Journal of Clinical and Basic Cardiology

An Independent International Scientific Journal

Journal of Clinical and Basic Cardiology 2002; 5 (1), 55-59

Magnesium in Cardiovascular Disease

Stühlinger H-G

Indexed in
Chemical Abstracts
EMBASE/Excerpta Medica

Krause & Pachernegg GmbH · VERLAG für MEDIZIN und WIRTSCHAFT · A-3003 Gablitz/Austria

Magnesium in Cardiovascular Disease

H. G. Stühlinger

In cardiovascular medicine, magnesium is of major importance in the treatment of arrhythmias and coronary artery disease. Magnesium raises the ventricular fibrillation threshold and prolongs the sinus node recovery time and atrioventricular conduction time. Main indications for magnesium are torsade de pointes tachycardias, digitalis induced ventricular tachyarrhythmias and multifocal atrial tachycardias. Additionally, magnesium has been used successfully in ventricular ectopies after overdose of neuroleptics or tricyclic antidepressants. Potential benefits can be expected in monomorphic ventricular tachycardias and in ventricular arrhythmias that did not respond to class III antiarrhythmic drugs. Recent studies have shown positive effects of magnesium in perioperative patients, where the incidence of atrial and ventricular arrhythmias could be reduced.

Oral magnesium has been used for years in patients with premature ventricular beats (PVB). Several studies have shown, that combined oral therapy with magnesium and potassium can effectively reduce the incidence of PVB.

Patients with coronary heart disease frequently suffer from magnesium deficiency. Oral combination therapy with magnesium and potassium improves the endothelial function in these patients and reduces platelet-dependent thrombosis. These encouraging results from basic science studies have now been confirmed in a large clinical trial showing that oral magnesium therapy improves exercise duration and quality of life in patients with coronary artery disease. *J Clin Basic Cardiol 2002; 5: 55–59.*

Key words: magnesium, arrhythmia, coronary artery disease

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 pointes, arrhythmias due to digitalis, 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.

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

Electrophysiological effects of low magnesium concentrations
• Reduced resting potential
• Reinforced sinus automaticity
• More frequent early afterdepolarisations
• Widening of the QRS complex
• Prolonged QT-intervals
• T-wave abnormalities, occurrence of U-waves
• Lowered atrial fibrillation threshold
• Lowered ventricular fibrillation threshold
Electrophysiological effects of high magnesium concentrations
• Reduced sinus automaticity
• Prolonged sinu-atrial conduction time
• Prolonged refractory period of atrium and AV-node
• Raised ventricular fibrillation threshold
• Reduction of drug-induced triggered activity
• Reduction of ischaemia-associated arrhythmias

From the Department of Emergency Medicine, University Hospital of Vienna, Austria
Correspondence to: H. Georg Stühlinger, Department of Emergency Medicine, University Hospital of Vienna, Waehringer Guertel 18–20, A-1090 Vienna, Austria; e-mail: h.georg.stuehlinger@akh-wien.ac.at

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 (hypomagnesaemia, hypokalaemia) and drugs that prolong the repolarisation phase (class Ia 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, Zwillinger 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 causative 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 astemizole, 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 antiarrhythmics 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

sinus rhythms with magnesium therapy in a study by Sager [53]. The mode of application provides one possible explanation for these discrepancies. Both studies used 8 mmol magnesium sulfate, albeit infused within 5 seconds by Wesley [52], and within 10 minutes by Sager [53]. A 1992 study comparing rapid bolus infusion of magnesium (within 15 seconds) with adenosine, found considerably higher cardioversion rates with adenosine [54]. These results indicate that magnesium should only be used in supraventricular tachycardia if adenosine treatment has failed [55].

Arrhythmias in Heart Failure and/or With Diuretics
In patients with congestive heart failure a negative correlation of magnesium concentration and occurrence of arrhythmias has been described [56]. There is suggestive evidence of an antiarrhythmic potential of elevated magnesium levels [57] and parenteral magnesium has been shown to reduce the incidence of arrhythmias [58]. Disappointingly, however, the same authors describe, that oral magnesium substitution could not change the incidence of arrhythmias in their patients [59].

In 1993, the PROMISE study found correlations of magnesium levels and the frequency of arrhythmias, however, the degree of severity and overall mortality were not influenced [60]. Nevertheless, the beneficial effects of parenteral magnesium in patients with congestive heart failure have repeatedly been proven [61, 62].

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 dose should be infused within 5 to 10 seconds.

Oral Magnesium in Arrhythmia

Overview
Proven indication:
- Premature ventricular beats without coexisting myocardial disease or with stable cardiac disease

Potential indication:
- Treatment with diuretics

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, Zehender 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 on the incidence of recurrent atrial fibrillation [78]. 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 could show that not only surrogate 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 improvement in the primary study endpoint, functional capacity, as measured by exercise testing (Table 2). This improvement 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 magnesium could be detected even though all patients received concurrent optimal treatment according to international guidelines (Aspirin 95 %, betablockers 48 %, ACE-inhibitors 40 %, lipid-lowering drugs 66 %).

The importance of these findings is emphasized by the association between exercise duration and cardiovascular mortality as well as overall mortality in patients with coronary artery 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 ischaemia. 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 vasculature [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. According 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 supraventricular 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 of myocardial cells as well as the myocardium as a whole, the drug appears valuable in a wide array of arrhythmias. The physiological basis of the therapeutic concept and the wide margin of safety provide convincing arguments.

Table 2. Maximal exercise duration in patients with stable coronary artery disease in minutes (Shechter et al. [12])

	Magnesium n = 94	Placebo n = 93	
At baseline	8.1 ± 2.7	7.8 ± 2.9	p = 0.168
After 6 months	8.7 ± 2.1	7.8 ± 2.9	p = 0.008
	p = 0.01	p = 0.162	

As studies have now transgressed 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.

References

1. Boyd LJ, Scherf D. Magnesium sulfate in paroxysmal tachycardia. Am J Med Sci 1943; 206: 43–8.
2. Szekely P. The action of magnesium on the heart. Br Heart J 1946; 8: 115–24.
3. Zwillinger L. Über die Magnesiumwirkung auf das Herz. Klin Wochenschr 1935; 14: 1429–33.
4. DiCarlo LA Jr, Morady F, de Buitleir M, Krol RB, Schurig L, Annesley TM. Effects of magnesium sulfate on cardiac conduction and refractoriness in humans. J Am Coll Cardiol 1986; 7: 1356–62.
5. Kulick DL, Hong R, Ryzen E, Rude RK, Rubin JN, Elkayam U, Rahimtoola SH, Bhandari AK. Electrophysiologic effects of intravenous magnesium in patients with normal conduction systems and no clinical evidence of significant cardiac disease. Am Heart J 1988; 115: 367–73.
6. Stark G, Stark U, Tritthart HA. Modulation of cardiac impulse generation and conduction by nifedipine and verapamil analyzed by a refined surface ECG technique in Langendorff perfused guinea pig hearts. Basic Res Cardiol 1988; 83: 202–12.
7. Askar AO, Mustafa SJ. Role of magnesium for the treatment of cardiac arrhythmias. Magnesium 2000; 2: 17–25.
8. Rasmussen HS, Larsen OG, Meier K, Larsen J. Hemodynamic effects of intravenously administered magnesium on patients with ischemic heart disease. Clin Cardiol 1988; 11: 824–8.
9. Shechter M, Kaplinsky E, Rabinowitz B. The rationale of magnesium supplementation in acute myocardial infarction. A review of the literature. Arch Intern Med 1992; 152: 2189–96.
10. Rosolova H, Mayer O Jr, Reaven G. Effect of variations in plasma magnesium concentration on resistance to insulin-mediated glucose disposal in nondiabetic subjects. J Clin Endocrinol Metab 1997; 82: 3783–5.
11. Shechter M, Sharir M, Labrador MJ, Forrester J, Silver B, Bairey Merz CN. Oral magnesium therapy improves endothelial function in patients with coronary artery disease. Circulation 2000; 102: 2353–8.
12. Shechter M, Bairey Merz CN, Stuehlinger HG, Sharir M, Matezki S, Pachinger O, Slany J. Oral magnesium supplementation improves exercise duration and quality of life in patients with coronary artery disease (Abstract). J Am Coll Cardiol 2001; 37: 149.
13. Ryzen E, Wagers PW, Singer FR, Rude RK. Magnesium deficiency in a medical ICU population. Crit Care Med 1985; 13: 19–21.
14. Wong ET, Rude RK, Singer FR, Shaw ST Jr. A high prevalence of hypomagnesemia and hypermagnesemia in hospitalized patients. Am J Clin Pathol 1983; 79: 348–52.
15. Perticone F, Adinolfi L, Bonaduce D. Efficacy of magnesium sulfate in the treatment of torsade de pointes. Am Heart J 1986; 112: 847–9.
16. Smith WM, Gallagher JJ. "Les torsades de pointes": an unusual ventricular arrhythmia. Ann Intern Med 1980; 93: 578–84.
17. Soffer J, Dreifus LS, Michelson EL. Polymorphous ventricular tachycardia associated with normal and long Q-T intervals. Am J Cardiol 1982; 49: 2021–9.
18. Kaseda S, Gilmour RF Jr, Zipes DP. Depressant effect of magnesium on early afterdepolarizations and triggered activity induced by cesium, quinidine, and 4-aminopyridine in canine cardiac Purkinje fibers. Am Heart J 1989; 118: 458–66.
19. Tzivoni D, Banai S, Schuger C, Benhorin J, Keren A, Gottlieb S, Stern S. Treatment of torsade de pointes with magnesium sulfate. Circulation 1988; 77: 392–7.
20. Tzivoni D, Keren A, Cohen AM, Loebel H, Zahavi I, Chenzbraun A, Stern S. Magnesium therapy for torsades de pointes. Am J Cardiol 1984; 53: 528–30.
21. Arnold DJ. Intravenous magnesium for the treatment of cardiac arrhythmias. Aust N Z J Med 2000; 30: 54–60.
22. Luderitz B, Manz M. The value of magnesium in intensive care medicine. Z Kardiol 1994; 83 (Suppl 6): 121–6.
23. Stuhlinger HG, Kiss K, Smetana R. Significance of magnesium in cardiac arrhythmias. Wien Med Wochenschr 2000; 150: 330–4.
24. Stuehlinger HG. The wider use of magnesium. Eur Heart J 2001; 22: 713–4.
25. Zehender M. Magnesium as an anti-arrhythmic therapy principle in supraventricular and ventricular cardiac arrhythmias. Z Kardiol 1996; 85 (Suppl 6): 135–45.
26. Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. Part 6: advanced cardiovascular life support: section 5: pharmacology I: agents for arrhythmias. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. Circulation 2000; 102: I112–28.
27. Iseri LT, Allen BJ, Ginkel ML, Brodsky MA. Ionic biology and ionic medicine in cardiac arrhythmias with particular reference to magnesium. Am Heart J 1992; 123: 1404–9.
28. Tzivoni D, Keren A. Suppression of ventricular arrhythmias by magnesium. Am J Cardiol 1990; 65: 1397–9.
29. Ghani MF, Smith JR. The effectiveness of magnesium chloride in the treatment of ventricular tachyarrhythmias due to digitalis intoxication. Am Heart J 1974; 88: 621–6.

30. Cohen L, Kitzes R. Magnesium sulfate and digitalis-toxic arrhythmias. JAMA 1983; 249: 2808–10.
31. Kinlay S, Buckley NA. Magnesium sulfate in the treatment of ventricular arrhythmias due to digoxin toxicity. J Toxicol Clin Toxicol 1995; 33: 55–9.
32. French JH, Thomas RG, Siskind AP, Brodsky M, Iseri LT. Magnesium therapy in massive digoxin intoxication. Ann Emerg Med 1984; 13: 562–6.
33. Keren A, Tzivoni D. Magnesium therapy in ventricular arrhythmias. Pacing Clin Electrophysiol 1990; 13: 937–45.
34. Iseri LT, Fairshter RD, Hardemann JL, Brodsky MA. Magnesium and potassium therapy in multifocal atrial tachycardia. Am Heart J 1985; 110: 789–94.
35. Iseri LT. Magnesium and cardiac arrhythmias. Magnesium 1986; 5: 111–26.
36. England MR, Gordon G, Salem M, Chernow B. Magnesium administration and dysrhythmias after cardiac surgery. A placebo-controlled, double-blind, randomized trial. JAMA 1992; 268: 2395–402.
37. Jensen BM, Alstrup P, Klitgard NA. Magnesium substitution and postoperative arrhythmias in patients undergoing coronary artery bypass grafting. Scand Cardiovasc J 1997; 31: 265–9.
38. Johnson CJ, Peterson DR, Smith EK. Myocardial tissue concentrations of magnesium and potassium in men dying suddenly from ischemic heart disease. Am J Clin Nutr 1979; 32: 967–70.
39. Parikka H, Toivonen L, Verkkala K, Jarvinen A, Nieminen MS. Ventricular arrhythmia suppression by magnesium treatment after coronary artery bypass surgery. Int J Angiol 1999; 8: 165–70.
40. Speziale G, Ruvolo G, Fattouch K, Macrina F, Tonelli E, Donnetti M, Marino B. Arrhythmia prophylaxis after coronary artery bypass grafting: regimens of magnesium sulfate administration. Thorac Cardiovasc Surg 2000; 48: 22–6.
41. Knudsen K, Abrahamsson J. Magnesium sulphate in the treatment of ventricular fibrillation in amitriptyline poisoning. Eur Heart J 1997; 18: 881–2.
42. Krahenbuhl S, Sauter B, Kupferschmidt H, Krause M, Wyss PA, Meier PJ. Case report: reversible QT prolongation with torsades de pointes in a patient with pimozide intoxication. Am J Med Sci 1995; 309: 315–6.
43. Rao KA, Adlakha A, Verma-Ansil B, Meloy TD, Stanton MS. Torsades de pointes ventricular tachycardia associated with overdose of astemizole. Mayo Clin Proc 1994; 69: 589–93.
44. Mletzko R, Jung W, Manz M, Kamradt T, Vogel F, Luderitz B. Arrhythmogenic effect of flecainide-treatment with i.v. magnesium. Z Kardiol 1989; 78: 602–6.
45. Baraka A, Ayoub C, Kawkabani N. Magnesium therapy for refractory ventricular fibrillation. J Cardiothorac Vasc Anesth 2000; 14: 196–9.
46. Tobey RC, Birnbaum GA, Allegra JR, Horowitz MS, Plosay JJ III. Successful resuscitation and neurologic recovery from refractory ventricular fibrillation after magnesium sulfate administration. Ann Emerg Med 1992; 21: 92–6.
47. Allen BJ, Brodsky MA, Capparelli EV, Luckett CR, Iseri LT. Magnesium sulfate therapy for sustained monomorphic ventricular tachycardia. Am J Cardiol 1989; 64: 1202–4.
48. Brooks R, McGovern BA, Brussel T. Limited effectiveness of magnesium infusions for suppressing inducible sustained monomorphic ventricular tachycardia (Abstract). Circulation 1992; 2: 659.
49. Hilton TC, Fredman C, Holt DJ, Bjerregaard P, Ira GH Jr, Janosik DL. Electrophysiologic and antiarrhythmic effects of magnesium in patients with inducible ventricular tachyarrhythmia. Clin Cardiol 1992; 15: 176–80.
50. North NE, Crandall BG, Halperin BD, Kron J, McAnulty JH. A double blind randomized trial of magnesium sulfate for ventricular tachycardia (Abstract). Circulation 1993; 88: 2401.
51. Manz M, Jung W, Tebbenjohanns J, Pfeiffer D, May F, Lüderitz B. Magnesium: Einfluß einer hochdosierten intravenösen Applikation auf monomorphe ventrikuläre Tachykardien (Abstract). Z Kardiol 1994; 83: 124.
52. Wesley RC Jr, Haines DE, Lerman BB, DiMarco JP, Crampton RS. Effect of intravenous magnesium sulfate on supraventricular tachycardia. Am J Cardiol 1989; 63: 1129–31.
53. Sager PT, Widerhorn J, Petersen R, Leon C, Ryzen E, Rude R, Rahimtoola SH, Bhandari AK. Prospective evaluation of parenteral magnesium sulfate in the treatment of patients with reentrant AV supraventricular tachycardia. Am Heart J 1990; 119: 308–16.
54. Viskin S, Belhassen B, Sheps D, Laniado S. Clinical and electrophysiologic effects of magnesium sulfate on paroxysmal supraventricular tachycardia and comparison with adenosine triphosphate. Am J Cardiol 1992; 70: 879–85.
55. Fazekas T, Scherlag BJ, Vos M, Wellens HJ, Lazzara R. Magnesium and the heart: antiarrhythmic therapy with magnesium. Clin Cardiol 1993; 16: 768–74.
56. Gottlieb SS, Baruch L, Kukin ML, Bernstein JL, Fisher ML, Packer M. Prognostic importance of the serum magnesium concentration in patients with congestive heart failure. J Am Coll Cardiol 1990; 16: 827–31.
57. Zehender M, Meinertz T, Faber T, Caspary A, Jeron A, Bremm K, Just H. Antiarrhythmic effects of increasing the daily intake of magnesium and potassium in patients with frequent ventricular arrhythmias. Magnesium in Cardiac Arrhythmias (MAGICA) Investigators. J Am Coll Cardiol 1997; 29: 1028–34.
58. Gottlieb SS, Fisher ML, Pressel MD, Patten RD, Weinberg M, Greenberg N. Effects of intravenous magnesium sulfate on arrhythmias in patients with congestive heart failure. Am Heart J 1993; 125: 1645–50.
59. Gottlieb SS, Fisher ML, Krichten C, Patten RD, Pressel MD, Brackett J. Is oral magnesium replacement antiarrhythmic in patients with congestive heart failure? (Abstract) J Am Coll Cardiol 1993; 21: 366A.
60. Eichhorn EJ, Tandon PK, DiBianco R, Timmis GC, Fenster PE, Shannon J, Packer M. Clinical and prognostic significance of serum magnesium concentration in patients with severe chronic congestive heart failure: the PROMISE Study. J Am Coll Cardiol 1993; 21: 634–40.
61. Ceremuzynski L, Gebalska J, Wolk R, Makowska E. Hypomagnesemia in heart failure with ventricular arrhythmias. Beneficial effects of magnesium supplementation. J Intern Med 2000; 247: 78–86.
62. Sueta CA, Clarke SW, Dunlap SH, Jensen L, Blauwet MB, Koch G, Patterson JH, Adams KF Jr. Effect of acute magnesium administration on the frequency of ventricular arrhythmia in patients with heart failure. Circulation 1994; 89: 660–6.
63. Dyckner T, Wester PO. Potassium/magnesium depletion in patients with cardiovascular disease. Am J Med 1987; 82: 11–7.
64. Dyckner T, Wester PO. Ventricular extrasystoles and intracellular electrolytes before and after potassium and magnesium infusions in patients on diuretic treatment. Am Heart J 1979; 97: 12–8.
65. Zehender M, Meinertz T, Just H. Magnesium deficiency and magnesium substitution. Effect on ventricular cardiac arrhythmias of various etiology. Herz 1997; 22 (Suppl 1): 56–62.
66. DeCarli C, Sprouse G, LaRosa JC. Serum magnesium levels in symptomatic atrial fibrillation and their relation to rhythm control by intravenous digoxin. Am J Cardiol 1986; 57: 956–9.
67. Brodsky MA, Orlov MV, Capparelli EV, Allen BJ, Iseri LT, Ginkel M, Orlov YS. Magnesium therapy in new-onset atrial fibrillation. Am J Cardiol 1994; 73: 1227–9.
68. Gullestad L, Birkeland K, Molstad P, Hoyer MM, Vanberg P, Kjekshus J. The effect of magnesium versus verapamil on supraventricular arrhythmias. Clin Cardiol 1993; 16: 429–34.
69. Moran JL, Gallagher J, Peake SL, Cunningham DN, Salagaras M, Leppard P. Parenteral magnesium sulfate versus amiodarone in the therapy of atrial tachyarrhythmias: a prospective, randomized study. Crit Care Med 1995; 23: 1816–24.
70. Hays JV, Gilman JK, Rubal BJ. Effect of magnesium sulfate on ventricular rate control in atrial fibrillation. Ann Emerg Med 1994; 24: 61–4.
71. Craddock L, Miller B, Clifton G, Krumbach B, Pluss W. Resuscitation from prolonged cardiac arrest with high-dose intravenous magnesium sulfate. J Emerg Med 1991; 9: 469–76.
72. Fatovich DM, Prentice DA, Dobb GJ. Magnesium in cardiac arrest (the magic trial). Resuscitation 1997; 35: 237–41.
73. Thel MC, Armstrong AL, McNulty SE, Califf RM, O'Connor CM. Randomised trial of magnesium in in-hospital cardiac arrest. Duke Internal Medicine Housestaff. Lancet 1997; 350: 1272–6.
74. Toivonen LK, Leinonen H. Limited effect of magnesium sulphate on torsades de pointes ventricular tachycardia. Int J Cardiol 1986; 12: 260–2.
75. Holzgartner H, Maier E, Vierling W. High-dosage oral magnesium therapy in arrhythmias. Results of an observational study in 1.160 patients with arrhythmia. Fortschr Med 1990; 108: 539–42.
76. Lewis RV, Tregaskis B, McLay J, Service E, McDevitt DG. Oral magnesium reduces ventricular ectopy in digitalised patients with chronic atrial fibrillation. Eur J Clin Pharmacol 1990; 38: 107–10.
77. Feyertag J, Laimer H, Herglotz P, Douglas T, Böttcher E, Ekmekcioglu C, Marktl W. Die Wirkung einer oralen Magnesiumsupplementation auf ventrikuläre Arrhythmien und Parameter des Magnesiumstoffwechsels. Mag Bull 1995; 17: 86–90.
78. Frick M, Darpo B, Ostergren J, Rosenqvist M. The effect of oral magnesium, alone or as an adjuvant to sotalol, after cardioversion in patients with persistent atrial fibrillation. Eur Heart J 2000; 21: 1177–85.
79. Anderson TW, Neri LC, Schreiber GB, Talbot FD, Zdrojewski A. Letter: Ischemic heart disease, water hardness and myocardial magnesium. Can Med Assoc J 1975; 113: 199–203.
80. Chipperfield B, Chipperfield JR. Heart-muscle magnesium, potassium, and zinc concentrations after sudden death from heart-disease. Lancet 1973; 2: 293–6.
81. Lichton IJ. Dietary intake levels and requirements of Mg and Ca for different segments of the U.S. population. Magnesium 1989; 8: 117–23.
82. Peterson DR, Thompson DJ, Nam JM. Water hardness, arteriosclerotic heart disease and sudden death. Am J Epidemiol 1970; 92: 90–3.
83. Shaper AG. Soft water, heart attacks, and stroke. JAMA 1974; 230: 130–1.
84. Shechter M, Paul-Labrador MJ, Rude RK, Bairey Merz CN. Intracellular magnesium predicts functional capacity in patients with coronary artery disease. Cardiology 1998; 90: 168–72.
85. Liao F, Folsom AR, Brancati FL. Is low magnesium concentration a risk factor for coronary heart disease? The Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J 1998; 136: 480–90.
86. Shechter M, Merz CN, Paul-Labrador M, Meisel SR, Rude RK, Molloy MD, Dwyer JH, Shah PK, Kaul S. Oral magnesium supplementation inhibits platelet-dependent thrombosis in patients with coronary artery disease. Am J Cardiol 1999; 84: 152–6.
87. Shechter M, Merz CN, Rude RK, Paul Labrador MJ, Meisel SR, Shah PK, Kaul S. Low intracellular magnesium levels promote platelet-dependent thrombosis in patients with coronary artery disease. Am Heart J 2000; 140: 212–8.
88. French JK, Hyde TA, Patel H, Amos DJ, McLaughlin SC, Webber BJ, White HD. Survival 12 years after randomization to streptokinase: the influence of thrombolysis in myocardial infarction flow at three to four weeks. J Am Coll Cardiol 1999; 34: 62–9.
89. Shechter M, Kaplinsky E, Rabinowitz B. Review of clinical evidence – is there a role for supplemental magnesium in acute myocardial infarction in high-risk populations (patients ineligible for thrombolysis and the elderly)? Coron Artery Dis 1996; 7: 352–8.
90. Iseri LT, French JH. Magnesium: nature's physiologic calcium blocker. Am Heart J 1984; 108: 188–93.
91. Paolisso G, Scheen A, D'Onofrio F, Lefebvre P. Magnesium and glucose homeostasis. Diabetologia 1990; 33: 511–4.