Magnesium chloride or magnesium sulfate: a genuine question

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Abstract. MgSO₄ is routinely used in therapeutics despite its toxicity. The aim of the present review was to compare MgSO₄ and MgCl₂ effects in order to answer the question whether MgSO₄ could be or not replaced by MgCl₂. Considering that the two salts have both similar and proper effects, a clear-cut conclusion is not easy to draw. However, choosing MgCl₂ seems advisable because of its more interesting clinical and pharmacological effects and its lower tissue toxicity as compared to MgSO₄.

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 (MgSO₄, 7H₂O) 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 MgSO₄ 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, MgSO₄ remains the first line pharmacological agent employed for tocolysis in North America. Finally, it seems that the large clinical use of MgSO₄ 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 MgSO₄.

All these considerations led us to highlight the differences between the pharmacological and toxicological properties of MgSO₄ and MgCl₂. MgSO₄ has the least interesting properties. Its absorption, cellular penetration, membrane effects and antihypoxic properties are low. Comparative studies between MgSO₄ and MgCl₂ have shown that absorption and retention are more efficient with MgCl₂ than with MgSO₄ [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 MgSO4 and MgCl2

Some recent MgSO4 and MgCl2 uses are reported hereafter.

Magnesium sulphate alone

In the last decade, many papers were published, dealing with MgSO4 uses. They may be classified as clinical and pharmacological data.

Pharmacological uses

- MgSO4 shows vaso- and neuro-protective properties after spinal cord injury [4];
- Postnatal MgSO4 infusion is safe and can improve short-term outcome in infants with severe birth asphyxia [5];
- MgSO4 has an effective antithrombotic activity in vivo, and treatment with MgSO4 may lower the risk of thromboembolic-related disorders [6];
- MgSO4 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];
- MgSO4 is given in cardioplegia [8];
- The mitochondrial respiratory function which decreases significantly after traumatic brain injury can be improved after MgSO4 infusion as shown by electron microscopy [9];
- A beneficial effect of MgSO4 has been also reported after severe traumatic brain injury in rats [10].

Clinical uses

- First of all, MgSO4 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.
- MgSO4 may be beneficial in the control of ventricular ectopy and supraventricular tachyarrhythmias after coronary artery bypass graft surgery [14];
- MgSO4 is used clinically to induce smooth muscle relaxation, mainly in airway smooth muscles [15];
- MgSO4 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 MgSO4 as an adjunct to the conventional use of nicardipine has been effective to manage a pediatric patient undergoing a laparoscopic operation [18];
- MgSO4 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

MgCl2 has been used less frequently. However, its usefulness was reported in various indications.

- MgCl2 is an efficient anaesthetic and narcotic agent for cephalopod molluscs [19];
- It has a valuable role as cardioprotective agent in rabbits [20];
- MgCl2 is a more advisable salt to use in cerebral palsy [21];
- Oral supplementation with MgCl2 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.

<table>
<thead>
<tr>
<th>Magnesium salts</th>
<th>Chloride MgCl2, 6H2O</th>
<th>Sulphate MgSO4, 7H2O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elemental Mg++/dose (mg)</td>
<td>25.54</td>
<td>20.2</td>
</tr>
<tr>
<td>Solubility in water</td>
<td>1 g dissolves in:</td>
<td>1g dissolves in:</td>
</tr>
<tr>
<td>- 0.6 ml water</td>
<td>- 0.8 ml water</td>
<td></td>
</tr>
<tr>
<td>- 0.3 ml boiling water</td>
<td>- 0.2 ml boiling water</td>
<td></td>
</tr>
<tr>
<td>- 2 ml alcohol</td>
<td>- slightly in alcohol</td>
<td></td>
</tr>
<tr>
<td>Density</td>
<td>1.56</td>
<td>1.67</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>good</td>
<td>low</td>
</tr>
<tr>
<td>Oral absorption % (mEq)</td>
<td>19.68 (1.04)</td>
<td>4 (oral dose), limited and variable extent</td>
</tr>
<tr>
<td>H2O molecules lost at 100°C</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Lethal doses (LD 50) (i.v.)</td>
<td>176 mg/kg (rats)</td>
<td>750 mg/kg (dogs)</td>
</tr>
</tbody>
</table>
Consequently, it appears very interesting to review, in the literature, the studies comparing the respective effects of MgSO₄ and MgCl₂, the magnesium salt which has the best fits with MgSO₄ in regard to elemental Mg²⁺/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 MgCl₂ and MgSO₄.

Pharmacological effects

- The comparison of the muscle relaxant activity of equimolar solutions of MgCl₂ and MgSO₄ 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 Mg²⁺ cation [23];
- No significant difference was seen between MgCl₂ and MgSO₄ infusions on the duration of epinephrine-induced cardiac arrhythmia [24];
- The two salts decrease the aldosterone production in a dose-dependent manner [25];
- MgCl₂ and MgSO₄ 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];
- MgCl₂ or MgSO₄ treatments are equally effective on diffuse axonal injury [27].

Clinical effects

- Both salts have a similar oral tocolytic role [28]. Compared with MgSO₄ and ritodrine, enteric-coated MgCl₂ was as effective in prolonging pregnancy and preventing recurrent preterm labor.
- MgCl₂ and MgSO₄ penetrate the blood-brain barrier after brain damage, enter injured tissue and improve neurologic outcomes [29].

These results demonstrate the possible use of MgCl₂ instead of MgSO₄ and reciprocally in pharmacological and clinical indications.

Different effects

Some recent studies indicate different or opposite effects between MgCl₂ and MgSO₄.

\[ MgSO₄ > MgCl₂ \]

- The poliovirus and measles vaccines [30] are stabilized by incorporating molar MgCl₂ or MgSO₄ respectively. The MgCl₂-stabilized poliovirus vaccine loses 0.5 log₁₀ units in three hours at 45°C whereas MgSO₄-stabilized measles vaccine loses only 0.3 log₁₀ in 30 minutes at 50°C.
- The effect of precalving magnesium source (MgO, MgSO₄ and MgCl₂) and post calving calcium supplementation were examined on calcemia and calcuria: postcalving plasma calcium concentration was affected by precalving magnesium source with MgSO₄ > MgCl₂ > MgO sequence [31].

\[ MgCl₂ > MgSO₄ \]

- Nishio et al. [32] studied the influence of magnesium salts (MgCl₂, MgSO₄, Mg aspartate HCl and Mg acetate) on rat mesenteric arteriole and venule reactivity to standard constrictor doses of epinephrine and BaCl₂ and showed that arteriolar constrictions were attenuated by systemic intravenous infusion of each Mg salt tested, except MgSO₄ which was insufficient.
- Grin et al. [33] studied, in dogs fed a normal diet, the antiarrhythmic and proarrythmic effects of MgCl₂ and MgSO₄ intravenous infusions and showed that infusion of MgSO₄ 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 MgCl₂ solution did not affect VFT and plasma potassium levels and prolonged also VERP.
- Durlach et al. [3] have pointed out that MgCl₂ was both more effective and less toxic than MgSO₄ in maintaining optimal aquaculture of scallops. From these data, they have indicated that MgCl₂ had a better “therapeutic ratio” (LD₅₀/ED₅₀) than MgSO₄, which could be relevant even in human beings. Such data raised the question as to whether the magnesium cation might be responsible for MgSO₄ 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 MgSO₄ and MgCl₂ are hexa-aqueous complexes. However MgCl₂ crystals consist of diions with magnesium coordinated to the six water molecules as a complex, [Mg(H₂O)₆]²⁺ and two independent chloride anions, Cl⁻. In MgSO₄, a seventh water molecule is associated
with the sulphate anion, $\text{[Mg(H_2O)_6]}^{2-} \cdot \text{[SO}_4 \cdot \text{H}_2\text{O]}$. 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$_4$ 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 placent 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].

- 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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MAGNESIUM CHLORIDE OR MAGNESIUM SULFATE


