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Role of Inhaled Isotonic Magnesium Sulphate in Pediatric Asthma Exacerbation

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Abstract: Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. Magnesium sulphate is a common medication in the hospital setting with a variety of uses. It currently holds many FDA approvals. Magnesium plays a role as a co-factor in more than 300 enzymatic reactions, including in particular, glycolysis and oxidative phosphorylation. Magnesium is accepted as the physiological antagonist of calcium. In addition to these functions, magnesium has also bronchodilatory and anti-inflammatory effects The mechanism of bronchodilation consists in making dose-dependent relaxation in bronchial smooth muscle.3 The inhibition of histamine from mast cells, acetylcholine from cholinergic nerve terminals and the release of calcium into the cytoplasm play a role in this formation. In children, the anti-inflammatory and bronchodilatory effect of magnesium is promising as an adjuvant treatment for patients who do not respond to treatment in severe asthma exacerbation. Inhaled MgSO(4) could used as a substitute for inhaled SABA. While this drug is used in addition to inhaled SABA (with or without inhaled ipratropium), no overall clear evidence for improved pulmonary function or reduced hospital admissions are stated. Studies investigating the usage of Mg in asthmatic children are rare. In these studies, mostly mild to moderate or moderate-to-severe asthmatic children were evaluated.

Keywords: Pediatric Asthma, Magnesium Sulphate

Introduction: *Incidence and prevalence of pediatric asthma in Egypt:*

The prevalence of asthma in Egyptian school children ranged from 10.9% to 18.7% with a mean of 15%. The asthma prevalence is more evident in urban areas as compared to rural areas. Exposure to environmental tobacco smoke, air pollution and bad housing conditions are important determinants of asthma and may explain the trend of increased asthma in Egyptian school children ***(1).***

In study of ***Abdallah et al., (2)*** they concluded that, bronchial asthma is a significant health problem among children and adolescents in Upper Egypt occurring in 6.2% of preparatory

school children. A study conducted by Halim in Ismailia, Governorate, Egypt, revealed that, the prevalence of asthma was (9.6%) ***(3)***.

Another study conducted by Abdelakher in Zigzag University, Egypt, revealed that, The prevalence of asthma was 12.5%, and allergy to food and drugs is the most important risk factor of bronchial asthma ***(3).***

Frequency of acute asthmatic attacks in asthmatic children in 2017 was 33.3% 1-2 times per year, 40.5% 3 times per year and 26.2% more than 4 times per year ***(2).***

Mortality and morbidity of asthma:

According to the WHO estimations, asthma deaths outnumbered more than 250,000 persons per year all over the world. The factors underlying increased asthma morbidity may include: increased severity of the disease, under-treatment of patients with anti-inflammatory therapy, over-reliance on bronchodilators, and delay in seeking medical help during an exacerbation. Poverty also appears to be a risk factor ***(2).***

Magnesium Sulphate in Pediatric Asthma

Magnesium sulphate is a common medication in the hospital setting with a variety of uses. It currently holds many FDA approvals.

FDA-approved Indications *(4).*

- Constipation
- Hypomagnesemia
- Acute nephritis (pediatric patients)
- Cardiac arrhythmias secondary to hypomagnesemia
- Soaking minor cuts or bruises

History of use

In 1912, Trendelenburg observed magnesium's bronchodilator effects in cows; in **1936, Rosello** and **Pla** demonstrated the same on patients. In vitro studies demonstrated the role of magnesium in the relaxation of bronchial cells. In smooth muscle, magnesium decreases intracellular calcium by blocking its entry and its release from the endoplasmic reticulum and by activating sodium-calcium pumps. Furthermore, inhibition of calcium's interaction with myosin results in muscle cell relaxation. Magnesium also stabilizes T cells and inhibits mast cell degranulation, leading to a reduction in inflammatory mediators. In cholinergic motor nerve terminals, magnesium depresses muscle fibre excitability by inhibiting acetylcholine release. Lastly, magnesium stimulates nitric oxide and prostacyclin synthesis, which might reduce asthma severity ***(5).***

Magnesium in health

Magnesium is the fourth most abundant mineral in the human body and is essential to good health. Magnesium is needed for more than 300 biochemical reactions in the body. Magnesium takes part in many metabolic processes in the human body, 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 regulates

the blood sugar level, keeps the heart rhythm and immune system and keeps bones strong. Magnesium is also an important coenzyme for various enzyme activities, helping maintain cellular homeostasis. Magnesium is also present in the muscles (25%), and in other cell types and body fluids. It has the ability to relax the muscles. This explains how magnesium deficiency can trigger muscle tension, muscle spasms, muscle cramps and muscle fatigue. Nerves also depend upon magnesium to avoid becoming overexcited ***(6).***

Magnesium is necessary for the maintaining of serum potassium and intracellular calcium levels due to its effect on the renal tubule. In the heart, magnesium acts as a calcium channel blocker. It also activates sodium–potassium ATPase in the cell membrane to promote resting polarisation and produce arrhythmias. In the central nervous system (CNS), magnesium prevents or controls seizures by blocking neuromuscular transmission and decreasing the amount of acetylcholine liberated at the end-plate by the motor nerve impulse. It also has a depressant effect on the CNS ***(7).***

MgSO4 is being used more frequently in patients with severe airflow limitation, in conjunction with aggressive treatment (e.g. systemic corticosteroids, b2-agonists and ipratropium bromide), and in patients who often required prolonged ED care or hospitalization. Moreover, MgSO4 effectiveness relies on early recognition and administration during a severe attack; widespread use of other effective asthma therapies would therefore not be expected to reduce the need for MgSO4 ***(8).***

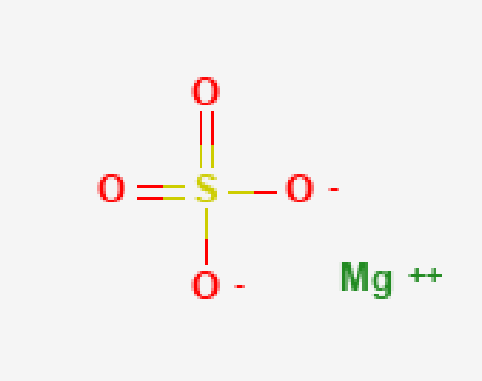

Figure (1): Magnesium Sulphate ***(9)***

Asthma and magnesium deficiency

Magnesium deficiency is a common electrolyte disorder in patients with acute asthma. There are some data suggesting lower levels of Mg2+ and increased Ca2+/Mg2+ ratios in asthmatic patients compared with non-asthmatics. In 1912, A study first recognised the potential bronchodilator effect of magnesium. He observed bronchial smoothmuscle relaxation in cows, after magnesium administration. In 1936, Other study also demonstrated a bronchodilator effect of magnesium in asthmatic patients ***(10)***

Magnesium (Mg) has been shown to relax bronchial smooth muscle in vitro and to bronchodilate asthmatic airways in vivo. Mg deficiency may then lead to an increased excitability of bronchial smooth muscle with a consequent bronchoconstriction, airway hyper-reactivity and self-reported wheezing. In addition, magnesium supplementation has

relaxant effect on vascular and bronchial tones in animals and asthmatic children. **De Valk** and **Kok**, found that intracellular Mg2+ content is reduced in patients with acute asthma, with exacerbation-induced bronchoconstriction ***(11).***

Haury stated that magnesium deficiency is a common electrolyte disorder in patients with acute asthma and hypomagnesaemia results in an increase in bronchi smooth muscles excitability and their contraction. He also found that the half of patients with asthma exacerbations had low serum magnesium levels. A study also showed a strong positive correlation between bronchial reactivity, as assessed by the metacholine provocation test, and the intracellular magnesium concentration ***(12)***

Mechanism of action of MgSO4 as a drug for asthma

Various mechanisms contributes to a larger improvement in pulmonary function using adjunct intravenous MgSO4:

(i) Calcium channel block in smooth muscle: in smooth muscle, magnesium decreases intracellular calcium by blocking Ca2+ entry (regulated by Ca/Mg-dependent membrane ATPase) and modulates prostaglandin and G-protein mediated vascular smooth-muscle relaxation and by activating sodium–calcium pumps causing airway smooth muscle relaxation ***(10)***

(ii) Inhibition of calcium's interaction with myosin results in muscle cell relaxation: Magnesium deficiency in asthmatic patients, intracellular calcium flows into the airway smooth muscle cells resulting in the muscles' contractility by enhancing myosin phosphorylation catalysed by Myosin kinase (regulated by magnesium) increase in the muscles' contractility, activation of secretory system in the mast cells and mucus producing cells. Thus, hypomagnesaemia results, then, in an increase in bronchi smooth muscles excitability and their contraction ***(13).***

(iii) Magnesium (Mg) prevents acetylcholine and histamine release from cholinergic motor nerve terminals to the axon terminal: Mg depresses muscle fibre excitability and promotes a bronchodilating effect. Some researchers found that laboratory animals severely deficient in magnesium had much higher blood levels of histamine when exposed to substances that trigger allergies than animals getting sufficient magnesium. Thus, hypomagnesaemia results, then, in an increase in bronchi smooth muscles excitability and their contraction ***(14).***

(iv) Magnesium has an anti-inflammatory action via stabilisation of T lymphocytes, inhibition of mast cell degranulation, and decreased superoxide production in neutrophils probably leads to sustained improvement in pulmonary function leading to a reduction in inflammatory mediators. Magnesium also exerts anti-inflammatory effect by decreasing the release of leukotriene and histamine from mast cells; therefore it may be useful in controlling inflammation in asthma exacerbations ***(14).***

(v) Magnesium stimulates nitric oxide and prostacyclin synthesis, which might reduce asthma severity. (vi) Magnesium inhibits the calcium release from the sarcoplasmic reticulum: magnesium's pharmacological action is based upon its ability to inhibit the release of calcium from vesicles in the resulting sarcoplasmic reticulum ***(12)***

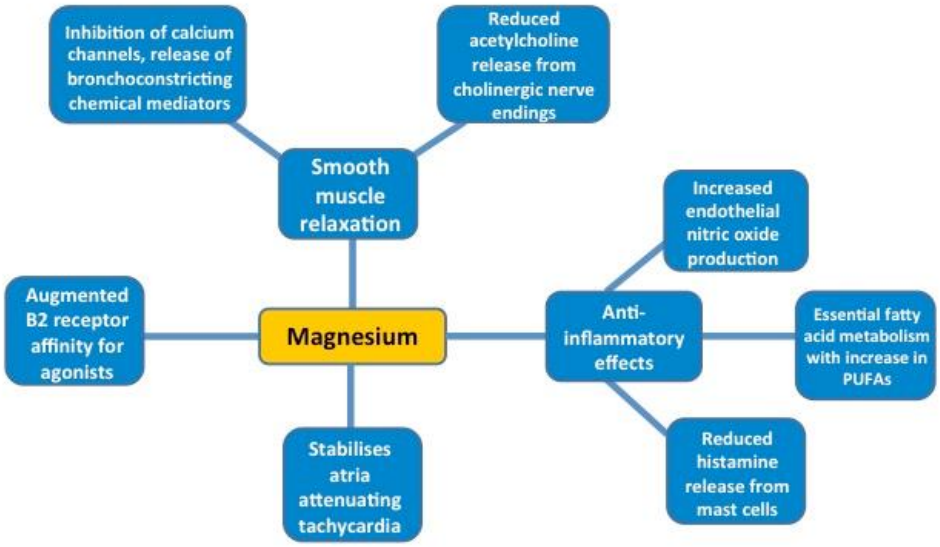

Figure (2): Magnesium sulphate physiology in acute asthma

Dose:

The optimal dose and mode of administration of magnesium sulphate have not been determined. Adult administration has ranged from 1.2 to 3.0g administered over 20 minutes to 10 to 20g infused over 1 hour. Pediatric administration has ranged from 25 to 40 mg/kg with a maximum of 2g. Other studies felt that plasma concentrations greater than 4 mg/dl were necessary to achieve significant bronchodilation. (Normal plasma levels are 1.5 to 2.2 mg/dl.). A study administered 50 mg/kg intravenously over 20 minutes to 10 asthmatic children aged 2 to 16 years. The average magnesium level rose from 2 to 3.3 mg/dl at the end of the 20-minute infusion and returned to 2.5 mg/dl 60 minutes after the start of the infusion. It appears that paediatric dosages of 50 mg/kg are both safe and well tolerated ***(15).***

Intravenous MgSO4 in pediatric asthma

Role of Inhaled MgSO4 in treatment of asthma exacerbation in children

Mg in children with asthma was published by Colin Powell et al. In this double-blind, randomised, placebo-controlled study, the effect of nebulized magnesium sulphate in severe acute asthma exacerbations was investigated. For this purpose, 508 patients with the age of 2–16 who did not respond to standard treatment were included in the study. Patients were divided into two groups including magnesium and placebo nebulized salbutamol+ipratropium bromide+2.5ml of magnesium sulphate (250mmol/L, tonicity 289 milliosmole; 151mg per dose) treatment was provided to the magnesium group three times

with 20min intervals and nebulised salbutamol+ipratropium bromide+2.5ml of isotonic saline treatment was provided to the placebo group with 20min intervals. Yung Asthma Severity Scores (ASS) in 60th min were compared. Average ASS was found as (4.72 [SD 1:37]) in the magnesium group and, (4.95 [SD 1:40]) in the placebo group. However, this difference was not considered as statistically significant. At the same time, it has been shown that the use of magnesium in serious exacerbation and exacerbation with short hospital admission time (fewer than 6h) is more effective. Mahajan et al. determined whether a combination of nebulised magnesium sulphate and albuterol as a single dose adds any benefit in management of children with mild to moderate asthma when compared to nebulised albuterol with saline. They compared FEV1 values at 10 and 20min. They found that the addition of magnesium to albuterol seemed to provide short-term benefits in children with acute exacerbations of mild to moderate asthma. In the study of Mangat et al. which includes adults and children (12–60 years of age), nebulised magnesium was compared with nebulised salbutamol 3ml magnesium sulphate (95mg) was given to the magnesium group and 3ml salbutamol was given to the salbutamol group. 100mg IV hydrocortisone was given to each patient. PEF values at the end of 2h were compared and any superior bronchodilator effect of magnesium to salbutamol was not been demonstrated. These results for children were similar with studies in adults. ***(10)***

Even though magnesium has a bronchodilator effect, there may be a few reasons for the lack of clinical benefit of adding nebulised salbutamol in patients with asthma exacerbation. Firstly, magnesium has a bronchodilator effect in a short term as nebulised. The study in which Meral et al. examined the effect of nebulised magnesium investigated that bronchodilator effect of Mg lasts 1h while salbutamol's effect lasts 6h. As mentioned above, Mahajan et al. found that adding nebulised Mg in mild to moderate asthma exacerbation in addition to albuterol provides short-term benefits. Wang et al. have investigated the effect of inhaled magnesium on bronchial hyperresponsiveness in children. Patients in the study including 84 children were divided into three groups; albuterol group, albuterol+magnesium group and magnesium group. Nebulised acetylcholine was given to all patients and then patients were treated in accordance with their group and their FEV1 values in 10th and 20th min were compared. As a result, a significant improvement in FEV1 was seen in each of the three groups, but more significant improvement in FEV1 on albuterol and magnesium+albuterol groups was achieved when compared to the magnesium group. Consequently, it is thought that magnesium has a bronchodilator effect; however it does not provide any additional benefit as adjuvant treatment. Secondly, Mg can be used in low concentrations. The concentration of nebulised magnesium to be used in asthma exacerbation is not clear. In GINA 2015, it is stated that isotonic solutions can be used. The bronchodilator effect of nebulised magnesium has already been shown to be dose-dependent. As hypertonic solutions could lead to bronchoconstriction in asthmatics, we used isotonic solution in our study. While Mg is used in doses as high as 40–50mg/kg (maximum 2g) in IV administration, it is used in 151mg/2.5ml dose in nebulised solutions to be isotonic.

But Hill et al. found that nebulised hypertonic Mg solutions deteriorated lung functions. Therefore, high concentrations of Mg should be avoided. ***(11)***

Nebulized (inhaled) MgSO4

Role of nebulized (inhaled) MgSO4 in treatment of asthmatic children

There are also some data suggesting a protective nature of MgSO4 inhalations in asthmatics. Researchers studied the effect of nebulized MgSO4 in animals in reversing bronchoconstriction induced by methacholine. They found that MgSO4 has a minimal bronchodilator effect. Researchers were also studied effect of nebulized magnesium in sodium metabisulfite (MBS) induced bronchoconstriction in subjects, and concluded that inhaled MgSO4 had protective effect. Researchers also found that nebulized MgSO4 (3 ml 3.2% solution) had significant bronchodilator effect similar to nebulized salbutamol. Inhaled MgSO4 has also been investigated in asthma children between 5 and 17 years of age. Nebulized MgSO4 was found to provide short-term bronchodilation. A study has been shown that inhaled MgSO4 is beneficial for the control of acute asthma in adults and children ***(11-13)***

Some previous studies used inhaled MgSO4 in the treatment of children with acute asthma. They found that the therapy with nebulized isotonic MgSO4 with or without b2-agonist can be safely administered at a variety of doses to children with acute moderate-to-severe asthma. They also reported that nebulization by isotonic MgSO4 solution with salbutamol provide early and better response as compared to conventional approach (e.g. salbutamol plus normal saline) in acute exacerbation of asthma in children. In addition, a study found significantly greater improvement in FEV1 with nebulized salbutamol plus isotonic MgSO4 solution than salbutamol plus normal saline. But other study reported that the administration of nebulized MgSO4 in combination with b2-agonists (usually salbutamol), improved pulmonary function but did not reduce the number of hospital admissions. ***(13-19)***

The use of magnesium sulphate (MgSO4) to reverse bronchospasm

A clinical trial concluded that nebulized magnesium sulphate has a minimal bronchodilator effect in asthmatic patients with methacholine induced bronchoconstriction. Responsiveness to magnesium sulphate may be dependent on the mechanism of induction of bronchospasm, and there probably is no role for nebulized magnesium sulphate in the treatment of acute bronchospasm due to cholinergic stimulation ***(19).***

Preparation of isotonic, sterile, aqueous solution of $MgSO_4$ for inhalation

1. ***mL dose (3.3% solution, 100 mg)***

Four grams of $MgSO_4 \cdot 7H_2O$ (molecular weight =246.48 g/mol) were dissolved in 100 mL sterile water for injection using ultrasonic stirrer. After $MgSO_4$ was completely dissolved, 132 mg of sodium chloride was added to adjust isotonicity of the solution. The pH of the solution was adjusted to 3.4, and the volume was adjusted to 120 mL with sterile water for

injection and mixed again. Finally, the solution was sterilized by passing through 0.22 µm filter unit and aliquoted into individual 3 mL volumes in sterile 10 mL falcon tubes ***(20).***

2. 5 mL dose (4% solution, 100 mg)

Four grams of $MgSO_4 \cdot 7H_2O$ (molecular weight =246.48 g/mol) were weighed and then dissolved in 80 mL sterile water for injection using ultrasonic stirrer. The pH of the solution was adjusted to 3.4, and the volume was adjusted to 100 mL with sterile water for injection and mixed again. Finally, the solution was sterilized by passing through 0.22 µ filter unit and aliquoted into individual 2.5 mL volumes in sterile 10 mL falcon tubes ***(20).***

The efficacy of nebulized magnesium sulphate alone and in combination with salbutamol

Magnesium may increase the bronchodilator response to salbutamol in acute asthma by increasing the affinity of β-receptors to salbutamol or by upregulating β-receptors. This agent has been shown to be easy to use, extremely safe, and inexpensive ***(20).***

A study concluded that nebulized $MgSO_4$ alone or combined with salbutamol has a clinically significant bronchodilator effect in acute asthma and leads to clinical improvement, increase in PEFR, reduction in HR, and reduction in RR. The response to nebulized $MgSO_4$ alone is comparable to that of nebulized salbutamol and is significantly less than that of nebulized combination ***(20).***

Nebulized magnesium sulphate plus albuterol in children.

Inhaled magnesium sulphate has been shown to be an effective bronchodilator when compared with albuterol, but its effect is not sustained. When magnesium sulphate was used as a vehicle for nebulized albuterol, it increased the peak flow response to treatment in comparison with albuterol and normal saline and thus seems to have an additive effect ***(21)***

A prospective, randomized study compared between nebulized magnesium sulphate plus albuterol to nebulized albuterol plus saline in children with acute exacerbations of mild to moderate asthma. The study concluded that The difference in FEV1 was significant at 10 and 20 min after a single dose of the combined treatment with magnesium and albuterol when compared with the albuterol and saline group. The addition of magnesium to albuterol seemed to provide short-term benefits in children with acute exacerbations of mild to moderate asthma ***(21)***

Magnesium Sulphate Side Effects

Magnesium sulphate is generally a safe drug to administer. In one trial there were some minor side effects reported, such as epigastric or facial warmth, flushing, pain and numbness at the infusion site, dry mouth, and malaise. Hypotension was also documented with rapid infusion ***(22).***

symptoms typically resolve spontaneously. If the patient is on a continuous magnesium sulphate infusion, serum levels must be accounted for as symptoms related to hypermagnesemia may become clinically evident. At supratherapeutic serum concentrations, absent reflexes, abnormal cardiac conduction, and muscle weakness may occur ***(4).***

Inhaled magnesium sulphate did not seem to cause any serious side effects ***(4).***

Magnesium Sulphate Toxicity

Toxicity might result in abnormalities in cardiac conduction, absent reflexes, muscle weakness, and respiratory depression ***(23).***

If patients exhibit signs and symptoms of hypermagnesemia, the recommendation is to discontinue magnesium sulphate products immediately. patients should receive parenteral doses of calcium gluconate to help alleviate symptoms, but continued doses may be necessary as the calcium provides temporary improvement. IV hydration should also occur if clinically appropriate. In patients with severe renal disease, then hemodialysis should be considered ***(4).***

Previous studies

4 studies with a total of 870 pediatric patients comprising 433 in the nebulized magnesium sulphate group and 437 in the control group. In a trial,20 lung function of children with acetylcholine-induced asthma was compared between 3 groups: magnesium sulphate (M), albuterol and saline (A + S), and a combination of magnesium sulphate and albuterol (M + A). Three studies were included for the analyses of the effects of nebulized magnesium sulphate on respiratory function. Two studies were included for the analyses of the effects on hospitalization and further treatment. Patients were treated with systemic steroids in 3 studies***. (21)***

References:

1. Deraz TE, Aboulfotouh A, Habib NM, (2009): Study of prevalence of asthma and other atopic diseases among school children in Dakalia c. Thesis Submitted for partial fulfillment of Master Degree in Pediatrics.
2. Abdallah AM, Sanusy KA, Said WS, Mahran, D. G., et al. (2012): Epidemiology of bronchial asthma among preparory school children in Assiut district. Egypt J Pediatr AllergyImmunol; 10(2):109-117.
3. Halim WB, Khalil KA, Sobhy SA, (2013): Prevalence of bronchial asthma among secondary schools students at Abu Khalifa village Ismailia Governorate. Medical Journal of Cairo University 81 (2): 19-24.
4. Hicks MA, Tyagi A. (2023): Magnesium sulphate. [Updated 2023 May 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm
5. Bichara, M. D., & Goldman, R. D. (2009): Magnesium for treatment of asthma in children. Canadian Family Physician, 55(9): 887–889.
6. Costello, R. B., Elin, R. J., Rosanoff, A., Wallace, T. C., Guerrero-Romero, F., Hruby, A., Lutsey, P. L., Nielsen, F. H., Rodriguez-Moran, M., Song, Y., & others. (2016): Perspective: the case for an evidence-based reference interval for serum magnesium: the time has come. Advances in Nutrition, 7(6): 977–993.
7. Tang, J., He, A., Li, N., Chen, X., Zhou, X., Fan, X., Liu, Y., Zhang, M., Qi, L., Tao, J., & others. (2018): Magnesium sulphate--Mediated vascular relaxation and calcium channel activity in placental vessels different from Nonplacental vessels. Journal of the American Heart Association, 7(14): e009896.

8. De Baaij, J. H. F., Hoenderop, J. G. J., & Bindels, R. J. M. (2015): Magnesium in man: implications for health and disease. Physiological Reviews.
9. Levonorgestrel, I. (2019): Drugs and Lactation Database (LactMed)[Internet]. Bethesda (MD): National Library of Medicine (US): 63–67.
10. Albuali, W. H. (2014): The use of intravenous and inhaled magnesium sulphate in management of children with bronchial asthma. The Journal of Maternal-Fetal \& Neonatal Medicine, 27(17): 1809–1815.
11. Shahi, A., Aslani, S., Ataollahi, M., & Mahmoudi, M. (2019): The role of magnesium in different inflammatory diseases. Inflammopharmacology, 27(4): 649–661.
12. K. Alansari, W. Ahmed, B.L. Davidson, M. Alamri, I. Zakaria, M. Alrifaai. Nebulized magnesium for moderate and severe pediatric asthma: a randomized trial. Pediatr Pulmonol, 50 (2015), pp. 1191-1199
13. H.S. Mangat, G.A. D'Souza, M.S. Jacob. Nebulized magnesium sulphate versus nebulized salbutamol in acute bronchial asthma: a clinical trial. Eur Respir J, 12 (1998), pp. 341-344
14. C.L. Carroll, A.K. Sekaran, T.J. Lerer, C.M. Schramm. A modified pulmonary index score with predictive value for pediatric asthma exacerbations. Ann Allergy Asthma Immunol, 94 (2005), pp. 355-359
15. N. Kokturk, H. Turktas, P. Kara, S. Mullaoglu, F. Yilmaz, A. Karamercan. A randomized clinical trial of magnesium sulphate as a vehicle for nebulized salbutamol in the treatment of moderate to severe asthma exacerbations. Pulm Pharmacol Ther, 18 (2005), pp. 416-421
16. O. Bessmertny, R.V. DiGregorio, H. Cohen, E. Becker, D. Looney, J. Golden, et al. A randomized clinical trial of nebulized magnesium sulfate in addition to albuterol in the treatment of acute mild-to-moderate asthma exacerbations in adults. Ann Emerg Med, 39 (2002), pp. 585-591
17. A. Meral, M. Coker, R. Tanaç. Inhalation therapy with magnesium sulfate and salbutamol sulfate in bronchial asthma. Turk J Pediatr, 38 (1996), pp. 169-175
18. H. Wang, Y. Xiong, C. Gong, L. Yin, L. Yan, X. Yuan, et al. Effect of inhaled magnesium sulfate on bronchial hyperresponsiveness. Indian J Pediatr, 82 (2015), pp. 321-327
19. J. Hill, J. Britton. Dose–response relationship and time-course of the effect of inhaled magnesium sulphate on airflow in normal and asthmatic subjects. Br J Clin Pharmacol, 40 (1995), pp. 539-544
20. Sarhan, H. A., EL-Garhy, O. H., Alhosseiny, M., & AlNokrashy, N. (2016): The efficacy of nebulized magnesium sulphate alone and in combination with salbutamol in acute asthma. Drug Design, Development and Therapy, 1927.
21. Mahajan, P., Haritos, D., Rosenberg, N., & Thomas, R. (2004a): Comparison of nebulized magnesium sulphate plus albuterol to nebulized albuterol plus saline in children with acute exacerbations of mild to moderate asthma. The Journal of Emergency Medicine, 27(1): 21–25.
22. Ochsenbein-Kölble, N., Krähenmann, F., Hüsler, M., Meuli, M., Moehrlen, U., Mazzone, L., Biro, P., & Zimmermann, R. (2018): Tocolysis for in utero surgery: atosiban performs distinctly better than magnesium sulphate. Fetal Diagnosis and Therapy, 44, 59–64.
23. Al Alawi, A. M., Majoni, S. W., & Falhammar, H. (2018): Magnesium and human health: perspectives and research directions. International Journal of Endocrinology, 2018.