Magnesium in the ICU: Sine qua non

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Introduction

Magnesium is the fourth most abundant cation in the body and the second most abundant intracellular cation. It activates many of the enzyme systems mainly involved in energy metabolism and acts as a natural calcium antagonist by regulating calcium access into the cell. Although magnesium was considered as the ‘forgotten ion’ for many years, its importance in critical care practice has been highlighted recently. One of the main reasons for this increased interest among critical care clinicians is the reports of a high incidence of hypomagnesemia in patients admitted to the intensive care unit (ICU); magnesium deficiency has been reported in 20 to 65% of patients in the ICU [1]. Reduction in serum total magnesium on admission to the ICU has been shown to be associated with increased morbidity and mortality [2]. Hypomagnesemia has been implicated in the development of organ dysfunction and the systemic inflammatory response syndrome (SIRS) in ICU patients [3]. However, there is little guidance related to when magnesium supplementation might be useful for clinicians treating critically ill patients [4].

There are variety of disorders in non-magnesium depleted patients where intravenous magnesium appears to have a therapeutic benefit. The traditional use, since the beginning of the last century, of parenteral magnesium therapy has been in the treatment of pre-eclampsia [5]. Magnesium is used in perioperative analgesia [6], postoperative shivering [7], and tetanus [8]. It has been, and is still being, studied in myocardial infarction [9], cardiac dysrhythmias [10], and asthmatic attacks [11] in the emergency department. Many of the studies in these clinical conditions have shown beneficial effects of magnesium administration and the guidelines for intravenous use have been presented with a specific focus on the low risk of adverse effects. However, the efficacy of therapeutic magnesium supplementation in terms of the dose-response relationship is not very clear since there are no certain data on how total magnesium concentrations reflect the biologically active state of magnesium. This chapter briefly considers magnesium physiology and metabolism as well as the pitfalls in assessing magnesium status in critical illness. Moreover, we review the novel approaches for the therapeutic use of magnesium independent of hypomagnesemia, such as for neuroprotection and in sepsis, and also examine magnesium use as an adjunct to analgesia and sedation.
Magnesium Physiology and Clinical Aspects

A brief overview of magnesium’s physiologic interactions is necessary since these may underlie the physiology and pharmacology of magnesium’s therapeutic role either as supplementation in a deficiency state or as a medical therapy.

Magnesium is a cofactor in hundreds of enzymatic reactions and it is important for those enzymes that use nucleotides as cofactors [12]. For enzymes like ATPase which is of central importance in energy metabolism, it is not the free nucleotide, but a magnesium complex that is the actual cofactor in its activation. Magnesium is also required for protein and nucleic acid synthesis, the cell cycle, cytoskeletal and mitochondrial integrity, and for the binding of substances to the plasma membranes [12]. Magnesium is, therefore, required not only for substrate formation as an activator of enzyme activity but also for membrane stability.

Magnesium modulates ion transport by pumps, carriers, and channels [13]. It intervenes in the action of calcium and sodium-potassium ATPase (Na+/K+-ATPase) activation. Serving as a cofactor in this enzyme system, it influences sodium and potassium flux across the cell membrane. Magnesium blocks outward movement of potassium through potassium channels in cardiac cells. Decreases in magnesium cause outward movement of potassium, inducing depolarization and, thereby, causing cardiac arrhythmias. Moreover, disorders of magnesium, by altering sodium/potassium gradients and transmembrane potentials, may result in neuromuscular excitability or irritability.

Magnesium acts as a calcium antagonist at intracellular sites and in membrane channels. The interaction of magnesium with calcium channels creates a competitive antagonist action against calcium inflow. By inhibiting calcium activation at the sarcoplasmic channel, magnesium also limits the outflow of calcium from the sarcoplasmic reticulum, which is the main site of intracellular calcium storage [14]. With this mechanism, magnesium regulates intracellular calcium levels and, thereby, influences smooth muscle tone. By regulating smooth muscle tone, magnesium deficiency has been proposed to cause hypertension, neuromuscular hyperexcitability, bronchial airway constriction, coronary spasms, and seizures [4]

Metabolism of Magnesium

The distribution of magnesium is regulated by metabolic and hormonal effects on gastrointestinal absorption and renal excretion [12]. Total body stores of magnesium average 2000 mEq and the normal serum range is considered as 1.4 to 2.1 mEq/l [14]. Magnesium is distributed in the body in the following percentages: 53 % in bone, 27 % in muscle, 19 % in soft tissue, 0.5 % in erythrocytes, and 0.3 % in serum. Extracellular magnesium in serum is 33 % protein bound, 12 % complexed to anions, and 55 % in a free ionized form [14]. Unlike other cations, magnesium is absorbed equally well in the ileum and the jejunum by passive absorption. This absorption varies according to the amount of magnesium in the diet. The kidney serves as the other major site regulating magnesium balance. Studies have demonstrated that only 5 % of filtered magnesium is excreted where 70 % is reabsorbed in the loop of Henle [4]. The maximum renal tubular reabsorption for magnesium is at the normal plasma magnesium level, thus elevated concentrations will decrease reabsorption and increase excretion. It has been demonstrated that a magnesium-restricted diet will result in significantly increased reabsorption without any changes.