Arrhythmogenic Threshold of the Myocardium under Conditions of Magnesium Deficiency

A. A. Spasov, I. N. Iezhitsa, M. V. Kharitonova, and N. A. Gurova

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 146, No. 7, pp. 69-71, July, 2008
Original article submitted June 6, 2007.

We studied the arrhythmogenic threshold of the myocardium after injection of $CaCl_2$ to magnesium-deficient rats receiving Mg^{2+} L-aspartate, $MgCl_2$, their combination with vitamin B_6, and reference preparations Magne B_6® and $MgSO_4$ until complete compensation of magnesium level in the plasma and erythrocytes. Magnesium-deficient diet and deionized water were used for inducing alimentary Mg^{2+} deficiency and modeling pathological changes in rats. After reducing Mg^{2+} level to 0.7 mmol/liter in the plasma and to 1.5 mmol/liter in erythrocytes, Mg L-aspartate, $MgCl_2$, their combination with vitamin B_6, as well as Mg^{2+} deficiency led to a decrease in the dose of $CaCl_2$ provoking heart rhythm disturbances in 50% animals and shortening of animal life span. Administration of the test magnesium salts increased the arrhythmogenic threshold; Mg^{2+} salts were comparable by their efficiency with Magne B_6® and were far superior to $MgSO_4$.

Key Words: *magnesium deficiency; arrhythmia; calcium chloride; magnesium; pyridoxine*

Antiarrhythmic effects of Mg^{2+} are used for the treatment of digitalis intoxication, vasospastic angina pectoris, and arrhythmias. Correction of Mg^{2+} deficiency (MD) eliminates rhythm disturbances in parenteral and/or peroral administration of Mg^{2+} salts.

The effect of various Mg^{2+} compounds such as $Mg(OH)_2$, MgO, $MgSO_4$ was evaluated in numerous experimental and clinical studies [4,7,8]. Holter monitoring showed that the incidence of ventricular and atrial arrhythmias in individuals with low blood Mg^{2+} content caused by insufficient alimentary Mg^{2+} intake is higher than in the group with normal Mg^{2+} content [6].

Mg^{2+} salts are characterized by different bioavailability [3]; combination of these salts with pyridoxine increases this parameter. Evaluation of the rate of compensation of alimentary MD with inorganic and organic Mg^{2+} salts [5] showed that Mg L-aspartate (MLA) and $MgCl_2$ are most effective organic and inorganic compounds, respectively. Intravenous administration under conditions of rhythm disturbances caused by $CaCl_2$, L-stereoisomer of Mg-aspartate was more effective than its DL- and D-stereoisomers [2].

The aim of the present study was to compare the effect of MLA, $MgCl_2$ and their combinations with vitamin B_6 on the course of $CaCl_2$-induced arrhythmias under conditions of alimentary MD.

MATERIALS AND METHODS

Experiments were carried out on 140 male Wistar rats weighing 170-250 g. Control animals (n=25) received magnesium-balanced diet. In other rats, alimentary MD was induced by magnesium-deficient diet (ICN Biomedicals Inc.). The rate and severity of hypomagnesiumemia was controlled by measuring the content of Mg^{2+} in the plasma and erythrocytes by the color reaction with titanium

Institute of Pharmacology; Department of Pharmacology, Volgograd State Medical University, Russia. ***Address for correspondence:*** farm@vlpost.ru. A. A. Spasov.

0007-4888/08/1461-0063

yellow (spectrophotometrically). After attaining medium-severe hypomagnesiumemia, the test magnesium salts MLA, $MgCl_2$, and their combination with vitamin B_6, and reference preparations Magne B_6® (Mg lactate with vitamin B_6) and $MgSO_4$ were administered *per os* in a dose of 50 mg Mg^{2+} per 1 kg body weight for 21 days until complete compensation of Mg^{2+} level in the plasma and erythrocytes. Vitamin B_6 was added to $MgCl_2$ and MLA in a dose of 5 mg/kg.

The values of compensation of Mg (X) deficiency was calculated by the formula:

$$X = \frac{C_{salt} - C_{diet}}{C_{intact} - C_{diet}} \times 100\%,$$

where C_{salt} is Mg^{2+} concentration in animals after administration of the salt, C_{diet} is Mg^{2+} concentration in animals receiving MD diet, and C_{intact} is Mg^{2+} concentration in intact animals.

Before the experiment, the animals were intraperitoneally narcotized with sodium ethaminal (40 mg/kg). The arrhythmogenic capacity of $CaCl_2$ was studied after its intraperitoneal injection of 10% solution in increasing doses. ECG in standard lead II was recorded using a medical oscilloscope OS2-01 and N-338-8 writter. Rhythm disturbances were controlled by changes in ECG waves. The dose of $CaCl_2$ (mg/kg) inducing arrhythmias in 50% animals (ATD_{50}) was calculated by probit analysis.

Prophylactic efficiency of Mg^{2+} salts after peroral treatment was evaluated by their capacity to prevent the development of arrhythmia, lengthen the arrhythmia latency and duration (from the appearance of arrhythmia to animal death), and lengthen animal survival time.

The data were processed statistically using one-way dispersion analysis and Dunkan test; regression analysis was also used.

RESULTS

Feeding MD for 7 weeks reduced Mg^{2+} content in the plasma (from 1.070±0.031 to 0.700±0.041 mmol/liter) and erythrocytes (from 1.900±0.031 to 1.04±0.024 mmol/liter). These changes were accompanied by body weight loss by 25% ($p<0.05$) and death of 32% animals in the MD group. Evaluation of proarrhythmogenic threshold for different $CaCl_2$ doses showed that ATD_{50} in MD rats was below the control value by 17.5% (Table 1).

Peroral treatment with magnesium salts restored the level of Mg^{2+} in the plasma and erythrocytes. The capacity to compensate MD in erythrocytes for the test salts decreases in the following order: MLA in combination with vitamin B_6 (151%)≥$MgCl_2$ in combination with vitamin B_6 (148%)>MLA (129%)≥ Magne B_6 (113%)≥$MgCl_2$ (105%)>$MgSO_4$ (97%). The concentration of Mg^{2+} in the plasma and erythrocytes did not exceed the upper boundaries of normal.

Compensation of MD was accompanied by an increase in the dose of $CaCl_2$ provoking heart rhythm disturbances (Table 1). MLA in combination with vitamin B_6, MLA, and $MgCl_2$ in combination with vitamin B_6 were most effective in reducing the proarrhythmogenic threshold of $CaCl_2$; $MgSO_4$ demonstrated minimum efficiency.

For evaluation of the nature and intensity of arrhythmia, we measured arrhythmia latency (from the moment of $CaCl_2$ administration) and duration. $CaCl_2$ in a dose of 170 mg/kg induced rhythm disturbances in most animals. In MD animals, the latency and duration of arrhythmia were shorter than in intact animals by 27 and 46%, respectively.

Peroral treatment with Mg^{2+} salts normalized these parameters. MLA in combination with vitamin B_6 was most effective in this respect and lengthened the time to arrhythmia by 95% (p=0.083).

MLA and $MgCl_2$ in combination with vitamin B_6 and MLA significantly prolonged the time of survival compared to MD animals. In groups receiving these salts this parameter surpassed the corresponding value in MD group by 85.38% (p=0.016), 70.54% (p=0.036), and 73.15% (p=0.032), respectively. MLA in combination with vitamin B_6 was more effective then $MgSO_4$ (p=0.041).

Thus, the decrease in arrhythmogenic threshold observed in our experiments agrees with published data. MD leads to a decrease in K^+ content in cardiomyocytes, increase the risk of ventricular arrhythmias, in particular extrasistoles and torsade de pointes tachycardia. Mg^{2+} can block slow inward Ca^{2+} current, which decreases the frequency of impulse generation by the sinus node, lengthen the time of atrioventricular conduction, and increases the time of its refractoriness. Apart from antagonism with Ca^{2+} ions, Mg^{2+} produces a membrane-stabilizing effect, prevents K^+ loss in cells, and interferes with sympathetic influences [1]. MLA alone and in combination with pyridoxine exhibited maximum activity. We previously demonstrated that MLA in intravenous administration more effectively prevents $CaCl_2$-induced arrhythmias than its D- and DL-stereoisomers [2] This can be explained by the fact that aspartate ion being a carrier of Mg^{2+} ions facilitates their transport into the intracellular space, while aspartate itself after entering the cell is integrated into cell metabolism. According to current

TABLE 1. Arrhythmogenic Threshold in Rats Receiving Peroral Mg^{2+} Preparations

Test preparation	ATD_{16}	ATD_{50}	ATD_{84}
Control	134.13 (129.88-138.52)	146.04 (141.41-150.83)	159.01 (153.97-164.22)
MD	108.51 (99.89-117.88)	120.56 (110.99-130.96)	133.95 (123.31-145.51)
MLA+vitamin B_6	137.55 (125.85-150.33)	162.17 (148.38-177.24)	181.39 (165.97-198.25)
$MgCl_2$+vitamin B_6	145.95 (133.31-159.78)	160.41 (146.52-175.61)	176.31 (161.04-193.04)
MLA	145.97 (130.71-163.02)	161.52 (144.63-180.38)	178.73 (160.04-199.60)
$MgCl_2$	144.85 (130.10-161.28)	155.85 (139.98-173.53)	167.69 (150.60-186.71)
Magne B_6®	145.81 (130.16-163.34)	156.22 (139.46-175.01)	167.38 (149.42-187.51)
$MgSO_4$	142.54 (129.04-157.45)	152.82 (138.35-168.81)	163.86 (148.34-181.00)

views on stereospecificity, L-isomers of amino acids are more actively assimilated and integrated into biochemical processes in human body.

Thus, we showed that Mg^{2+} level in the plasma and erythrocytes decreases on week 7 of MD diet. MD was associated with increased sensitivity of experimental animals to the arrhythmogenic effect of $CaCl_2$, which manifested in a decrease in the dose of $CaCl_2$ inducing arrhythmia in 50% animals and shortening of the latency and duration of arrhythmias. Prophylactic peroral treatment with Mg^{2+} salts compensated MD. The capacity to compensate MD in erythrocytes for the test salts decreases in the following order: MLA in combination with vitamin $B_6 \geq MgCl_2$ in combination with vitamin $B_6 >$ MLA$\geq$Magne $B_6 \geq MgCl_2 > MgSO_4$. Treatment with Mg^{2+} salts increased the arrhythmogenic dose of $CaCl_2$ and lengthened the latency and duration of arrhythmia. $MgCl_2$ and MLA alone and in combinations with pyridoxine were most effective by the majority of parameters, MLA was more effective than $MgSO_4$ and comparable to Magne B_6.

REFERENCES

1. A. A. Spasov, *Magnesium in Medical Practice* [in Russian], Volgograd (2000).
2. A. A. Spasov, I. N. Iezhitsa, N. V. Zhuravleva, *et al.*, *Kardiologiya*, **46**, No. 7, 62-65 (2006).
3. M. Firoz and M. Graber, *Magnes. Res.* **14**, No. 4, 257-262 (2001).
4. S. Ichikawa, *Jpn. J. Thorac. Cardiovasc. Surg.*, **46**, No. 3, 287-298 (1998).
5. I. N. Iezhitsa, A. A. Spasov, M. S. Kravchenko, *et al., J. Jpn. Soc. Magnes. Res.*, **25**, No. 2, 99 (2006).
6. L. M. Klevay and D. B. Milne, *Am. J. Clin. Nutr.*, **75**, No. 3, 550-554 (2002).
7. C. Meenagh, C. Mulholland, and M. F. Ryan, *J. Psychopharmacol.*, **8**, No. 3, 438-439 (2004).
8. A. Tsuji, K. Araki, K. Maeyama, and Ê. Hashimoto, *J. Cardiovasc. Pharmacol. Ther.,* **10**, No. 3, 205-208 (2005).