

Effects of Magnesium Sulfate on Cardiac Conduction and Refractoriness in Humans

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Magnesium has been used empirically for several decades in the treatment of atrial and ventricular arrhythmias in patients with normal and decreased serum magnesium levels. However, a systematic evaluation of the effects of magnesium on cardiac conduction and refractoriness in humans has not been described. In this study, the electrocardiographic and electrophysiologic effects of magnesium were determined in 10 patients with normal baseline serum magnesium and other electrolyte levels. Six grams of magnesium sulfate was administered intravenously over 6 minutes followed by a continuous infusion of 1 additional gram over 1 hour. Serum magnesium levels rose significantly from a baseline of 2.0 ± 0.2 to 5.4 ± 0.4 mg/dl ($p < 0.001$).

No significant change occurred in heart rate at rest, or in duration of the QRS complex or QT or QTc intervals during sinus rhythm. There were significant increases in sinus node recovery time ($1,000 \pm 211$ to $1,106 \pm 223$ ms, $p < 0.01$) and corrected sinus node recovery

time (279 ± 87 to 336 ± 104 ms, $p < 0.05$). Significant increases occurred in atrioventricular (AV) node conduction time during sinus rhythm (82 ± 22 to 97 ± 17 ms, $p < 0.02$), in the atrial paced cycle length at which AV node Wenckebach block occurred (350 ± 46 to 419 ± 65 ms, $p < 0.01$) and in the AV node relative refractory period (397 ± 27 to 422 ± 18 ms, $p < 0.05$), functional refractory period (395 ± 41 to 415 ± 33 ms, $p < 0.05$) and effective refractory period (306 ± 67 to 338 ± 38 ms, $p < 0.05$). During rapid ventricular pacing at 500 and 250 ms, QRS duration increased significantly (154 ± 15 to 164 ± 20 ms, $p < 0.01$) but was not rate dependent. There was no significant change in atrial or ventricular refractory periods.

Acute intravenous administration of magnesium has several electrophysiologic effects that may be beneficial in the treatment of atrial and ventricular arrhythmias.

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The sulfate and chloride salts of magnesium have been used intravenously for several decades in the short-term treatment of patients with atrial and ventricular arrhythmias (1-6). In these uncontrolled studies, variable doses of magnesium were administered over several seconds or minutes to terminate paroxysmal atrial tachycardia (1,2), to decrease the ventricular rate during atrial fibrillation (2,3) and to suppress ventricular extrasystoles associated with digitalis intoxication (2,3). Magnesium has also been used empirically, often in conjunction with other antiarrhythmic drugs or interventions, in the treatment of intractable ventricular tachycardia, ventricular fibrillation and torsade de pointes in patients with normal and decreased serum magnesium levels (4-7). The

antiarrhythmic effects of magnesium have been reported to last from several minutes to as long as 24 hours (2); however, the serum half-life of intravenously administered magnesium is very short. It is excreted by the kidney almost entirely within 4 to 8 hours in patients with normal renal function (8).

Although the electrocardiographic and electrophysiologic effects of intravenous magnesium administration have been described in experimental animals, a systematic evaluation of the effects of magnesium in humans has not been reported. The purpose of this study, therefore, was to determine the effects of intravenously administered magnesium sulfate on cardiac conduction and refractoriness in humans.

Methods

Patients studied. Approval for administration of intravenous magnesium sulfate was obtained from the Institutional Review Board at our medical center. Subjects for this study were recruited from patients undergoing a routine

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electrophysiologic evaluation for clinical indications. Because our study was intended to examine only the effects of magnesium on cardiac conduction and refractoriness, we excluded patients in whom sustained atrial or ventricular tachycardia was initiated during their clinical electrophysiologic evaluation.

There were seven men and three women in this study with a mean age of 54 ± 12 years. Three patients had ischemic cardiomyopathy, two had idiopathic dilated cardiomyopathy, one had alcoholic cardiomyopathy and four had no clinical evidence of heart disease. One patient had left bundle branch block, one had a nonspecific intraventricular conduction delay that exceeded 120 ms, five had a nonspecific intraventricular conduction delay of less than 120 ms, and three had normal intraventricular conduction on a 12 lead electrocardiogram at rest before administration of magnesium. Clinical indications for electrophysiologic study were evaluation of ventricular tachycardia (four patients) and syncope (six patients). All patients had normal serum sodium, potassium chloride, bicarbonate, calcium and magnesium levels at the time of study.

Protocol of electrophysiologic study. All antiarrhythmic drugs were withheld for at least five half-lives before study. Electrophysiologic studies were performed with patients in the fasting nonsedated state after written, informed consent was obtained. Two or three 6F quadripolar electrode catheters (USCI) with a 1 cm interelectrode distance were introduced percutaneously into the right femoral vein and positioned under fluoroscopic guidance in the high right atrium, across the tricuspid valve in the region of the His bundle and in the right ventricular apex. Systemic blood pressure was monitored continuously with a 5F indwelling cannula introduced percutaneously into the right femoral artery and connected to a Statham P23-ID pressure transducer (Gould Medical Products). Intracardiac electrograms were filtered below 30 and above 500 Hz and were displayed simultaneously with scalar electrocardiographic leads V_1 , I and III on a multichannel oscilloscope (Electronics-for-Medicine, VR-16). Signals were recorded on photographic paper at speeds of 50 to 150 mm/s. Programmed cardiac stimulation was performed with a programmable constant current stimulator (Bloom Associates) that delivered rectangular pulses of 2 ms duration at twice diastolic threshold.

After measuring the heart rate at rest and scalar electrocardiographic P wave, PR, QRS and QT intervals and baseline atrial-His (AH), His-ventricular (HV) and P wave-(high right) atrial (PA) intervals, atrial overdrive pacing was performed for durations of 1 minute at cycle lengths of 600 ms down to 300 ms in 50 ms decrements. This was done to determine uncorrected and corrected sinus node recovery times, AH and HV intervals and the paced cycle length at which atrioventricular (AV) Wenckebach block occurred. Atrial and ventricular effective refractory periods were determined in duplicate at atrial and ventricular drive cycle

lengths of 500 ms using a drive train of 8 paced cycles with a 3 second intertrain pause. Right ventricular pacing was then performed for at least 15 beats at cycle lengths of 500 and 250 ms. The last five QRS complexes of each pacing train were recorded at a paper speed of 150 mm/s.

Magnesium administration. Immediately after completion of the protocol, 6 g of 4% magnesium sulfate solution was intravenously administered at a rate of 1 g/min.* Because of the short half-life of intravenous magnesium, a continuous infusion of 4% magnesium sulfate solution was then initiated at a rate of 1 g/hour.† Ten minutes later, the entire pacing protocol was repeated. Serum magnesium levels were obtained immediately before intravenous administration of magnesium sulfate and immediately after the pacing protocol was repeated. Serum magnesium content was determined using the methylthymol blue complex colorimetric procedure (DuPont aca III analyzer) (9).

Data analysis. Uncorrected and corrected sinus node recovery times, AH and HV intervals and atrial and ventricular effective refractory periods were determined using standard methods and previously described definitions (10). The scalar electrocardiographic QT interval was corrected (QTc) using Bazett's formula (11). Using a previously described method (12), the duration of the last QRS complex recorded during ventricular pacing at cycle lengths of 500 and 250 ms was measured as an index of intraventricular conduction from electrocardiographic lead III which, in all cases, provided the best definition of the onset and termination of the QRS complex. The duration of this QRS complex train was measured in blinded fashion by two investigators. Reproducibility was within 5%.

Because of practical considerations, data acquisition was limited in 4 of the 10 cases. In one patient, who demonstrated accelerated AV node conduction during the baseline study, QRS, QT and QTc intervals recorded during sinus rhythm, all AH and HV intervals and the paced cycle length causing AV node Wenckebach conduction were excluded. In two patients, who demonstrated Wenckebach block at a paced cycle length of at least 500 ms after magnesium was administered, and in the fourth patient, in whom a stable His bundle depolarization could not be consistently recorded, AV node effective, functional and relative refractory periods could not be determined.

Statistical analysis was performed using the paired *t* test. All values are expressed as mean \pm SD.

Results

Patients uniformly experienced a sensation of increased warmth with flushing and diaphoresis associated with cu-

*This dose was chosen to represent a midrange dose when compared with the administered doses reported in previous studies (1-7,13,16).

†This dose was given because of short excretion time of magnesium and because of previous use of continuous intravenous infusion (4,5,7).

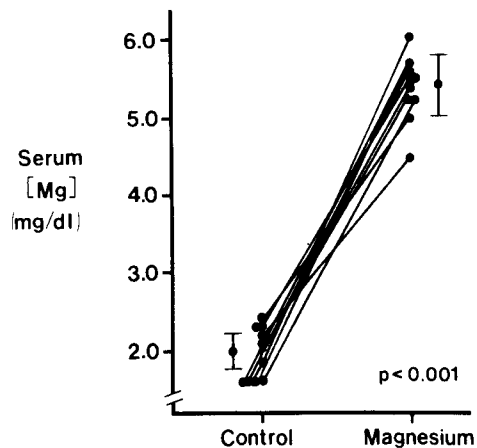


Figure 1. Serum magnesium concentrations before and after administration of magnesium sulfate in 10 patients.

taneous vasodilation and a transient decrease in blood pressure during short-term loading with magnesium sulfate. No depression of respiratory rate occurred in any patient. All symptoms and signs resolved spontaneously and heart rate and blood pressure returned to baseline within 2 to 3 minutes after loading was completed, and did not recur during continued infusion of 1 g magnesium sulfate over the next hour.

Serum magnesium levels rose significantly (from 2.0 ± 0.2 to 5.4 ± 0.4 mg/dl, $p < 0.001$) after intravenous administration of magnesium sulfate (Fig. 1).

Electrocardiographic effects (Table 1). Magnesium caused a significant increase in the electrocardiographic PR interval (167 ± 19 to 187 ± 18 ms, $p < 0.001$) (Fig. 2). No significant change occurred in heart rate (81 ± 19 versus 78 ± 14 beats/min, $p = \text{NS}$), P wave duration (106 ± 27 versus 113 ± 39 ms, $p = \text{NS}$), QRS duration (113 ± 27 versus 117 ± 31 ms, $p = \text{NS}$), QT interval (383 ± 35 versus 388 ± 30 ms, $p = \text{NS}$) or corrected QT interval (QTc) (443 ± 37 versus 451 ± 42 ms, $p = \text{NS}$). Comparison of 12 lead electrocardiograms before and after magnesium administration demonstrated no changes in P wave, QRS complex, ST segment or T wave configuration.

Electrophysiologic effects (Table 2). *Sinus node function.* No significant change in spontaneous sinus cycle length occurred after administration of magnesium (737 ± 178 to

768 ± 139 ms, $p = \text{NS}$). However, significant increases were noted in the longest sinus node recovery time ($1,000 \pm 211$ to $1,106 \pm 223$ ms, $p < 0.01$) and the longest corrected sinus node recovery time (279 ± 87 to 336 ± 104 ms, $p < 0.05$) measured after administration of magnesium (Fig. 3).

Atrioventricular conduction. Magnesium caused a significant increase in the AH interval (82 ± 22 to 97 ± 17 ms, $p < 0.02$) during sinus rhythm without a significant change in scalar electrocardiographic P wave duration (106 ± 27 to 113 ± 39 ms, $p = \text{NS}$), intracardiac atrial electrogram duration (60 ± 12 to 64 ± 10 ms, $p = \text{NS}$) or P-A interval (16 ± 12 to 17 ± 11 ms, $p = \text{NS}$). The atrial paced cycle length at which AV node Wenckebach block occurred was significantly prolonged after administration of magnesium (350 ± 46 to 419 ± 65 ms, $p < 0.01$) (Fig. 2). Magnesium caused no significant change in HV interval during sinus rhythm (47 ± 4 to 47 ± 5 ms, $p = \text{NS}$) or during atrial overdrive pacing.

Atrioventricular node refractoriness. After administration of magnesium sulfate, significant increases occurred in the AV node functional refractory period (395 ± 41 to 415 ± 33 ms, $p < 0.05$), relative refractory period (397 ± 27 to 422 ± 18 ms, $p < 0.05$) and effective refractory period (306 ± 67 to 338 ± 38 ms, $p < 0.05$) (Fig. 4).

Intraventricular conduction. The duration of intraventricular conduction was similar during rapid ventricular pacing at cycle lengths of 500 and 250 ms before administration of magnesium (154 ± 15 versus 154 ± 15 ms, $p = \text{NS}$). After administration of magnesium, it increased significantly during ventricular pacing at cycle lengths of 500 ms (154 ± 15 to 164 ± 20 ms, $p < 0.01$) and 250 ms (154 ± 15 to 164 ± 18 ms, $p < 0.01$) (Fig. 5).

Atrial refractoriness. Magnesium caused no significant change in the atrial functional refractory period (253 ± 20 to 261 ± 21 ms, $p = \text{NS}$), relative refractory period (246 ± 27 to 285 ± 80 ms, $p = \text{NS}$) or effective refractory period (213 ± 18 to 235 ± 33 ms, $p = \text{NS}$).

Ventricular refractoriness. Magnesium caused no significant change in ventricular effective refractory period (233 ± 20 to 235 ± 15 ms, $p = \text{NS}$).

Table 1. Electrocardiographic Effects of Magnesium Sulfate*

	Baseline	Magnesium	p Value
Heart rate (beats/min) (n = 10)	81 ± 19	78 ± 14	NS
P wave duration (ms) (n = 10)	106 ± 27	113 ± 39	NS
Interval			
PR (ms) (n = 9)	167 ± 19	187 ± 18	< 0.01
QRS (ms) (n = 9)	113 ± 27	117 ± 31	NS
QT (ms) (n = 9)	383 ± 35	388 ± 30	NS
QTc (ms) (n = 9)	443 ± 37	451 ± 42	NS

*All data recorded on scalar electrocardiogram during sinus rhythm. n = number of patients; NS = not significant; QTc = QT interval corrected for heart rate (Bazett's formula).

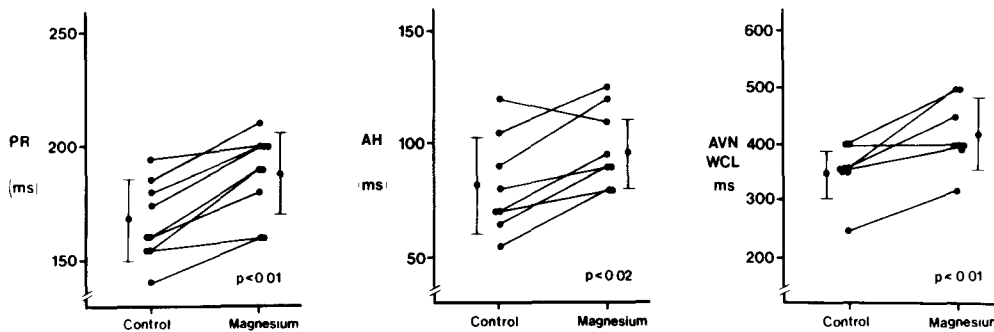


Figure 2. PR and atrial-His (AH) intervals, and the longest paced atrial cycle length causing AV node Wenckebach block (AVN WCL) before and after administration of magnesium sulfate in nine patients.

Discussion

Electrocardiographic effects. The electrocardiographic effects of magnesium sulfate demonstrated in this study are in general agreement with those described by previous authors. A strict comparison is not possible, however, because

of variability in the quantity of magnesium administered, the varying duration of intravenous administration and the absence of serum magnesium determinations before and after treatment in earlier studies. No significant change in heart rate or duration of QRS complex or QT interval occurred in this study after administration of 6 g magnesium sulfate over 6 minutes. Previous authors (6,13) noted no change in heart rate or QT interval after administration of 1 to 2 g magnesium sulfate over 10 seconds to 1 to 2 minutes. After giving 4 g magnesium sulfate over 4 to 10 seconds,

Table 2. Electrophysiologic Effects of Magnesium Sulfate

	Baseline	Magnesium	p Value
Sinus node function			
SSCL (n = 10)	737 ± 178	768 ± 139	NS
SNRT (n = 10)	1,000 ± 211	1,106 ± 223	< 0.01
SNRTc (n = 10)	279 ± 87	336 ± 104	< 0.05
Atrioventricular conduction			
A (n = 10)	60 ± 12	64 ± 10	NS
AH (n = 8)	82 ± 22	97 ± 17	< 0.02
AVN WBB (n = 9)	350 ± 46	419 ± 65	< 0.01
HV (n = 8)	47 ± 4	47 ± 5	NS
P-A (n = 10)	16 ± 12	17 ± 11	NS
AV node refractoriness			
AVNERP (n = 6)	306 ± 67	338 ± 38	< 0.05
AVNFRP (n = 6)	395 ± 41	415 ± 33	< 0.05
AVNRRP (n = 6)	397 ± 27	422 ± 18	< 0.05
Intraventricular conduction			
QRS ₅₀₀ (n = 10)	154 ± 15	164 ± 20	< 0.01
QRS ₂₅₀ (n = 10)	154 ± 15	164 ± 18	< 0.01
Atrial refractoriness			
AERP (n = 7)	213 ± 18	235 ± 33	NS
AFRP (n = 7)	253 ± 20	261 ± 21	NS
ARRP (n = 7)	246 ± 27	285 ± 80	NS
Ventricular refractoriness			
VERP (n = 10)	233 ± 20	235 ± 15	NS

All values in ms. A = atrial septal electrogram duration; AERP = atrial effective refractory period; AFRP = atrial functional refractory period; AH = atrial-His interval; ARRP = atrial relative refractory period; AVN = atrioventricular node; AVNERP, AVNFRP and AVNRRP = atrioventricular node effective, functional and relative refractory period, respectively; AVN WBB = atrial paced cycle length causing atrioventricular node Wenckebach conduction; HV = His-ventricular interval; n = number of patients; P = scalar electrocardiographic P wave duration; P-A = scalar electrocardiographic P wave-intracardiac (high right) atrial electrogram interval; QRS₂₅₀ and QRS₅₀₀ = QRS duration during ventricular pacing at a cycle length of 250 and 500 ms, respectively; SNRT = sinus node recovery time; SNRTc = corrected SNRT; SSCL = spontaneous sinus cycle length; VERP = right ventricular apex effective refractory period.

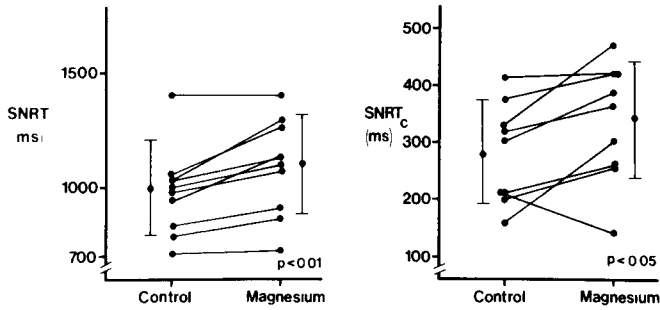


Figure 3. The longest measured sinus node recovery time (SNRT) and the longest measured corrected sinus node recovery time (SNRTc) before and after administration of magnesium sulfate in nine patients.

Enselberg et al. (3) reported an initial increase followed by slowing of the heart rate, whereas Szekely (2) found minor alterations in heart rate in only 4 of 10 patients given a similar dose over 2 minutes. During administration of 10 g of magnesium sulfate over 30 to 60 minutes with continuous electrocardiographic monitoring, Winkler et al. (14) observed no significant slowing of heart rate.

Sinus node effects. Although no significant change in heart rate at rest occurred after administration of magnesium sulfate in this study, sinus node recovery time and corrected sinus node recovery time were significantly prolonged. Several studies in animals suggest that this may be mediated by both indirect and direct inhibitory effects of magnesium on the sinoatrial node. Magnesium has been demonstrated (15) to slow the heart rate at rest by inducing a short-lived blockade of the nictating membrane of the sympathetic ganglia and by preventing the stimulating effects of potassium and acetylcholine on the superior cervical ganglion of anesthetized cats. Magnesium does not release the heart from vagal inhibition; conversely, it continues to have a negative chronotropic effect after administration of atropine or sectioning of the vagus nerve (16). It continues to slow the heart rate at rest in a dose-dependent fashion even after the heart has been decentralized by crushing of the cervical sympatheticovagal trunks (15).

Atrioventricular node effects. Magnesium induced a prolongation of AV node conduction time during sinus rhythm and an increase in the paced cycle length at which AV node Wenckebach block occurred. These findings are compatible with previous observations of prolongation of the PR and AV intervals during sinus rhythm and a decrease in ventricular rate during atrial fibrillation after administration of intravenous magnesium (1-3,5,17). Significant increases in AV node functional, relative and effective refractory periods caused by magnesium were also observed in our study. In vitro studies (18) have demonstrated an increase in AV node conduction time and a decrease in the spontaneous firing frequency of the AV node in isolated rabbit hearts exposed to a 5 mM concentration of magnesium cation as compared with the mean serum concentration of 2.2 mM achieved after administration of magnesium in this study. Although magnesium has been proposed by some authors (19) as nature's calcium antagonist, it appears to exert its negative dromotropic and chronotropic effects on the AV node indirectly. Magnesium induces an inward shift of the background potassium-mediated current, causing a secondary voltage-dependent inactivation of the slow inward current which mediates AV node depolarization (18). Magnesium exhibits a different mode of action, therefore, than the direct inactivation of the slow inward current observed with other calcium channel antagonists, such as verapamil (20).

Myocardial effects. Magnesium had no significant effect on His-Purkinje conduction time or QRS duration at heart rates at rest. These findings are consistent with those of previous studies (2,5) that reported no increase in QRS duration or development of intraventricular block in humans given intravenous magnesium. An increase in QRS duration was reported in dogs (16,21), but only when they were given lethal doses of magnesium. In our study, magnesium was demonstrated to have a small but statistically significant effect on intraventricular conduction during rapid ventricular

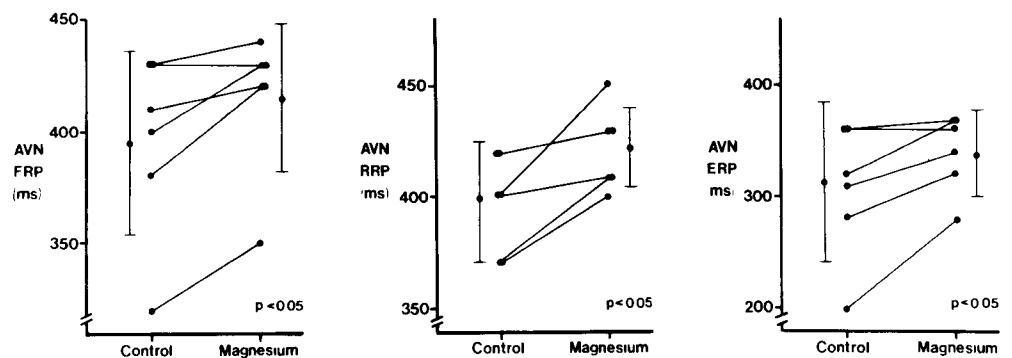


Figure 4. Atrioventricular node (AVN) functional refractory period (FRP), relative refractory period (RRP) and effective refractory period (ERP) before and after administration of magnesium sulfate in six patients.

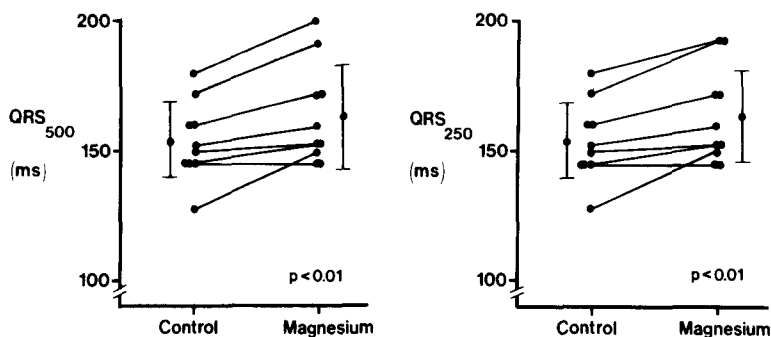


Figure 5. QRS duration during ventricular pacing at cycle lengths of 500 ms (QRS₅₀₀) and 250 ms (QRS₂₅₀) before and after administration of magnesium sulfate in 10 patients.

pacing. Individual increases ranged from 0 to 18% with a mean increase of 6% for the patient group. The observed increases were similar at paced cycle lengths of 500 and 250 ms, suggesting that the effect of magnesium on ventricular conduction is tonic and unlike the rate-dependent increase in intraventricular conduction observed with type 1 and type 3 antiarrhythmic drugs (12). Although this tonic effect on intraventricular conduction could not be demonstrated during sinus rhythm, such an effect cannot be excluded with certainty. The scalar electrocardiographic QRS complex recorded during sinus rhythm was much narrower than the broad QRS complex recorded during ventricular pacing; this may have made a subsequently small but significant increase in intraventricular conduction much more difficult to detect. Alternatively, the lack of effect of magnesium on QRS duration during sinus rhythm may reflect an absence of effect on the His-Purkinje system, which initiates ventricular depolarization, whereas an increase in QRS duration during ventricular pacing may reflect the effect of magnesium on the myocardial tissue which is initiating and propagating ventricular depolarization.

Several lines of evidence suggest that the effects of magnesium on myocardial muscle fibers do not occur as a result of interaction with the fast sodium-mediated channel or the slow calcium-mediated channel in the excited myocardial sarcolemma membrane. The effects of magnesium on action potential are not blocked by tetrodotoxin, lidocaine or calcium antagonists such as verapamil, D600, nifedipine or diltiazem (22). Magnesium may instead have a direct effect on potassium channels in the sarcolemmic membrane (22-24).

Watanabe and Dreifus (24) observed minimal changes in action potential amplitude, rest potential and maximal rate of depolarization of isolated ventricular muscle fibers exposed to a 7.5 mM concentration of magnesium ion. A small but significant (4.3%) increase in action potential duration and a 10 to 30 ms prolongation of the ventricular effective refractory period were observed. Although magnesium sulfate appeared to have no significant effect on atrial or ventricular refractoriness in their study, the mean serum concentration was much lower (2.2 mM). Furthermore, it is possible that other compensatory neurogenic mechanisms

occur in vivo which may offset any direct effect of magnesium on myocardial muscle repolarization.

Antiarrhythmic effects of magnesium. Magnesium has been used empirically for more than 40 years (1-7) to treat atrial and ventricular arrhythmias in a variety of clinical settings including hypoxemia, myocardial ischemia and infarction, electrolyte depletion due to malnutrition or diuretic therapy and complications of treatment with digitalis glycosides and type 1 or type 3 antiarrhythmic drugs, for example, drug-induced torsade de pointes (6,7). However, the specific role of magnesium in the treatment of cardiac arrhythmias has been unclear. In the clinical studies published to date, serum magnesium levels before treatment have often been unknown, or serum magnesium and other electrolyte levels have been normal, making it difficult to distinguish whether subsequently successful treatment with magnesium was due to repletion of a magnesium deficiency or to a separate antiarrhythmic effect. In many cases, the mechanism of the treated arrhythmia has not been defined and other antiarrhythmic drugs or interventions have been used concurrently with intravenous magnesium, preventing a clear determination of the antiarrhythmic effects of magnesium alone.

In this study, administration of intravenous magnesium to patients with normal serum electrolyte levels caused a significant decrease in sinus node and AV node functions. In some patients, therefore, magnesium might be useful in the treatment of arrhythmias whose mechanism depends on participation of the sinoatrial or AV node (such as supra-ventricular arrhythmias due to sinoatrial reentry, AV node reentry or reciprocating tachycardia) or arrhythmias whose mechanism depends on slow channel activity (for example, ventricular arrhythmias due to digitalis toxicity or triggered automaticity) (3,25).

When administered in a dose that met or exceeded many of the doses previously reported to be effective in the treatment of ventricular arrhythmias, magnesium had no effect on ventricular refractoriness and caused a small but statistically significant decrease in intraventricular conduction in the patients participating in this study. It is noteworthy, however, that the observed decrease in ventricular conduc-

tion was minimal when compared with that reported (12) for other antiarrhythmic agents known to decrease the fast sodium-dependent channel activity that mediates ventricular muscle depolarization. These findings suggest that magnesium might be unlikely to have a significant antiarrhythmic effect in the treatment of ventricular tachycardia due to a reentrant mechanism (26,27).

Conclusions. Although intravenously administered magnesium has several significant electrophysiologic effects in humans, the relation of these electrophysiologic findings to the potential antiarrhythmic effects of magnesium is not clear. Despite several decades of use in treatment of cardiac arrhythmias, the clinical use of magnesium has been sporadic and infrequent and its antiarrhythmic effects have been poorly understood. Additional studies may be helpful in determining its antiarrhythmic efficacy.

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