Magnesium suppression of early afterdepolarizations and ventricular tachyarrhythmias induced by cesium in dogs

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ABSTRACT The mechanism by which magnesium therapy suppresses some ventricular tachyarrhythmias characterized by a prolonged QT interval (e.g., torsades de pointes) is unknown. Since early afterdepolarizations have been proposed as a cause of the long QT syndrome and the related ventricular tachyarrhythmias, we hypothesized that magnesium therapy would suppress both the early afterdepolarizations and the ventricular arrhythmias. The present study was performed to test that hypothesis. Using monophasic action potentials (MAP) recorded with a contact electrode from the right ventricular endocardium to demonstrate early afterdepolarizations, cesium chloride (168 mg/kg iv) was administered before, during, and 1 to 2 hr after discontinuation of a magnesium infusion (1 to 2 mg/kg/min for 20 to 30 min). Before magnesium infusion, cesium induced early afterdepolarizations that were 49.7 ± 1.6% (mean ± SE) of the amplitude of the corresponding monophasic action potential. The amplitude of the early afterdepolarization decreased to 31.2 ± 3.8% of the MAP amplitude during magnesium infusion (p<.003) and increased to 48.0 ± 4.0% 1 to 2 hr after termination of the magnesium infusion (p<.003). Cesium induced sustained monomorphic ventricular tachycardia, torsades de pointes, or ventricular fibrillation in 12 of 13 dogs before magnesium infusion, and in eight of 11 dogs 1 to 2 hr after stopping infusion, but in only three of 13 dogs during magnesium infusion. Cesium prolonged the corrected QT interval from 338 ± 16 msec (control) to 387 ± 14 msec before (p<.003), 356 ± 12 msec during (p<.003), and 406 ± 16 msec after stopping the magnesium infusion (p<.003). Magnesium also suppressed early afterdepolarizations induced with cesium in isolated canine Purkinje fibers. These data support the conclusion that magnesium's mechanism of action is to suppress early afterdepolarizations, prolonged QT interval, and ventricular tachyarrhythmias induced by cesium. Successful responses in patients may occur by a similar mechanism of early afterdepolarization suppression.

Methods

Surgical preparation. Mongrel dogs of either sex weighing 17 to 29 kg were anesthetized with sodium secobarbital (30 mg/kg iv) and ventilated with room air with use of constant-volume respirator (Harvard model 607). Additional secobarbital was administered as needed to maintain anesthesia. Saline-filled polyethylene catheters were placed in the right femoral artery to monitor arterial blood pressure (Statham transducer P23 BD) and in both femoral veins to infuse drugs and normal saline (0.9%) to replace spontaneous fluid losses. A median sternotomy exposed the heart, which was suspended in a pericardial cradle. The right internal jugular vein was isolated for later introduction of a catheter to record MAPs from the right ventricle. Bipolar electrograms were obtained by inserting two Teflon-coated stainless steel hook electrodes 5 mm apart in the left ventricle and the right atrial appendage. Each dog was placed on a heating pad and the sternotomy was covered by a plastic sheet. An operating room table lamp was used to maintain epicardial temperature between 37° and 39° C.

Recording MAPs in vivo. MAPs were recorded from the antero-apical right ventricular endocardium with a No. 4F bipolar contact catheter with a silver–silver chloride distal electrode and a reference lead 5 mm away (Bard Critical Care). In five dogs, a No. 7F multipurpose catheter (Cordis) with a hole cut at the tip was inserted into the right ventricular cavity via the right internal jugular vein. The contact electrode catheter was either advanced directly to the right ventricular endocardial surface via the right internal jugular vein (n = 13) or through the lumen of the multipurpose catheter (n = 5). The latter method was used to stiffen the assembly and minimize movement of the contact electrode catheter within the heart if a secure position could not be found for the contact electrode alone. The tip of the endocardial electrode was visible as a bulge in the right ventricular free wall and was monitored visually and electrocardiographically for stability. Lead II, bipolar atrial and ventricular electrograms, and MAPs were recorded simultaneously on a strip-chart (Electronics for Medicine) at paper speeds of 25 to 100 mm/sec. Signals were amplified and filtered at a frequency of 0.04 to 500 Hz for the bipolar ventricular electrogram, lead II, and the MAPs, and at a frequency of 50 to 500 Hz for the bipolar atrial electrogram. Baseline recordings were obtained 10 to 20 min after placement of all electrodes and only when the MAP recording appeared to be stable (see below).1

In this study, delays in repolarization occurring during phase 3 were termed EADS.6 Because catheter movement or changes in myocardial contractility may produce artifacts appearing as extra “humps” in the MAP, data acceptable for MAP analysis were derived only from stable recordings, which were judged on the basis of: (1) constant amplitude, morphology, and stable resting membrane potential at control, during magnesium infusion alone, and during each cesium injection, (2) isoelectric phase 4 with no suggestion of afterdepolarizations during control, during magnesium infusion alone, or immediately before each cesium injection, (3) stable amplitude of phase 2 exceeding 10 mV during control and before each cesium injection, (4) appearance of an interruption in the smooth repolarization contour during phase 3 of the MAP within 30 to 60 sec of the cesium injection without a shift in catheter position (EAD, figures 1 and 2), and (5) attenuation of EAD amplitude at rapid rates and amplification at slow rates (unlikely changes if due to motion artifact). The amplitude of the MAP was defined as the difference between phase 2 and the maximum diastolic potential during phase 4.4,6 The amplitude of the EAD was determined in the same manner as for EADs obtained from transmembrane recordings and was defined as the potential difference between phase 4 and the first deviation from the smooth contour during phase 3 repolarization (figure 1).4,6 A second deviation occasion-
blood samples were obtained before each cesium injection to determine serum magnesium concentration.

Control dogs. To assess the possible cumulative effects of repeated injections of cesium, the amplitude of EADs and the incidence of ventricular tachyarrhythmias were determined in four dogs that received cesium injections according to the same time course and doses noted above for the study group. However, these dogs did not receive MgSO₄ infusions.

Definitions. In the present study, ventricular tachyarrhythmias were defined as follows: (1) Nonsustained ventricular tachycardia: Three or more consecutive premature ventricular complexes at a cycle length of 300 msec or less and terminating spontaneously within 25 sec. (2) Sustained monomorphic ventricular tachycardia: Regular repetitive ventricular complexes having similar morphologies and lasting 25 sec or more at a cycle length of 300 msec or less. (3) Torsades de pointes: Sustained ventricular tachycardia as defined above associated with a prolonged QT interval and having the typical QRS contour of twisting about an axis. (4) Ventricular fibrillation: Disorganized, rapid, irregular ventricular complexes with changing contours resulting in absence of systemic arterial pressure and requiring immediate defibrillating shock for termination.

In vitro experimental protocol. Hearts were excised rapidly from dogs anesthetized with secobarbital sodium (30 mg/kg iv). Unbranched free-running false tendons were removed and quickly mounted in a Lucite tissue bath chamber and superfused at a rate of approximately 10 to 15 ml/min with Tyrode’s solution gassed with 95% O₂ and 5% CO₂ and maintained at 37.0 ± 0.5°C and pH 7.35 ± 0.05. The composition of the Tyrode’s solution was (in mM): MgCl₂ 0.7, NaH₂PO₄ 0.9, CaCl₂ 2.0, NaCl 124.0, NaHCO₃ 24.0, KCl 4.0, and glucose 5.5. The false tendon was driven with a Teflon-coated platinum bipolar electrode, with a 2.0 msec stimulus 1.5 times late diastolic threshold. By conventional recording techniques, glass microelectrodes filled with 3M KCl (direct-current resistance 10 to 30 MΩ) were used to record transmembrane potentials. Recordings were displayed on a storage oscilloscope from which they were photographed.

Fibers were superfused with normal Tyrode’s solution and paced at a cycle length of 400 msec for a 60 to 120 minute period of stabilization. At that point, the superfusate was switched to 5 mM (three preparations) or 12 mM (one preparation) cesium chloride dissolved in 2.7 mM KCl Tyrode’s solution. When EADs appeared and were stable, MgCl₂ (5 to 7 mM) was added to the low-potassium Tyrode’s-cesium superfusate and continued for 10 min. Superfusion with the low-potassium Tyrode’s-cesium solution was then resumed, and the MgCl₂ was washed out.

Data analysis. Data are expressed as the mean ± SE. Mean values were compared by an analysis of variance for repeated measures. Multiple comparisons were made with the t test modified by the Bonferroni method. Comparisons of paired mean values were analyzed with the paired t test. McNemar’s chi-square test for matched pairs was used to compare the frequency of ventricular tachyarrhythmia induction. A p < .05 was considered indicative of a statistically significant difference.

Results

Effects of cesium on MAPs, QT interval, and ventricular tachyarrhythmias

Study dogs. MAPs recorded from 11 of 18 dogs were analyzed. Data from the remaining seven dogs were not used for the analysis of MAPs either because of premature death before protocol completion or technical difficulties resulting in the failure to obtain satisfactory stable MAP recordings (see earlier criteria) at all phases of the experiment. Control MAP amplitudes ranged from 11.4 to 26.8 mV (mean 17.2 ± 1.1 mV). No EADs were observed in these baseline recordings.

A delay in phase 3 repolarization (figure 2) occurred in all experiments during cesium chloride injections made before and 1 to 2 hr after the infusion of MgSO₄. The mean amplitude of the cesium-induced EAD before infusion of magnesium was 8.2 ± 0.8 mV and the mean amplitude of the MAP was 16.6 ± 1.6 mV (EAD 49.7 ± 1.6% of MAP amplitude). One to two hours after terminating the magnesium infusion, the mean amplitude of the EAD was 7.6 ± 0.6 mV and the mean amplitude of the MAP was 16.1 ± 0.8 mV (EAD 48.0 ± 4.0% of MAP amplitude).

QT interval. Cesium injected before magnesium infusion lengthened the QT interval from 202 ± 12 (control) to 248 ± 11 msec (p < .003). When cesium was injected 1 to 2 hr after the termination of the magnesium infusion, the QT interval increased from 240 ± 7 msec (control 1 to 2 hr after stopping the magnesium infusion) to 256 ± 13 msec (p < .003). Before magne-
cesium infusion, cesium increased the QTc to 387 ± 14 msec from a control value of 338 ± 16 msec (p<.003). One to two hours after stopping the magnesium infusion, the QTc was lengthened from 347 ± 14 (control) to 406 ± 16 msec (p<.003). Cesium increased the RR interval from a control value of 361 ± 23 to 409 ± 18 msec before magnesium infusion and to 400 ± 19 msec 1 to 2 hr after stopping the infusion.

Ventricular tachyarrhythmias. After the administration of cesium chloride (range 168 to 672 mg/kg; mean 390 mg/kg) before magnesium infusion, ventricular tachyarrhythmias appeared in 16 of 18 dogs. Of these animals, 10 developed sustained ventricular tachycardia (mean cycle length = 227 ± 5 msec) and six developed ventricular fibrillation. One dog developed sinus arrest and one dog maintained normal sinus rhythm without developing a ventricular tachyarrhythmia. Figure 3 shows the arrhythmias that developed in each dog after cesium injection before, during, and 1 to 2 hr after stopping magnesium infusion. Only the 13 dogs that lived to receive the magnesium infusion are represented. Eleven of these dogs survived to receive another cesium injection 1 to 2 hr after termination of the magnesium infusion. Of these 11 animals, four developed ventricular fibrillation, two developed sustained ventricular tachycardia, two developed torsades de pointes, and three developed nonsustained ventricular tachycardia. In all cases in which a ventricular tachyarrhythmia developed, prominent EADs appeared in the MAP tracing within 20 sec after the injection of cesium chloride and gradually disappeared within 10 min after the termination of the tachyarrhythmia. In addition to the arrhythmias noted above, there were 17 episodes of persistent (> 1 min) ventricular bigeminy, five episodes of atrial quiescence, and four episodes of third-degree atrioventricular block when cesium was administered before or 1 to 2 hr after stopping the magnesium infusion. Periods of sinus arrest (> 2 sec duration) occurred just before the onset of tachyarrhythmias in all experiments and all arrhythmias developed spontaneously.

Control dogs. The amplitude of the EADs and the prevalence and the type of ventricular tachyarrhythmia did not change over time with repeated doses of cesium chloride (table 1, p = .7).

Effects of magnesium on cesium-induced EADs, QT prolongation, and ventricular tachyarrhythmias. Magnesium was administered to 13 dogs. Two of these dogs developed severe systemic hypotension and cardiac arrest during the cesium injection at the time of the magnesium infusion. Data from these dogs were excluded from the MAP and QT interval analyses. In the 11 dogs used for MAP analysis, cesium injected during magnesium infusion resulted in EADs with significantly smaller amplitudes compared with cesium injected before or after termination of the magnesium infusion: EAD = 5.5 ± 0.7 mV, MAP 18.4 ± 0.5 mV, EAD 31.2 ± 3.8% of MAP amplitude (p<.002). Figure 4 demonstrates tracings from one representative experiment in which a prominent cesium-induced EAD developed before (panel B) and 1 to 2 hr after magnesium infusion (panel D), but was significantly decreased in the presence of magnesium (panel C). Cesium injected during magnesium infusion prolonged the QT interval to 247 ± 7 msec (p<.003), but the RR interval also lengthened from 402 ± 19 (control with magnesium alone) to 472 ± 37 msec (p<.03). The QTc interval was significantly shorter (356 ± 12 msec, p<.003) when compared with values obtained during all other cesium injections.

Cesium injected during magnesium infusion in-

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**FIGURE 3.** Descriptive classification of ventricular tachyarrhythmias (ordinate) induced by cesium injections (abscissa). All points within any one arrhythmia classification are the same arrhythmia. Each plot represents the progression of one dog through the experimental protocol. Only dogs that survived to receive the magnesium infusion are represented. Two dogs (*) died after the cesium injection during magnesium infusion. Two dogs developed torsades de pointes during the cesium injection 1 to 2 hr after the magnesium infusion was stopped, but are not differentiated in this figure from those that developed SVT. No VT = no ventricular tachycardia; NSVT = nonsustained VT; SVT = sustained VT; VF = ventricular fibrillation.
produced sustained ventricular tachycardia in three dogs, nonsustained ventricular tachycardia in four dogs, and no tachyarrhythmia in six dogs (figure 3). Ventricular bigeminy and atrial quiescence occurred during this intervention in only two dogs.

The serum magnesium concentration significantly increased during the magnesium infusion from a control value of 1.8 ± 0.1 to 5.2 ± 0.5 mg/dl (p<.002). Serum magnesium concentration decreased 1 hr after stopping the infusion to 3.5 ± 0.3 mg/dl (p<.01). In four of the 11 dogs studied, repeated magnesium infusions were necessary to prevent cesium-induced tachyarrhythmias. Three of the animals required one additional infusion and one animal required two additional infusions. In these dogs, the serum magnesium levels increased from 4.1 ± 0.4 mg/dl after the first infusion to 5.5 ± 0.5 mg/dl after the final infusion (p<.05).

Experimental observations in vitro. In two preparations, 5 mM cesium induced one EAD that reached threshold after each action potential. In two preparations, 5 or 12 mM cesium induced EADs that frequently were followed by four to five regenerative responses (figure 5). MgCl₂, 5 mM in two preparations and 7 mM in two preparations, eliminated all EADs that reached threshold. MgCl₂ entirely suppressed all EADs in three preparations and reduced their amplitude, similar to the results in vivo, in one preparation. Suppression of EADs resulted within 5 min in three and within 15 min in one preparation and was reversible within 5 min of MgCl₂ washout.

Discussion

Major findings. The present study confirms previous observations that cesium given in vivo induces EADs, QT prolongation, and ventricular tachyarrhythmias

| TABLE 1 |
| Control dogs |
| VT prevalence (%) | Time (min) |
| VTNS | 0 | 30 | 60 | 120 | 180 | 210 |
| 25 | 50 | 50 | 50 | 75 | 75 |
| VTS | 25 | 0 | 50 | 50 | 25 | 0 |
| VF | 25 | 25 | 0 | 0 | 0 | 0 |
| Total | 75 | 75 | 100 | 100 | 100 | 75 |
| EAD amplitude (% MAP) | 33.1±11.5 | 35.0±11.6 | 30.4±5.9 | 35.9±6.9 | 36.7±6.8 | 36.9±4.0 |

VTA = ventricular tachyarrhythmias; VTNS = nonsustained ventricular tachycardia; VTS = sustained VT; VF = ventricular fibrillation.

FIGURE 4. Changes in MAP morphology during each intervention from one representative experiment. A, Normal MAP morphology recorded during control. B, The presence of a prominent EAD 20 sec after the injection of cesium chloride. Note the apparent prolongation of phase 2 in the MAP and the lengthened QT interval on the surface electrocardiogram. C, Recorded during cesium injection in the presence of magnesium. The EAD amplitude was greatly reduced and the QTc interval was significantly shortened. D, The return of prominent EADs when cesium chloride was injected 1 hr after stopping the magnesium infusion. Note also the early arrhythmogenic effects of cesium 20 sec after injection. Paper speed = 50 mm/sec; time lines = 1 sec intervals; 0 = 0 mV; 5 = 5 mV.
that may be due to triggered activity.\textsuperscript{4, 6} The new observation is that, in the presence of magnesium, the cesium-induced EADs, prolonged QTc interval, and triggered ventricular tachyarrhythmia were significantly diminished or suppressed. This observation provides support for the use of magnesium to treat torsades de pointes and other ventricular tachyarrhythmias accompanying the acquired long QT syndrome in patients. It also furnishes evidence consistent with the hypothesis that these ventricular tachyarrhythmias are caused by EADs and that suppression of the EADs eliminates the ventricular tachyarrhythmias.

Whether EADs actually are responsible for the ventricular tachyarrhythmias can only be inferred from previous studies because the EADs were not “manipulated,” i.e., increased or decreased, to demonstrate a causal relation to ventricular arrhythmias. While it is possible that in the present study cesium-induced ventricular tachycardia was causally unrelated to cesium-induced EADs and that magnesium suppressed both independently, in view of the data obtained in vivo and in vitro, the logic is compelling that magnesium suppressed cesium-induced EADs that were responsible for the ventricular arrhythmia. Extrapolating further, this study also supports the concept that some forms of the acquired long QT syndrome and torsades de pointes are caused by EADs.\textsuperscript{4-9} Naturally, this conclusion must be tempered by recognition of the potential problems of applying data gained from animal experiments to the clinical situation.

**Effects of magnesium on cesium-induced EADs.** Cesium chloride injected before and 1 to 2 hr after termination of the magnesium infusion elicited prominent EADs (figures 1, 2, and 4) and ventricular tachyarrhythmias in all but one animal (figure 3). In the absence of magnesium, the amplitude of the EAD gradually increased in size until ventricular ectopic activity developed.\textsuperscript{4} When magnesium was given as a 20 to 30 min infusion, cesium-induced tachyarrhythmias were suppressed and the EAD amplitude was significantly decreased. This observation supports the previous correlation of EADs and triggered activity.\textsuperscript{4-9} Magnesium may not totally abolish the EAD. However, if its amplitude is reduced sufficiently, it may not reach threshold to produce a regenerative, propagating response. Other mechanisms of action for magnesium cannot be excluded, however. Stable EADs were maintained in vitro. In that setting, MgCl\textsubscript{2} reversibly suppressed the EADs within minutes.\textsuperscript{17}

An important characteristic of EADs is that they are potentiated by long cycle lengths.\textsuperscript{4-7} In this study, the cycle length was significantly increased when cesium was injected during the infusion of magnesium. Hence, it would be expected that the EAD amplitude would be increased during this intervention. Our data demonstrate that, despite the long cycle length favorable to developing EADs with increased amplitudes, the opposite resulted. This observation eliminates the possibility that magnesium suppression of EADs is a rate-related phenomenon.

**Experimental considerations.** Maintaining the position of the contact electrode catheter was sometimes difficult under the present experimental conditions. To replicate the clinical situation as closely as possible, particularly the characteristic cycle length changes preceding the spontaneous onset of torsades de pointes, we did not attempt to maintain a constant cycle length with atrial or ventricular pacing, as we ordinarily would. Cesium induced periods of sinus arrest, just before the onset of the tachyarrhythmia, during which the heart often dilated. During two experiments, these periods were sufficiently long to cause the electrode catheter to lose contact with the ventricular endocardial surface and prevent MAP recordings.
We did not record MAPs from the left ventricle. However, because cesium was injected intravenously, EADs should have occurred throughout both ventricles and probably would have been detected at virtually any position of contact between the electrode and the ventricular endocardium. Cesium induced well-defined EADs in all experiments in which acceptable MAP recordings could be made. The EAD and MAP amplitudes recorded from the right ventricular endocardium in the present study were comparable to those recorded from the left ventricular endocardium in a previous report. In a separate study we have shown that the amplitude of MAPs recorded simultaneously from the right and left ventricular endocardium are also comparable. Thus, the right ventricular recording was probably appropriate and sufficient for the present study. We cannot be certain that the EAD recorded was the particular EAD that gave rise to ventricular tachyarrhythmia since we could not tell whether the electrode tip was in the exact location of the ectopic focus. Also, using an extracellular recording technique, we could not eliminate the compounding variable of electrotonus, effects of reflection, summating action potentials, and the like. Yet, it is likely that the events recorded at any position along the endocardium were representative of other areas of the heart tissue, including the site of the ectopic focus.

We also cannot be absolutely certain of the mechanism responsible for the ventricular tachyarrhythmia. While the circumstantial evidence suggests that the EADs gave rise to triggered events leading to the arrhythmia, since these mechanisms are only incompletely worked out in vitro, results in vivo obtained by the extracellular recording technique are less definitive. The arrhythmia may be due to sustained rapid EADs, oscillatory potentials triggered by the first EAD, reentry resulting from the electrical heterogeneity caused by the EADs, or other mechanisms.

The actual amplitude of the potential at which the EADs occurred could not be determined accurately for technical reasons. The amplitude of the MAP varied from dog to dog and between interventions in the same dog. The degree to which the electrode catheter tip made contact with the endocardial surface was the primary factor contributing to this variation. We found no method of maintaining the same endocardial contact pressure from one recording to the next. Also, the control MAP decreased slightly in amplitude over a period of 1 min from the time of initial electrode positioning before reaching a stable amplitude exceeding 10 mV. We attributed this change to variations in the degree of injury created by the electrode tip in contact with the endocardial surface. Initial injury was probably different from chronic injury. Therefore, we used the amplitude of the EAD relative to the corresponding MAP amplitude for analysis. This seemed to be an acceptable method of analysis since the MAP amplitudes remained stable and greater than 10 mV and EADs remained a constant percentage of the MAP amplitude during the course of cesium injection.

**Mechanisms.** EADs may result when an inward depolarizing current exceeds an outward repolarizing current during phase 2 or 3 of the cardiac action potential. Interventions that increase the former and/or decrease the latter should facilitate EAD development. Cesium, which reduces potassium conductance, has been used to induce EADs. The mechanism by which magnesium suppresses the EADs and ventricular arrhythmias is unknown. Magnesium at a concentration of 6.3 mM tends to increase action potential duration in rabbit ventricular myocardium in vitro, an effect that theoretically should be more conducive to EAD development. In isolated rabbit hearts, magnesium did not alter the duration of the action potential or the QT interval unless calcium was omitted or was significantly reduced in the perfusate. Magnesium (2 to 7 mM) slightly shortened action potential duration at 50% repolarization in isolated canine Purkinje fibers and suppressed EADs by possibly reducing the sodium window current. In humans, magnesium in doses sufficient to raise serum levels to 5.4 ± 0.4 mg/dL does not change atrial or ventricular refractory periods or the QT or QTc intervals during sinus rhythm, even in patients with torsade de pointes. One possible effect of magnesium might be to increase intracellular potassium by affecting the Na-K-ATPase, a change that might increase potassium conductance and the outward repolarizing current. Increasing the latter would suppress EADs and the associated ventricular tachyarrhythmia. Magnesium also may block the inward current(s), such as the slow inward current, that may be responsible for the EADs.

**Clinical relevance.** The results of this study support the hypothesis that EADs prolong the QT interval and cause ventricular tachyarrhythmias. Magnesium attenuates the amplitude of the EADs and suppresses the ventricular arrhythmias. While the clinical parallels are obvious, EADs have only been reported in man infrequently. The present data suggest that MAP recordings be performed more frequently during electrophysiologic studies in patients, particularly when a long QT interval is present or suspected.

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