Correction of Furosemide-Induced Magnesium Deficiency with Different Stereoisomers of Organic Magnesium Salts: A Comparative Study

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We compared the efficiency of different stereoisomers of organic magnesium salts (Mg DL-, Mg D-, and Mg L-aspartate and Mg L- and Mg DL-glutamate) after oral administration under conditions of furosemide-induced magnesium deficiency. The time to complete compensation of erythrocyte magnesium level was 5 days for Mg L-aspartate, 10 and 8 days for Mg L-glutamate and Mg D-aspartate, respectively, and 11 days for Mg DL-aspartate and Mg DL-glutamate. These findings attest to better bioavailability of Mg complex with L-stereoisomer of aspartate in comparison with DL and D-stereoisomers and stereoisomers of Mg glutamate.

Key Words: *magnesium deficiency; furosemide; stereoisomers; magnesium aspartate; magnesium glutamate*

Loop diuretics are now widely used in clinical practice, particularly in the treatment of heart failure and essential hypertension. This group of drugs possesses wide therapeutic potential, but they promote loss of potassium and magnesium, which worsens the existing pathology [1]; therefore, correction of drug-induced magnesium deficiency is an urgent problem.

According to modern views on stereospecificity, L-isomers of amino acids are more effectively consumed and utilized in biochemical processes in human body [2].

The objective of this study was to investigate compensation rate of furosemide-induced magnesium deficiency by magnesium salts of different isomers of aspartic and glutamic acids.

MATERIALS AND METHODS

The experiments were carried out on white mongrel male rats (n=43) weighing 190-250 g. Group 1 (control) comprised intact animals. Group 2 rats received furosemide (30 mg/kg intraperitoneally, 1% solution; Polifarm) for 15 days, which led to moderate magnesium deficiency. Then, the animals received the test magnesium salts (orally throught a tube in dose of 50 mg of elementary magnesium per 1 kg of body weight; Fig. 1) for 11 days against the background of furosemide treatment. Blood samples for measurement of magnesium concentrations in blood plasma and erythrocytes were taken before the experiment, on days 8 and 15 of furosemide administration, and then on days 3, 7, and 11 of magnesium salt administration. The rate and magnitude of magnesium deficiency development were monitored spectrophotometrically by measuring magnesium levels in the plasma and red blood cells using color reaction with titanium yellow [3].

Magnitude of magnesium deficiency compensation (X) was estimated by the formula:

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

where C_{salt} is magnesium concentration in animals receiving magnesium salts; $C_{furosemide}$ is magnesium con-

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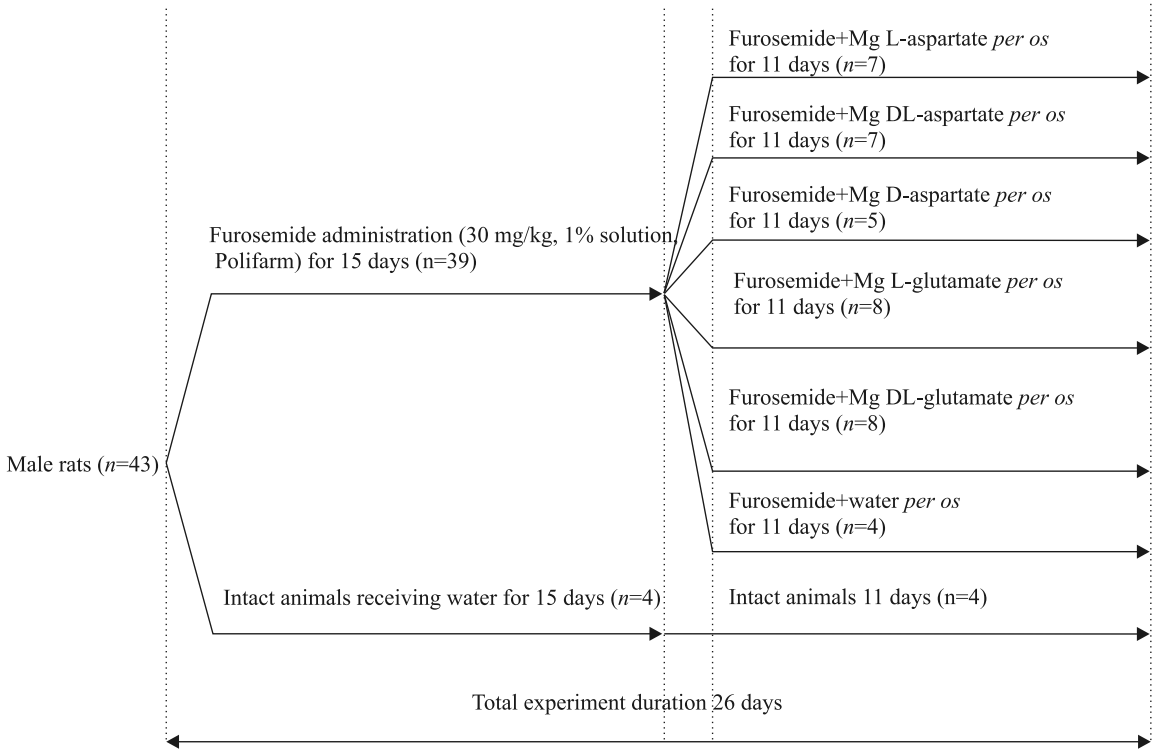

Fig. 1. Evaluation of compensation rate of furesemide-induced magnesium deficiency with stereoisomers of organic magnesium salts (scheme of experiment).

centration in animals receiving furosemide (30 mg/kg) alone; C_{intact} is magnesium concentration in intact controls.

The data were processed by one-way ANOVA and Scheffé's test using Statistica 6.0 software.

Averaged time (days) to compensation of magnesium deficiency in red blood cells and plasma of magnesium-deficient animals receiving magnesium salts was calculated using regression analysis.

RESULTS

On day 15 of the experiment, body weight decrease, sparse hair, and hyperemia of open body parts, *i.e.* sings of general dystrophy associated with magnesium deficiency were observed in animals treated with furosemide. Magnesium level in rats from this group decreased from 1.43±0.04 to 0.47±0.01 mmol/liter in blood plasma and from 2.07±0.04 to 1.10±0.02 mmol/liter in erythrocytes in comparison with the control group.

In furosemide intoxication, magnesium salts shifted the balance between renal magnesium losses and its income from external sources, which led to replenishment of its concentration in blood plasma and red blood cells (Fig. 2).

In addition, the time to complete compensation of magnesium deficiency calculated using regression analysis model, was 7 days for Mg L-aspartate group, 10 days for Mg D-aspartate groups, 11 days for Mg DL-aspartate group, and 13 days for Mg L-, DL-glutamate groups (Table 1).

Complete compensation of erythrocyte magnesium level was reached in Mg L-aspartate group on day 5; in animals receiving Mg L-glutamate and Mg

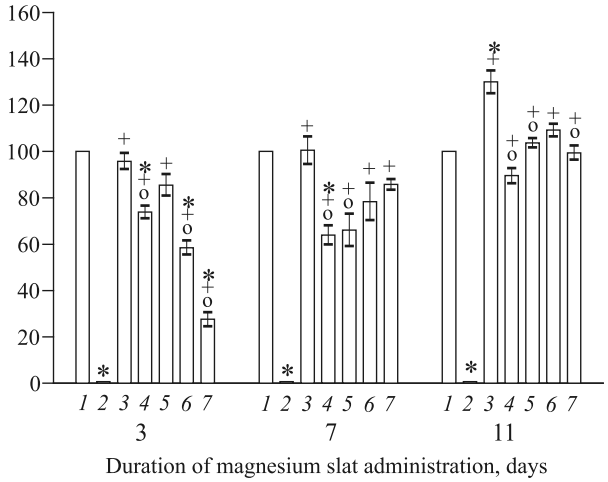

Fig. 2. Effects of organic magnesium salts on the magnitude of magnesium deficiency compensation (X) in erythrocytes under conditions of furosemide intoxication. Ordinate: changes in the percent of magnesium deficiency compensation (X) in erythrocytes. *1*) intact rats; *2*) furosemide; *3*) Mg L-aspartate; *4*) Mg DL- aspartate; *5*) Mg D-aspartate; *6*) Mg L-glutamate; *7*) Mg DL-glutamate. $p<0.05$ compared to: **1*, +*2*, °*3*.

TABLE 1. Averaged Times Magnesium Level Compensation in Erythrocytes and Blood Plasma in Animals Receiving Organic Magnesium Salts (50 mg of elementary magnesium per kg body weight) under Conditions of Furosemide-Induced Magnesium Deficiency

Agent	50% compensation level, days		100% compensation level, days	
	plasma	erythrocytes	plasma	erythrocytes
Mg L-aspartate	1.46 (0.90±2.37)	1.06 (0.64±1.75)	6.96 (4.28±11.32)	4.72 (2.86±7.79)
Mg DL- aspartate	2.74 (2.13±3.53)	3.36 (1.47±7.68)	10.67 (8.28±13.75)	10.82 (4.73±24.78)
Mg D- aspartate	3.77 (1.71±8.31)	4.12 (1.70±9.97)	9.02 (4.09±19.87)	7.26 (3.00±17.56)
Mg L-glutamate	1.75 (1.58±1.92)	2.79 (2.11±3.67)	13.56 (12.31±14.94)	9.56 (7.26±12.60)
Mg DL- glutamate	2.79 (2.16±3.60)	4.29 (3.66±5.03)	12.97 (10.05±16.73)	10.07 (8.58±11.80)

D-aspartate it was attained on days 10 and 8, respectively, and in animals receiving Mg DL-aspartate and Mg DL-glutamate on day 11 (Table 1). Thus, the level of the magnesium deficiency compensation on day 11 of administration of the test salts was maximum in animals treated with Mg L-aspartate. The animals receiving all other test salts, except Mg L-glutamate, lagged behind the leading group in terms of erythrocyte magnesium level (Fig. 2).

Different pharmacological activity of the stereoisomers can be explained by differences in compound entry into the body. These differences may be associated with peculiarities in the structure and functioning of biological membranes consisting of optically active, asymmetric material, as well as with the presence of special membrane systems responsible for transmembrane transport of metabolites [4]. Stereospecific transmembrane transport systems are known, which act in such a way that intracellular concentration of L-amino acids increases approximately 500-fold in comparison with their concentrations in extracellular space, whereas D-amino acids are not transported by these systems. In addition, D-amino acids entering the body are metabolized to α-oxo acids by D-amino acid oxidase (DAO) or D-aspartate oxidase [1]. L-amino acids acting as acid forming residue and being the endogenous compound will exhibit higher distribution and utilization rate in the body.

The use of L-aspartate, but not its racemate, as a chelating agent will contribute to better magnesium ion penetration into the intercellular space, and as a consequence, eliminate intracellular deficiency of these cations and associated heart rate disturbances. Seeming to support of this phenomenon, H. A. Nieper proposed the theory of mineral transporters, according to which L-aspartate promotes more rapid potassium and magnesium entry into the cell (compared to D-aspartate), and as a consequence, more rapidly restores the balance of these cations [5].

These findings attest to higher bioavailability of magnesium complex with L-stereoisomer of aspartate in comparison with DL and D-stereoisomers, as well as with stereoisomers of magnesium glutamate. Although ionization of magnesium salts occurs in the organism, it is possible that chelating agent plays an important role in the transport of this cation through biological barriers, along with such transporters as TRPM6 and TRPM7 [6], and L-aspariginate appears more effective in this respect.

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