What do you need to know as medical laboratory scientists when performing plasma electrolyte analysis? What new information should you consider regarding best laboratory practice in electrolyte analysis? This review article will answer some of these questions.

**Background**

In human physiology it is best to refer to electrolytes, the main component in bodily fluids, in the context of extracellular fluid (ECF) volume and total water (H₂O) content in the body. Electrolytes are also best referenced collectively rather than individually because they are part of an integrated physiological mechanism of H₂O and ionic balance. Thirst, renal function, and hormonal response help to maintain homeostasis of electrolytes.¹

These entities play a role in general functions of metabolic pathways, enzyme activation, acid-base balance, muscular-function regulation, and nervous-tissue contractions. Control of electrolyte levels is based on H₂O and pH balance and is enacted by the renal glands through processes such as active transport in the proximal convoluted tubules, osmosis, and passive diffusion. At a cellular level, sodium (Na) and potassium (K) levels are maintained by the Na-K–adenosine triphosphatase (ATPase) pump.¹ The endocrine system influences the distal convoluted tubules via the renin-aldosterone system and the circulating levels of vasopressin and natriuretic peptides in bodily fluids.

**Clinical Significance**

Potassium maintains cardiac rhythm and contributes to neuromuscular conduction. Imbalances in K level, as indicated by hyperkalemia or hypokalemia, will cause cardiac arrhythmias and neuromuscular weakness. Chloride (Cl) helps to maintain electrical neutrality with Na. Cl also contributes to the maintenance of acid-base balance by participating in the isohydric shift to buffer H⁺ and the Cl shift to maintain electrical neutrality with movement of bicarbonate (HCO₃⁻) ions. Renal and endocrine disorders often are characterized by electrolyte imbalances that can be reflected in plasma electrolyte levels. Changes in electrolyte levels, compared with total H₂O content in the body, are associated with pathological consequences and increased mortality.²,³,⁴

Hypernatremia is caused by renal and nonrenal disorders; it is closely tied to total H₂O levels in the body. A common nonrenal cause for hypernatremia is hypotonic dehydration resulting from severe diarrhea, extensive burns, or excessive sweating without proper fluid replacement. Infants, elderly individuals, and other patients will also experience hypernatremia due to dehydration if they are deprived of sufficient amounts of H₂O or are not properly hydrated. Hypernatremia can also be caused by renal loss of H₂O, such as from nephrogenic diabetes insipidus. Serum osmolality and urinary Na levels can help to differentiate the cause of hypernatremia, be it renal loss of H₂O or nonrenal in nature.⁴
Hyponatremia, also of renal and nonrenal origins, is classified based on extracellular fluid (ECF) levels. However, clinical assessment of hyponatremia and ECF volume status is difficult without measuring the concentration of Na in a spot urine sample. In situations in which there is increased ECF volume, there may be an actual increase in total Na levels in the body but a dilutional effect of plasma Na levels due to ascites, nephrotic syndrome, or congestive heart failure. Urine Na levels are usually normal or decreased in hyponatremia due to edema. Decreased total Na levels in the body, even in the context of decreased ECF levels, are found in salt-losing renal nephritis, renal tubular acidosis, and treatment with certain types of diuretics or in the syndrome of inappropriate antidiuretic hormone secretion (SIADH) with resulting renal loss of Na. These causes of hyponatremia may be evaluated by testing for the presence of excess urinary Na levels. This illustrates the value of measuring urine Na levels along with serum Na levels.

Because of the high concentration of Na in extracellular fluid, such as plasma H2O, Na plays a major role in maintaining osmotic pressure. Extremely high or low Na concentrations in plasma will cause severe osmotic pressure changes that can induce serious consequences to several organs. The most immediate effect is swelling on the brain and potential coma.

Hyperkalemia may be caused by decreased renal excretion in acute or chronic renal failure, treatment with certain diuretics, or hormonal imbalances such as hyperaldosteronism or hypocortisolism. Hyperkalemia may also be caused by ionic shift, as may be observed in cases of diabetic ketoacidosis or other metabolic acidosis; hyperkalemia is also associated with leukemia, excessive muscle activity, and hemolysis. Finally, hyperkalemia is associated with iatrogenic causes of excessive K administered intravenously or orally. Maintaining serum K levels in the normal reference range in patients with cardiac conditions may decrease life-threatening complications because abnormal serum K levels are associated with increased mortality.

Hypokalemia is caused by renal loss such as renal tubular acidosis, hyperaldosteronism, hypocortisolism, and treatment of patients using certain diuretics. Potassium levels can also be low due to gastrointestinal dietary deficit or loss from severe vomiting, diarrhea, nasogastric suctioning, laxatives, and/or malabsorption. Transcellular ionic shifts that take place during insulin overdose and in metabolic alkalosis can also cause hypokalemia.

Chloride is the major extracellular anion that balances with Na to maintain electrical neutrality. Chloride levels outside of reference ranges, even when considered by themselves, usually indicate a more serious underlying metabolic disorder, such as metabolic acidosis or alkalosis. Testing for Cl levels is diagnostically important and should be evaluated in a wide variety of clinical situations, especially those dependent on total H2O levels in the body. Thus, hyperchloremia, like hypernatremia, occurs most commonly due to dehydration.

Hypochloremia may occur due to loss of Cl from the ECF or excess extracellular fluid levels, such as in edema or similar causes including hyponatremia. Cl loss can occur in the gastrointestinal tract, in compensation for respiratory acidosis, or in primary metabolic alkalosis. The typical close inverse relationship between serum Cl and HCO3− concentrations is often less correlated when patients also exhibit significant changes in H2O balances and concurrent acidosis with anion gap disturbances.

HCO3−, the metabolic component of the plasma buffer system, is the major component of the extracellular buffer system; renal tubular cells and erythrocytes serve as its reservoirs. Changes in plasma tCO2 and HCO3− levels indicate the presence of an acid-base disturbance but must be evaluated in the context of clinical information and several sequential electrolyte and anion gap results. Decreased plasma levels of total CO2 or HCO3− usually result from primary metabolic acidosis or as part of compensation for respiratory alkalosis. Extremely low levels of HCO3− in plasma almost always point to metabolic acidosis, such as in ketosis, renal failure, or other metabolic causes that limit compensation for respiratory alkalosis.

Increased plasma levels of total CO2 result from primary metabolic alkalosis or compensation for acute respiratory acidosis, such as in emphysema or respiratory failure. Mixed metabolic and respiratory acidosis due to respiratory failure, in combination with hyponatremia or hypochloremia due to fluid imbalances such as edema, can yield serious complications and require prolonged treatment.

Methods of Analysis

The reference method for these electrolytes, other than HCO3−, is flame emission photometry. However, ion-selective electrodes (ISEs) are the most commonly used instruments of electrolyte analysis in clinical laboratories.
Only the free unbound ion is measured by the ISE; conditions that affect binding and ionization can affect the accuracy of measurements. ISEs consist of or are covered by a unique material that is more selective for a certain ion in solution than for other ions. When the selected ion comes in contact with the electrode, a change in the potential can be observed, compared with the reference electrode; this is measured as a voltage change, due to the ionic activity.

Turnaround time (TAT) for urgent electrolyte-level testing orders is a consideration when choosing methodology platforms. It is common to set the completion time for urgent electrolyte-test requests at 15 minutes, although health care professionals would prefer a TAT of 5 minutes. This is possible with use of point-of-care (POC) devices to achieve this TAT. However, laboratorians must consider various technical aspects, such as issues of the reliability of results, before instituting this option. POC devices can produce unreliable results due to variable levels of experience among testing staff, less care taken by certain testing-staff members, the effects of sample integrity, and the general assumption that simpler testing equates error-proof results. Given less control over the testing process, tracking and managing errors generated by POC electrolyte devices may be more difficult than doing so in the centralized laboratory testing environment.

Principles

The ISEs for Na and K are similar; they only possess differences in the composition of the membrane that provides for selectivity of the unique ion. For Na, the ISE membrane is often made of a lithium aluminum silicate or other composite silicon dioxide glass compound that selects for Na+ more readily than K+ or H+. The ISE for K typically uses a selective membrane containing valinomycin.

Chloride can be measured by an ISE consisting of a silver chloride (AgCl)–membrane solid-state electrode. When the ion comes in contact with the electrode, a change occurs in the potential compared with the reference electrode; this change can be measured as a voltage change due to the ionic activity. Chloride can also be measured via coulometric-amperometric titration, with silver (Ag) ions released at a constant rate and forming insoluble AgCl. The time of titration is proportional to the Cl activity in the sample. This method is commonly used for sweat Cl analysis.

The total plasma CO2 (tCO2) gas cell/electrode contains an acid to convert HCO3− to gas, which diffuses through a silicone membrane and reacts with an HCO3−/carbonic acid buffer to produce H+ in proportion to the amount of tCO2 in the plasma. The H+ molecules are detected by an ISE made of silicon dioxide/lithium and calcium oxide glass that selects for Na+ over H+ and registers a change in potential versus the AgCl reference electrode. Total CO2 can be measured via ISE or by an enzymatic/photometric method. A spectrophotometric/ enzymatic methodology for total CO2 measurement uses urea amidolyase. The enzyme catalyzes the reaction of HCO3− with urea to form several products, including ammonium. Ammonium is then measured using glutamate dehydrogenase (after first assessing the endogenous ammonium ion concentration) to produce nicotinamide adenine dinucleotide phosphate (NADP+), which produces change in absorbance at 340 nm.

The Specimen

Venous serum, lithium heparinized whole blood or plasma, or heparinized arterial whole blood should be collected using a method that does not trigger hemolysis, release from muscle activity, or leakage from erythrocytes. Heparinized plasma is the specimen of choice; it contains less K, namely, 0.3 to 0.7 mmol per L, than serum due to platelet release during coagulation. Laboratorians may also analyze electrolytes in bodily fluids such as urine, sweat, cerebrospinal fluid (CSF) and gastric fluids; specimens of these fluids are stable if maintained in closed containers and analyzed promptly. The specimen type may be the cause of a consistent difference between direct and indirect ISE methods, especially when POC devices are used. This difference may occur due to the differing ratios of the volume of anticoagulant to patient specimen used in central laboratory testing versus capillary whole blood that is tested in POC devices.

Interferences

Several preanalytical variables affect electrolyte results, including type of anticoagulant, storage conditions, and hemolysis. Hemolysis of blood causes a false increase in plasma K results by releasing intracellular K; however, grossly hemolyzed specimens will affect the analyses of Na and Cl levels due to a dilutional effect. The presence of excess anticoagulant when small volumes of blood are collected will similarly cause a dilutional effect and falsely decreased plasma levels of Na and Cl. Refrigeration of
unseparated whole blood may actually enhance the intracellular release of K from erythrocytes.

Some anticoagulants, such as trisodium citrate (Na$_3$C$_6$H$_5$O$_7$) or ethylenediaminetetraacetic acid (EDTA), chelate cations and should be avoided to prevent a false decrease in plasma results. Ammonium or sodium heparin may falsely add electrolytes to results. Therefore, lithium heparin is the only recommended anticoagulant for plasma electrolyte analysis.

Analytical variables may also cause limitations. Flame emission and ISE systems that dilute the sample before analysis with the electrode are termed indirect methods. The results are compromised by hyperlipidemia or hyperproteinemia because the large lipid or protein molecules that occur in unusually high amounts in those conditions displace some of the volume of the plasma within the dilution. For example, if triglycerides or total protein are significantly elevated, the laboratorian may begin to experience interference. The effect of hyperlipidemia or hyperproteinemia is to falsely lower the measured Na levels and sometimes the Cl levels in plasma due to this dilutional effect. Direct systems do not dilute the sample before analysis. Even with normal plasma H$_2$O concentration, a slight difference in ionic activity would be measured via direct and indirect ISE systems. Direct ISE systems generally have a conversion factor that yields results in concentration terms that are comparable to the reference method (flame photometry) for specimens with normal plasma H$_2$O levels.

Analytical limitations may be more pronounced in some methodologies than others. For example, a study of a POC device that measures blood gases and electrolytes reported significantly different Na levels than a bench-top analyzer in paired sample tests. The researchers recommend that critical decisions could safely be made based on POC K values but that Na results might not be as reliable.

Variation will also occur in the spectrophotometric method for determining the total CO$_2$ level, due to the presence of interfering chemicals that are absorbed at wavelengths that overlap with the wavelengths established for the test analysis. The enzymatic/photometric method for total CO$_2$ may yield a false decrease in the results due to turbidity production, which alters the reaction kinetics of the enzymatic assay and causes an initial increase in absorbance and a falsely low total CO$_2$ value. Turbidity may have resulted from precipitation of paraproteinsor an endogenous antibody that binds with an animal protein included in the assay reagents.

Reference ranges vary with populations, geographical locations, methods, and other conditions. A study suggests the need for separate reference intervals for neonates versus infants. The historical reference ranges for electrolytes used by the National Institute of Health are as follows: Na, 135 to 144 mmol/L; K, 3.3 to 5.1 mmol/L; Cl, 99 to 107 mmol/L; and total CO$_2$, 21 to 31 mmol/L.

Developing specific standardized reference ranges and critical values can be useful in making clinical decisions.

Accurate electrolyte analysis and valid results are vital for patient outcomes. It is important to use a well-maintained and well-calibrated instrument; to pay critical attention to standard operating procedures; to refer to information provided by the manufacturers of analyzers; and to test methodologies to minimize preanalytical, analytical and postanalytical errors. In conclusion, standardization of methods of specimen handling, analysis, and reporting, as well as following best practices in confirmation by cross-checking results, is essential in the quest to eliminate errors in the laboratory.

References


