 147 mmol/L. That is, we found patients who had alkalosis and coexisting hyperchloraemia.

REFERENCES

1. Peters J, Van Slyke D. Quantitive clinical chemistry. Baltimore: Williams and Wilkins, 1931.
2. Sirker AA, Rhodes A, Grounds RM, Bennett ED. Acid-base physiology: the 'traditional' and the 'modern' approaches. Anaesthesia 2002;57:348-356.
3. Siggard-Anderson O. The Acid-Base Status of the blood. 4th ed. Copenhagen: Munksgaard, 1974.
4. Gamble J. Chemical Anatomy, Physiology and Pathology of Extracellular Fluid. A lecture syllabus. Cambridge: Harvard University Press, 1954.
5. Haldane JBS. Experimental and therapeutic alterations of human tissue alkalinity. Lancet 1924:537-538.
6. Abelow B. Understanding Acid-Base. First ed. Baltimore: Williams and Wilkins, 1998:1 - B20.
7. Henderson LJ. Blood as a physicochemical system. J Biol Chem 1921;44:411-419.
8. Lathem W. Hyperchloremic acidosis in chronic pyelonephritis. N Engl J Med 1958;258:1031-1036.
9. Worthley LIG. Acid-base balance and disorders. In: Bersten AD, Soni N, editors. Oh's Intensive Care Manual. Sydney: Butterworth-Heinmann, 2003:873-883.
10. Scheingraber S, Rehm M, Sehmisch C, Finsterer U. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology 1999;90:1265-1270.
11. Prough DS, Bidani A. Hyperchloremic metabolic acidosis is a predictable consequence of intraoperative infusion of 0.9% saline. Anesthesiology 1999;90:1247-1249.
12. Liskaser FJ, Bellomo R, Hayhoe M, et al. Role of Pump Prime in the Etiology and Pathogenesis of Cardiopulmonary Bypass-associated Acidosis. Anesthesiology 2000;93:1170-1173.
13. Constable PD. Hyperchloremic acidosis: the classic example of strong ion acidosis. Anesth Analg 2003;96:919-922.
14. Hayhoe M, Bellomo R, Liu G, McNicol L, Buxton B. The aetiology and pathogenesis of cardiopulmonary bypass-associated metabolic acidosis using polygeline pump prime. Intensive Care Med 1999;25:680-685.
15. Odaira T. Influence of some neutral salt solutions, intravenously administered , on the alkalai reserve of the blood. Tohoku J Exp Med 1923;4:523-526.
16. Gabow PA, Kaehny WD, Fennessey PV, Goodman SI, Gross PA, Schrier RW. Diagnostic importance of an

increased serum anion gap. N Engl J Med 1980;303:854-858.
17. Kellum JA, Kramer DJ, Pinsky MR. Strong ion gap: a methodology for exploring unexplained anions. J Crit Care 1995;10:51-55.
18. Story DA, Morimatsu H, Bellomo R. Strong ions, weak acids and base excess: a simplified Fencl-Stewart approach to clinical acid-base disorders. Br J Anaesth 2004;92:54-60.
19. Figge J, Jabor A, Kazda A, Fencl V. Anion gap and hypoalbuminemia. Crit Care Med 1998;26:1807-1810.
20. Christensen. Anions versus cations. Am J Med 1957;27:163-165.
21. Frazer S, Stewart C. Acidosis and alkalosis: A modern view. J Clin Path 1959;12:195-206.
22. Relman A. What are "acids" and "bases"? Am J Med 1954;17:435-437.
23. Stewart PA. How to understand acid-base. New York: Elsevier, 1981:4-179.
24. Stewart PA. Modern quantitative acid-base chemistry. Can J Physiol Pharmacol 1983;61:1444-1461.
25. Gilfix BM, Bique M, Magder S. A physical chemical approach to the analysis of acid-base balance in the clinical setting. J Crit Care 1993;8:187-197.
26. DuBoise. Acid-base disorders. In: Brenner BM, editor. Brenner and Rector's The Kidney. 6th ed. Philadelphia: W.B. Saunders Company, 2000:925-997.
27. McFarlane C, Lee A. A comparison of Plasmalyte 148 and 0.9% saline for intra-operative fluid replacement. Anaesthesia 1994;49:779-781.
28. Williams EL, Hildebrand KL, McCormick SA, Bedel MJ. The effect of intravenous lactated Ringer's solution versus 0.9% sodium chloride solution on serum osmolality in human volunteers. Anesth Analg 1999;88:999-1003.
29. Waters JH, Gottlieb A, Schoenwald P, Popovich MJ, Sprung J, Nelson DR. Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. Anesth Analg 2001;93:817-822.
30. Rehm M, Finsterer U. Treating intraoperative hyperchloremic acidosis with sodium bicarbonate or tris-hydroxymethyl aminomethane: a randomized prospective study. Anesth Analg 2003;96:1201-1208.
31. Reid F, Lobo DN, Williams RN, Rowlands BJ, Allison SP. (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study. Clin Sci (Lond) 2003;104:17-24.
32. Wilkes NJ, Woolf R, Mutch M, et al. The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. Anesth Analg 2001;93:811-816.
33. Kellum JA. Fluid resuscitation and hyperchloremic acidosis in experimental sepsis: improved short-term survival and acid-base balance with Hextend compared with saline. Crit Care Med 2002;30:300-305.
34. Kellum JA. Determinants of blood pH in health and disease. Crit Care 2000;4:6-14.
35. Kellum JA. Metabolic acidosis in the critically ill: lessons from physical chemistry. Kidney Int Suppl 1998;66:S81-S86.
36. White SA, Goldhill DR. Is Hartmann's the solution? Anaesthesia 1997;52:422-427.
37. Staempfli HR, Constable PD. Experimental determination of net protein charge and A(tot) and K(a) of nonvolatile buffers in human plasma. J Appl Physiol 2003;95:620-630.
38. Prough DS, White RT. Acidosis associated with perioperative saline administration: dilution or delusion? Anesthesiology 2000;9:1167-1169.