HIGH SCHOOL EDITION
Journal of Student Research
Volume 13 Issue 4 (2024)

The Effects of Sodium Bicarbonate on Acid-Base. Imbalances: Balancing the pH: Mechanistic Insights and Clinical Impact

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ABSTRACT

Increasing levels of bicarbonate in human blood influence the buffering capacity, thereby stabilizing blood pH levels and improving overall acid-base homeostasis. About fifteen percent of individuals worldwide suffer from chronic kidney disease (CKD), in which the kidney loses its ability to soak up the excess acid circulating throughout the human body [1]. Metabolic acidosis is the term given when an individual's body system carries an excess amount of acid, which puts the individual at risk for cardiovascular diseases, respiratory diseases, and many more. This literary review aims to answer the problem presented by excess acid or base in the bloodstream through an increase in the blood buffer capacity. Although sodium bicarbonate is not a viable option in every situation, it can surely be used to treat and alleviate aggregations in certain contexts. Sodium bicarbonate provides the means by which the blood system can remain at homeostasis throughout different conditions, but this homeostasis is often short-lived.

Introduction

Both genetics and environmental influences play a role in chronic kidney disease. This disease increases the individual's susceptibility to an array of diseases. Renal failure or kidney disease causes the individual's acid-base levels in the blood to fluctuate from homeostasis, often causing a lower than average pH and resulting in acidosis. The blood system is naturally built with a buffer system, which consists of bicarbonate. This system allows for acid and base to naturally flow into the blood streams to allow for homeostasis and keep the blood near the pH of 7.40, which is the necessary pH for human survival. Patients suffering from CKD often have a lower than average pH level, and this occurs as a result of the kidney's inefficiency to excrete the hydrogen ions, which leads to metabolic acidosis. This is just one of the many pathways to acidosis, which is a problem faced by a multitude of individuals who may have reached this consequence in an array of different ways. One of the primary therapeutic agents used to treat this imbalance in the blood system is sodium bicarbonate. Sodium bicarbonate is a buffer that helps neutralize excess acid in the bloodstream. This buffer has uses in an array of conditions, such as chronic kidney disease, severe lactic acidosis, and many more. The goal of sodium bicarbonate is to restore acid-base equilibrium in order to improve organ function in the human body system. This literature review will explore the efficacy, benefits, and potential risks of sodium bicarbonate administration in patients with acid-base discrepancies. It will first demonstrate the basics of sodium bicarbonate administration and then analyze current research and clinical studies to better understand the controversy surrounding sodium bicarbonate therapy.

Sodium Bicarbonate vs. Serum Bicarbonate

Before understanding the different effects that the addition of sodium bicarbonate has on the human blood buffer system, it is important to note the different uses of bicarbonate. Sodium bicarbonate often describes the compound

itself and its administration as a treatment. It is used to correct acid-base imbalances, such as metabolic acidosis. It does so by increasing bicarbonate levels in the blood, allowing for extra acid to be removed and for homeostasis to regain prominence. It is a compound that can be administered orally or intravenously. The method of administration is solely dependent on the severity of the situation. This compound contains sodium, which is a cation, and bicarbonate, which acts as an anion in this chemical compound. It must be used carefully and only in certain situations, as will become clearer throughout this literature review. If given at an excessive level, it can lead to detrimental problems such as metabolic alkalosis (opposite of metabolic acidosis) and electrolyte imbalances. On the other hand, serum bicarbonate is used to describe the overall bicarbonate concentration in the blood. It is often heard of during the diagnosis of a patient. The term diagnostic marker is often given to it as it assesses a patient's acid-base balance and also their overall metabolic state. Lower serum bicarbonate numbers are most likely associated with a decline in kidney function. Serum bicarbonate is a part of the official bicarbonate-carbonic acid buffer system. The measurement of serum bicarbonate in an individual is done through a blood test, which is normally included in an electrolyte panel or blood gas analysis. Normal serum bicarbonate levels range from 22 to 28 mEq/L [1].

Effect of Serum Bicarbonate on CKD Patients

The estimated glomerular rate (eGFR) is used to understand how well an individual's kidneys are filtering. Many studies have shown that patients with a lower serum bicarbonate were most associated with a decline in eGFR, or kidney failure [1]. An increase in serum bicarbonate primarily influences the eGFR in a positive manner, which is shown by an increase in the value, meaning that the kidney has gained a better ability to filter. This increase occurs in multiple steps. First, the addition of the serum allows for the reduction of metabolic acidosis, which in turn results in the kidneys' increased ability to excrete acid. Along with this benefit, an improvement in renal blood flow is presented, as metabolic acidosis can lead to vasoconstriction (narrowing of blood vessels) and reduced renal blood flow. Reducing the metabolic acidosis allows for improved renal perfusion and, consequently, glomerular filtration rate (GFR) [2]. Acidosis is a known factor that promotes renal injury through mechanisms such as increased ammoniagenesis, activation of the complement system, and promotion of tubulointerstitial fibrosis. But the increased serum bicarbonate mitigates these dangerous occurrences, which protects the kidneys from damage. Another benefit of the addition of bicarbonate is that it can improve tubular function, which allows the kidneys to better maintain electrolyte and fluid balance, which indirectly supports the maintenance of GFR. Lastly, acidosis greatly affects the secretion and action of various hormones, which play roles in phosphate metabolism and kidney function. These hormones include parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23). Correcting the detrimental process known as acidosis helps in equalizing these hormonal balances, which in turn contributes to better kidney function. When used on patients with chronic diseases, the effect, on the contrary, would be very detrimental. Sodium bicarbonate can only be used as a remedy for acute diseases.

Formation of Metabolic Acidosis Through the Accumulation of Plasma Anions

Metabolic acidosis is indicated by an acidic pH in the bloodstream. This occurs through the relative accumulation of plasma anions in excess of cations [4]. Sodium bicarbonate has been proven to be of great use when patients lose their necessary amount of bicarbonate through renal proximal tubular acidosis, but there isn't much evidence of its effect on those with more severe problems such as metabolic acidosis, including diabetic ketoacidosis, lactic acidosis, septic shock, intraoperative metabolic acidosis, or cardiac arrest. CKD patients often show signs of metabolic acidosis as a result of increased anions and hyperchloremia [4]. The therapy, which involves the injection of serum bicarbonate, comes with an array of side effects, which include hypercapnia, hypokalemia, ionized hypocalcemia, and QTc interval prolongation. The main plasma (pCO_2) is measured by blood gas analyzers to indicate the pressure put out by the small portion of CO_2 dissolved in the aqueous phase of plasma. The concentration of plasma bicarbonate is used to

measure pH and pCO1 values. Laboratory analyzers are used to measure the tCO2, which reflects the total amount of CO2 present in the blood. This primarily corresponds to the sum of bicarbonate and dissolved carbon dioxide, or pCO2 [4]. This relationship between the pH and the pCO2 can be used to calculate plasma bicarbonate concentration through the application of the Henderson-Hasselbalch equation.

$$CO_2 + H_2O \longleftrightarrow H_2CO_3$$
$$H_2CO_3 \longleftrightarrow H^+ + HCO_3^-$$

$$K_1 = \frac{[H_2CO_3]}{[CO_2][H_2O]}.$$

$$K_2 = \frac{[H^+][HCO_3^-]}{[H_2CO_3]}.$$

$$pH = pK_a + \log \frac{[HCO_3^-]}{\alpha \times pCO_2}.$$

$$pH = 6.1 + \log \frac{[HCO_3^-]}{0.03 \times pCO_2}.$$

[4] Equations 1-5

*Note: K_2 is known as Ka as referred to by the H-H equation.

The relationship configured through the Henderson-Hasselbalch equation has the possibility of being flawed as a result of the isoenzymes of carbonic anhydrase (CA) [4]. To better understand, this occurs because the hydration of carbon dioxide requires the action of isoenzymes of carbonic anhydrase, which can be anchored to the plasma membrane of red blood cells or lie inside the erythrocytes [4]. Isoenzymes refer to enzymes that differ in amino acid sequence but catalyze the same chemical reaction [5]. Carbonic anhydrase is an important part of this process, as its action is required for further results [4]. The carbonic anhydrase functions to promote rapid buffering to stabilize the pH [6]. CAs are found in almost every living organism and are encoded by seven different gene families (α, β, γ, δ, ξ, η, and θ) [6]. Out of these families, the α-family has the greatest role in human body systems. Another possible reason for the changes in blood levels of CO_2 and HCO_3- is the $RPTP_\gamma$, which may act as a dual sensor for extracellular CO_2 and HCO_3- and is responsible for the physiological response of renal proximal tubules [6]. It is important to note that this CA-dependent acid-base system via the renal epithelial plays a vital role in regulating and stabilizing the acid-base balance in the body, which is clear through the cell pH. This stability is of dire importance for biochemical reactions such as gluconeogenesis and lipogenesis in the cell. If the CA is overexpressed, many pathological states may appear, such as calcification and epilepsy. For this reason, many scientists have been investing in different designs of CA-selective inhibitors, which could play out as therapeutic agents [6]. In the past century, physiologists have developed Davenport diagrams in which the normal buffers are converted into a single buffer that protonates linearly with the pH scale [6]. This has brought about a greater understanding of the competition among buffer reactions. Along with this, a closed buffer system is one that doesn't allow any property to leave. This enhances the buffering power of the system, which is reflected in the pH stability.

Sodium Bicarbonate Therapy for Patients

Currently, supplemental usage of sodium bicarbonate has been proven useful for patients who suffer from renal tubular acidosis, but in harsher conditions, it has been proven to be unhelpful. Patients with diabetic ketoacidosis are one of the many groups of patients who have found sodium bicarbonate therapy to be unhelpful. Many cases of CKD come with an anion gap, which remains normal in early cases, but later on, as it becomes larger, there are therapies such as the addition of plasma ions such as albumin, phosphate, and potassium [4]. Recent studies also show the negative results seen in vegetarian diets. The consumption of vegetable protein diets instead of animal protein diets results in a lower GFR and renal plasma flow. A study was done to confirm the relationship between low serum bicarbonate concentrations and the progression of kidney disease [4]. Along with this, it has been made certain that a higher concentration of serum bicarbonate reflects a reduced risk of CKD progression. An analysis done by the African American Study of Kidney Disease and Hypertension came to a direct statistic that arrived after the adjustment of baseline iothalamate clearance and baseline proteinuria. The conclusion that was reached was that a 1 mM increase in serum bicarbonate reflects a four percent lower hazard, dialysis, or GFR decrease. Although so, the trials done by these groups resulted in the death, or end-stage renal disease, after 10 years for more than fifty percent of the participants [4]. Patients with chronic kidney disease have actually fallen into detrimental situations as a result of sodium bicarbonate input. Although a general consensus cannot be reached as every individual reacts differently to this treatment, it is overall shown that sodium bicarbonate is unhelpful in chronic diseases such as CKD. Patients who have CKD alongside metabolic acidosis have been shown to benefit from the treatment of sodium bicarbonate at times, but the usage of this solution is tricky at times as it has controversial effects [11].

Applications in Severe Hyperkalemia

Sodium bicarbonate has many other applications, such as in hyperkalemia, which is a medical problem that can cause fatal arrhythmias (heart rate disruptions). Severe hyperkalemia is linked to a serum potassium concentration level greater than 6.0 or 5.5 mmol/l and severe arrhythmia or hyperkalemic electrocardiographic changes [7]. This disease is multifactorial, which means that it is caused by multiple factors. Renal failure, potassium supplements, drugs that impair renal potassium excretion, and the movement of potassium out of cells as a result of inorganic metabolic acidosis are all different factors contributing to the severity of this process. Severe hyperkalemia is a life-threatening disease that can result in fatal consequences. This is why sodium bicarbonate can be used as a remedy [8]. One concern about this is that sodium bicarbonate only comes into effect in patients with severe hyperkalemia after several hours, which then proves to be unhelpful with patients suffering from an acute disease[7]. Sodium bicarb should be given to patients who suffer from severe hyperkalemia and have significant metabolic acidosis [8]. It should not be given to hypovolemic patients, as it could increase the risk of pulmonary edema. Along with this, patients with organic acidosis (lactic or ketoacidosis) in which their acidosis does not contribute to hyperkalemia should avoid this method of treatment [8]. Sodium bicarbonate therapy is a specific therapy that differs by person. This is why not one dose will suit all individuals. Each individual reacts differently to different amounts of sodium bicarbonate. Research shows that it is reasonable to start by giving 150 mEq in 1 liter of dextrose over 3 to 4 hours and then to decrease the concentration [8]. To reiterate, severe hyperkalemia leads to an immediate increase in serum potassium of 2.1 to 3.0 mmol/l, and a decrease in this fatal problem has been found using hypertonic sodium bicarbonate, but only in severely acidotic patients (pH 7.10–7.18) [8].

Controversy of Sodium Bicarbonate Usage in Patients with Cardiac Arrest

Safety and its affiliation with cardiac arrest have long been debated. Clinical and experimental data has brought to light concerns about the safety and effectiveness of sodium bicarbonate's usage during cardiac arrest [9]. The use of

sodium bicarbonate was once considered to be of stellar importance, especially in patients with severe metabolic acidosis in cardiac arrest, as it normalized extracellular and intracellular pH and guided the system to resuscitation [9]. However, through the years, advanced cardiac life support (ACLS+) altered their recommendation; around the year 2010 they had recommended to not use sodium bicarbonate at all. The revised publication of ACLS revealed the usage of sodium bicarbonate in only severe and acute cases. A cohort study was published by Stiell in 1995. It tested 529 patients, all of whom suffered from cardiac arrest. The result of the trial showed that SB did not have any great affiliation with survival, but the researchers reached the conclusion that the timing of the administration of drugs could be a vital piece of information. Many studies revealed inaccurate data regarding the usage of SB, as it was put into use later than it should have been. One study published by Bar-Joseph, which was based on the brain resuscitation clinical trial III, found a linear relationship between the duration of ACLS and bicarbonate use. From this, the scientists concluded that the use of bicarbonate was often late and suggested that it should be used earlier during the development of severe metabolic acidosis [9]. Even after all these trials, it is still uncertain as to the direct effect that SB holds on patients with a differing range of cardiac arrest. Each individual reacts in a different manner to this treatment, but overall, earlier usage of this solution brings more positive results. The latest ACLS guidelines published by the AHA make it clear that routine SB usage is not recommended in the ACLS protocol for pulseless electrical activity, and this conclusion is derived from a single randomized trial [9]. Although this is so, SB is still a part of resuscitation in cardiac arrest, and research is still needed to further understand the effects of SB.

Role of Sodium Bicarbonate in Lactic Acidosis

Lactic acidosis is one of the many forms of metabolic acidemia. The higher the serum levels of lactate, the worse the clinical prognosis for patients [12]. Those who state that lactate directly contributes to mortality advocate the use of buffers to raise the blood pH, hoping that this will support the cardiovascular system and its function [12]. This leads back to the idea of bicarbonate as a therapy only for severely acidic patients suffering from acute diseases. To better understand this diagnosis, the following passage will expand on the intricacies of lactic acidosis. Lactate is produced through lactate dehydrogenase from an oxidation-reduction paired reaction with NADH from pyruvate. An increase in pyruvate or in the ratio of reduced and oxidized nicotinamide adenine dinucleotide (NADH/NAD+) results in hyperlactatemia [12]. An elevated lactate level does not always imply acidemia. Hyperlactatemia without acidemia happens most often when hypoxia is not present and the buffering systems are not severely impacted [12]. Increased aerobic glycolysis during strenuous exercise, seizures, or hypermetabolic malignancy are common causes of isolated hyperlactatemia [12]. Advocates of correcting lactic acidosis through a buffer such as sodium bicarbonate argue that acidemia produces harsh physiological consequences that can only be eased through the normalization of the pH [12]. The use of bicarbonate during bicarbonate losses, which could occur due to chronic diarrhea or renal tubular losses, is less controversial [12]. Animal studies have shown no significant hemodynamic benefits of sodium bicarbonate administration but have actually shown a decreased cardiac output, lower intracellular pH levels, and an increased or unchanged lactate level [12]. Sodium bicarbonate can lead to many detrimental outcomes, especially if used at any level of excess. The vasomotor tone may be decreased by bicarbonate [12]. Many of these findings prove that external buffer additions fail to fully diffuse into myocardial cells, and in addition to that, they worsen intracellular acidosis and myocardial function [12]. Sodium bicarbonate also decreases myocardial oxygen extraction, which results in myocardial ischemia, which decreases myocardial contractility [12]. Overall, the effects that the addition of an exogenous buffer has on the system are short-lived and have mixed results. Although symptomatic relief is felt by patients, the negatives of the treatment have long outweighed its benefits. This has led to selective usage of the solution, which is used cautiously and only in specific circumstances.

Conclusion

The overall previous research done on the usage of sodium bicarbonate to address acid-base imbalances in various medical conditions highlights its role as an effective buffering agent under specific circumstances. In patients with chronic kidney disease, sodium bicarbonate assists in the mitigation of metabolic acidosis, which in turn improves renal function and stabilizes blood pH levels. This stabilization is of great importance for reducing the risk of cardiovascular and respiratory diseases linked to chronic acidosis. However, its efficacy varies, and overuse of it can lead to dangerous outcomes such as metabolic alkalosis and electrolyte imbalances. Sodium bicarbonate's usage in acute conditions such as severe hyperkalemia and certain drug overdoses shows its potential benefits when used correctly. For example, it helps in the rapid correction of life-threatening hyperkalemia by adding potassium to cells. On the other hand, its use in lactic acidosis and cardiac arrest remains controversial due to a variety of clinical outcomes that have demonstrated a potential for worsening intracellular acidosis. Clinical guidelines recommend the selective use of sodium bicarbonate, specifically in severe cases of metabolic acidosis with critically low pH levels. This decision to administer the treatment must always be rooted in an intricate assessment of a patient's conditions, along with careful monitoring as a precautionary measure to avoid complications. To conclude, although sodium bicarbonate can be a valuable tool for managing acid-base imbalances, its administration requires a detailed approach in order to maximize benefits while minimizing risks.

Acknowledgments

I would like to thank my advisor for the valuable insight provided to me on this topic.

References

[1] Kidney Disease: The Basics. (2021, April 8). National Kidney Foundation. https://www.kidney.org/news/newsroom/fsindex#:~:text=Kidney%20disease%20affects%20an%20estimated

[2] Hultin S, Hood C, Campbell KL, Toussaint ND, Johnson DW, Badve SV. A Systematic Review and Meta-Analysis on Effects of Bicarbonate Therapy on Kidney Outcomes. Kidney Int Rep. 2020 Dec 31;6(3):695-705. doi: 10.1016/j.ekir.2020.12.019. PMID: 33732984; PMCID: PMC7938083.

[3] Tangri N, Ferguson TW, Reaven NL, Lai J, Funk SE, Mathur V. Increasing Serum Bicarbonate is Associated With Reduced Risk of Adverse Kidney Outcomes in Patients with CKD and Metabolic Acidosis. Kidney Int Rep. 2023 Feb 1;8(4):796-804. doi: 10.1016/j.ekir.2023.01.029. PMID: 37069991; PMCID: PMC10105060.

[4] Adeva-Andany MM, Fernández-Fernández C, Mouriño-Bayolo D, Castro-Quintela E, Domínguez-Montero A. Sodium bicarbonate therapy in patients with metabolic acidosis. ScientificWorldJournal. 2014;2014:627673. doi: 10.1155/2014/627673. Epub 2014 Oct 21. PMID: 25405229; PMCID: PMC4227445.

[5] Wikipedia contributors. (2023, December 14). Isozyme. Wikipedia. https://en.wikipedia.org/wiki/Isozyme

[6] Occhipinti R, Boron WF. Role of Carbonic Anhydrases and Inhibitors in Acid-Base Physiology: Insights from Mathematical Modeling. Int J Mol Sci. 2019 Aug 6;20(15):3841. doi: 10.3390/ijms20153841. PMID: 31390837; PMCID: PMC6695913.

[7] Abuelo JG. Treatment of Severe Hyperkalemia: Confronting 4 Fallacies. Kidney Int Rep. 2017 Oct 7;3(1):47-55. doi: 10.1016/j.ekir.2017.10.001. PMID: 29340313; PMCID: PMC5762976.

[8] Simon LV, Hashmi MF, Farrell MW. Hyperkalemia. [Updated 2023 Sep 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470284/

[9] Velissaris D, Karamouzos V, Pierrakos C, Koniari I, Apostolopoulou C, Karanikolas M. Use of Sodium Bicarbonate in Cardiac Arrest: Current Guidelines and Literature Review. J Clin Med Res. 2016 Apr;8(4):277-83. doi: 10.14740/jocmr2456w. Epub 2016 Feb 27. PMID: 26985247; PMCID: PMC4780490.

[10] Senewiratne NL, Woodall A, Can AS. Sodium Bicarbonate. [Updated 2024 Feb 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559139/

[11]Healthline Media. (n.d.). Sodium bicarbonate for kidney disease: Benefits and more. Healthline. https://www.healthline.com/health/sodium-bicarbonate-kidney-disease

[12] Rudnick MR, Blair GJ, Kuschner WG, Barr J. Lactic Acidosis and the Role of Sodium Bicarbonate: A Narrative Opinion. Shock. 2020 May;53(5):528-536. doi: 10.1097/SHK.0000000000001415. PMID: 31318832.

[13] Mustaqeem R, Arif A. Renal Tubular Acidosis. [Updated 2023 Jul 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519044/