THE EFFECT OF SLOW RELEASING ORAL MAGNESIUM CHLORIDE ON THE QT_c INTERVAL OF THE ELECTROCARDIOGRAM DURING OPEN HEART SURGERY

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ABSTRACT

Recent work in both animal and human studies emphasizes the value of magnesium in the maintenance of the functional and structural integrity of cardiac muscle. Both intracellular and extracellular magnesium concentrations can vary independently and the serum and red cell magnesium levels may not give an accurate account of intracellular cardiac magnesium deficiency. However, electrocardiographic studies of magnesium levels could provide an accurate index of intracellular cardiac magnesium levels.

Twenty-four patients scheduled electively for mitral valve replacement were studied to evaluate the effect of slow releasing oral magnesium chloride on the QT_c interval of the electrocardiogram. Although pretreatment QT_c values in all patients were not significantly different, there was a highly significant difference between the control group and the treatment group after four days of preoperative treatment with oral magnesium chloride. During the postoperative phase of the trial, all patients developed a similar pattern of increase in QT_c interval, reaching a peak at the end of the second day and followed by a decrease over the final two days. All patients who developed arrhythmias postoperatively had not been pretreated (primed) with oral magnesium chloride and had abnormal QT_c intervals both before and after operation.

The results of this study demonstrate the usefulness of oral magnesium chloride in reducing the QT_c interval of the electrocardiogram and so protecting the myocardium against possible arrhythmias.

KEY WORDS: HEART, electrocardiogram, QT_c interval, magnesium.

RECENT WORK in both animal[1-3] and human studies[4-7] emphasizes the value of magnesium in the maintenance of the functional and structural integrity of cardiac muscle. Intracellular and extracellular magnesium concentrations can vary independently and a deficit in one compartment may not be accompanied by a significant change in the other.[8] The assessment of the serum magnesium is therefore not a true and reliable index of the intracellular magnesium level. Furthermore, the exchange of magnesium ions occurs much more rapidly in heart muscle than in other tissues.[9]

The QT_c interval of the electrocardiogram represents the total duration of ventricular systole and should not exceed 0.42 seconds in men and 0.43 seconds in women.[10] A prolonged QT_c interval results from delayed repolarization of the ventricular myocardium. It is during this period that the patient is highly vulnerable to cardiac arrhythmias with myocardial infarction and death.[11]. It has been predicted that certain individuals with congenitally prolonged QT_c intervals are at increased risk of fatal ventricular fibrillation when conditions causing hypoxia or sympathetic discharge occur[16] Based on measurement of the QT_c intervals and clinical observations during magnesium therapy for anxiety states,[11] it was decided to study the effects of slow releasing oral magnesium chloride on the electrocardiogram during cardiopulmonary bypass procedures.

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METHODS

Twenty-four patients ranging in age from 14 to 58 years scheduled electively for mitral valve replacement utilizing cardiopulmonary bypass were selected to participate in the study. All patients had been using some type of diuretic agent and had been digitalized for at least two months before operation. All patients had not

been taking magnesium-containing drugs for the same period of time. It was not necessary to administer diuretics or to digitialize any of the patients during the immediate preoperative period. Informed consent and institutional approval were obtained for all patients participating in the investigation. Upon hospitalization baseline electrocardiographic studies and a full blood count were done, and serum electrolytes were determined on all 24 patients. The rate and rhythm of all preoperative electrocardiographic tracings were normal. The average preoperative QT_c interval of the electrocardiogram for all patients was 0.425 seconds with a standard deviation of 0.025 seconds. The patients were then randomly assigned to one of two treatment arms: Group I (treatment): patients who received oral magnesium tablets for four days preoperatively. Each tablet contained 535 mg $MgCl_2 \cdot 6H_2O$. The oral dosage was 80mg per kilogram body weight. Group II (control): patients who received oral placebo tablets identical in size, shape, and colour to the magnesium chloride tables. The tablets were administered to the patients from coded bottles by the nursing staff and at the beginning of the fifth day, open heart surgery was done. All patients were premedicated using morphine 0.1 $mg \cdot kg^{-1}$ and atropine 0.05 $mg \cdot kg^{-1}$. Anaesthesia was induced using thiopentone sodium and neuromuscular blockade attained using succinylcholine 1.5 $mg \cdot kg^{-1}$. Following tracheal intubation ventilation was controlled to maintain Pa_{CO_2} of 4.66–5.32 kPa (35–40 torr). Anaesthesia was maintained with a mixture of nitrous oxide and oxygen (50:50), pancuronium 0.1 $mg \cdot kg^{-1}$ and morphine sulphate 0.15 $mg \cdot kg^{-1}$ increments intravenously.

During cardiopulmonary bypass the composition of the pump priming solution was two units of fresh blood and one unit of plasmalyte B (1000 ml). Plasmalyte B is a balanced solution of electrolytes containing sodium 130 mmol per litre, potassium 4 mmol per litre, bicarbonate 28 mmol per litre, and the pH of solution is 7.4. The exact composition of cardioplegic solution was the same in all cases and consisted of 1000 ml of plasmalyte B to which was added 30 mmol potassium, 16 ml 50 per cent dextrose, 2.5 ml sodium bicarbonate 8.4% solution, 1.0 ml calcium chloride 10% solution, 500 mg solumedrol. The osmolarity of the solution was approximately 330 and the pH was 7.38. All patients were cooled to 28°C during bypass.

Immediately after operation electrocardiographic studies were made and the QT_c intervals were measured for four consecutive postoperative days. Any arrhythmias that occurred during the postoperative phases were also noted and recorded.

Groups I and II were compared for the average per patient change in QT_c interval from initial admission to the time just before the operation four days later, using a paired t-test. The comparison of postoperative QT_c interval changes was done using repeated measure analysis of variance techniques. Finally, if enough arrhythmias occurred during the trial, a comparison of this subgroup of patients with the arrhythmia-free group of patients was made.

Results

After the allocation of patients to Group I (treatment) and Group II (control) was made, average pretreatment QT_c intervals $\pm$ one standard deviation were: Group I: 0.428 ± 0.026 and Group II: 0.422 ± 0.024. These were not significantly different.

At the end of the four day preoperative treatment, those patients on oral magnesium chloride had an average decrease in QT_c interval of 0.0279 seconds. The untreated control patients had an average increase in QT_c interval of + 0.0076 seconds. This difference in the average change was statistically significant ($t = 7.15$ $p < 0.001$). (Figure 1).

During the postoperative phase of the trial, all patients had a similar pattern of a rise in the QT_c interval during the first two postoperative days, followed by a decrease in the last two days of observation. This pattern is shown in Figure 1, and can be represented mathematically by a quadratic function. Using least squares a quadratic equation was fitted to both the treated groups and to the control group. A plot of the two fitted equations shows them parallel, with the distance between them indicating the effect of oral magnesium chloride priming on the QT_c interval. This difference was 0.0293 seconds QT_c interval less for the treated group during the four postoperative days. This was statistically significant ($p < 0.01$).

Figure 2 shows the patterns in QT_c intervals for the two control groups and the treated group. Again, the patterns are almost identical and the same general quadratic function described previously holds here as well. Thus, once the preoperative QT_c level has been established, the QT_c response curves for the three groups are

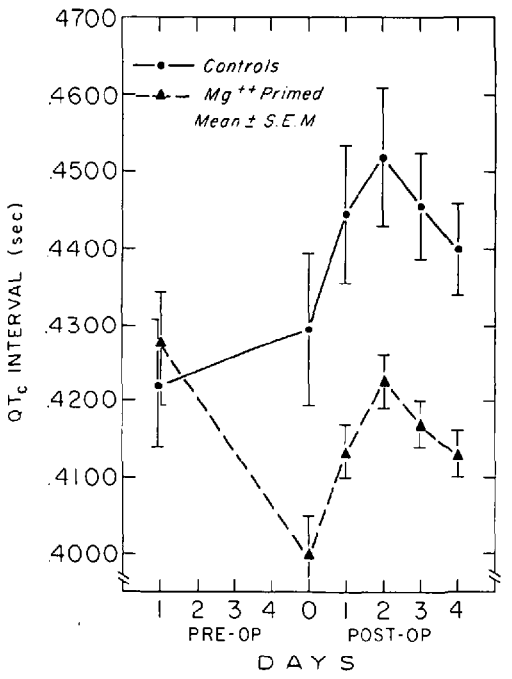

FIGURE 1 Comparison of QT_c intervals in control and treated groups.
● = controls.
▲ = Mg^{++} primed.

quadratic and parallel. Using repeated measures ANOVA, the F for parallelism was F (4, 12) = 0.76 (N.S.).

Five patients developed arrhythmias postoperatively. Three developed ventricular extrasystoles, one a bigeminal rhythm and one paroxysmal atrial tachycardia. All five of these patients were on the control arm of the trial. Retrospectively, a re-analysis of the data was done by dividing Group II (control) into two groups, controls with dysrhythmias and controls without dysrhythmias. Table I shows the preoperative changes in QT_c intervals for all three groups (the two control groups and the treated groups). While the change in QT_c interval was larger for those in the control who developed DYS; i.e. + 0.0132, compared to those in the control who did not develop DYS; i.e. = 0.0036, statistically they were not significantly different ($t = 1.38$, $p > 0.15$).

DISCUSSION

Magnesium is involved in normal mitochondrial contraction with the formation of the magnesium-ATP complex which is the true substrate

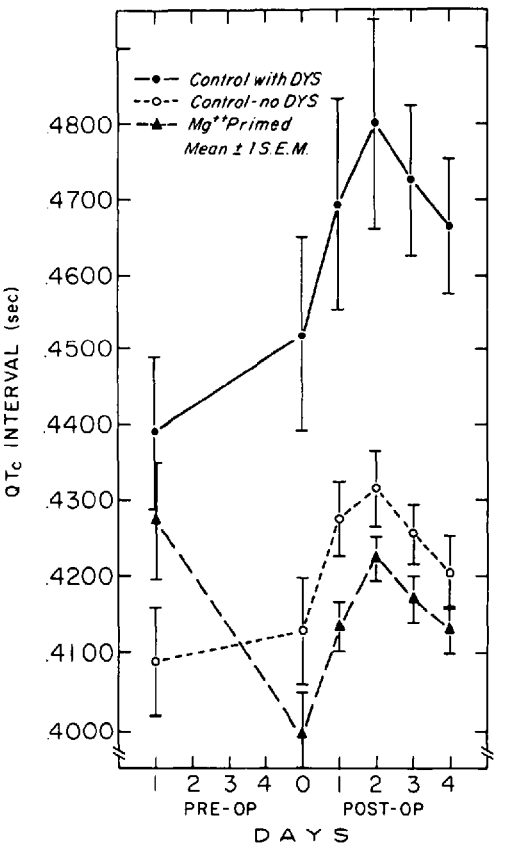

FIGURE 2 Comparison of QT_c intervals in controls with dysrhythmias, controls with no dysrhythmias and treated group.
● = control with dysrhythmias.
○ = control with no dysrhythmias.
▲ = Mg^{++} primed.

for all reactions involving ATP[14]. Magnesium also affects the sodium-potassium ATPase of heart membranes, and activates adenyl cyclase in heart muscle.[15] With depletion of cardiac magnesium as a result of ischaemia, anoxia or the administration of cardiotoxic drugs, ATPase becomes inactivated and oxidative phosphorylation is inhibited. Cellular potassium efflux and sodium influx takes place and mitochondrial swelling occurs, ultimately resulting in myocardial fibre necrosis.[11–13] Magnesium is thus vital in the maintenance of mitochondrial integrity and in the retention of myocardial potassium. Several factors may contribute to the postoperative fall in magnesium levels and the development of arrhythmias in patients undergoing open heart surgery using cardiopulmonary bypass. These include a preoperative magnesium deficiency in

TABLE I
QT_c INTERVAL CHANGES PREOPERATIVELY
(Mean ± S.E.M.)

Group	Pre-Mg Level	Post-Mg Pre-op Level	Average Change
Control with DYS (n = 5)	0.4390 ± 0.0098	0.4522 ± 0.0127	+0.0132 ± 0.0036
Control without DYS (n = 7)	0.4090 ± 0.0068	0.4126 ± 0.0069	+0.0036 ± 0.0008
Treated (Primed) with Mg (n = 12)	0.4275 ± 0.0076	0.3996 ± 0.0047	−0.0279 ± 0.0045

DYS = dysrhythmia.

patients with cardiac pathology, anaesthesia using artificial ventilation with hyperventilation, haemodilution, acid-base disturbances, duration of perfusion, and the use of drugs. The careful monitoring of intracellular magnesium levels is thus of prime importance. The serum and red cell magnesium levels may not be an accurate reflection of intracellular cardiac magnesium deficiency. However, electrocardiographic studies could provide an accurate index of intracellular cardiac magnesium levels and can be a valuable way of detecting changes in the electrophysiological events in the myocardium during magnesium deficiency and magnesium therapy.

The effect of an enteric-coated slow releasing oral tablet of magnesium chloride on the QT_c interval during open heart surgery was interesting statistically. Although pretreatment QT_c values were not significantly different, there was a highly significant difference between the treatment and control groups following four days of oral magnesium chloride treatment in the preoperative period. It was also very interesting to note that during the postoperative phase of the trial, all patients developed a similar pattern of a rise in the QT_c interval, reaching a peak at the end of the second day, followed by a decrease over the next two days. Finally, it should be noted that all five patients who developed arrhythmias postoperatively had not been pretreated (primed) with oral magnesium chloride and that those patients had an abnormal QT_c interval both before and after operation.

The results of this study demonstrate the use of oral magnesium chloride in reducing the QT_c interval of the electrocardiogram and so protecting the myocardium against possible arrhythmias. The potential of prophylactic use of oral magnesium in heart disease is illustrated.

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RÉSUMÉ

Des études récentes effectuées chez l'homme et chez l'animal ont souligné le rôle important du magnésium dans le maintien de l'intégrité structurelle et fonctionnelle du muscle cardiaque. Comme les concentrations intra et extra-cellulaires du magnésium peuvent varier de façon indépendante, les déterminations dex taux de magnésium dans les globules rouges et dans le sérum peuvent ne pas révéler des déficiences de cet ion dans la cellule myocardique. L'étude des modifications électrocardiographiques pourrait d'autre part fournir un index précis de la concentration de cet ion au niveau de la cellule myocardique.

Vingt quatre patients devant subir un remplacement valvulaire mitral ont fait l'objet d'une étude dont le but était d'évaluer l'influence d'une administration orale de chlorure de magnésium à libération lente sur la durée de l'intervalle QT_c de l'électrocardiogramme. Une différence hautement significative a été observée dans la durée de l'intervalle QT_c des malades ainsi traités au chlorure de magnésium pendant quatre jours avant la chirurgie par rapport à celle trouvée chez les patients non traités. Après l'intervention, la durée de l'intervalle QT_c s'est prolongée chez tous les patients, le maximum de prolongation survenant au deuxième jour post-opératoire pour ensuite se raccourcir durant les deux jours suivants. Tous les cas d'arythmie observés sont survenus chez des patients n'ayant pas reçu de chlorure de magnésium avant l'intervention et les intervalles QT_c de tous ces patients étaient anormaux avant et après la chirurgie.

Les résultats de ce travail démontrent que l'administration de chlorure de magnésium se traduit au niveau de l'électrocardiogramme par un raccourcissement de l'intervalle QT_c et contribue à prévenir des arythmies éventuelles.