Magnesium in Cardiovascular Disease

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Magnesium, an essential mineral, plays an important role in the regulation of transmembrane electrolyte transfer. Publications as early as the 1930s document that magnesium deficiency can precipitate ventricular arrhythmias and that treatment with magnesium has antiarrhythmic potency on the supraventricular as well as ventricular level [1–3]. These cardiac effects of magnesium are induced by activation of the Na/K-ATPase, which stabilizes the membrane potential. Magnesium raises the ventricular fibrillation threshold. Impulse initiation and propagation are altered by a decrease of sinus rate, and prolongation of sinus node recovery time and atrioventricular refractory period [4, 5]. These characteristic actions on sinus and atrioventricular node place magnesium in the group of physiologic calcium antagonists [6]. Additionally, magnesium influences the occurrence of arrhythmias by altering early and late afterpotentials.

Within the myocardial cell, low magnesium concentrations are associated with membrane destabilization, while high magnesium concentrations are membrane stabilizing, and therefore antiarrhythmic. Table 1 shows the electrophysiological consequences of high and low magnesium concentrations.

Therapeutic strategies for life-threatening arrhythmias have mostly been studied in uncontrolled settings. Torsades de points, arrhythmias due to digitals, multifocal atrial tachycardias, sustained ventricular tachycardias or ventricular tachyarrhythmias after class III antiarrhythmic drugs pose difficult methodological problems for controlled studies.

The interaction between magnesium and coronary heart disease has been studied for four decades. There is ample evidence that a significant percentage of patients with coronary artery disease suffer from magnesium deficiency. Magnesium is a potent vasodilator [7, 8] and plays an important role in muscle contraction [9]. During ischaemia, it exerts cellular protective effects against calcium ion influx and reduces vascular resistance and systolic blood pressure [10]. In 2000 Shechter described a significant improvement of endothelial function in patients with stable coronary artery disease through magnesium therapy [11]. A recently completed study finally provides the link from basic science to clinically relevant parameters [12]. The investigators were able to show the effects of oral magnesium therapy on the exercise duration and quality of life in patients with documented coronary heart disease.

10% of hospitalized patients can be presumed to be magnesium deficient, for patients in intensive care this figure might be as high as 50% [13, 14]. The low magnesium levels are mainly due to renal magnesium losses through diuretics or digitalis treatment or to the secondary hyperaldosteronism of heart failure.

In general, serum magnesium levels do not adequately reflect a patient’s magnesium status and cannot be used to monitor therapeutic interventions. Only intracellular magnesium measurements can detect magnesium deficiency.

**Key words:** magnesium, arrhythmia, coronary artery disease

### Table 1. Effects of magnesium on electrical features of myocardial cells

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<thead>
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<th>Electrophysiological effects of low magnesium concentrations</th>
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<tr>
<td>• Reduced resting potential</td>
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<td>• Reinforced sinus automaticity</td>
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<td>• More frequent early afterdepolarisations</td>
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<td>• Widening of the QRS complex</td>
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<td>• Prolonged QT-intervals</td>
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<td>• T-wave abnormalities, occurrence of U-waves</td>
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<td>• Lowered atrial fibrillation threshold</td>
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<td>• Lowered ventricular fibrillation threshold</td>
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<td>• Prolonged refractory period of atrium and AV-node</td>
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<td>• Raised ventricular fibrillation threshold</td>
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<td>• Reduction of drug-induced triggered activity</td>
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<td>• Reduction of ischaemia-associated arrhythmias</td>
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Parenteral Magnesium in Arrhythmia

Overview
Proven indication:
• Torsades de pointes tachycardia
• Digitalis-induced ventricular tachyarrhythmias
• Multifocal atrial tachycardias
• Perioperative patients
Reasonable indication:
• Ventricular arrhythmias due to overdose of neuroleptics or tricyclic antidepressant drugs
• Rescue treatment of ventricular arrhythmias, after class III antiarrhythmic drugs
• Refractory ventricular fibrillation
Potential indication:
• Monomorphic ventricular tachycardias
• Supraventricular tachycardias not responding to adenosine
• Arrhythmias in heart failure and/or with diuretics
Not an indication:
• Atrial fibrillation
• Cardiac arrest

Torsades de Pointes Tachycardia
The term torsades de pointes characterizes a special form of polymorphic ventricular tachycardia with a baseline prolonged QT interval. The ECG shows a typical oscillating “sine wave” pattern and polarity switching from negative to positive. Major triggering events are bradycardias (sinus arrest, AV-block III), electrolyte disturbances (hypoamnesia, hypokalaemia) and drugs that prolong the repolarisation phase (class 1a or III antiarrhythmics, tricyclic antidepressants) [15–17]. In most cases structural myocardial disease is present. The electrical mechanism is related to dispersion of repolarisation or to triggered activity with afterdepolarisation, which can be suppressed by magnesium [18]. The potency of magnesium in this indication has been documented in numerous studies [15, 19, 20]. Today, parenteral magnesium is the drug of choice in all torsades de pointes tachycardias [21–25]. Accordingly, the guidelines of the American Heart Association recommend magnesium in this indication [26].

Digitalis-Induced Ventricular Tachyarrhythmia
Various types of arrhythmias can be observed in patients with digitalis overdose. As early as 1935, Zwilling described the effects of magnesium on digitalis-induced arrhythmias [3]. Digitalis inactivates the Na/K-ATPase, inducing the classic hyperkalaemia of severe digitalis overdose [27]. The positive influence of magnesium on the Na/K-ATPase antagonizes this effect [28]. Animal experiments documented a magnesium induced raise of the fibrillation threshold even in the presence of digitalis [29]. Due to methodological problems no controlled studies are available to date, however, for lack of safe alternatives, the use of parenteral magnesium in this indication is unchallenged [24, 30–33]. The electrical cardioversion of digitalis-induced tachyarrhythmias is problematic and the systemic treatment with specific antibodies is costly and may not be available everywhere. Thus, magnesium is the preferred therapeutic option [21–23].

Multifocal Atrial Tachycardias (MAT)
This rare form of tachycardia is characterized by at least 3 different sites of atrial activity and p wave morphologies, a heart rate of more than 100 beats per minute, and variable PP and PQ intervals. Postoperative patients, those in intensive care and patients with decompensated chronic obstructive pulmonary disease are particularly prone to develop these arrhythmias. The proposed mechanism of MAT is an increased automaticity, which can usually be interrupted by magnesium [34, 35].

Perioperative Use
The efficacy of magnesium against peri- and postoperative arrhythmias in cardiac surgery is well documented. A controlled study by England in 1992 found a 50 % reduction in the incidence of ventricular arrhythmias with perioperative administration of parenteral magnesium. Supraventricular arrhythmic events were reduced from 37 % to 17 % [36]. Recent publications have confirmed these results and underline the potentials of perioperative magnesium therapy [37–40]. All studies show a significant reduction in incidence and duration of atrial (ectopias, atrial fibrillation) and ventricular events.

Ventricular Arrhythmias Due to Intoxication With Neuroleptics or Tricyclic Antidepressant Drugs
Magnesium is successfully used for ventricular ectopias in intoxications with amitriptyline, neuroleptic drugs or tricyclic antidepressants [41–43]. Again, case reports and observational studies have to substitute for controlled settings, but clinical experience and pharmacological considerations support the use of parenteral magnesium in these indications [22, 23].

Rescue Treatment of Ventricular Arrhythmias Occurring After Class III Antiarrhythmic Drugs
A major argument for the use of magnesium in ventricular arrhythmias after class III antiarrhythmic drugs have failed is the lack of interaction of magnesium with conventional antiarrhythmics [44]. In patients who have received antiarrhythmic drugs, rapid recurrences of tachyarrhythmias that occur despite repeat defibrillation and widening QRS complexes pose a therapeutic dilemma. The interaction of multiple arrhythmics creates unpredictable and often proarrhythmogenic effects. In these situations magnesium provides a valuable therapeutic option [22, 24].

Refractory Ventricular Fibrillation
Despite the lack of controlled studies, magnesium provides a valuable therapeutic option in these dramatic clinical situations [45, 46]. According to the American Heart Association guidelines parenteral magnesium should be considered alternative treatment (class indeterminate) for ventricular fibrillation refractory to standard therapy [26].

Monomorphic Ventricular Tachycardias
The diversity of pathophysiological processes underlying ventricular tachycardias might in part explain the conflicting results that the mostly small studies on magnesium in monomorphic tachycardias have produced [47–49]. In a randomized, double blind study by North, magnesium successfully terminated ventricular tachycardia in one third of the patients [50]. Manz and coworkers showed similar cardioversion rates [51]. However, successful cardioversion seems to be dependent on the dose of magnesium. A bolus dose of 2 g magnesium sulphate has been recommended [25].

Supraventricular Tachycardias
In electrophysiological studies in humans, magnesium has been shown to prolong the refractory period [4, 5]. This fact provides the rationale for the use of magnesium in supraventricular tachycardias (SVT). However, existing results are inconsistent. While Wesley describes successful cardioversion of SVT in 70 % of patients [52], only 29 % of episodes of induced supraventricular reentry tachycardias converted to
Proven indication

Overview

Dose Recommendations and Mode of Administration

Potential indication:

Not an indication:

Premature Ventricular Beats Without Coexisting Myocardial Disease or With Stable Cardiac Disease

Patients who suffer from frequent premature ventricular beats in the absence of or with stable cardiac disease represent one of the most interesting and promising patient groups for antiarrhythmic treatment with magnesium. Holzgartner described marked subjective improvements in a cohort of more than 1,000 patients treated with oral magnesium [75]. A controlled study by Lewis found a significant reduction of premature ventricular beats in patients with chronic atrial fibrillation after four weeks of oral magnesium [76]. Treatment with 15 mmol magnesium daily for 3 weeks reduced ventricular arrhythmias by 57% in a small controlled trial [77]. In 1997, Zehnder showed in a randomized, controlled trial, that three weeks of daily oral potassium and magnesium aspartate reduced the incidence of premature ventricular beats by 17% and significantly suppressed ventricular arrhythmias [57]. Interestingly, these positive effects occurred irrespective of pretreatment magnesium or potassium levels and were not limited to patients with deficiencies in either substance.

Treatment With Diuretics

Chronic intake of loop diuretics or thiazides induces magnesium deficiency [63]. This is mainly due to an increase in excretion. While it has been shown that ventricular arrhythmias in patients on diuretics can be reduced through parenteral potassium and magnesium substitution [64], there is currently insufficient data to recommend routine substitution for all patients on diuretic treatment [33, 65].

Atrial Fibrillation

Magnesium deficiency can be detected in approximately 20% of patients with paroxysmal atrial fibrillation [66]. Several controlled studies have examined the use of magnesium in atrial fibrillation [67–69], however, only one placebo-controlled study exists [70]. While the heart rate could be reliably lowered with magnesium, the authors did not see any improvements in cardioversion rates.

Cardiac Arrest

A few case reports describe the successful use of magnesium in cardiac arrest [46, 71]. However, no controlled study confirms these results [72, 73]. The use of magnesium in resuscitation is limited to refractory ventricular fibrillation [26].

Dose Recommendations and Mode of Administration

Any parenteral magnesium therapy that is supposed to influence cardiac rhythm should be administered as an intravenous bolus infusion, followed by a continuous infusion via infusion pump. Only cases of prompt cardioversion do not need to be infused further. No universally valid optimal dose can be recommended from the available evidence. Based on the results of Toivonen [74], however, bolus doses of less than 8 mmol do not appear to be reasonable. Additionally, the studies by Sager [53] and Wesley [52] indicate, that the bolus should be infused within 5 to 10 seconds.

Potential indication:

Not an indication:

Atrial fibrillation

Premature Ventricular Beats Without Coexisting Myocardial Disease or With Stable Cardiac Disease

Patients who suffer from frequent premature ventricular beats in the absence of or with stable cardiac disease represent one of the most interesting and promising patient groups for antiarrhythmic treatment with magnesium. Holzgartner described marked subjective improvements in a cohort of more than 1,000 patients treated with oral magnesium [75]. A controlled study by Lewis found a significant reduction of premature ventricular beats in patients with chronic atrial fibrillation after four weeks of oral magnesium [76]. Treatment with 15 mmol magnesium daily for 3 weeks reduced ventricular arrhythmias by 57% in a small controlled trial [77]. In 1997, Zehnder showed in a randomized, controlled trial, that three weeks of daily oral potassium and magnesium aspartate reduced the incidence of premature ventricular beats by 17% and significantly suppressed ventricular arrhythmias [57]. Interestingly, these positive effects occurred irrespective of pretreatment magnesium or potassium levels and were not limited to patients with deficiencies in either substance.

Treatment With Diuretics

Chronic intake of loop diuretics or thiazides induces magnesium deficiency [63]. This is mainly due to an increase in excretion. However, a clear-cut clinical benefit of routine magnesium substitution has not been proven to date [23, 33, 65].

Atrial Fibrillation

Magnesium deficiency can be detected in approximately 20% of patients with paroxysmal atrial fibrillation [66]. However, a recently published study by Frick did not detect any effect of oral magnesium [66]. This is mainly due to an increase in excretion. As there are a number of established drugs for rate control, cardioversion and prophylaxis of recurrences, the use of magnesium in atrial fibrillation cannot be recommended [23, 55].

Dose Recommendations and Mode of Administration

The oral magnesium dose in the treatment of arrhythmias should not be below 6 mmol per day. Concurrent potassium substitution is recommended [57]. Patients should take their medication 2 hours apart from any meal [23].

Oral Magnesium in Coronary Artery Disease

Proven indication:

Stable coronary artery disease

Stable Coronary Artery Disease

For four decades, the association between magnesium deficiency and coronary artery disease has been studied intensively. Patients with coronary artery disease frequently suffer from magnesium deficiency [79–83]. Myocardial tissue magnesium concentration predicts functional capacity [84] and is negatively correlated with mortality in this patient group [38]. Thus, low magnesium levels seem to play a role in the pathogenesis of coronary artery disease [85]. A controlled trial by Shechter in 50 patients with coronary artery disease demonstrated a significant improvement of endothelial function with oral magnesium therapy [11]. Furthermore, 3 months of oral magnesium reduced the development of
platelet-dependent thrombosis in patients with coronary artery disease [86]. The latter finding is corroborated by data showing a promotion of platelet-dependent thrombosis by low intracellular magnesium concentrations [87].

The clinical significance of these magnesium effects were impressively documented in a study presented at the 2001 ACC in Orlando [12]. For the first time, a study in patients with coronary artery disease showed that not only surro-
gate parameter such as endothelial function and the incidence of platelet-dependent thrombosis but also hard clinical end points can be influenced by oral magnesium therapy. This prospective, double-blind, randomized, placebo-controlled study analyzed 187 patients from 5 international centers. After 6 months, the magnesium group showed a significant im-
provement in the primary study endpoint, functional capac-
ty, as measured by exercise testing (Table 2). This improve-
ment was significant versus baseline and versus the placebo group. Additionally, quality of life questionnaires analyzed at 1, 3 and 6 months showed a significant improvement in quality of life with magnesium. The positive effects of mag-
nesium could be detected even though all patients received con-
current optimal treatment according to international guide-
lines [Aspin 95 %, betablockers 48 %, ACE-inhibitors 40 %, lip-
oid-lowering drugs 66 %].

The importance of these findings is emphasized by the as-
sociation between exercise duration and cardiovascular mor-
tality as well as overall mortality in patients with coronary ar-
tery disease [88].

Multiple mechanisms could explain the benefits seen in the magnesium group. Magnesium acts as a systemic [8] and coronary vasodilator [7] and is integrated in many metabolic processes such as in muscle contraction [9]. It is a cofactor of ATPase [89] and acts as a physiological calcium antagonist [9, 89, 90], thereby preventing intracellular calcium overload in is-
chaemia. Magnesium reduces the vascular resistance, which subsequently increases the cardiac index [10, 89, 91]. A high extracellular magnesium concentration not only reduces the vascular tone in systemic, coronary and pulmonary vascula-
ture [89] but also lowers the systemic blood pressure [10].

Recommendations for Dose and Administration

For oral magnesium therapy in patients with coronary artery disease 15 to 30 mmol should be prescribed per day. Accord-
ing to the results of published studies concurrent potassium substitution is recommended. Patients should take their medication 2 hours apart from any meal.

Conclusion

The use of magnesium as an antiarrhythmic drug for supra-
ventricular and ventricular arrhythmias has been a matter of increasing interest and controversy over recent years. In view of the influence of magnesium on electrical stability and function and of myocardial cells as well as the myocardium as a whole, the drug appears valuable in a wide array of arrhyth-
mias. The physiological basis of the therapeutic concept and the wide margin of safety provide convincing arguments.

As studies have now transcended from basic science to evidence of clinical efficacy, coronary heart disease features prominently among the indications for oral magnesium therapy. It could be shown that magnesium improves exercise duration and general well being in these patients.

The easy and safe handling of the drug as well as the low treatment costs justifies the increasing interest in magnesium for clinical use and scientific research.

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FOCUS ON MAGNESIUM: MAGNESIUM DEFICIENCY AND CARDIOVASCULAR DISEASE


