Introduction

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Magnesium ions are essential to all living cells. As the second most abundant intracellular cation, magnesium has a crucial role in fundamental metabolic processes such as DNA and protein synthesis, oxidative phosphorylation, enzyme function, ion channel regulation, and neuromuscular excitability. **(Naderi and Reilly, 2008).**

Magnesium is one of the four major cations in the human body and the second most abundant within the cell. Observational studies have shown the fundamental role of magnesium in treatment of different cardiovascular disorders, connected with magnesium deficiency. As co-factor of many enzymes, especially those involved in phosphate transfer, it plays a role in regulation of intracellular reactions in the organism. By influence on sodium pump and calcium pump, it regulates flowing of Na+, Ca2+, K+ ions through channels in cell membrane and therefore, it decreases lack of K+ ions, protects the cell from Ca2+ ions overloading and inhibits sodium influx into the cell. **(Anna and Kazimierz, 2004).**

Magnesium is an important cofactor for many biological processes, such as protein synthesis, nucleic acid

stability, or neuromuscular excitability. **(Konrad, et al., 2004).**

Magnesium role is achieved through two important properties of magnesium; the ability to form chelates with important intracellular anionic-ligands, especially ATP, and its ability to compete with calcium for binding sites on proteins and membranes. **(Ryan, 1991).**

Magnesium is an often overlooked electrolyte that is essential to life. Magnesium plays a role in more than 300 enzymatic reactions and is critically involved in energy metabolism, glucose utilization, protein synthesis, fatty acid synthesis and breakdown, ATPase functions, and virtually all hormonal reactions. Magnesium is closely involved in maintaining cellular ionic balance through its association with sodium, potassium, and calcium. **(Guns, 2004).**

Magnesium deficiency and hypomagnesaemia can result from a variety of causes including gastrointestinal and renal losses. Magnesium deficiency can cause a wide variety of features including hypocalcaemia, hypokalaemia and cardiac and neurological manifestations. **(Swaminathan, 2003).**

Magnesium reduces catecholamine release and thus allows better control of adrenergic response during intubation or pheochromocytoma surgery. It also decreases the frequency of postoperative rhythm disorders in cardiac surgery as well as convulsive seizures in preeclampsia and their recurrence in eclampsia . Mg is used in different surgical situations, obstetrics and perioperative analgesia and has various interactions with the drugs used in anesthesia. The use of adjuvant magnesium during perioperative analgesia may be beneficial for its antagonist effects on N- methyl-D-aspartate receptors. Dysmagnesemia, particularly hypomagnesaemia is frequent in the perioperative period and in the intensive care unit and causes considerable morbidity. Hypermagnesemia is relatively infrequent and often iatrogenic, especially in patients with renal insufficiency for whom magnesium should prescribed with much care. **(Dube and Granry, 2003).**

CHAPTER 1

Physiological Considerations

Magnesium physiology

Mg in the organism:

Mg is a bivalent ion; the human body contains one mole (24 g) of Mg. It is the fourth most common mineral salt in the organism after phosphorus, calcium and potassium, the second intracellular cation after potassium, and the fourth plasma cation after sodium, potassium and calcium. Extracellular Mg represents only 1% of the total. **(Saris, et al., 2000).**

Requirements & Absorption:

The recommended Mg requirement is 250 to 350 mg per day (10.4–14.6 mmol) in adults and an additional 100 to 150 mg in children and pregnant or nursing women. Food input is ensured essentially by cocoa powder, chocolate, almonds, peanuts, walnuts, vegetables, cereals and seafood. From 30 to 50% of ingested Mg is absorbed (5 mmol per day) in decreasing quantity from the small intestine to the colon. Fibres, phytates and oxalic acid appear to reduce Mg absorption moderately through the formation of a complex that cannot be easily

dissociated. The binding of Mg to anions (phosphates) or fatty acids reduces the quantity of absorbable Mg. **(Sanders, et al., 1999).**

Administration of Mg:

Mg can be administered orally or intravenously. Intramuscular injection is also possible but painful. Oral administration of a daily dose of more than 50 mmol can cause vomiting and diarrhea.In anesthesia and intensive care, the preferred administration route is IV. Two injectable forms of Mg are available, namely Mg chloride and sulfate. Ten millilitres of a 10% Mg chloride ($MgCl_2$) solution provide 1 g of Mg salts (= 118 mg elemental Mg), and 10 mL of a 10% Mg sulfate ($MgSO_4$) solution provide 1 g of Mg salts (= 98 mg elemental Mg). **(Dacy, et al., 2001).**

Dosage of Mg:

Dose of Mg differs according to indications, and several dosage recommendations have been proposed. When Mg sulfate is used to correct a Mg deficit, the objective is to restore normal serum concentrations, in which case slow infusion of up to 10 g per day is appropriate. When Mg is used for its pharmacological properties, more rapid infusion is often necessary to obtain the high plasma concentrations desired. The recommended procedure is rapid I.V infusion of

1 to 2 g of $MgSO_4$ over a ten-minute period followed by continuous I.V infusion of 0.5 to one g per hr (reduced to 0.25 g per hr for patients with renal insufficiency). Administration is performed under continuous electrocardiographic monitoring, and serum concentrations of Mg or ionized Mg are determined every six hours. **(Dacy, et al., 2001).**

Mg when given too quickly, flushing can occur, and bradycardia, cardiac arrhythmia, and cardiac arrest have been reported. There is also the increased risk of the toxic effects of Mg resulting in renal impairment. **(Walker, 2000).**

When Mg was used for tocolysis, adverse effects (flushing and headache) were more frequent with high (5 g per hr) than with low doses (2 g per hr). **(Terrone, et al., 2000).**

Distribution of magnesium:

Mg is concentrated mainly in bone (60%), muscle (20%), and soft tissues (19%). Extracellular Mg represents only 1% of the total. Only a fourth of the Mg contained in bone and muscle is exchangeable and functions as a reservoir to stabilize the serum concentration. **(Sanders, et al., 1999).**

The concentration of magnesium in CSF is around 1.1 mmol /L, of which 55% is free and 45% is complexed with other compounds. The higher ultrafiltrable magnesium in CSF compared to serum is due to active transport of magnesium across the blood-brain barrier. **(Morris, 1992).**

Serum Mg:

In serum, Mg is divided into three fractions: ionized (active form), protein-bound and that contained in anion complexes (phosphates and citrates). These three fractions account respectively for 65, 27 and 8% of serum content. Three-fourths of plasma Mg is ultrafiltrable**.** Total serum Mg is 16.8–26.4 mg/L, 1.4-2.2 m Eq /L or 0.7-1.1 mmol /L. **(Saris, et al., 2000).**

Intracellular Mg:

Mg is mainly intracellular, existing largely (90%) in bound form in adenosine triphosphate (ATP) molecules of the cytoskeleton (nucleus, mitochondria and endoplasmic reticulum), in nucleotides, or in enzyme complexes. A small portion of intracellular Mg (about 10 %, depending on the cells) is found in ionized free form within the cell.

Heart muscle cells have a high concentration of total Mg. **(Kelepouris, et al., 1998).**

Excretion of Mg:

Urinary excretion of Mg is normally 5 mmol /day, but can be reduced to 0.5 mmol /day in the event of severe deficiency. The level is regulated by variations in renal reabsorption, as a function of magnesemia, relative to inputs and bone mobilization. **(Sanders, et al., 1999).**

Within the kidney, Mg filtered by the glomerulus is handled in different ways along the nephron. About 10-20% of Mg is reabsorbed by the proximal convoluted tubule. The bulk of Mg (about 50-70%) is reabsorbed by the cortical thick ascending limb of the loop of Henle. In this region, Mg moves across the epithelium through the paracellular pathway, driven by the positive lumenal transepithelial voltage. A recently cloned human gene, paracellin-1 was shown to encode a protein localized to the tight junctions of the cortical thick ascending limb and is thought to mediate Mg transport via the paracellular space of this epithelium. The distal convoluted tubule reabsorbs the remaining 5-10% of filtered Mg. This segment seems to play an important role in determining final urinary excretion, since there is no

evidence for significant Mg absorption beyond the distal convoluted tubule. **(Satoh, and Romero, 2002).**

Under normal circumstances, about 80% of the total plasma magnesium is ultrafiltrable, 84 mmol of magnesium is filtered daily and 95% of this reabsorbed leaving about 3–5 mmol to appear in the urine. Approximately 15–20% of filtered magnesium is reabsorbed in the proximal tubular segments, 65–75% in the ascending limb of Henle's loop and the rest in the distal segments. **(Yu, 2001).**

Mg is reabsorbed through the reabsorption of Na and K by creating an electropositive gradient from tubular lumen to extra-cellular space. Mg reabsorption in loop of henle is linked to Na-Cl co-transport and inversely related to the flow so, diuretics and other that increase tubular flow can result in decreased Mg reabsorption. **(Topf and Murray, 2003).**

Hormonal Regulation:

No single hormone has been shown to be specifically related to magnesium homeostasis. Several hormones including PTH, antidiuretic hormone (ADH), calcitonin, glucagon and insulin have been shown to affect magnesium reabsorption. Of these, PTH is the most important. PTH

increases reabsorption in the distal tubules by a cyclic AMP mediated process. **(Dai, et al., 2001).**

Several hormones are involved in the regulation of Mg metabolism, namely parathyroid hormone (PTH), calcitonin, vitamin D, insulin, glucagon, epinephrine, antidiuretic hormone, aldosterone and sex hormones. PTH and vitamin D increase intestinal absorption, PTH favours renal reabsorption of Mg and facilitates its bone reuptake, insulin induces intracellular shift of Mg and glucagon is concerned with its renal reabsorption. **(Quamme,1997).**

Biological considerations:

Assay of total plasma Mg by spectrophotometry is precise and easy to perform (0.7–1.1 mmol/L or 1.4–2.2 mEq/L, or 16.8–26.4 mg/L). However, owing to the intracellular nature of this ion, these values are not exactly indicative of the Mg pool in the organism or of a possible state of deficiency. **(Fawcett, et al., 1999).**

Because of the long life of Mg and its slow turnover, erythrocytic Mg might be a better indicator of deficiency. Lymphocytic Mg would appear to be a better indicator of the Mg content of muscle and myocardium and of ionized Mg. **(Delhumeau and Granry, 1995).**

Cellular physiological properties of Mg:

Action on membrane and membrane pumps:

Magnesium is required for the active transport of ions like potassium and calcium across cell membranes. Through its role in ion transport systems, magnesium affects the conduction of nerve impulses, muscle contraction, and normal heart rhythm. **(Rude, et al., 2006)**.

Mg intervenes in the activation of membrane Ca ATPase and Na-K ATPase involved in transmembrane ion exchanges during depolarization and repolarization phases. Mg deficiency impairs the action of ATPase pumps and leads to a reduction of intracellular ATP as well as to increased concentrations of sodium and calcium and decreased concentrations of potassium within the cell. **(Dacy, et al., 2001).**

It was found that Mg appears to act as a stabilizer of cell membrane and intra-cytoplasmic organelles**. (Reinhart, 1991).**

Action on ion channels:

Mg is considered to act as a regulator of different ion channels. A low intracellular Mg concentration allows potassium to leave the cell, thereby altering conduction and cellular metabolism. **(Dacy, et al., 2001).**

Mg is a calcium channel blocker and a modulator of calcium channel activity, which means that a rise in intracellular calcium occurs during hypomagnesaemia**. (Sanders, et al., 1999).**

Enzyme activation:

Intracellular free Mg is involved in the energy reactions of phosphorylation and is necessary for the activation of hundreds of enzymatic reactions concerning ATP. **(Reinhart, 1991).**

Inorganic phosphate and ATP within the cell reduce free Mg, whereas the conversion of ATP to adenosine diphosphate (ADP) increases it. **(Saris, et al., 2000).**

In fact, Mg interacts with the outer two phosphate groups of ATP to form the enzymatic substrate. Intracellular Mg deficiency is correlated with the impaired function of many enzymes utilizing high-energy phosphate bonds, as in the case of glucose metabolism. **(Sanders, et al., 1999).**

Table (1): Physiological functions of magnesium

Enzyme function:
Enzyme substrate (ATPmg, GTPmg)
Kinases B: Hexokinase, Creatine kinase, Protein kinase
ATPases or GTPases : Na^+-K^+ ATPase ,Ca^+ ATPase
Cyclases : Adenylate cyclase ,Guamylate cyclase
Direct enzyme activation:
Phosphofructokinase
Creatine kinase
5-phosphoribosyl-pyrophosphate synthetase
Adenylate cyclase
Na^+,K^+-ATPase
Membrane function:
Cell adhesion
Transmembrane electrolyte flux
Calcium antagonist:
Muscle contraction/relaxation
Neurotransmitter release
Action potential conduction in nodal tissue
Structural function:
Protein
Polyribosomes
Nucleic acids
Multiple enzyme complexes
Mitochondria

(Swaminathan, 2003).