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Acid-base balance

K.T. Saracoglu (*), A. Saracoglu (**), S. Pence (***)

Abstract : Acid-base balance is the balance of the hydrogen ion concentrations in body fluids. The hydrogen ion (H^+) concentration in body fluids is regulated within a narrow range to achieve normal metabolic and enzymatic functions as well as critical functions including fertilization, growth, protein synthesis, and cell volume regulation. Acid-base balance is under a multi-system control involving the brain, lungs, liver and kidneys. Many acid-base disorders occur due to the loss of body fluids or electrolytes from the body or their entry into the body. Electroneutrality and buffer systems are the key factors in ensuring this balance.

Key words : acidosis; alkalosis; buffer; anion gap

Introduction

All metabolic processes in the body are maintained in a narrow range where acidity and alkalinity play a key role. The body activates the lungs, kidneys and various buffer systems together in order to achieve it. The principles governing the acid-base balance are corner stones of medical sciences. In this opinion paper, we aimed at reviewing the current concepts of acid-base balance regulation.

Bicarbonate, hydrogenion and carbon dioxide

The hydrogen ion (H^+) concentration in body fluids is regulated within a narrow range to achieve normal metabolic and enzymatic functions, as well as critical functions including fertilization, growth, protein synthesis, and cell volume regulation. H^+ sources include proteins and weak acids, like hydrogen phosphate ($H_2PO_4^{-2}$).

The human metabolism generates H^+ ions, which in turn react with bicarbonate to produce carbonic acid ($H_2CO_3^-$). Subsequently, carbonic acid is broken down into water (H_2O) and carbon dioxide (CO_2) by carbonic anhydrase. CO_2 is expelled from the lungs. The CO_2 acid charge is called volatile acid, and equals approximately 13000 mEq/day. While urination is the major way of water excretion, it can be also excreted through sweating, defecation and respiration.

H^+ ions are involved in several oxidation-reduction reactions, and in the synthesis of adenosine triphosphate (ATP). Conventionally, acidity is expressed as pH, whichis the logarithm of the inverse of H^+ concentration (log $1/[H^+]$). There is a linear correlation between pH and log PCO_2. However, most cells have a mechanism to defend themselves against intense increases or declines of pH. Elimination of acids into urine is a part of this mechanism. As a result, extracellular pH value stays stable between 7.35 and 7.45. The intracellular pH is lower than the extracellular one, and ranges from 7.0 to 7.3. H^+ concentration is 10^6-fold lower than serum Na^+ concentration, and normal levels lie between 35 and 45 nmol L^{-1}.

Both volatile acids like carbonic acid and nonvolatile acids like lactic acid contribute to cellular H^+ concentration. While nonvolatile acids are excreted through the kidneys, volatile acids like CO_2 can be expelled from the lungs. Cellular carbonic acid production is one of the sources of acid in the body. The amount of carbon dioxide and water contained in the carbonic acid is equal. CO_2 is formed through the oxidation of carbohydrates, keto acids, fats, and amino acids. Although the amount of produced acid is low, it should be fully expellable with urination. There is a urinary buffering system to excrete the daily acid load of 50-100 mEq H^+.

Kemal Tolga Saracoglu, Ayten Saracoglu, Sadrettin Pence
(*) Department of Anesthesiology and Intensive Care, Health Sciences University, Istanbul, Turkey.
(**) Department of Anesthesiology and Intensive Care, Marmara University, Istanbul, Turkey
(***) Department of Physiology, Health Sciences University, Istanbul, Turkey.
Corresponding author : Dr. K. Tolga Saracoglu, Saglik Bilimleri Universitesi, Derince SUAM Kocaeli, Turkey. Tel : +90 262 317 80 00. Fax : +90 262 233 55 36.
E-mail: saracoglukt@gmail.com

The Henderson-Hasselbalch equation and the buffer systems

The acid-base balance is the balance of H^+ concentrations in body fluids. Although this concentration is very low, even small changes impact enzymatic reactions and physiological events. The normal range of H^+ concentration in healthy people is between 36 and 40 nmol L^{-1}. A pH of 7.40 corresponds to a H^+ concentration of approximately 40 nmol L^{-1}, and is considered a physiological pH. There is a mathematical relationship between pH, HCO_3^- concentration, and $PaCO_2$. A change in the acid-base balance always results from a change in one or two of these elements. According to the Henderson-Hasselbalch equation, pH = pK+ log (HCO_3^-/ $H_2CO_3^-$), or pH = 6.1+ log (HCO_3^-/ 0.03x$PaCO_2$), or pH = Constant × (HCO_3^-) / $PaCO_2$.

A normal pH in the arterial blood ranges between 7.35 and 7.45. In the venous blood, however, it is 0.03 to 0.05 lower. The acid-base balance is maintained within physiological limits through various systems (Table 2). Chemical buffer systems change the state by taking up or losing one hydrogen ion. The buffering time of plasma bicarbonate is very short, the one of interstitial bicarbonate is 15-20 min, and the one of intracellular proteins ranges between 2 and 4 hours.

Phosphate and proteins are the intracellular buffer systems. Contrarily to the bicarbonate buffer, hemoglobin (Hb) buffers both carbonic and non-carbonic acids. Intracellular buffer systems have a large capacity, and constitute approximately 75% of all chemical buffers in the body. Ph and $PaCO_2$ pressure affect respiration through central and peripheral chemoreceptors.

The brain and the acid-base balance

Brain pH is closely correlated with cerebrospinal fluid (CSF) pH, and crucially important for the functions of the central nervous system (CNS). Brain pH is controlled through different mechanisms than peripheral ones, and involves cellular adaptation in a narrow range. These mechanisms help brain adaptation to changes in pH, which is set to levels close to the normal range when metabolic and respiratory acidosis or alkalosis occurs.

The brain is one of the vital organs that regulate body pH, including during systemic diseases. Aortic and carotid chemoreceptors send inputs to the CNS, which in turn regulate alveolar ventilation. While acidification of the CNS interstitial fluid lead to an increase in ventilation, alkalization of the medullary interstitial fluid results in a depression of ventilation (1). As the blood-brain-barrier has different permeability for CO_2, H^+, and bicarbonate, each of these molecules move into the CNS with different time courses, which may result in transitional changes in CNS pH. These transitions may be paradoxical as compared to peripheral pH at times. For example, a paradoxical pH change occurs when a patient is given sodium bicarbonate to correct peripheral acidosis. The fact that the produced CO_2 can more easily diffuse into the brain than the bicarbonate anion may cause temporary cerebral acidification. Although bicarbonate is administered to the extracellular fluid, the acidification of the cerebrospinal fluid leads to systemic respiratory alkalosis, as a result of hyperventilation.

Table 2
Buffer systems.

Chemical buffer system - Bicarbonate- carbonic acid - Phosphate - Proteins and hemoglobin
Respiratory system compensation
Renal compensation

Cerebral pH regulation also involves lactate production in case of alkalosis. According to the oxyhemoglobin dissociation curve, oxygen delivery to the cells decreases during metabolic alkalosis. Moreover, during acute alkalemia, the cerebral blood flow also falls due to vasoconstriction. As a result, more lactate is produced through anaerobic glycolysis. Phosphofructokinase I is a rate-limiting pH-sensitive glycolytic enzyme, which stimulates glycolysis in the presence of high intracellular pH. During acidosis, the brain converts glutamine into glutamate to protect its own pH. In this way, ammonia, which is a proton acceptor, is released and contributes to pH elevation (2).

Lungs and renal system

Nearly 100% of CO_2 is produced in the mitochondria. The amount of CO_2 in the blood of pulmonary capillaries is higher than in the alveoli. As a consequence, it is expelled through ventilation. The elimination rate depends on CO_2 production, pulmonary blood flow, and alveolar ventilation. CO_2 is transported into the blood as dissolved in solution, as bicarbonate, or as a carbamino group bounded to plasma proteins and albumin. Whereas most of CO_2 is transported by Hb, plasma proteins still carry a small portion. Reduced Hb has a 3-fold higher affinity for CO_2 as compared to O_2. CO_2 binds

to N-terminal amino groups in the alpha and beta chains. However, there is a competition between CO_2 and 2,3-bisphosphoglycerate (2,3-DPG) for the binding site.

According to Henry's law, $[CO_2] = PCO_2 \times$ dissociation constant of carbon dioxide in plasma. Chemically speaking, $CO_2 + H_2O \neq H_2CO_3^- \neq HCO_3^- + H^+$.

The carbonic anhydrase enzyme is found in the erythrocytes, nephron, stomach, pancreas, as well as in cardiac and skeletal muscles and pulmonary vascular endothelium, but it is not present in the plasma.

At a 7.4 pH, approximately 96% of $H_2CO_3^-$ is dissolved. Acidosis occurs when bicarbonate concentration decreases. The signals to the lung modulate the control of ventilation in respiratory disorders and metabolic disorders. For instance, in acute respiratory acidosis, the increase in CO_2 reaches the cerebellar medullary center, and stimulates the central ventilatory response, suppressing hypoventilation, and preventing hypercapnia.

Not only pulmonary ventilatory responses but also elaborate renal mechanisms can compensate for metabolic disorders (3). The excretion of acids by the kidneys is almost 75 mmol day^{-1}. H^+phosphate and ammonium ions are the main buffers that play an important role in acid excretion and in bicarbonate formation. The kidneys absorb 99% of bicarbonate, and help to regenerating lost bicarbonate. Almost 90% of the filtered bicarbonate is reabsorbed by the proximal tubules. Luminal bicarbonate combines with H^+ ion to produce carbonic acid. In the presence of carbonic anhydrase, it is converted into CO_2 and H_2O, so that it can easily diffuse into the cells. Inside the luminal cells, CO_2 is hydrolyzed by the carbonic anhydrase isoenzym II, to form carbonic acid, which decomposes into bicarbonate and H^+ (4). Thereafter, bicarbonate and sodium (Na^+) are transferred to the cell membrane together. The absorption of bicarbonate is proportional to PCO_2. The amount of generated acid must be equal to the amount of excreted acid, in order to maintain a stable acid-base balance. The clearance of the acid anions depends on the complete absorption of the filtered bicarbonate. Ammonium is generated through the absorption of phosphate and chloride, and excreted in the urine. Alveolar ventilation eliminates CO_2. Any inequality or imbalance between the production and elimination of CO_2 results in respiratory and metabolic disorders.

Approximately 10% of the filtered bicarbonate is reabsorbed in the distal tubules. The reabsorption of bicarbonate depends on 2 systems : the H^+/ATPase and the aldosterone-dependent Na^+/ H^+ exchanger. Similarly, secreted H^+ react with bicarbonate in the urine to form carbonic acid, which is then transported into the cells in the proximal tubule. Ammonium and H^+ phosphate function as urinary buffers. Glutamine is hydrolysed to glutamate and ammonium (NH4+) by the glutaminase in the proximal renal tubules. Glutamate is oxidized into 2-oxo-glutarete and more NH4+ is generated. Subsequently, ammonium decomposes into ammonia and H^+ ions, and then it generates bicarbonate. In other words, the deamination of glutamate creates NH_4^+ which buffers H^+ ions and produce bicarbonate for the plasma. If NH_4^+ is not eliminated from the body, it forms urea by combining with bicarbonate. The thick ascending limb of Henle's loop absorbates 50% of the NH_4^+ in the proximal tube. The absorbed NH_4^+ is taken up into the medullary interstitium. The elimination of NH_4 increases with acidosis since a) the deamination enzymes are stimulated by acidosis; b) there is an elevation in the conversion of NH_3^+ (ammonia) to NH_4^+ (ammonium) in the collecting ducts when the secretion of H ions is high. In the distal tubes, the phosphate buffering system plays a role in bicarbonate production. H^+ compounds with phosphate and form $H_2PO_4^-$. In systemic acidosis, phosphate reabsorption is inhibited.

The total H^+ secretion is equal to bicarbonate reabsorption and phosphate excretion plus ammonium excretion. Phosphate can be titrated only using acids. The 3 factors determining H^+ concentration are identified in Table 1.

Normally, kidneys regulate the acid-base balance through two ways. High amounts of bicarbonate are filtered in the glomerule. The kidneys also generate acid by combining H^+ with phosphate and ammonium. The kidneys play a role in the production and reabsorption of bicarbonate, as well as in the elimination of titratable acids and ammonia. If HCO_3^- is affected first, it is defined as a metabolic disorder, if $PaCO_2$ is affected first, it is defined as a respiratory disturbance.

Table 1
Factors determining the H^+ ion concentration

PCO_2
SID: the sum of cation concentrations in the solution (K^+, Na^+, Ca^{+2}, Mg^{+2}) – total anion concentration (chloride, lactate) (mEq/l).
Total concentration of weak acids: plasma proteins, albumin and phosphates

PCO_2: partial carbon dioxide pressure
SID: strong ion difference. Normal range: 42-46 $mmol^{-1}$
Na^+: sodium, K^+: potassium, Ca^{+2}: calcium, Mg^{+2}: magnesium

In the advanced stages of respiratory acidosis, kidneys excrete H^+ and uptake bicarbonate ions for compensation. In acute respiratory acidosis, there is an increase of 1 mEq L^{-1} pf bicarbonate for every 10 mmHg rise in CO_2, while in chronic respiratory acidosis, bicarbonate elevates by 4 mEq L^{-1} for each 10 mmHg CO_2 increase. If $PaCO_2$ is below 40 mmHg, the plasma HCO_3^- generally falls by 2 mEq L^{-1} for every 10 mmHg acute decline in the PCO_2. The kidneys compensate respiratory alkalosis by holding H^+ and excreting bicarbonate ions.

There is a relationship between the acid-base balance and the hepatic urea , insofar as urea originates from the reaction between bicarbonate and ammonium. The ammonium produced by the cells is transported to the liver by the erythrocytes (5). They participate in the urea cycle with the carbamoyl phosphate synthetase enzyme. Metabolic acidosis functions as a stress response, and causes an increase in glucocorticoid catecholamines production. In this way, protein catabolism occurs and low bicarbonate levels are accompanied with increased ammonium production. Acidosis decreases hepatic ureagenesis, and thus, leads to the production of hepatic glutamine instead of urea. As a result, the loss of bicarbonate is prevented, and bicarbonate can be stocked (6).

Glutamine intake into the renal proximal tubule cells increases with acidosis, and, also, acidosis stimulates the renal glutaminase. Consequently, there is an elevation in renal ammonium generation. This is how metabolic acidosis increases the production of glutamine in the liver, and ammonium in the kidneys.

Decreased renal perfusion and reduced urination limit renal acidification mechanisms, causing metabolic acidosis. Nevertheless, respiratory alkalosis develops as a result of the hyperventilation driven by the CNS.

Patients with renal failure show a higher tendency to develop acidemia because, in such patients, renal ammonium generation is limited and glutamine metabolism is disordered. Patients with a low glomerular filtration rate have a higher risk of developing acidosis if receiving a rich protein diet than normal patients. If there is a damage in the renal tubules where acid secretion occurs, the severity of acidemia will be enhanced. Chronic tubulointerstitial diseases are frequently associated with renal acidosis and hyperkalemia. A lower glomerular filtration rate also reduces the amount of filtered bicarbonate. In case of acidosis, on the other hand, bicarbonate loss is cushioned through urination. Decreased bicarbonate filtration in proximal renal tubular acidosis (RTA) will reduce the severity of proximal acidosis. Attempting to alkalinize the urine of a patient, who is non-acidemic due to decreased bicarbonate filtration, leads to the alkalinization of the patient's blood, while the urine pH continues to be acidic.

Table 3
Main changes that occur during metabolic ascidosis.

1.	Sympathetic nervous system becomes active
2.	Corticosteroids are released
3.	Leukocytosis and hypercatabolic process occur
4.	Acidic pH and low bicarbonate stimulate peripheral chemoreceptors
5.	Ventilation increases through medullary center
6.	Energy consumption elevates in muscles including respiratory muscles
7.	Intercostal muscles occurs causing Kussmaul breathing
8.	Respiration rate increases
9.	Patients with COPD have a blue bloater in the presence of hypoventilation, but have a pink buffer in the presence hyperventilation

COPD: Chronic Obstructive Pulmonary Disease

The main changes in metabolic acidosis are summarized in Table 3. In case of insufficiency in renal compensation of metabolic acidosis, ammonium production will be limited, and new bicarbonate ions will not be produced despite an adaptation in the mechanisms of H+ secretion.

Type 2 proximal renal tubular acidosis results from a decreased reabsorption of bicarbonate, which occurs due to a generalized defect in tubule function. Additionally, there may be disturbances in Na^+-H^+ conversion, H^+ ATPase, carbonic anhydrase or sodium bicarbonate transporter. The maintenance of metabolic alkalosis is mediated by hypovolemia, hypokalemia, hypochloremia, and elevated PCO_2 levels.

The failure of kidneys that normally regulate the balance of water, sodium and potassium, also impairs the compensation of metabolic alkalosis. However, accompanying hypokalemia, fluid loss and hyperaldosteronism play a role in the continuation of metabolic alkalosis.

During vomiting, bicarbonate is lost, metabolic alkalosis develops, and paradoxical aciduria occurs in urine. As a result of fluid losses and hypokalemia, there is an increase in angiotensin II level. Respiratory compensation for metabolic alkalosis occurs as follows: increased pH value and bicarbonate concentration are detected by peripheral chemoreceptors. Hypoventilation is then generated. For oxygen areterial partial pressure,

the threshold for chemoreceptors sensitivity is 60 mmHg, corresponding to 90% hemoglobin saturation. Venti-lation is stimulated following the decrease of these levels in the brain interstitial fluid.

Respiratory acidosis is compensated by kidneys through sodium bicarbonate reabsorption and new bicarbonate formation in the distal nephron. Decreased glomerular filtration rate resulting from hypoxemia and hypercarbia, and increased bicarbonate reabsorption caused by elevated PCO_2 lead to extracellular volume expansion, and possibly to pulmonary edema. If the functions of renal tubules are intact in chronic respiratory alkalosis, the reabsorption of bicarbonate goes down.

Diagnostic approach in determining the acid-base disorders

Medical history and physical examination are important. Vomiting, diarrhea, COPD, and pneumonia must alert to eventual metabolic alkalosis, metabolic acidosis, respiratory acidosis, and respiratory alkalosis, respectively (7).

Winters equation can be used in the presence of mixed metabolic acidosis and alkalosis. It is useful for determining the serum anion gap (AG) when high chloride acidity and low chloride alkalosis are present at the same time. Anion gap defines the state, in which there are more cations than anions in the serum. If AG is positive, there must be non-measurable anions corresponding to alkalosis. On the other hand, if AG is negative, there must be non-measurable cations corresponding to acidosis. It is calculated by subtracting the sum of chloride and bicarbonate from the sodium concentration. The normal AG range is between 10 and 12 mEq L^{-1}. An elevated anion gap indicates metabolic acidosis. An elevated anion gap (> 12mmol/L) can be encountered in conditions of endogenous or exogenous acid excess.

Causes of anion gap metabolic acidosis and hyperchloremic acidosis

Anion gap is useful both in the diagnosis of metabolic acidosis and in determining the presence of mixed metabolic disturbances. If the rate of change in anion gap is higher than the decrease in bicarbonate, there must be a factor that raises the bicarbonate level, which is possible in the case of hypokalemia-related metabolic alkalosis. For example, a mixed disorder may be seen in a patient with the complaint of vomiting. Metabolic alkalosis may be accompanied by lactic acidosis or ketoacidosis. In the isohydric approach, traditionally, pH and PCO_2 are assessed to determine the acid-base impairment (8). In the equation $CO_2 + H_2O \neq H_2CO_3^- \neq HCO_3^- + H^+$, or $pH = PK + \log (HCO_3^-)/0.03\ (pCO_2)$, 0.03 is the dissolution constant for carbon dioxide in the solution. PK is the total dissociation constant for carbon dioxide and bicarbonate. According to the isohydric principle, H^+ concentration is equal to the ratio of the acids to the bases multiplied by the dissociation constant. This principle applies to H^+-retaining buffers including phosphate, albumin, hemoglobin and other proteins.

The bicarbonate deficit can be defined as (desired bicarbonate-available bicarbonate) x 0.3 x body weight, or HCO_3^- gap = 0.5 x body weight (kg) x (desired HCO_3^-– serum HCO_3^-), or HCO_3^- need = 0.3 x body weight (kg) x BE (base excess).

In the case of impaired elimination of CO_2, bicarbonate treatment may lead to paradoxical intracellular acidosis, because the resulting CO_2 easily enters the cell while HCO_3^- cannot.

Normal HCO_3^- concentration ranges between 22 and 26 mEq L^{-1}, and normal BE ranges between -3 and +3 mEq L^{-1}.

Many acid-base disorders result from body fluids or electrolytes loss or gain. The resulting Na^+ and Cl^- ratios are important. For instance, there is more Na^+ than Cl^- in the gastric fluid. Pancreatic secretion in the small intestine contains more Na^+ than Cl^-. In diarrhea-related losses, Na^+ loss is usually greater than Cl^- loss. Potassium enters the cell through K^+- Na^+ exchange.

According to Steward, if OH^- ions are equal to H^+ ions, the solution is neutral ; if H^+ ions are higher, the solution is extremely acidic; and if OH^- ions are higher, the solution is extremely basic. The ions that are poorly soluble in water are referred to as weak ions, while the electrolytes that are highly soluble in water are referred to as strong ions. Strong ions include Na^+, K^+, Mg^{+2}, Ca^{+2}, SO_4^{-2} and chloride. Weak ions include protein, phosphate and bicarbonate. The factors that depend on acid-base balance in different areas of the body include water, PCO_2, as well as strong and weak ions.

Hypochloremia arises from the loss of chloride-rich gastric and intestinal fluids. Hypochloremia may also occur as a result of the intake of sodium salts that are poor in chloride, such as sodium citrate, sodium lactate or acetate, plasmapheresis, and dialysis. The consequences of chloride increase on bicarbonate level are the following. In order to reestablish the balance, cations must be equal to anions. Simply, if the chloride concentration increases while the Na^+ concentration remains constant, there must be

a decrease in the amount of another anion. On the other side, if the chloride amount decreases, while sodium remains stable, there must be a rise in the amount of another anion. With regard to this, the plasma anion to maintain the electroneutrality is bicarbonate.

According to the rule of electroneutrality, the concentration of negatively charged anions in solutions must be equal to the concentration of positively charged cations. For example, $Na^+ + H^+ \neq Cl^- + OH^-$.

In brief, we consider metabolic acidosis in the presence of hyperchloremia and metabolic alkalosis in the presence of hypochloremia. However, when there is an abnormality in the non-chloride ions, we need to take the increases and decreases in bicarbonate levels into consideration. For instance, the loss of negative charge due to hypoalbuminemia will result in an increase in bicarbonate levels, which is known as hypoproteinemic alkalosis (9). There is a need for 2.5 mEq L^{-1} of negative charge for each 1 g dL^{-1} albumin (10). Another form of metabolic alkalosis occurs in case of hypochloremia resulting from increased sodium reabsorption in the collecting duct of the kidney. Hyperaldosteronism is associated with hypertension and hypokalemia. Hyperchloremic acidosis, nevertheless, occurs with hypertension and hyperkalemia. It is important to indicate the relation between serum Na^+ and Cl^-. Also, it is necessary to correct the anion deficit if hypoalbuminemia develops. Anion deficit is generally expressed as Na^+-Cl^--HCO_3^-. In case there is a rise in the level of non-measurable non-chloride anions, the bicarbonate level will decrease to compensate that rise, which is called anion gap acidosis.

Urinary electrolytes should be analyzed to understand the role of renal function in the acid-base balance. The amount of sodium, potassium, and chloride present in the urine shows the acidifying or alkalizing effect of urine on the extracellular fluid. For example, if the amount of Na^+ and K^+ in urine is high, it means that there is a tendency towards acidification of body fluids. If metabolic acidosis is present in blood and the amount of Na^+ and K^+ excreted through urine is higher than Cl^-, kidneys are likely to be responsible for metabolic acidosis. On the other hand, if urine chloride level is high, plasma must have an alkalizing effect.

Renal compensation of respiratory disorders can also be understood by a urine analysis. The purpose of renal compensation developing in respiratory acidosis must be extracellular alkalization. By this way, the chloride level excreted in urine in response to the increasing bicarbonate level will be higher than the excreted Na^+ and K^+. Ammonium is the accompanying cation for chloride.

Hypochloremic Alkalosis

There is loss of HCl^- from the stomach through vomiting or gastric drainage, which causes the secretion of bicarbonate from the parietal cell to the extracellular space. As chloride ions come in, bicarbonate ions go out of the cell. The acidification of gastric fluids is carried out by the recreation of luminal H^+-K^+- ATPase and chloride. There is a chloride-bicarbonate exchanger in the basolateral membrane. Normally, bicarbonate goes out of the cell after meals, and thus, there is a postprandial increase in urine pH. However, as the losses become severe after vomiting, metabolic alkalosis develops. According to the isohydric principle, the increasing volume of bicarbonate in the extracellular fluid is not equal to the loss of chloride. Bicarbonate is associated with the extracellular H^+ concentration; however, chloride does not have a pH-dependent distribution. In order to correct alkalosis, the volume of bicarbonate secreted into the proximal tubule increases.

Bicarbonaturia is accompanied by natriuresis, leading to polyuria. Ongoing vomiting results in extracellular volume loss, due to the loss of Na^+ and chloride. In response, the renin-angiotensin-aldosterone system is activated. Angiotensin II stimulates the Na^+- H^+ exchange in the proximal tubule, and protects from water and Na^+ loss through the reabsorption of sodium bicarbonate. Another effect of bicarbonate reaching the distal nephron in case of increased aldosterone is the increase in sodium-potassium exchange in urine. In this situation, urine pH is high but starts to fall, and the urinary Na^+/ K^+ ratio changes in favor of K^+. As a result, hypokalemia occurs and leads to not only an increase in Na^+-H^+ exchange, but also in Na-bicarbonate co-transport. Thus, the proximal retention of Na^+ and bicarbonate increases. Due to the rise of aldosterone in the distal nephron, the reabsorption of Na^+ increases through the epithelial Na^+ channels of the primary cells in the collecting ducts. Aldosterone also increases intercalated cell proton secretion, and causes bicarbonate reabsorption. Consequently, depending on hypokalemia, it reabsorbs K^+, through the K^+-H^+ modulator in intercalated cells, and regulates the secretion of hydrogen. The process terminates with a net bicarbonate reabsorption. As long as vomiting goes on, hypokalemia and fluid loss continue,

leading to bicarbonate reabsorption and metabolic alkalosis. As bicarbonate is reabsorbed from the urine, the urinary pH becomes acidic. Urine is concentrated, and contains low sodium, bicarbonate and even potassium amount. Since bicarbonate has a caliuric effect, the reduction of bicarbonate volume in urine mitigates the loss of K^+. The proximal and distal Cl^- reabsorption scales up, because of the low extracellular Cl^-. It is important to administer KCl because volume expansion would multiply the intake of bicarbonate and the loss of potassium.

Extracellular chloride loss will be compensated by the increase of bicarbonate, an anion, in order to achieve electroneutrality. Hypochloremic alkalosis can develop secondary to chloride losses, resulting from the use of chloro diuretics including loop and thiazide diuretics. Besides, channelopathies like Bartter's and Gitelman's Syndrome may be other renal causes. A cause of alkalosis, other than vomiting, is the losses through sweating in cystic fibrosis. Whereas non-renal metabolic alkalosis will result in low urinary chloride, renal alkalosis results in high urinary chloride.

Non-hypochloremic metabolic alkalosis

Another type of metabolic alkalosis is associated with hypertension and involves the diseases with elevated mineralocorticoids. It is characterized with various grades of volumetric expansion, hypertension, moderate alkalosis, which is usually considered or occurs in low potassium situations. Sodium is retained in the principal cells of the renal collecting channels, which causes the levels of Na^+ and K^+ to exceed the normal ranges, but the elevation in Na^+ is more severe. This is due to the fact that mineralcorticoids have a reabsorption effect on Na but not on chloride. The amount of bicarbonate is multiplied to ensure the electroneutrality between Na^+ and Cl^-.

Sedimentary downregulation occurs in the thiazide sensitive sodium chloride transporter due to hyperaldosteronism. This situation, which causes chloride losses, is called aldosterone escape (11). Hypocalcemia also maintains metabolic alkalosis through its influence on the proximal tubule and, at the same time, it leads to chloruria by reducing chloride reabsorption.

Elevated aldosterone induces Na^+ reabsorption and K^+ secretion. Through the negativity of the lumen and the aldosterone-dependent electronic proton secretion, a small amount of bicarbonate is added to the circulation. In case a lower amount of bicarbonate reaches the distal nephron, there is more Na^+ absorption and new bicarbonate formation. Also, the augmentation of K^+ can cure the metabolic alkalosis. The co-occurrence of hypokalemia and hypertension suggests that there is a defect in the principal cells located in the collecting ducts. There is a rise in Na^+ level also in the Liddle Syndrome. There is an increase in aldosterone functions due to a defect in 11β-hydroxysteroid dehydrogenase. Cushing's Syndrome and ectopic ACTH secretion are other conditions that need to be considered in the differential diagnosis. If aldosterone rises together with renin, the source of the problem is the kidneys. In that case, it may be a unilateral renal artery stenosis or a renal secretory tumor.

Hyperchloremic acidosis

Metabolic acidosis can occur following intestinal and renal losses, or due to adrenal disturbances. For instance, a patient with ileostomy may develop metabolic acidosis in the small intestines due to the loss of alkaline, which contains high amounts of Na^+ and bicarbonate. Hyperchloremic metabolic acidosis develops when the patient's major loss is serum bicarbonate. High intestinal losses cause activation in the aldosterone system of renin-angiotensin, due to volume loss at the same time. In this case, kidneys will start to secrete more chloride as a result of excessive chloride losses through the interstitial fluid. Since ammonium production is induced in case of acidosis, the kidneys secrete chloride but retain Na^+ and K^+. In this way, cations are spared for fluid and K^+ balance. In the cases where diuretics like carbonic anhydrase inhibitors are used intensively, kidneys may also be a source of bicarbonate defect and renal tubular acidosis.

Even if bicarbonate, instead of chloride, accompanies the losses of Na^+ and K^+, the result will be hyperchloremic acidosis. In pseudohypoaldosteronism, the renin and aldosterone levels are expected to increase; however, there is a decrease in receptor functions. If aldosterone levels are low, adrenal of aldosterone insufficiency must be considered. In such a case, the renin level excessively increases in order to compensate for the loss of salt, resulting in volume deficiencies. If the level of renin is also low, hyporeninemic hypoaldosteronism is present. This time, renin inhibitors, non-steroidal anti-inflammatory drugs, and diseases affecting tubular function should be considered in the differential diagnosis.

Conclusion

In conclusion, acid-base balance is under a multi-system control, involving the brain, the lungs, the liver and the kidneys. These organs need to be intact for compensation. Moreover, electroneutrality plays an important role in ensuring the balance.

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