REVIEW

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The use of magnesium in bronchial asthma: a new approach to an old problem

Aneta Kowal, Bernard Panaszek, Wojciech Barg and Andrzej Obojski

Department of Internal Medicine and Allergology, Wrocław Medical University, Wrocław, Poland

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Abstract

Magnesium deficiency is a common electrolyte disorder in patients with acute severe asthma, but intracellular magnesium content better reflects its homeostasis than does its serum concentration. Magnesium takes part in many metabolic processes in the organism, including energy metabolism, protein and nucleic acid synthesis, cell cycle, the binding of substances to the plasma membrane, and maintenance of cytoskeletal and mitochondrial integrity. It also modulates ion transport and influences intracellular calcium concentration. Maintenance of the cells' transmembrane gradient depends on the presence of magnesium, and hypomagnesemia may result in an increase in neuromuscular cell excitability. Magnesium is a cation modulating the smooth muscle contractility of different tissues: hypomagnesemia causes their contraction and hypermagnesemia their relaxation. Suggestions of a positive influence of magnesium in the treatment of asthma exacerbation have been known for a long time, but research results differ. A single dose of intravenous magnesium sulfate given to patients with acute asthma exacerbation has been shown to be safe, but its efficiency is still under discussion. According to the Global Initiative for Asthma GINA-2005, magnesium sulfate administration is not recommended for routine treatment, but it is permitted in patients with severe asthma exacerbation not responding to treatment (evidence category A). Recommendations of the British Thoracic Society allow one dose of magnesium sulfate to patients with acute severe asthma exacerbation and inadequate initial response to broncho-dilating inhalation treatment (evidence category A). Future investigations should help to establish the indications for magnesium use in the treatment of acute asthma exacerbations as well as the magnesium dose and the scheme of its administration.

Key words: magnesium, hypomagnesemia, smooth muscle contractility, acute asthma exacerbation.

Abbreviations: DNA – deoxyribonucleic acid, ATP – adenosine-5`-triphosphate, IgE – immunoglobulin E, $MgSO_4$ – magnesium sulfate, PEFR – peak expiratory flow ratio, FEV_1 – forced expiratory volume during the first second of expiration.

Corresponding author: Aneta Kowal, M.D., Department of Internal Medicine and Allergology, Wrocław Medical University, Traugutta 57/59, 50-417 Wrocław, Poland, tel.: +48 71 733-24-00, fax: +48 71 733-24-09, e-mail: akowal2@op.pl

INTRODUCTION

Magnesium has never awoken as much interest as calcium, sodium, or potassium. The daily magnesium requirement depends on sex and age: for children it is about 150–250 mg, for women about 300 mg, and for men 350–400 mg. Its normal serum levels are from 0.8 to 1.0 mmol/l (1.9–2.5 mg/dl). Most of the human body's magnesium is found in the bones (approximately 60%) and soft tissues, and only about 1% is found in serum [19]. Most clinical laboratories assess only total serum Mg, which consists of three Mg fractions: Mg^{2+} bound to proteins, Mg^{2+} complexed to small anion ligands, and free ionized Mg^{2+}. Using ion-selective electrodes, Altura and Altura [3] demonstrated that the mean concentration of ionized Mg^{2+} in the blood is about 600 μmole/l (0.54–0.65 mmol/l), with 65–72% of the total Mg being free or biologically active Mg^{2+}. The ion serum concentration is usually correlated with total human body magnesium content, but its normal serum concentration still sometimes does not reflect the human body's magnesium real stores. Connective tissue, skin, and soft tissues of the abdominal cavity, which can deliver magnesium to the serum relatively fast, are the routes of easy access to reservoirs of this ion, while magnesium circulation among bones, muscles, and erythrocytes is slow [19]. The human body's supply of this bioelement is regulated by metabolic and hormonal mechanisms which influence its intestinal absorption and renal excretion [17]. Kidneys are the main organs regulating magnesium homeostasis and the renal excretion of this ion depends on its serum concentration.

Magnesium can also be lost due to perspiration. At high temperatures even 10–15% of excreted magnesium can be present in sweat [19].

The main reasons for magnesium deficiency are reduced intake, impaired intestinal absorption, increased renal loss, alcohol, diuretics (with the exception of potassium-sparing agents), antibiotics (gentamicin, carbenicillin, ticarcillin), hyper- and hypo-parathyroidism, excess sweating, and idiopathic hypomagnesemia [19]. The main clinical manifestations of hypomagnesemia are neuromuscular disturbances, cardiac arrhythmias such as premature ventricular contractions, atrial fibrillation, and torsade de pointes and electrocardiographic changes such as T-wave flattening, metabolic disorders (refractory hypokalemia, hypocalcemia, hypercholesterolemia), and mental disorders [19].

Renal insufficiency is the main cause of hypermagnesemia, especially when medications containing magnesium are used. It is difficult to induce hypermagnesemia in a patient with normal renal function [19]. A moderate increase in magnesium concentration is safe for the organism, and only its considerable increase may cause clinical manifestations.

MAGNESIUM'S PARTICIPATION IN INTRACELLULAR METABOLIC PROCESSES

Magnesium takes part in many very important metabolic processes in the organism, including energy metabolism, protein and nucleic acid synthesis, cell cycle, the binding of substances to the plasma membrane, and the maintenance of cytoskeletal and mitochondrial integrity. It also modulates ion transport and influences intracellular calcium and potassium concentrations [26]. Its flow across the cell membrane is regulated by many hormones and depends on the cell type [15].

Magnesium is a co-factor of more than 300 intracellular enzymic reactions utilizing high-energy phosphate bonds [9]. All cell reactions, whether producing (oxidative phosphorylation) or utilizing energy, depend on magnesium. DNA synthesis and degradation also require its presence [15]. Magnesium joined to the adenosine-5`--triphosphate (ATP) molecule forms a substrate whose terminal phosphate bond is labile, making it easier to transfer the phosphate to other molecules. The ion neutralizes the negatively charged ATP molecule and facilitates binding the ATP to other enzymes participating in the reaction [19]. The presence of magnesium is fundamental to all ATPas activities, including those responsible for calcium flow both across cell membranes either into the cell and within the cell. The cell's excitability depends on the electrochemical transmembrane potential gradient, which is essential for impulse formation and propagation. By influencing the Na-K-ATPase system, magnesium takes part in maintaining the cell's transmembrane gradient. Hypomagnesemia, by reducing transmembrane potentials, results in an increase in the excitability of neuromuscular cells [17].

MAGNESIUM'S INFLUENCE ON SMOOTH MUSCLE FUNCTION

Magnesium is a cation modulating the contractility of the smooth muscles of different tissues, so hypomagnesemia results in their contraction and hypermagnesemia in their relaxation [9]. The contraction and dilation of smooth muscles of the bronchi are a result of phosphorylation and dephosphorylation of the myofibrillar proteins conducted by specific enzymes and regulated by intracellular calcium concentration. Calcium is transported into the cell by Ca/Mg-dependent membrane ATPase and by voltage- and receptor-regulated calcium channels. The phosphorylation and dephosphorylation reactions are carried out by enzymes of two classes, i.e. protein kinases and phosphoprotein phosphatases. Myosin kinase, which phosphorylates myosin chains, belongs to the first group and depends on magnesium. Myosin phosphatase, which dephosphatases the light chains of myosin, belongs to the second group and depends on calcium. The intracellular calcium level is a result of its magnitude of transport through the cell membrane. Magnesium is one of the agents regulating this process. It can be said that the intracellular magnesium concentration influences the activity of those two most important enzymes taking part in the contraction and relaxation of the bronchi smooth muscles either in a direct (myosin kinase) or an indirect way (myosin phosphatase). Magnesium deficiency in asthmatic patients may potentiate calcium intracellular flow into the smooth muscle cells, which leads to enhanced myosin phosphorylation and to an increase in the muscles' contractility. Magnesium deficiency increases acetylcholine cell depolarization as well. Hypomagnesemia results, then, in an increase in bronchi smooth muscles excitability and their contraction [15]. Magnesium delivery may reverse these processes. The potential mechanisms of magnesium dilation include the phenomena shown in Table 1.

Iseri and French [13] showed that elevation of the magnesium level inhibits and its deficiency increases calcium activity. The physiological magnesium level regulates calcium influx into the smooth muscle cells. Magnesium

Table 1. Mechanisms of magnesium dilation

- calcium channel block [9]
- inhibition of cholinergic neuromuscular transmission with decreased sensitivity to the depolarizing action of acetylocholine [9]
- stabilization of mast cells and T lymphocytes [9]
- stimulation of nitric oxide and dilatation prostacyclins [9]
- inhibition of calcium release from the sarcoplasmic reticulum [13]
- stimulation of reticulum calcium uptake [16]
- stimulation of Ca-ATPase activity and the calcium drive into the reticulum [13]
- competition with calcium at certain binding sites on troponin-C and myosin and reduction of muscle tension development [13]

deficiency may result in disturbances in calcium removal from the cells by magnesium-dependent Ca-ATPase, the intracellular calcium drive to the mitochondria, and its excessive distribution in the sarcoplasmic reticulum.

A high concentration of magnesium reduces basic muscle tension, while a low concentration increases it rapidly. Hypomagnesemia increases muscle reactivity to catecholamines and reduces prostaglandin relaxant action [15]. A decrease in magnesium concentration was noted during adrenaline or salbutamol infusion, which are used in acute asthma. It is suggested that magnesium flow between the extracellular and intracellular compartments may be under the influence of β-adrenergic receptors [16]. During a stress reaction, which is an acute asthma exacerbation, magnesium escapes from the cells and calcium enters the cells [15].

The problem is the fact that when considering only the serum level of magnesium level, intracellular hypomagnesemia may be overlooked, as the extracellular level of the ion may not reflect its intracellular deficiency. Thus we cannot anticipate the patient's response to our magnesium treatment based on his magnesium serum level. Intracellular magnesium content better reflects its homeostasis than does its serum concentration, but we still do not know which tissue is the best qualified for testing.

THE CALCIUM ASTHMA HYPOTHESIS

Bronchial hyperreactivity, i.e. excessive contraction of the airways as a response to physical, chemical, and pharmacological stimuli, is a characteristic feature of asthma. Exposure to specific (allergen) and nonspecific (viral, bacterial, physical, and chemical) factors finally result in disturbances in calcium homeostasis and lead to airway contraction. The intracellular calcium concentration increase is caused by its release from the endoplasmic reticulum due to inositol phosphate activity, which is formed by phospholipase C activation. The enzyme's activation may be in an immunoglobulin (Ig)E-dependent way, where the allergen joins to the antibody, thus changing the IgE receptor conformation, or in an IgE-independent way, where the agonist binds directly to the receptor, which activates the G-protein of the cell membrane [14]. An increase in the concentration of ionized calcium in the cytosol results in releasing allergic reaction mediators (histamine, prostaglandin D_2) by mastocytes and basophiles and acetylcholine by cholinergic nerve endings. This induces smooth muscle contraction. This is the so-called calcium asthma hypothesis [15]. Magnesium may influence each of the above stages of muscle contraction and it can effectively inhibit them [15]. The results of research published in 1998 by Dominguez et al. [9] suggest a strong positive correlation between bronchial reactivity as assessed by the metacholine provocation test and the intracellular magnesium concentration measured by spectophotometry in the erythrocytes. There are also some data suggesting a protective nature of $MgSO_4$ inhalations, expressed by decreased histamine- and metacholine--induced bronchoconstriction in asthmatics [21, 22].

THE USE OF MAGNESIUM IN TREATING BRONCHIAL ASTHMA EXACERBATION

Magnesium deficiency is a common electrolyte disorder in patients with acute asthma. There are some data suggesting lower levels of Mg^{2+} and increased Ca^{2+}/Mg^{2+} ratios in asthmatic patients compared with nonasthmatics [28]. In 1912, Trendelenburg (quoted in ref. [12]) discovered bronchi smooth muscle relaxation in the presence of magnesium. The first use of magnesium in asthma treatment was reported in 1936 [23]. In 1938, Haury [12] published crucial experimental results demonstrating a dilation effect of magnesium on bronchoconstriction caused by pilocarpine, histamine, and barium chloride in guinea pigs. Haury's next study [11] discovered that half of patients with severe asthma exacerbations had low serum magnesium levels. $MgSO_4$ administration to two of them improved their clinical state. In 1989, McNamara et al. [18] reported that $MgSO_4$ infusion in a patient with respiratory insufficiency caused by asthma exacerbation improved his state so that he could avoid intubation and mechanical ventilation. Recently, a few randomized, placebo-controlled clinical trials have been conducted with magnesium sulfate used as a supplemental therapy in treating acute asthma exacerbation. Skobeloff et al. [29] gave patients with moderate and severe asthma exacerbations 1.2 g $MgSO_4$ (9.6 mEq) or 50 ml of physiological saline. The patients' status was monitored by peak expiratory flow ratio (PEFR). At 90 min of the treatment, PEFR had increased from 225 to 297 l/min in the magnesium-treated group, while it increased only from 208 to 216 l/min in the placebo-treated group ($p<0.01$). In another trial, carried out by Tiffany et al. [31], a beneficial effect of magnesium was not, however, found. In this study were 48 patients with asthma exacerbation divided into three groups: the first was given 2 g $MgSO_4$ (16 mEq) over 20 min followed by a continuous magnesium infusion of 2 g/h (16 mEq) over 4 h, the second was given 2 g $MgSO_4$ (16 mEq) over 20 min followed by a placebo infusion, and the third was given a placebo bolus followed by a placebo infusion. This trial did not show increases in FEV_1 or PEFR after magnesium treatment. In 1995, Bloch et al. [5] carried out a trial with 135 patients being treated for asthma exacerbation. They were given 2 g $MgSO_4$ (16 mEq) or physiological saline over 20 min. Analyzing the outcomes they noted that patients with severe bronchoconstriction (FEV_1 <25% predicted) were characterized by statistically significant improvement, while patients with FEV_1 >25% predicted did not respond that way. Silverman et al. [27] reported the same results in his trial. Infusion of 2 g $MgSO_4$ (16 mEq) in 50 ml of normal saline for 10–15 min considerably improved

the effect of patients treated for severe asthma exacerbation, but only when the initial FEV_1 was less than 25% predicted. The final FEV_1 after 240 min reached 45.3% in those patients, while it reached only 35.6% of the predicted value in the placebo-treated group. When the initial FEV_1 was more than 25% predicted, the final FEV_1 in the magnesium group reached 51.1% in the placebo group and 53.9%. There were 248 patients randomized in the study. Similar trials with magnesium used in asthma exacerbations were conducted in children. In 1995, Ciarallo et al. [7] published their trial results with 31 children included. They showed a significant FEV_1 improvement in the magnesium-treated group compared with the placebo group. Benefits of magnesium treatment in children were suggested by Devi et al. [8] as well.

It seems the results of the trials do not explicitly answer the question about the efficacy of intravenous magnesium sulfate used as an additional treatment in acute asthma exacerbations. The divergences were confirmed by three meta-analyses presenting the results discussed [2, 24, 20]. Cheuk et al. [6] published a meta-analysis in 2005 on intravenous magnesium sulfate for treating acute asthma in children. Four out of five studies showed that magnesium sulfate was effective.

The other way of magnesium delivery is by inhalation. Some trials were conducted with nebulized magnesium sulfate in patients with acute asthma. Aggarwal et al. [1] recently published results of their trial. They compared nebulized magnesium sulfate and salbutamol with salbutamol alone in the treatment of acute asthma and concluded there were no therapeutic benefits of adding nebulized $MgSO_4$. A meta-analysis of six trials with inhaled magnesium sulfate by Blitz et al. [4] suggests that this treatment of patients with severe astma may have some benefits, such as lung function improvement, but it does not reduce hospital admissions rates.

The basic limitation of using magnesium in treating asthma exacerbation is the fear of overdosing it. Administration of 2 g $MgSO_4$ (16 mEq) in a bolus increases the magnesium serum concentration from 1.8 to 3.1 mEq/l (0.9–1.55 mmol/l) 30 min after the infusion. Experiments suggest that administration of 2–4 g $MgSO_4$ (16–32 mEq) to patients with normal renal function over 30–60 min has a low probability of side effects [15]. Fast infusions (1–2 min) of 2 g $MgSO_4$ (16 mEq) also caused minimal side effects, but they required patient monitoring [17]. Hypermagnesemia treatment consists of magnesium administration cessation, 1 g calcium gluconate infusion, and dialysis may sometimes be needed [19].

Establishing the correct dosage and the scheme of its administration in the treatment of asthma exacerbations is also a major problem. Magnesium is rapidly removed from the vascular space by the kidneys. The cellular exchange is slow. More beneficial may be continuous infusion or repeated doses to replete magnesium-deficient cells [19].

In severe hypomagnesemia, the suggested scheme of $MgSO_4$ administration is: 6 g $MgSO_4$ (48 mEq) over 3 h, followed by 2 liters of intravenous fluid with 5 g $MgSO_4$ (40 mEq) per liter over the next 21 h, and 6 g $MgSO_4$ (48 mEq) every 24 h for the next 4 days in a slow infusion [17].

A final problem is that it is also difficult to relate the patient's clinical state of improvement definitively to the magnesium treatment without knowing its real initial cellular deficit. Ryzen et al. [25] worked out a practical method of magnesium metabolism evaluation. This is a parenteral magnesium loading test with measurement of 24-hour urinary magnesium retention. Twenty-four--hour magnesium urinary excretion may also be a good indicator. Magnesium less than 0.5 mEq in 24-hour urine collection can manifest its deficiency [17].

FINAL REMARKS

A single dose of intravenous magnesium sulfate given to patients with acute asthma exacerbation has been shown to be safe, but its efficiency is still being discussed. According to trials, a positive effect of magnesium is suggested in a subpopulation with severe asthma. The safety of magnesium treatment should be emphasized, as there were no life-threatening side effects noted in any of the trials. The most common were transient skin flushing, feeling warm, and burning at the IV site. According to the Global Initiative for Asthma GINA-2005 [10], magnesium sulfate administration is not recommended for routine treatment, but it is permitted in patients with severe asthma exacerbation not responding to treatment (evidence category A). The British Thoracic Society recommendations [30] allow one dose of magnesium sulfate administration to patients with acute severe asthma exacerbation and inadequate initial response to bronchodilating inhalation treatment (evidence category A). Future investigations should help to establish the indications for magnesium treatment in acute asthma exacerbation as well as the magnesium dose and scheme of its administration.

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