Acid base disorders in hospitalized cattle

Distúrbios ácido-base em bovinos hospitalizados

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ABSTRACT

The objectives of this retrospective study were to determine the main acid-base and electrolytes disorders in hospitalized cattle, using both Henderson-Hasselbalch and the physicochemical approach and to compare their diagnostic and therapeutic utility. A total of 31 medical records were reviewed of bovines admitted to the Large Animal Hospital at Universidad Nacional de Colombia, that met the inclusion criteria of the measurement of blood gases, blood electrolytes and plasma protein on admission before providing any treatment. Using the Henderson-Hasselbalch approach, acid base abnormalities were found in 83.3% of the patients, compared to 93.5% using the physicochemical approach. The principal acid-base disorders found were strong ion acidosis (61.29%) and weak acid acidosis (38.7%); strong ion gap (SIG) acidosis was found in 73.68% of cases showing strong ion acidosis. These results highlight the importance of the diagnosis of acid-base disorders in sick cattle for proper recognition of pathophysiological phenomena and its understanding to guide treatment decisions.

Keywords: Bovine. Physicochemical approach. Strong ion acidosis. Hyponatremia.

Introduction

Acid base and electrolytic disorders are frequent findings in sick cattle (Constable et al., 2005; Gomez et al., 2013b; Roussel et al., 1998). There are two approaches to describe
acid-base balance in mammals. One approach is the Henderson-Hasselbalch equation, which is a descriptive method that explains how plasma pH is influenced by the interaction of CO₂ pressure (pCO₂), bicarbonate concentration [HCO₃⁻], the equilibrium constant (PK') and the solubility of CO₂ in plasma (SCO₂) (Henderson, 1913). The other approach is the physicochemical method, which is a quantitative model that combines in polynomial equations the laws of electroneutrality, mass conservation and dissociation equilibrium of weak acids to determine the plasma pH based on three independent variables: strong ion difference (SID), pCO₂ and total weak acid concentration (A) (Stewart, 1983).

Many studies using the physicochemical approach have been carried out in horses (Gomez et al., 2013a), pigs (Reinhold et al., 2010) and dogs (Slawuta et al., 2010); and acid base disorders in cattle have been widely described using the Henderson-Hasselbalch equation in gastrointestinal disorders in adult cattle (Braun et al., 1990; Ward et al., 1994), neonatal calf diarrhea (Naylor, 1989; Tennant et al., 1972), feeding changes in healthy animals (Oetzel et al., 1991) and normal newborn calves (Butler et al., 1971). However, fewer studies have been done using the physicochemical approach (Gomez et al., 2013b; Stämpfli & Oliver, 2002; Stämpfli et al., 2012).

The objectives of this retrospective study were to determine the main acid-base and electrolytes disorders in hospitalized cattle by different diseases, using both Henderson-Hasselbalch and the physicochemical approach and to compare their diagnostic and therapeutic utility.

Materials and Methods

Study population

All the medical records (n=245) were reviewed of bovines admitted between January 2005 and July 2013 to the Large Animal Hospital at the Universidad Nacional de Colombia. Animals were included if the complete results of arterial or venous blood gases (pO₂ (mmHg) and pCO₂ (mmHg)) and electrolytes ([Na⁺] (mmol/L), [K⁺] (mmol/L) y [Cl⁻] (mmol/L)) were measured. Blood samples that were taken between 2005 and February 2012 were sent to an external laboratory in Bogota, Colombia and analyzed using the Cobas® b 221 Blood gas system (Roche OMNI® S) for blood gases and pH, and Vitros® 350 Chemistry System (Ortho-Clinical Diagnostics-Johnson & Johnson company®) for electrolytes measurement. After May 2012, all blood samples were analyzed using the EPOC® Host Blood Analysis system (HH-0005-XU-00) for pH and blood gases and using an ion selective electrode (EPOC® BGE- Test Cards) for electrolytes measurement at the Clinical Pathology Laboratory, Faculty of Veterinary Medicine and Zootechnics, Universidad Nacional de Colombia, Bogota, Colombia.

The bicarbonate [HCO₃⁻] (mmol/L) (Constable, 2000), base excess (BEℰCPP) (mmol/L) (Constable, 2002; Gomez et al., 2013a) and anion GAP (mmol/L) (Constable et al., 1997; Constable, 2000) were calculated. For the physicochemical approach, the SID and A⁺ variables were calculated using the Software by Stämpfli (2019) (Stewart Acid-Base Analysis®) and the calculation of the SIG was performed according to the simplified strong ion model for the acid-base balance (Constable et al., 1997; Constable, 2000).

Acid base disorder definitions according to the Henderson-Hasselbalch and physicochemical approaches are presented in Tables 1 and 2.

| Acid base disorder        | Arterial Blood | Venous Blood |
|---------------------------|---------------|-------------|
| Metabolic Acidosis        | BEℰCPP<4.45 mmol/L | BEℰCPP<2.7 mmol/L |
|                           | [HCO₃⁻]<18.4 mmol/L | [HCO₃⁻]<21.66 mmol/L |
| Metabolic Alkalosis       | BEℰCPP>6.63 mmol/L | BEℰCPP<5.93 mmol/L |
|                           | [HCO₃⁻]>30.1 mmol/L | [HCO₃⁻]>30.34 mmol/L |
| Respiratory Acidosis      | pCO₂>43.85 mmHg | pCO₂>50.98 mmHg |
| Respiratory Alkalosis     | pCO₂<31.65 mmHg | pCO₂<37.14 mmHg |

BEℰCPP = base excess of extracellular fluid; [HCO₃⁻] = bicarbonate concentration; pCO₂ = partial pressure of carbon dioxide.
Table 2 – Acid base disorders according to the physicochemical approach, based on the values reported by Stämpfli & Oliver (2002)

| Acid base disorder | Definition |
|--------------------|------------|
| SID Acidosis       | SID >38 mmol/L |
| SID Alkalosis      | SID >44 mmol/L |
| A- Acidosis        | A- >13 mmol/L  |
| A- Alkalosis       | A- <12 mmol/L  |
| SIG Acidosis       | SIG < -3 mEq/L |

SID = strong ion difference; A- = total weak acid concentration; SIG = strong ion gap.

Two animals (6.45%) had chronic suppurative pneumonia, 1 (3.22%) enzootic pneumonia, 2 (6.45%) aspiration pneumonia, 4 (12.9%) neonatal septicemia, 4 (12.9%) left abomasal displacement, 2 (6.45%) intestinal accidents, 2 (6.45%) hemoparasitism, 2 (6.45%) neonatal calf diarrhea, 2 (6.45%) bovine viral diarrhea, 2 (6.45%) vagal indigestion, 1 (3.22%) ruminal lactic acidosis, 1 (3.22%) atresia coli, 1 (3.22%) high mountain disease, 1 (3.22%) toxic metritis, 1 (3.22%) esophageal obstruction, 1 (3.22%) urethral obstruction, 1 (3.22%) pharyngeal paralysis, and 1 (3.22%), salmonellosis. Eleven (35.48%) animals were euthanized, 9 (29%) were discharged, 7 (22.58%) died, and 4 patients (12.9%), the outcome was not registered.

Electrolytes derangements were diagnosed in 23 (74.2%) of the animals and were classified as hyponatremia in 10 (32.25%), hypernatremia in 2 (6.45%), hypokalemia in 12 (38.7%), hyperkalemia in 4 (12.96%), hypochloremia in 13 (41.93%) and hyperchloremia in 5 (16.12%) animals. Two different electrolyte derangements were diagnosed in 10 animals and were classified as hyponatremia with hyperchloremia in 2 (6.45%) and hyponatremia with hypochloremia in 8 (25.8%) animals. (Table 3)

Acid-base disturbances classified by the Henderson-Hasselbalch approach were diagnosed in 26 (83.87%) patients, a single metabolic disorder was diagnosed in 11 patients. There were 2 cases (18.18%) of metabolic acidosis based on BE_{(ECF)} (<-4.45 (arterial); <-2.07 (venous) (mmol/L)) , 5 (45.45%) metabolic acidosis by BE_{(ECF)} and plasma [HCO$_3^-$] (<18.24 (arterial) < 21.66 (venous) mmol/L), 4 (36.36%) metabolic alkalosis by BE_{(ECF)} and plasma [HCO$_3^-$] (>30.12 (arterial); >30.34 (venous) mmol/L). A single respiratory disorder was found in 8 patients (30.76%), respiratory acidosis (pCO$_2$ >43.85 (arterial); >50.98 (venous) mmHg) and respiratory alkalosis (pCO$_2$ <31.65 (arterial); <37.14 (venous) mmHg) were found in 4 and 4 of the patients, respectively. Mixed metabolic acid-base abnormalities were diagnosed in 7 patients (26.92%): 4 cases of metabolic acidosis by BE_{(ECF)} and plasma [HCO$_3^-$] with respiratory acidosis; 1 case of metabolic alkalosis by BE_{(ECF)} and plasma [HCO$_3^-$] with respiratory alkalosis, and 2 cases of metabolic alkalosis by BE_{(ECF)} and plasma [HCO$_3^-$] with respiratory alkalosis. Furthermore, anion GAP acidosis (<14 mEq/L) was found in 10 patients with metabolic acidosis. Acid base disorders according to the Henderson-Hasselbalch approach are presented in Figure 1.

Acid-base disturbances classified by the physicochemical approach were diagnosed in 29 (93.54%) patients (Figure 2), a single disorder was diagnosed in 9 patients. There were 4 (44.44%) cases of weak acid acidosis (A- >13 mmol/L), 2 (22.22%) strong ion alkalosis (SID >44 mmol/L), 2 (22.22%) strong ion acidosis (SID <38 mmol/L), and 1 (11.11%) weak

Results

Two hundred forty-five bovines were admitted to the Large Animal Hospital at Universidad Nacional de Colombia between January 2005 and July 2013 and 31 met the inclusion criteria. Twenty-four animals (77.41%) were Holstein, 7 (22.58%) females and 7 (22.58%) were males. The breeds in the study included 14 (45.16%) that were Holstein, 7 (22.58%) Angus, 1 (3.22%) Brangus, 1 (3.22%) Charolais, 3 (9.67%) Brahman, 2 (6.45%) Normande, 1 (3.22%) Brahman, 1 (3.22%) Brown Swiss, and in 1 (3.22%), the type of breed was not available. The median age was 18 months, ranging from 1 day to 9 years of age.

Statistical analysis

Due to the fact that a retrospective study was conducted and all data were collected as part of routine diagnosis and treatment, but any intervention was carried out, no approval from the ethics committee was necessary.

Data were checked for normality using the Shapiro-Wilk test. Data that were normally distributed were expressed as mean ± standard deviation and data with a non-normal distribution were expressed as median and range. Data were analyzed using Statgraphics®1 statistical software.

For the pH, pO$_2$, pCO$_2$, BE$_{(ECF)}$, and [HCO$_3^-$] data, the values found by Cañaneda et al. (2002) in cattle at 2.600 meters above sea level (the same altitude for animals included in the present study), were used as reference ranges, but using 2 standard deviations of the mean, assuming that data had a gaussian distribution; therefore, 95% of the distribution would include all data that were between 2 standard deviations of the mean.

The degree of agreement between both diagnostic approaches was determined using the Kappa statistic (Gordis, 2009). Receiver operating characteristic (ROC) curves analysis was used to evaluate the accuracy of both approaches as diagnostic tests for acid base disorders (Swets, 1988).

Electrolytes derangements were diagnosed in 23 (74.2%) of the animals and were classified as hyponatremia in 10 (32.25%), hypernatremia in 2 (6.45%), hypokalemia in 12 (38.7%), hyperkalemia in 4 (12.96%), hypochloremia in 13 (41.93%) and hyperchloremia in 5 (16.12%) animals. Two different electrolyte derangements were diagnosed in 10 animals and were classified as hyponatremia with hyperchloremia in 2 (6.45%) and hyponatremia with hypochloremia in 8 (25.8%) animals. (Table 3)
Table 3 – Acid base variables from 31 bovine patients (Reference values reported by Castañeda et al., 2002; Ontario Veterinary College, 1992; Stämpfli & Oliver, 2002)

| Parameter                  | Values                                         | Ref. Value       |
|----------------------------|------------------------------------------------|------------------|
| **pH**<sub>arterial</sub>  | 7.38 ± 0.15 (6.99-7.59)                        | 7.38-7.46        |
| **pH**<sub>venous</sub>    | 7.33-7.42                                      |                  |
| pCO<sub>2</sub><sup>arterial</sup> (mmHg) | 39.82 ± 12.29 (19.9-71.9) | 31.65-43.85      |
| pCO<sub>2</sub><sup>venous</sup> (mmHg)   | 37.14-50.98                                   |                  |
| HCO<sub>3</sub>-<sup>arterial</sup> (mmol/L)  | 24.66 ± 9.37 (5.6-48.2)                        | 18.24-30.12      |
| HCO<sub>3</sub>-<sup>venous</sup> (mmol/L)    | 21.66-30.34                                   |                  |
| BE<sub>ECF</sub><sup>arterial</sup> (mmol/L) | -0.39 ± 11.27 (-25.11-29.35)                    | -4.45-6.63       |
| BE<sub>ECF</sub><sup>venous</sup> (mmol/L)    | -2.07-5.93                                    |                  |
| Na<sup>+</sup> (mmol/L)    | 135.35 ± 12.72 (104-170)                        | 132-152          |
| K<sup>+</sup> (mmol/L)     | 4.04 ± 1.11 (2-6.92)                            | 3.9-5.2          |
| Cl<sup>-</sup> (mmol/L)    | 96.71 ± 15.47 (62-129)                         | 97-111           |
| SID (mEq/L)                | 37.49 ± 10.25 (26.7-62.5)                      | 8-44             |
| A- (mEq/L)                 | 12.83 ± 2.83 (8.1-20.8)                         | 12-13            |
| AG (mEq/L)                 | 18.01 ± 8.66 (-1.05-40.96)                      | 14-20            |
| SIG (mEq/L)                | -5.17 ± 8.24 (-20.16-14.90)                     | -3 + 3           |
| TP (g/L)                   | 70 (46-122)                                    | 67-75            |

\( pCO_2 \) = partial pressure of carbon dioxide; \([HCO_3^-]\) = bicarbonate concentration; BE<sub>ECF</sub> = base excess of extracellular fluid; Na<sup>+</sup> = sodium; K<sup>+</sup> = potassium; Cl<sup>-</sup> = chloride; SID = strong ion difference; A- = total weak acid concentration; AG = anion gap; SIG = strong ion gap; TP = total plasma proteins.

Figure 1 – Acid-base disorders according to the Henderson-Hasselbalch approach. (A) Metabolic acidosis, respiratory alkalosis and anion gap (AG) acidosis; (B) Metabolic alkalosis, respiratory alkalosis and acidosis.

Figure 2 – Acid-base disorders according to the physicochemical approach. (A) Strong ion (SID) acidosis, SID acidosis, Weak acid (A-) acidosis and alkalosis, respiratory acidosis and alkalosis; (B) SID alkalosis, A- acidosis, respiratory acidosis, respiratory alkalosis and strong ion gap (SIG) acidosis.
acidosis (A- <12 mmol/L). Concomitant disorders were diagnosed in 20 (64.51%) patients: 4 (20%) had SID alkalosis and weak acid acidosis, 10 (50%) had SID acidosis and weak acid alkalosis, and 6 (30%) had both SID and weak acid acidosis. Altogether, strong ion acidosis was diagnosed in 19 patients, weak acid acidosis in 12, strong ion alkalosis in 5 and weak acid alkalosis in 12. Also, 10 (52.63%) of the SID acidosis cases had decreased SIG (SIG <-3 mEq/L), 5 (26.31%) were hyponatremic, 2 (10.52%) hyponatremic and had decreased SIG, and 2 (10.52%) had decreased SIG and were hyperchloremic. All cases of SID alkalosis were also hypochloremic. (Figure 2)

The Kappa statistic showed a 38.1% agreement between the Henderson-Hasselbalch and physicochemical approaches. ROC analysis showed an area under the curve of 0.838 and 0.75 for the diagnosis of alkalosis and 0.875 and 0.848 for the diagnosis of acidosis, according to the physicochemical and Henderson-Hasselbalch approaches, respectively (Figure 3).

Discussion

The most common disorder found, following the Henderson-Hasselbalch approach, was metabolic acidosis by BE\textsubscript{ECF} and also by plasma [HCO\textsubscript{3}-]. In patients younger than 3 months, the main disorder was metabolic acidosis by BE\textsubscript{ECF} and/or by plasma [HCO\textsubscript{3}-]; meanwhile, in patients older than 3 months, the most common disorder was the metabolic alkalosis. This difference may be the result of physiological changes related to rumen development during the first months of life (Drackley, 2008) and also, as a consequence of metabolic acidosis occasioned by the presentation of neonatal diarrhea, which is the most important disease in neonatal calves (Barrington et al., 2002). Conversely, the most common disorder in older patients may be associated with abomasal disturbances involving the sequestration of chloride in the fore-stomach (Ward et al., 1994).

Metabolic acidosis has been described as a frequent acid base alteration in calves (Tennant et al., 1972; Naylor, 1987) and has been attributed in diarrheic calves, mainly to bicarbonate ion losses and in dehydrated patients, to decreased renal excretion of hydrogen ions, besides plasma lactic acid accumulation, secondary to anaerobic glycolysis caused by poor tissue hypoperfusion (Kasari & Naylor, 1986; Naylor, 1987; Tennant et al., 1972) or D-lactic acid gain due to bacterial fermentation (Ewaschuk et al., 2005; Omole et al., 2001). In adult cattle, metabolic alkalosis has been described related to gastrointestinal disorders as right abomasal displacement, abomasal volvulus, small intestinal obstruction and vagal indigestion (Braun et al., 1990; Roussel et al., 1998), as well as cattle treated with oral magnesium hydroxide (Kasari et al., 1990; Ogilvie et al., 1983). Due to the limited number of cases, a statistical correlation between etiologies and acid base disorders was not feasible. However, a hypochloremic metabolic alkalosis was identified in patients diagnosed with abomasal ulcer, vagal indigestion, small intestine intussusception and intestinal accident, in agreement with the expected clinical pathology findings of these etiologies in which abomasal reflux occurs and chloride and hydrogen ions are sequestered into the forestomach compartments known as functional pyloric stenosis (Braun et al., 1990; Ward et al., 1994).

AG acidosis was found in 10 patients. All calves < 3 months diagnosed with metabolic acidosis by BE\textsubscript{ECF} or plasma [HCO\textsubscript{3}-], had also an increased anion GAP, probably due to increased plasma either D- or L-lactic acid (Omole et al., 2001). Metabolic acidosis in calves used to be attributed to the increased AG, secondary to L-hyperlactatemia (Naylor, 1987), although, in most recent studies, this association has
not been found (Kasari & Naylor, 1984). Meanwhile, blood D-lactate (which is produced by bacterial fermentation in the gastrointestinal tract) has been related to metabolic acidosis in calves without dehydration (Ewaschuk et al., 2004; Lorenz, 2009) and only a moderate association between anion GAP and L-lactate in adult cattle has been described, limiting the usefulness to predict blood concentration of L-lactate in sick cattle (Constable et al., 1997).

Despite the clinical relevance of the Henderson-Hasselbalch approach, the accuracy of the model is affected in sick animals as a consequence of alterations in pH, plasma protein and sodium concentrations (Constable et al., 1997).

According to the physicochemical approach, the most common acid base disorder was strong ion acidosis, as well as weak acid alkalosis and strong ion acidosis concurrent with weak acid alkalosis. SID acidosis may be occasioned by the decrease in [Na⁺], increase in [Cl⁻] or accumulation of metabolically produced organic acids (lactate, acetoacetate or β-hydroxybutyrate) (Whitehair et al., 1995). Hyponatremia has been widely studied in diarrheic calves, as a consequence of increased water losses in the gastrointestinal tract along with electrolytes (mainly sodium and potassium) (Roussel et al., 1998; Tennant et al., 1972) and for reduced milk intake (Berchtold, 2009). Moreover, hyponatremia has been an important finding in acidotic sick calves with or without diarrhea (Constable et al., 2005; Gomez et al., 2013b), in agreement with the findings of the present study.

Hyperchloremic acidosis has been ascribed to the therapeutic use of 0.9% NaCl solutions (Stämpfli & Constable, 2003), and has been experimentally induced in calves to resemble metabolic acidosis secondary to diarrhea or ruminal acidosis (Gentile et al., 2008). Nonetheless, in this study, there were two cases of hyperchloremic acidosis along with increased SIG; therefore, acidosis could not be ascribed exclusively to the increased [Cl⁻] in those patients.

In a study carried out in 264 calves with neonatal diarrhea, strong ion gap (SIG) acidosis was the principal disorder and was diagnosed in 80% of the calves (Gomez et al., 2013b). Strong ion acidosis with increased SIG, has been attributed to the increased [lactate], both L and D isomers, as a consequence of hypoperfusion and hypovolemia secondary to dehydration, which results on an increased anaerobic glycolysis and organic acids (L-lactate) (Tennant et al., 1972), and bacterial production of D-Lactate in gastrointestinal tract, due to carbohydrate malabsorption (Ewaschuk et al., 2004; Omole et al., 2001).

Total plasma proteins are the main component of A- therefore, their concentration affect, in an independent way, the acid base balance. Hence, hypoproteinemina and hyperproteinemina caused alkalemia and acidemia, respectively (Stämpfli & Constable, 2003). In a retrospective study of 231 diarrheic calves, ruminal drinkers and septic diarrheic calves, weak acid acidosis was found due to the increased total plasma protein (Constable et al., 2005). Changes in plasma protein in sick animals may be related to the hydration status (Constable et al., 1998), but it may occur as consequence of other factors. As such, weak acid alkalosis may be due to decreased synthesis (hepatic failure, malnutrition, malabsorption), increased loss (urinary losses with nephropathy or enteropathy with protein loss) and increased capillary permeability (Wilkes, 1998). In this study, the cause of hypoproteinemina could not be identified, although, in three patients it could be caused by hepatic failure reflected by an increased in liver enzymes (AST and GGT).

The ROC analysis showed that the accuracy detecting acid-base disorders is higher in the physicochemical than in the Henderson-Hasselbalch approach. This approach allowed detecting more abnormalities, which may affect the selected treatment, and probably enhances the odds of a more positive outcome of these patients. The kappa statistic showed a fair agreement between the two approaches, due to the higher sensitivity of the physicochemical approach, especially in the diagnosis of alkalosis. Therefore, acid base disturbances following the Henderson-Hasselbalch approach may be misdiagnosed and the prognosis of those patients may be aggravated.

In conclusion, the physicochemical approach allowed detection of more acid base disturbances in hospitalized cattle than the Henderson-Hasselbalch approach. These results indicate the need to determine accurately the acid-base disorders in hospitalized cattle for their adequate treatment.

The limitations of this retrospective study are the limited number of clinical cases, which precluded eliciting statistical correlations between the etiology and the acid-base disorder, and use of two different blood gas analyzers, which may affect the accuracy of the blood gas measures.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the work presented in this report. The authors are responsible for the content and the writing of the paper.

Ethics Statement

This study was a retrospective study of records of patients already treated at Large Animal Hospital at Universidad Nacional de Colombia that did not involve direct animal use.

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