Effect of Intravenously Administered Crystalloid Solutions on Acid-Base Balance in Domestic Animals

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Intravenous fluid therapy can alter plasma acid-base balance. The Stewart approach to acid-base balance is uniquely suited to identify and quantify the effects of the cationic and anionic constituents of crystalloid solutions on plasma pH. The plasma strong ion difference (SID) and weak acid concentrations are similar to those of the administered fluid, more so at higher administration rates and with larger volumes. A crystalloid’s in vivo effects on plasma pH are described by 3 general rules: SID > [HCO₃⁻] increases plasma pH (alkalosis); SID < [HCO₃⁻] decreases plasma pH (alkalosis); and SID = [HCO₃⁻] yields no change in plasma pH. The in vitro pH of commercially prepared crystalloid solutions has little to no effect on plasma pH because of their low titratable acidity. Appreciation of IV fluid composition and an understanding of basic physicochemical principles provide therapeutically valuable insights about how and why fluid therapy can produce and correct alterations of plasma acid-base equilibrium. The ideal balanced crystalloid should (1) contain species-specific concentrations of key electrolytes (Na⁺, Cl⁻, K⁺, Ca²⁺, Mg²⁺), particularly Na⁺ and Cl⁻; (2) maintain or normalize acid-base balance (provide an appropriate SID); and (3) be isosmotic and isotonic (not induce inappropriate fluid shifts) with normal plasma.

Key words: Acid-base balance; Base replacement; Fluid therapy; Metabolic acidosis; Physiology.

Intravenous salt solutions ("crystalloids") are routinely administered to animals and are considered an established standard of care in many veterinary practices. They are administered to maintain or restore vascular volume, electrolyte concentrations, and acid-base balance and are utilized as diluents for large (>30 kD) molecular weight insoluble molecules to produce a colloid suspension ("colloids") that helps preserve plasma colloid osmotic pressure. Fluids are drugs, and although often considered to produce beneficial effects, they should only be administered after thorough consideration of the indication for which they are prescribed.2,3 Reasons for administering IV fluids include the prevention or treatment of dehydration, replacement of ongoing fluid losses, correction of electrolyte imbalances, restoration of tissue perfusion, treatment of hypotension, and correction of acid-base abnormalities.1,4 Although the beneficial volume effects of IV fluids have been appreciated for more than 100 years, their impact on the extracellular and intracellular concentrations of electrolytes, acid-base balance, and survival is only beginning to be appreciated.5–10

Improvements in hydration status and hemodynamic parameters (macrocirculatory features such as arterial blood pressure, blood flow) are frequently the primary goals of IV fluid therapy. Macrocirculatory improvements, however, do not always insure an improvement in capillary perfusion (microcirculatory effect), cellular homeostasis, or survival.11–13 The maintenance of normal blood hydrogen ion (H⁺) activity is a key factor linked to survival, and its regulation is one of the most tightly controlled homeostatic processes in the body.14–18 Use of the term hydrogen ion concentration ([H⁺]), although commonplace in the acid-base literature, is misleading and should be discouraged because it is hydrogen ion activity (pH) that is measured by pH electrodes. Hydrogen ions are considerably smaller than other chemicals in aqueous solutions but have the highest charge density of any electrolyte in plasma.19 Hydrogen ions (protons) are chemically active because of the electromotive force (activity) they produce. Furthermore, hydrogen ion concentration cannot be accurately determined in vivo because it is calculated assuming an activity coefficient of 1, but its activity coefficient in plasma is uncertain. Comparatively small changes in H⁺ activity (pH) can produce substantial and potentially life-threatening alterations in cellular metabolism (Fig 1).20,21 Acidemia (decreased blood pH) and alkalosis (increased blood pH) directly impact morbidity and mortality and are decidedly influenced by the administration of IV fluids.21–24 This review will summarize the various methods used to identify and

Abbreviations:
AG anion gap
A tot nonvolatile weak acids
NHE1 Na⁺/H⁺ exchanger
PCO₂ partial pressure of carbon dioxide
pKa pH at which the acid and conjugate base are equal
SID apparent SID
SIDe effective SID
SIDv in vivo SID
S ID strong ion difference
SIG strong ion gap
THAM trishydroxymethyl aminomethane
UA unmeasured anion
describe acid-base abnormalities, provide a modern definition for what is considered to be a balanced crystalloid solution, and explain how IV fluid therapy can alter acid-base balance. The use of different IV fluids for the treatment of metabolic acidosis will be reviewed, and the influence of commercially prepared IV fluid solutions on acid-base balance will be discussed.

**Diagnosing and Describing Acid-Base Disorders**

Regrettably, conflicting opinions, ambiguous terminology, computational complexity, and, until recently, the absence of simplified and versatile monitoring equipment have hindered the assessment and diagnosis of acid-base abnormalities in veterinary clinical practice. The various approaches employed for the diagnosis and description of acid-base abnormalities are based upon changes in blood pH (negative base 10 logarithm of activity) or the principal analytes responsible for its alteration (Fig 2). They include (1) the Henderson-Hasselbalch approach; (2) the anion gap (AG) approach; (3) the Astrup and Siggaard-Andersen (base excess [BE]) approach; and (4) the physiochemical or Stewart approach.

The Henderson-Hasselbalch approach is based on the relationship among pH, PCO₂, and HCO₃⁻. The Henderson-Hasselbalch equation is

$$\text{pH} = \text{pK} + \log \left( \frac{[\text{HCO}_3^-]}{\text{PCO}_2/0.308} \right)$$

where PCO₂ is measured in mmHg at 37°C and is the basis of [HCO₃⁻] determination by blood gas analyzers. The anion gap (AG) approach attempts to identify changes in acid-base balance by determining the difference between the principal cations and anions (AG = ([Na⁺] + [K⁺]) - ([Cl⁻] + [HCO₃⁻])). An increase in the AG is considered indicative of an increase in fixed (nonvolatile) acid and metabolic (nonrespiratory) acidosis. Increased AG acidosis (e.g., lactic or ketoacidosis) is characterized by decreased plasma bicarbonate concentration without hyperchloremia. Increased plasma chloride concentration (i.e., hyperchloremia) is accompanied by a decrease in plasma [HCO₃⁻] with no increase in the AG, a condition referred to as “normal AG acidosis” or “hyperchloremic acidosis.”

Discontent with the Henderson-Hasselbalch approach prompted Singer and Hastings to introduce the BE concept and propose that plasma pH be determined by 2 independent factors, PCO₂ and net strong (highly dissociable) ion charge, equivalent to the SID. Base excess is comparable to the difference between an animal’s SID and the normal SID for that species. Discontent with the Henderson-Hasselbalch approach prompted Singer and Hastings to introduce the BE concept and propose that plasma pH be determined by 2 independent factors, PCO₂ and net strong (highly dissociable) ion charge, equivalent to the SID. Base excess is comparable to the difference between an animal’s SID and the normal SID for that species.

**Fig 1.** Relationship between approximate pH values and mortality in 754 critically ill human patients.

**Fig 2.** The different approaches used to diagnose and describe acid-base disorders can be categorized as descriptive, semiquantitative, and quantitative. The physiochemical (Stewart) approach can be used in all 3 capacities. Aₜot = total weak acids; PCO₂ = partial pressure of carbon dioxide; SBE = standard base excess; SID = strong ion difference; SIG = strong ion gap.

**Fig 3.** Principal independent factors that determine pH.
and the administration of crystalloid solutions can alter acid-base balance (Table 1).15,31,33–39

**Physicochemical or Stewart Approach to Acid-base Abnormalities**

Strong ions behave as though nearly completely dissociated at physiologic pH, and the SID characterizes the net charge that must be balanced by all of the nonvolatile weak acids (A\text{rot}, primarily albumin, and phosphate) in order to maintain electrical neutrality.31 The plasma SID is typically calculated as the difference between all measurable strong cations ([Na\textsuperscript{+}] + [K\textsuperscript{+}] + [Ca\textsuperscript{2+}] + [Mg\textsuperscript{2+}]) and anions ([Cl\textsuperscript{−}] + [other strong anions, e.g., lactate]) and is frequently referred to as the apparent SID (SID\textsubscript{a}) because this value is representative of the majority of ions found in plasma. The SID\textsubscript{a} is normally positive (+40–45 mEq/L), and this net charge is balanced by the negative charge of the fixed weak anion components of phosphate and proteins (A\text{rot}), and bicarbonate.40–42 As stated earlier, the sum of the nonvolatile weak acids, A\text{rot}, is an independent variable that impacts hydrogen ion activity and therefore pH (Fig 3). An increase in the concentration of lactate and unmeasured anions (other organic acids) from any cause (e.g., hemorrhage, trauma, hypoxia) will increase hydrogen ion activity creating metabolic acidosis.43–45 Importantly, fluid selection and infusion strategies are key factors that can influence the production of unmeasured anions (UA).46 The [UA] can be derived by subtracting the effective SID (SID\textsubscript{e}, the sum of the negatively charged substances) from SID\textsubscript{a}, thereby defining the strong ion gap (SIG, SIG = SID\textsubscript{a} – SID\textsubscript{e} = UA; Fig 4).47 Delayed metabolism or elimination of any UA\textsuperscript{−} decreases SID\textsubscript{e}, thereby increasing the SIG and contributing to metabolic acidosis.47 Notably, the SID\textsubscript{a} minus SID\textsubscript{e} (SIG) is equal to or near zero when plasma pH is 7.4 and PCO\textsubscript{2} is 40 mmHg. The SID\textsubscript{e} and SIG have been used clinically in both humans and animals to identify acid-base imbalances and predicting mortality, respectively.37–35 Current evidence, however, suggests that directly measured serial arterial lactate concentrations may provide as good or better prognostic ability than SIG for discriminating between survivors and nonsurvivors.53,54 Simplified versions of the Stewart approach have substantially improved the recognition and contribution of electrolyte abnormalities (alterations in SID) in maintaining acid-base balance and highlight the importance of fluid selection as a potential therapy.34,37–39,52–56

**Table 1.** Stewart approach to acid-base balance

| Independent Variable | Change | Acid-base Effect | pH |
|----------------------|--------|------------------|----|
| PCO\textsubscript{2} mmHg | ↑ | Respiratory acidosis | ↓ |
| SID mEq/L | ↓ | Respiratory alkalosis | ↑ |
| A\text{rot} mmol/L | ↓ | Metabolic alkalosis | ↑ |
| | ↑ | Metabolic acidosis | ↓ |
| | ↓ | Metabolic alkalosis | ↑ |

↑ = increase; ↓ = decrease.

**Crystalloids and Balanced Crystalloids**

Crystalloid solutions are prepared by diluting relatively small amounts of the salts of physiologically relevant elements (Na\textsuperscript{+}, K\textsuperscript{+}, Ca\textsuperscript{2+}, Mg\textsuperscript{2+}, Cl\textsuperscript{−}) in water. These elements are electrically balanced (law of electrical neutrality) but fully dissociate (e.g., strong cations and anions) in water because their pKa (pH at which the acid and conjugate base are equal) value is considerably different (e.g., the pKa of lactic acid = 3.86, and therefore it is fully dissociated) from that of normal plasma pH (7.40). Compounded crystalloids may contain added NaHCO\textsubscript{3} in order to treat (buffer) or resist pH changes from nonrespiratory causes of acidosis. Most commercial manufacturers of crystalloid solutions have abandoned the addition of Na\textsuperscript{+} HCO\textsubscript{3} to replace chloride ion when stored in plastic bags that allow equilibration with atmospheric CO\textsubscript{2} because of the potential to form divalent carbonate (CO\textsubscript{3}\textsuperscript{2−}) and precipitates with calcium and magnesium.57,58 Most manufacturers have replaced HCO\textsubscript{3} with an organic anion (lactate, acetate, citrate) with the expectation that it will act as a “precursor” or stable surrogate for bicarbonate (Table 2).59,60 In addition, replacing some of the Cl\textsuperscript{−} with an organic anion maintains electrical neutrality and lowers the solution’s [Cl\textsuperscript{−}].59 Organic anions are strong anions (pK < 4) combined with Na\textsuperscript{+}. Their role is not to generate HCO\textsubscript{3}, as often taught, but to be rapidly metabolized and disappear from solution, thus increasing the in vivo SID\textsubscript{a}.60–63 This requirement is met in most animals but is likely to be species dependent, compromised in sick animals, and dependent upon the rate and amount of organic ion administered.64–69 The in vivo fate of organic anions as HCO\textsubscript{3} generators in animals with naturally occurring diseases (hypovolemic shock; sepsis) requires further investigation.

The term “balanced” was originally devised to describe mixtures of various salts in water that produced electrolyte concentrations similar to normal plasma.5–7,56,57,59 This term, however, has become both confusing and misleading because it is not always applicable.
apparent what is balanced (e.g., [Na⁺] or [Cl⁻]), effective osmolality, pH relative to plasma) and because the fate of organic anions is not always predictable.⁷⁰,⁷¹ Normal or physiologic saline (0.9% NaCl), Ringer’s solution, lactated Ringer’s solution (LRS), and compound sodium lactate (Hartmann’s) are historically popular resuscitation fluids in both human and veterinary medicine.⁵–⁷,⁷² Saline (0.6–0.9% NaCl) evolved from in vitro experiments designed to prevent hemolysis of human red blood cells whereas Ringer’s solution was formulated in order to improve the contraction of beating frog hearts in vitro.⁷²,⁷³ Lactated Ringer’s and Hartmann’s solutions soon followed by adding lactate to Ringer’s solution in order to buffer dehydration-associated acidosis in humans.⁷⁴ Although the concentrations of 1 or more electrolytes in each of these 3 solutions are comparable to those found in plasma, none are truly “normal,” “physiologic,” “plasma adapted,” or balanced, especially when different species of animals are considered (Table 2).⁵⁶,⁵⁷,⁶⁹,⁷¹ If “balanced” is meant to imply a solution that has an electrolyte composition close to plasma, normal [Cl⁻], and 1 that maintains normal (effective) osmolality, tonicity, and pH values, then the composition of most commercially prepared “balanced” crystalloids can be challenged.⁵⁶,⁷⁵,⁷⁶ I propose that balanced crystalloid solutions should (1) contain species-specific concentrations of key electrolytes (Na⁺, Cl⁻, K⁺, Ca²⁺, Mg²⁺), particularly [Na⁺] and [Cl⁻]; (2) maintain or normalize acid-base balance (provide an appropriate SID); and (3) be isosmotic and isotonic (not induce inappropriate fluid shifts) with normal plasma.

### pH of Commercial Crystalloid Solutions

The pH of most commercially prepared crystalloids varies between 4.0 and 6.5 unless specified otherwise (e.g., Normosol-R⁸ [pH 7.4], Plasma-Lyte A⁸ [pH 7.4], Plasma-Lyte 148⁸ [pH 7.4]). A solution’s in vitro pH is a measure of the degree of acidity or alkalinity of the solution and not the total reservoir (or lack thereof) of hydrogen ions available.⁷⁸ Three factors determine the in vitro pH of commercially prepared solutions: the container (glass or polyvinyl chloride [PVC]), the temperature-dependent solubility of CO₂ in water, and the concentration of electrolytes (strong ions) added to the solution. Glass containers are considered to be inert, but autoclaving of PVC packaged solutions generates small quantities of acetic and formic acid, lowering the solution’s pH.⁷⁸,⁷⁹ This source of acidity, however, is inconsequential based upon the miniscule amounts of H⁺ produced.⁷³ Carbon dioxide absorbed from air is the largest contributor to hydrogen ion activity and a decrease in pH in commercial solutions. Finally, the addition of physiologically relevant concentrations of salts to water is believed to influence the formation of hydronium ions (H₃O⁺) favoring an increase in hydrogen ion activity and a decrease in pH.⁷⁹ The

### Table 2. Characteristics of crystalloid and colloid solutions.

| Fluid          | pH    | Na⁺ (mEq/L) | Cl⁻ (mEq/L) | K⁺ (mEq/L) | Ca²⁺ (mEq/L) | Mg²⁺ (mEq/L) | Buffer      | Osmolarity (mOsm/L) | COP (mmHg) | SID (mEq/L) | Viscosity (cP) |
|----------------|-------|-------------|-------------|------------|--------------|--------------|-------------|-------------------|-------------|--------------|----------------|
| 0.9% NaCl      | 5.5   | 154         | 154         | 0          | 0            | 0            | 308         | 0                 | 0           | 0           | ≈1            |
| 7.5% Saline    | 5.5   | 1283        | 1283        | 0          | 0            | 0            | 2,566       | 0                 | 0           | 0           | ≈1            |
| 1.4% NaHCO₃    | 7.4   | 140         | 98          | 5          | 0            | 3            | Lactate 28  | 273               | 0           | 27          | ≈1            |
| 8.4% NaHCO₃    | 7.4   | 140         | 98          | 5          | 0            | 3            | Lactate 27  | 295               | 0           | 27–50        | ≈1            |
| 3% NaLactate   | 7.0   | 504         | 7           | 4          | 2.7          | 0            | Lactate 504 | 1,020              | 0           | 500         | ≈1            |
| LRS            | 6.5   | 130         | 109         | 4          | 3            | 0            | Acetate 27  | 273               | 0           | 27–50        | ≈1            |
| Normosol-R     | 7.4   | 140         | 98          | 5          | 0            | 3            | Acetate 27  | 295               | 0           | 27–50        | ≈1            |
| Plasma-Lyte A  | 7.4   | 140         | 98          | 5          | 0            | 3            | Acetate 27  | 294               | 0           | 27–50        | ≈1            |
| Plasma-Lyte 148| 6.0   | 140         | 98          | 5          | 0            | 3            | Acetate 27  | 294               | 0           | 27–50        | ≈1            |
| 5% Albumin     | 5.5   | 154         | 154         | 0          | 0            | 0            | 308         | 19                | 0           | 1.2–1.5      |               |
| 6% Het/Saline  | 5.5   | 154         | 154         | 0          | 0            | 0            | 308         | 3                 | 0           | 4.3          |               |
| 6% Het/LRS     | 6.5   | 143         | 124         | 3          | 5            | 0.9          | 28          | 303               | 28          | 4.3          |               |
| 6% Tetra/Saline| 5.5   | 154         | 154         | 0          | 0            | 0            | 308         | 42                | 0           | 4           | ≈4            |
| Blood          | 7.4   | ≈150        | ≈105        | ≈4         | ≈5           | ≈2           | 40          | 300–305           | 20–25       | 40           | 3.5           |

Common properties of crystalloid and colloid solutions used for fluid therapy. LRS, Lactated Ringer’s solution.

⁸Hospira, Inc., Lake Forest, IL 60045.

⁸Baxter Healthcare Corporation Deerfield, IL 60015.

⁺l-lactate; Het, hetastarch; Tetra, tetrastarch.

⁷Glutonate is a mixed nonmetabolizable strong ion.
concentration of the electrolytes in 0.9% NaCl, for example, is responsible for lowering the pH approximately 0.01 pH unit.70 Sterile distilled water has a pH of approximately 5.6 at sea level and at 25°C due to the absorption of CO₂ from the atmosphere;70 the same process is the largest contributor to hydrogen ion activity in commercial solutions stored in plastic containers.70

Titratable acidity, as measured by the titration of any commercial crystalloid solution with NaOH to pH = 7.4, is clinically negligible in all commercial crystalloids and ranges from 0.126–0.152 mEq/L for 0.9% NaCl.70 The low titratable acidity of 0.9% NaCl implies that it is not the solution’s in vitro pH that is responsible for its potential to produce an in vivo metabolic acidosis but rather the solution’s effect (0.9% NaCl = 0) on the in vivo SID.

The Acid-Base Effects of Intravenous Fluid Therapy

All crystalloids have the potential to significantly alter acid-base balance because of differences in their physicochemical composition relative to plasma.56,71

The SIDₜ of normal plasma is approximately 40–44 mEq/L (mM/L), suggesting that administration of a crystalloid with an in vivo SID (SIDᵢₚ) of 40–44 mEq/L should maintain plasma SID within the normal reference range. Infusion of a solution with an SIDᵢₚ of 40–44 mEq/L, however, results in the development of metabolic alkalosis because of progressive dilution of SIDₜ.56 Acid-base balance is achieved when the SIDᵢₚ of the infused fluid is similar to the normal plasma [HCO₃⁻] of the species (omnivore versus herbivore) being treated.

The in vitro SID of all crystalloid and colloid solutions is zero (law of electrical neutrality) but ranges from 0 to 50 mEq/L in vivo because of the addition of metabolizable organic anions (e.g., lactate, acetate, citrate, gluconate; Table 2). Because commercially prepared crystalloids do not contain HCO₃⁻, final plasma pH is determined by the net charge difference produced by the crystalloid’s SIDᵢₚ after metabolism of the crystalloid’s organic anion(s) in proportion to the rate and volume of fluid administered.70 The rapid infusion of large volumes of any crystalloid, for example, will cause the extracellular fluid (plasma and interstitial fluid) to become metabolizable because of poor metabolism. Other issues associated with the infused fluid are the principal determinants of the solution’s effect on plasma pH. A low infusion rate (10 mL/kg/h) of 0.9% NaCl, Hartmann’s solution, or a polyionic glucose-free maintenance solution for 2 hours (total volume = 20 mL/kg) to 60 normal dogs, for example, produced no significant differences in plasma electrolytes, total protein, plasma osmolality, SIG, or pH.71,77

Acute Metabolic Acidosis: Causes, Consequences, and Treatment

Acute metabolic (nonrespiratory) acidosis is caused by diseases that increase the production or decrease the elimination of nonvolatile fixed acids or decrease the body’s buffering capabilities. Metabolic acidosis can be characterized by a decrease in SIDₜ or increase in Aᵦᵩᵩ with resultant decreases in [HCO₃⁻] and secondary (compensatory) decreases in PCO₂ (approximately 0.7 mmHg for each 1 mEq/L decrease in [HCO₃⁻]). Metabolic acidosis also may coexist with respiratory acidosis in animals that have impaired pulmonary function.91,92 Acute metabolic acidosis can be further classified as normal (nonion gap acidosis, hyperchloremic metabolic acidosis) or high anion gap
Acidosis, lactic acidosis (hyperlactatemia > 2 mmol/L), a high anion gap acidosis, is considered evidence for tissue hypoxia, tissue hypoperfusion, and anaerobic metabolism and is used as a prognostic indicator for increased morbidity and mortality in humans and animals. Lactic acidosis in sepsis is multifactorial and may be caused by regional tissue hypoxia and increased aerobic glycolysis secondary to cytokine-stimulated cellular glucose uptake and catecholamine stimulation of Na-K ATPase. SID, difference between strong cations and strong anions.

Acidemia decreases cardiac contractility, decreases blood flow (cardiac output), increases susceptibility to cardiac arrhythmias, impairs responsiveness to catecholamines, alters the immune response, and promotes a systemic inflammatory state. Severe metabolic acidosis (pH < 7.15) may decrease systemic and increase pulmonary vascular resistance, worsening hypotension and tissue perfusion. Intracellular acidification (decreased pH) also activates Na-dependent acid/base transporters. The Na+/H+ exchanger (NHE1) is a ubiquitous and integral membrane transporter involved in regulating cell volume and pH. Activation of NHE1 increases intracellular [Na+] and [Ca+++] resulting in alterations in cellular metabolism and cell membrane potential and is likely the principal cause for poor cardiac function, arrhythmias, and increased concentrations of proinflammatory cytokines.

Treating acute acidemia (pH < 7.2) is not simple and should be based upon identification and control of the pathophysiologic process(s) responsible for its production. Ideally, species-specific crystalloids containing appropriate quantities of electrolytes and metabolizable organic anions are preferred for maintaining tissue perfusion and correcting mild acid-base abnormalities in otherwise normal healthy animals. Alkaline therapies including NaHCO₃ or carbon dioxide-consuming bases (trishydroxymethyl aminomethane: THAM) and Carbicarb (combination of NaHCO₃ and Na₂CO₃) are more effective treatments for acute severe metabolic acidosis than abnormal saline because of their high SIDₜ (Table 2). Carbicarb (SIDₜ = 210; 300 mOsm/L) generates less CO₂ than NaHCO₃ and therefore is less likely to produce intracellular acidosis whereas THAM (SIDₜ = 201; 300 mOsm/L) increases the buffering capacity of blood without generating CO₂ and does not produce hypernatremia or hypokalemia. Neither THAM nor Carbicarb, however, has therapeutic advantages compared to NaHCO₃ in clinical practice. All 3 therapies remain controversial because

**Table 3. Misconceptions of acid-base balance and fluid therapy.**

| Misconception | Fact |
|---------------|------|
| The pH of plasma is determined by the partial pressure of carbon dioxide (PCO₂) and the bicarbonate ion (HCO₃⁻) | Partially true: the plasma pH is determined by 3 primary independent variables: PCO₂, A⁰, and SID. Changes in [HCO₃⁻] are dependent on these same 3 factors |
| Most commercially available fluids produce no effect on plasma acid-base balance | All commercially available fluids produce changes in plasma acid-base balance dependent upon their ability to change in vivo strong ion difference: Their effects on plasma SID become more pronounced when larger fluid volumes are administered rapidly |
| Fluid administration produces acidosis by dilution of plasma [HCO₃⁻] | Fluid administration does dilute [HCO₃⁻] producing metabolic acidosis but also dilutes A⁰ producing metabolic alkalosis. Crystalloid-induced changes in plasma pH are primarily caused by a change in SID, not dilution |
| The in vitro pH of commercial crystalloid solutions can acidify the plasma | The titratable acidity of all commercially available IV crystalloid solutions has no clinically relevant effect on plasma pH |
| Physiologic saline solution (0.9% NaCl) has no effect on plasma pH | 0.9% NaCl in vivo SID (SIDₜ) = 0 and produces hyperchloremic metabolic acidosis; effect is related to dose and administration rate |
| Physiologic saline solution is harmful to animals | 0.9% NaCl effect on [H⁺] is usually negligible in normal healthy animals unless large volumes (>30 mL/kg) are administered over a short period (<1 h) or administered to animals that already have metabolic acidosis |
| Lactated Ringer’s solution (LRS) is a “balanced” crystalloid | LRS is hypotonic (273 mOsm/L): Tonicity is the effective osmolality of a solution |
| The lactate in LRS is a bicarbonate precursor or bicarbonate substitute | The role of lactate (like all organic anions) in LRS is to be rapidly metabolized (disappear), thereby increasing SID |
| The lactate in LRS is an ideal organic anion to substitute for bicarbonate | LRS contains a racemic mixture of D and L-lactate as an inorganic ion. D-lactate is proinflammatory and can cause CNS depression |
| Normosol-R and Plasma-Lyte maintain normal plasma pH | Normosol-R and Plasma-Lyte have an SIDₜ = 50 increasing plasma pH |
| Sodium bicarbonate solution administration produces CNS and intracellular acidosis (paradoxical acidosis) | Possibly true but the effect is dose and rate of administration related, usually transient and clinically irrelevant in animals that are adequately ventilated |

[A], concentration; pH, negative log of [H⁺]; PCO₂, partial pressure of carbon dioxide; A⁰, weak nonvolatile acids, inorganic phosphate, serum proteins, and albumin; SID, difference between strong cations and strong anions.
of selective or uncertain long-term benefit and the potential for complications.\textsuperscript{126,127} More specifically, the Surviving Sepsis Campaign guidelines of 2016 recommend “against the use of sodium bicarbonate therapy to improve hemodynamics or to reduce vasopressor requirements in patients with hypoperfusion-induced lactic acidemia.”\textsuperscript{128} In addition, sodium bicarbonate has the potential to produce hyperosmolality, hypernatremia, hypokalemia, decreased ionized calcium concentration, and increased hemoglobin affinity for oxygen.\textsuperscript{129,130} Sodium bicarbonate also is believed to produce paradoxical intracellular and CNS acidosis (decreased pHi as plasma pH increases) an effect that is not observed in ventilated animals.\textsuperscript{131,132} Regardless, the IV administration or addition of various commercially available or compounded hypertonic NaHCO\textsubscript{3} solutions (8.4%: SID \textsuperscript{154}mEq/L, 2,000 mOsm/L; 5.0%: SID = 595 mEq/L, 1190 mOsm/L; 1.3%: SID = 154 mEq/L, 310 mOsm/L) have been shown to be more effective than balanced crystalloid solutions for treating diarrheic calves.\textsuperscript{135,136} More recently, the co-administration of NHE exchange inhibitors (e.g., sabiporide) and sodium bicarbonate or hypertonic sodium L-lactate (3%) has been shown to restore acid-base balance, improve cardiac performance and hemodynamic parameters, promote urine formation, improve endothelial function, and decrease extracellular fluid accumulation in acidotic, hemorrhaged, hypotensive, endotoxic, and traumatized animals, in addition to preventing intracranial hypertension after severe traumatic brain injury.\textsuperscript{137,145} Hypoosmolar sodium L-lactate also may serve as a potential energy substrate (3.61 kcal/g).\textsuperscript{144} Collectively, these studies suggest that restoration of vascular volume and tissue perfusion and removal of tissue oxygen debt in conjunction with normalization of plasma pH are key factors in the success or failure of alkalinizing and cell protective therapies.\textsuperscript{136,137,141,144–148}

Concluding Comments

Misconceptions regarding the interpretation and influence of crystalloid therapy on acid-base balance can confound fluid selection (Table 3). Balanced crystalloids should (1) contain species-specific concentrations of key electrolytes (Na\textsuperscript{+}, Cl\textsuperscript{−}, K\textsuperscript{+}, Ca\textsuperscript{2+}, Mg\textsuperscript{2+}), particularly Na\textsuperscript{+} and Cl\textsuperscript{−}; (2) maintain or normalize acid-base balance (provide an appropriate SID); (3) be isosmotic and isoionic (not induce inappropriate fluid shifts) with normal plasma; and (4) consider the temperature dependence of H\textsubscript{2}CO\textsubscript{3}. New insights regarding the mechanisms responsible for acid-base balance, the role and efficacy of organic anions as buffers, and the importance of a crystalloid’s SID\textsubscript{v} have helped clarify and determine fluid selection. The administration of large volumes of solutions containing high concentrations of chloride (e.g., 0.9% NaCl) can no longer be supported because of their potential to produce hyperchloremic metabolic acidosis, impair renal function, and increase mortality.\textsuperscript{75,147–150} A small volume of hypertonic sodium bicarbonate solution is an effective treatment for metabolic acidosis and hyperkalemia in dehydrated, hypovolemic, septic animals as long as larger volumes of balanced solutions also are administered to restore tissue perfusion.\textsuperscript{135,136} More species-specific research is required to identify appropriate fluid choices within the context for which they are prescribed.\textsuperscript{3} Ideally, fluid administration should be continuously monitored, frequently reassessed, and focused upon the restoration cardiovascular function, vascular volume, electrolyte concentrations, effective osmolality, tonicity, plasma SID, and pH.

“We are still confused – but on a much higher level”
W. Churchill.

Footnotes

\textsuperscript{a} Hospira, Inc., Lake Forest, IL 60045
\textsuperscript{b} Baxter Healthcare Corporation Deerfield, IL 60015
\textsuperscript{c} Abbott Laboratories, North Chicago, Ill 60064
\textsuperscript{d} International Medication Systems, South El Monte, CA 91733
\textsuperscript{e} Berchtold, J., H. Hartmann, and W. Hofmann. “The comparative effectiveness of Carbicarb-R, Tribonate-R and bicarbonate in the treatment of acidosis in neonatal calves.” In: Proceedings of the 30th Annual Conference of the American Association of Bovine Practitioners, Montreal, CAN. 1997.p.135

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