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Balanced versus unbalanced salt solutions: What difference does it make?

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Background: The infusion of crystalloid solutions is a fundamental part of the management of critically ill patients. These solutions are used to maintain the balance of water and essential electrolytes and replace losses when patients have limited gastrointestinal intake. They also act as carriers for intravenous infusion of medication and red cells. The most commonly used solution, 0.9% saline, has equal concentrations of Na^+ and Cl^- even though the plasma concentration of Na^+ normally is 40 meq/L higher than that of Cl^-. The use of this fluid thus can produce a hyperchloremic acidosis in a dose-dependent manner, but it is not known whether this has clinical significance.

Approach: The first part of this article deals with the significance of Na^+ and Cl^- in normal physiology. This begins with examination of their roles in the regulation of osmolality, acid–base balance, and generation of electrochemical gradients and why the concentration of Cl^- normally is considerably lower than that of Na^+. The next part deals with how their concentrations are regulated by the gastrointestinal tract and kidney. Based on the physiology, it would seem that solutions in which the concentration of Na^+ is "balanced" by a substance other than Cl^- would be advantageous. The final part examines the evidence to support that point.

Conclusions: There are strong observational data that support the notion that avoiding an elevated Cl^- concentration or using fluids that reduce the rise in Cl^- reduces renal dysfunction, infections, and possibly even mortality. However, observational studies only can indicate an association and cannot indicate causality. Unfortunately, randomized trials to date are far too limited to address this crucial issue. What is clear is that appropriate randomized trials will require very large populations. It also is not known

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whether the important variable is the concentration of Cl^-, the difference in concentrations of Na^+ and Cl^-, or the total body mass of Cl^-.

Introduction

Single-atom electrolytes such as sodium, potassium, and chloride play a unique role in biology [1–4]. Because they are not metabolized, their quantity in the body must be regulated through intake and excretion. They are primarily dissolved in water although there are exceptions, such as the formation of boney structures by calcium and the interaction of calcium ion with the many calcium-binding proteins. Sodium ion (Na^+), too, can be sequestered by glycosaminoglycans in the skin in a process that is tightly regulated by monocyte phagocytic cells and vascular endothelial growth factor C (VEGF-C) [5,6]. However, these bound ions do not contribute to the osmotic activity of solutions. Electrolytes in solutions play three crucial biological roles. They are major determinants of the osmolality of the extracellular and intracellular compartments, which is essential for the maintenance of constant cell volume relative to the external environment [4]. Second, gradients in strong electrolytes across cell membranes create a transmembrane potential energy that can be used to move charged substances across the walls of cells and to regulate intracellular processes [4]. Third, strong electrolytes are important regulators of hydrogen ion (H^+) concentration, that is, pH [7]. I will first review the physiological significance of electrolytes in general and chloride (Cl^-) in particular and then discuss the empiric evidence for the clinical use of intravenous solutions in which the concentration of Cl^- is less than that of Na^+. Some of these issues have been well discussed in two recent reviews, one especially focused on specific issues related to Cl^- [8] and the other on the nature of substitutes for Cl^- [9].

Osmolality

Water is the essential solvent of living organisms and the volume of water in cells needs to be regulated to maintain normal cell function. Water does not flow freely, but rather follows along concentration gradients. Accordingly, water volume is regulated by regulating the concentrations of solutes. Since single-atom electrolytes are not metabolized, they provide ideal substances for regulating water distribution.

Life evolved out of the sea in which the two most common elements (not including oxygen and hydrogen ion) are Cl^- and Na^+. Thus, it is not surprising that these two electrolytes which dominated the extracellular environment of early organisms still dominate the extracellular environment of multicellular organisms. Typical NaCl concentration of seawater is in the range of 3%, whereas that of extracellular space is <1% and that of fresh water is 0.05%. In early multicellular organisms, seawater moved freely through the gastrointestinal and respiratory systems. This allowed these organisms to freely secrete seawater into their body cavities, pump it around, and use it to clear waste [10]. When organisms moved into water with lower salinity, they had to evolve relatively impermeable exterior systems to avoid taking up too much water from their surrounding for this would have resulted in swelling of cells and compromised cell structures. At the same time, filtering off excess water resulted in salt loss and mechanisms had to develop to reabsorb electrolytes from the filtrate [10]. When life evolved onto land the problem shifted to conservation of water for now organisms were no longer surrounded by water and water had to taken in by the gastrointestinal tract and conserved. An early need in the evolutionary process was to take in an appropriate amount of Na^+ and Cl^- from the environment and differentiating the concentrations inside impermeable structures from the surrounding environment. For example, fish developed very sophisticated mechanisms in their gills that regulate internal Na^+ and Cl^- ion concentrations [11–13]. Some fish even can adapt these processes rapidly so that they can move from the high salt environment of seawater to the low salt concentration