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Review paper

Magnesium chloride or magnesium sulfate: a genuine question

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Abstract. $MgSO_4$ is routinely used in therapeutics despite its toxicity. The aim of the present review was to compare $MgSO_4$ and $MgCl_2$ effects in order to answer the question whether $MgSO_4$ could be or not replaced by $MgCl_2$. Considering that the two salts have both similar and proper effects, a clear-cut conclusion is not easy to draw. However, choosing $MgCl_2$ seems advisable because of its more interesting clinical and pharmacological effects and its lower tissue toxicity as compared to $MgSO_4$.

Keywords: chloride, magnesium, sulfate

Magnesium ions are known to play a central role in cellular function and to strongly influence the cardiovascular and neuromuscular excitability. They are also an important factor in both the growth and maintenance of living cells and an essential co-factor for many intracellular enzymes involved in both glycolytic metabolism and ion movements mediated by Na and Ca pumps [1]. Magnesium sulphate ($MgSO_4$, $7H_2O$) is commonly used, in the United States, as prophylactic and clinical treatment of eclamptic seizures whereas in Europe, its use is highly debated in that indication. Conversely, magnesium chloride is not frequently used in either physiology or physiopathology. Nonetheless, it has been postulated, but not established, that the anion associated with magnesium other than sulphate could have a less toxic, or even beneficial effects on neonate health outcomes.
Several scholarly reviews have concluded that $MgSO_4$ was not an effective tocolytic agent, and have recommended to ban it in that indication [2]. Nevertheless, in spite of the lack of supporting data and the ongoing absence of an international consensus, $MgSO_4$ remains the first line pharmacological agent employed for tocolysis in North America. Finally, it seems that the large clinical use of $MgSO_4$ results more from routine habits than from clinical, pharmacological or toxicological data. However, other magnesium compounds such as oxide, gluconate and chloride may be successfully used in various pathological situations. For example, these magnesium salts are effective in promoting continued uterine quiescence in patients recently treated for preterm labor [2]. In addition they are generally less toxic than $MgSO_4$.

All these considerations led us to highlight the differences between the pharmacological and toxicological properties of $MgSO_4$ and $MgCl_2$. $MgSO_4$ has the least interesting properties. Its absorption, cellular penetration, membrane effects and antihypoxic properties are low. Comparative studies between $MgSO_4$ and $MgCl_2$ have shown that absorption and retention are more efficient with $MgCl_2$ than with $MgSO_4$ [3].

Consequently, the aim of the present review was to compare the properties and the effects of both magnesium sulphate and chloride.

Physical comparison

The main physical and chemical properties of each magnesium salts are summarized in the *table 1*.

Examples of physiological and clinical utilisation of $MgSO_4$ and $MgCl_2$

Some recent $MgSO_4$ and $MgCl_2$ uses are reported hereafter.

Magnesium sulphate alone

In the last decade, many papers were published, dealing with $MgSO_4$ uses. They may be classified as clinical and pharmacological data.

Pharmacological uses

– $MgSO_4$ shows vaso- and neuro-protective properties after spinal cord injury [4];

– Postnatal $MgSO_4$ infusion is safe and can improve short-term outcome in infants with severe birth asphyxia [5];

– $MgSO_4$ has an effective antithrombotic activity *in vivo*, and treatment with $MgSO_4$ may lower the risk of thromboembolic-related disorders [6];

– $MgSO_4$ is an effective and safe antiarrhythmic agent for arrhythmias developed after open-heart surgery. Its antiarrhythmic effect may be related to its pharmacological properties and not to the normalization of the circulating magnesium concentrations [7];

– $MgSO_4$ is given in cardioplegia [8];

– The mitochondrial respiratory function which decreases significantly after traumatic brain injury can be improved after $MgSO_4$ infusion as shown by electron microscopy [9];

– A beneficial effect of $MgSO_4$ has been also reported after severe traumatic brain injury in rats [10].

Clinical uses

– First of all, $MgSO_4$ has been often used in case of preeclamptic-eclamptic seizures [11-13] but it has been also successfully used in other clinical indications, as reported hereafter.

– $MgSO_4$ may be beneficial in the control of ventricular ectopy and supraventricular tachyarrhythmias after coronary artery bypass graft surgery [14];

– $MgSO_4$ is used clinically to induce smooth muscle relaxation, mainly in airway smooth muscles [15];

– $MgSO_4$ administration may lead to a significant reduction of anaesthetic drugs during total intravenous anaesthesia with propofol, remifentanil and vecuronium [16-17]. In addition, the intraoperative use of $MgSO_4$ as an adjunct to the conventional use of nicardipine has been effective to manage a pediatric patient undergoing a laparoscopic operation [18];

– $MgSO_4$ may be considered as an alternative treatment in persistent pulmonary hypertension of the newborn when no other modalities exist since it is a non aggressive and low cost treatment [15].

Magnesium chloride clinical uses

$MgCl_2$ has been used less frequently. However, its usefulness was reported in various indications.

– $MgCl_2$ is an efficient anaesthetic and narcotic agent for cephalopod molluscs [19];

– It has a valuable role as cardioprotective agent in rabbits [20];

– $MgCl_2$ is a more advisable salt to use in cerebral palsy [21];

– Oral supplementation with $MgCl_2$ solution restored serum magnesium levels, improving insulin sensitivity and metabolic control of type 2 diabetic patients with decreased serum magnesium levels [22].

Table 1. Comparison of each magnesium salts properties.

Magnesium salts	**Chloride $MgCl_2, 6H_2O$**	**Sulphate $MgSO_4, 7H_2O$**
Elemental Mg^{++}/dose (mg)	25.54	20.2
Solubility in water	1 g dissolves in: - 0.6 ml water - 0.3 ml boiling water - 2 ml alcohol	1g dissolves in: - 0.8 ml water - 0.2 ml boiling water - slightly in alcohol
Density	1.56	1.67
Bioavailability	good	low
Oral absorption % (mEq)	19.68 (1.04)	4 (oral dose), limited and variable extent
H_2O molecules lost at 100°C	2	5
Lethal doses (LD 50) (i.v.)	176 mg/kg (rats)	750 mg/kg (dogs)

Consequently, it appears very interesting to review, in the literature, the studies comparing the respective effects of $MgSO_4$ and $MgCl_2$, the magnesium salt which has the best fits with $MgSO_4$ in regard to elemental Mg^{++}/dose (in mEq).

Comparison between magnesium chloride and magnesium sulphate

The publications comparing the two magnesium salts are very scarce but allow to distinguish similar and proper effects to each magnesium salt.

Similar effects

In the literature, there are some examples of similar pharmacological and clinical effects between $MgCl_2$ and $MgSO_4$.

Pharmacological effects

– The comparison of the muscle relaxant activity of equimolar solutions of $MgCl_2$ and $MgSO_4$ using the head drop method in rabbits shows no statistical difference between the two salts with regard to their potency and duration of action, suggesting that these activities are not influenced by the anion associated with the Mg^{2+} cation [23];

– No significant difference was seen between $MgCl_2$ and $MgSO_4$ infusions on the duration of epinephrine-induced cardiac arrhythmia [24];

– The two salts decrease the aldosterone production in a dose-dependent manner [25];

– $MgCl_2$ and $MgSO_4$ have similar effects on the isolated and perfused rat heart: decreasing heart rate, left ventricular systolic pressure, voltage epicardial electrogram and increasing coronary flow rate [26];

– $MgCl_2$ or $MgSO_4$ treatments are equally effective on diffuse axonal injury [27].

Clinical effects

– Both salts have a similar oral tocolytic role [28]. Compared with $MgSO_4$ and ritodrine, enteric-coated $MgCl_2$ was as effective in prolonging pregnancy and preventing recurrent preterm labor.

– $MgCl_2$ and $MgSO_4$ penetrate the blood-brain barrier after brain damage, enter injured tissue and improve neurologic outcomes [29].

These results demonstrate the possible use of $MgCl_2$ instead of $MgSO_4$ and reciprocally in pharmacological and clinical indications.

Different effects

Some recent studies indicate different or/opposite effects between $MgCl_2$ and $MgSO_4$.

$MgSO_4$ > $MgCl_2$

– The poliovirus and measles vaccines [30] are stabilized by incorporating molar $MgCl_2$ or $MgSO_4$ respectively. The $MgCl_2$-stabilized poliovirus vaccine loses 0.5 log10 units in three hours at 45°C whereas $MgSO_4$-stabilized measles vaccine loses only 0.3 log10 in 30 minutes at 50°C.

– The effect of precalving magnesium source (MgO, $MgSO_4$ and $MgCl_2$) and post calving calcium supplementation were examined on calcemia and calciuria: postcalving plasma calcium concentration was affected by precalving magnesium source with $MgSO_4$ > $MgCl_2$ > MgO sequence [31].

$MgCl_2$ > $MgSO_4$

– Nishio *et al.* [32] studied the influence of magnesium salts ($MgCl_2$, $MgSO_4$, Mg aspartate HCl and Mg acetate) on rat mesenteric arteriole and venule reactivity to standard constrictor doses of epinephrine and $BaCl_2$ and showed that arteriolar constrictions were attenuated by systemic intravenous infusion of each Mg salt tested, except $MgSO_4$ which was insufficient.

– Grin *et al.* [33] studied, in dogs fed a normal diet, the antiarrhythmic and proarrythmic effects of $MgCl_2$ and $MgSO_4$ intravenous infusions and showed that infusion of $MgSO_4$ solution decreased plasma sodium, potassium and ventricular fibrillation threshold (VFT) (a proarrhythmic effect), prolonged the ventricular effective refractory period (VERP) and increased the urinary excretion of potassium. By contrast, infusion of $MgCl_2$ solution did not affect VFT and plasma potassium levels and prolonged also VERP.

– Durlach *et al.* [3] have pointed out that $MgCl_2$ was both more effective and less toxic than $MgSO_4$ in maintaining optimal aquaculture of scallops. From these data, they have indicated that $MgCl_2$ had a better "therapeutic ratio" (LD50/ED50) than $MgSO_4$, which could be relevant even in human beings. Such data raised the question as to whether the magnesium cation might be responsible for $MgSO_4$ toxicity or if such toxicity was instead attributable to the associated sulphate anion.

The reason of the toxicity of magnesium pharmacological doses of magnesium using the sulphate anion rather than the chloride anion may perhaps arise from the respective chemical structures of both the two magnesium salts. Chemically, both $MgSO_4$ and $MgCl_2$ are hexa-aqueous complexes. However $MgCl_2$ crystals consist of dianions with magnesium coordinated to the six water molecules as a complex, $[Mg(H_2O)_6]^{2+}$ and two independent chloride anions, Cl^-. In $MgSO_4$, a seventh water molecule is associated

with the sulphate anion, $[Mg(H_2O)_6]^{2+}[SO_4.\ H_2O]$. Consequently, the more hydrated $MgSO_4$ molecule may have chemical interactions with paracellular components, rather than with cellular components, presumably potentiating toxic manifestations while reducing therapeutic effect [11].

Finally, to corroborate these explanations, two experimental *in vitro* studies in the physiology of human gestational physiology – amniotic membrane and allantochorial placental vessels – must be considered. Since 1984, the research group associating M. Bara, A. Guiet-Bara and J. Durlach has studied the interrelation between Mg salts and various elements of the placental unit [34-41].

– Human amniotic membrane [34-37]

These experiments associated electrophysiological and morphological studies. The main results were as follows.

– Scanning and transmission electron microscopy results, analysed by a stereological method which indicates the ratio between the volume of the intercellular space (R1), the microvilli (R2) and the podocytes (R3) versus the cell volume, showed that (i) at low concentration, $MgSO_4$ increased R1 and R2 but decreased R3, whereas $MgCl_2$ decreased R1 and R3 and had no significant effect on R2; (ii) at high concentration, $MgCl_2$ decreased R1 and increased R2 and R3, while $MgSO_4$ had no significant effect on R1, increased R2 and decreased R3 [34].

– The study of the ionic fluxes in the two directions between the mother and the fetus indicated that, when the $MgCl_2$ concentration increased, the ratio between influx and efflux being was two-fold increased, whereas when the $MgSO_4$ concentration increased, influx and efflux became equal. Consequently, $MgSO_4$ could not guarantee the fetal needs in sodium and potassium provided across the human amnion [35].

– In addition, it has been demonstrated that $MgCl_2$ interacts with all the exchangers in the membrane, while the effect of $MgSO_4$ effect is limited to paracellular components without interaction with cellular components, with exception of the antiport Na/H [36, 37].

To sum up, $MgCl_2$ interacts with all exchangers while the interaction of $MgSO_4$ is limited to paracellular exchangers, and $MgCl_2$ increases the flux ratio between mother to fetus while $MgSO_4$ decreases it.

– Human allantochorial placental vessels [38-42]

– $MgCl_2$ or $MgSO_4$ added *in vitro* induced a depolarization of the human placental chorionic cells (from arteries and veins with or without endothelium), but the depolarization thresholds were different and higher with $MgSO_4$. This difference indicated that $MgCl_2$ influences the cell membrane potential directly, whereas $MgSO_4$ interferes first with endothelial cells and then with muscle cells [38, 39].

– $MgCl_2$ and $MgSO_4$ both regulated the cell tonus and the Ca^{2+} influx through voltage-gated Ca^{2+} channels in smooth muscle and endothelial cells but the depolarization reduction was more important with $MgCl_2$ than with $MgSO_4$ [40].

– Moreover, $MgCl_2$ blocked the ATP-dependent K^+ channels and opened the delayed (K(df)) K^+ channels, while $MgSO_4$ blocked the current through voltage-gated and ATP dependent K^+ channels but had no effect on K(df) [41]. These results were confirmed by micro-particle induced X-ray emission studies [42].

To sum up, the differences between $MgCl_2$ and $MgSO_4$ were less important in allantochorial vessels than in amniotic membranes, but the effects of $MgCl_2$ effects seemed more interesting than those of $MgSO_4$ ones.

The comparison reveals that it is very difficult to reach a conclude conclusion on the possible utilisation of a one salt instead of another but it indicates that $MgSO_4$ is not always the appropriate salt in clinical therapeutics and that $MgCl_2$ seems the better anion-cation association to be used in many clinical and pharmacological indications.

Conclusions

This review showed shows that it is difficult to elicit identify $MgSO_4$ or $MgCl_2$ as the reference magnesium salt to be used as a therapeutic agent, since each salt displayed valuable clinical properties in various cases situations. The comparison did not allow to a preference of one salt to over the another other, but the studies indicated that $MgSO_4$ is not the alone only magnesium salt which may be used in severe injuries.

It is attractive tempting to explain the differences between $MgCl_2$ and $MgSO_4$ by their crystal structures. Magnesium chloride forms a stable hexahydrate, while magnesium sulphate forms a stable heptahydrate [43]. In the two crystals, magnesium has the same complex form. Consequently, the different effects observed might be attributed to the anions. As a result, the biological properties of magnesium salts might depend on their interactions with water and with the polar groups at the membrane surface by screening and/or binding processes [44].

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