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Use of magnesium oxide in hemodialysis patients

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It has been reported that long-term administration of magnesium oxide causes hypermagnesemia and therefore particular attention should be exercised in hemodialysis patients. However, few studies have examined the effect of magnesium oxide in hemodialysis patients. Here, we present 7 hemodialysis patients who maintained good bowel movements without any symptoms of hypermagnesemia by 1.5g of magnesium oxide per day. We examined the serum and erythrocyte magnesium levels in these patients. While the serum and erythrocyte magnesium levels were significantly high in these hemodialysis patients compared with those in hemodialysis patients and healthy subjects without taking magnesium oxide , no symptoms of hypermagnesemia such as hypotension and bradycardia were observed. Furthermore, the serum and erythrocyte magnesium levels were not tended to influence by the duration of drug use. The result suggests that administration of 1.5g of magnesium oxide per day to hemodialysis patients maintains good bowel movements without any symptoms of hypermagnesemia. However, serum potassium level was tended to elevate in 5 patients after taking 1.5g of magnesium oxide per day, which was significant in 3 of them. This finding demonstrated that the serum potassium level should be measured when magnesium oxide is administrated to hemodialysis patients because there is a possibility that the use of magnesium oxide induces hyperkalemia and can result in fatal arrhythmia in hemodialysis patients.

Keywords: Hemodialysis, Hyperkalemia, Laxatives, Magnesium oxide, Serum magnesium level,

INTRODUCTION

It is known that various complications occur in hemodialysis patients ; constipation is one such common complaint. As a protective measure, various laxatives have been used. However, bulk-forming laxatives and infiltrating laxatives are unsuitable for hemodialysis patients under fluid restrictions because these laxatives require a large volume of water, saline laxative causes hypermagnesemia[1] and saccharide laxative is cost prohibitive as it is not covered by medical insurance. Hemodialysis patients have difficulty controlling bowel movements. Our previous study on bowel movements in 142 outpatients on hemodialysis three times a week found that 69 of them took laxatives. Furthermore, more than 60 percent of the hemodialysis patients taking laxatives admitted that they abstained from taking a laxative on the day before hemodialysis even if they had constipation in order to avoid defecation during hemodialysis[2]. In these circumstances, we present 7 hemodialysis patients maintaining good bowel movements without any symptoms of hypermagnesemia by taking 1.5g of magnesium oxide per day. The Ministry of Health, Labour and Welfare alerted the possibility of occurrence of hypermagnesemia due to magnesium oxide in Pharmaceuticals and Medical Devices Safety Information[3]. Furthermore, it has been reported that

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administration of 3g of magnesium oxide per day to hemodialysis patients causes hypermagnesemia[1]. In this study, however, daily dosage of magnesium oxide is 1.5g, and very few studies concerning relationship between hemodialysis and magnesium oxide have been reported afterwards. We evaluated the effect of magnesium oxide in these hemodialysis patients in comparison with hemodialysis patients and healthy subjects without taking magnesium oxide.

METHODS

Subjects

We enrolled 7 hemodialysis outpatients taking 1.5g of magnesium oxide per day (HD-Mg group), 7 hemodialysis outpatients (HD group) and 7 healthy subjects (N group) without taking magnesium oxide. The study was conducted in accordance with the Declaration of Helsinki. Sanai Memorial Hospital' s Institutional Review Board approved the study design, and we explained the aim of the study and obtained written informed consent from all the subjects prior to the study.

Blood sampling point

Blood samples were collected pre-hemodialysis with a 2-day hemodialysis interval (Fig. 1).

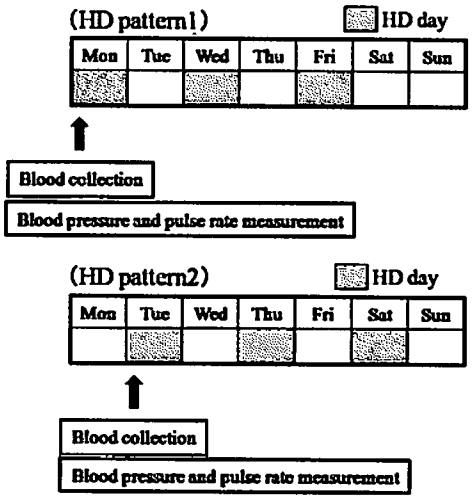


Fig.1 HD patterns, sampling days, blood pressure and pulse rate measurement days. HD, hemodialysis.

Methods

1. Bowel movement

Bowel movement data were recorded by patient interviews in HD-Mg group.

2. Changes in blood pressure and pulse rate after taking magnesium oxide

Blood pressure and pulse rate were recorded pre-hemodialysis with a 2-day hemodialysis interval (Fig.1) from patient charts in HD-Mg group. Mean blood pressure and pulse rate in 3 months before and after taking magnesium oxide were recorded in order to evaluate the effect of magnesium oxide on these parameters.

3. Serum magnesium level and erythrocyte magnesium level

The serum magnesium level was measured by the xylidyl blue method pre-hemodialysis on blood sampling days shown in Fig. 1. Erythrocyte magnesium level was measured from sampled blood in the same way as serum magnesium level. Sampled blood was washed three times with 0.9% saline solution after removal of blood plasma by the centrifugation (3000 rpm, 10 min) to obtain erythrocytes. Then, they were hemolyzed and measured by atomic absorption spectrometer (Hitachi High-Technologies Co., Tokyo, Japan). In addition, these levels were also measured 3 and 6 months after the first measurement in order to evaluate the effect of the duration of magnesium oxide use in HD-Mg group.

4. The ratio of intracellular and extracellular magnesium level

The ratio of intracellular and extracellular magnesium level was calculated by dividing the erythrocyte magnesium level by the serum magnesium level.

5. Changes in serum potassium level after taking magnesium oxide

Serum potassium level was measured by the ion selective electrode method pre-hemodialysis on sampling days shown in Fig.1 twice a month in HD-Mg group. Mean of that in 3 months before and after taking magnesium oxide was calculated in order to evaluate the effect of taking magnesium oxide on this parameter.

Statistical analysis

The data were expressed as mean ±SD. The statistical tests were performed using the Mann-Whitney U test and the ANOVA.

RESULTS

1. Bowel movement

Table 1 shows the characteristics of subjects. There were no significant differences in age or gender among the three groups. There was no significant difference in the duration of hemodialysis between HD group and HD-Mg group. The dialysate magnesium level was 1.2mg/dL in HD group and HD-Mg group.

The duration of magnesium oxide use was 6 to 44 months in HD-Mg group. Table 2 shows bowel movement conditions in HD-Mg group. All patients in HD-Mg group maintained a good bowel movement ; 3 of them took magnesium oxide only and the other 4 patients took magnesium oxide combined with large intestine stimulant laxative. Taking this laxative before bedtime facilitated good bowel movement following morning.

TABLE.1 Characteristics of the subjects

	N group (n=7)	HD group (n=7)	HD-Mg group (n=7)	P-value
Age (years) (mean±SD)	51~68 (61.0±6.55)	45~73 (63.3±8.86)	44~73 (61.7±10.21)	NS (p=0.88)
Gender Male	5	4	5	NS
Female	2	3	2	(p=0.83)
Duration of dialysis (years) (mean±SD)	—	3.1~34.0 (18.0±10.56)	6.1~12.8 (9.4±2.61)	NS (p=0.07)
Dialysate magnesium level (mg/dL)	—	1.2	1.2	—
Rate of vitamin D3 use	0%	100%	100%	—
Rate of magnesium-containing drug use	0%	0%	0%	—
Doses of magnesium oxide (g/day)	—	—	1.5	—
Duration of magnesium oxide use (months) (mean±SD)	—	—	6~44 (20.4±12.1)	—

NS, not significant.

TABLE.2 Characteristics and bowel movement conditions of HD-Mg group

Case number	Age (years)	Gender	Duration of dialysis (years)	Duration of magnesium oxide use (months)	Laxative being taken	Dosage/day	Bowel movement condition
1	60	M	7.5	12	Magnesium oxide	1.5g	Each morning
2	72	M	11	25	Magnesium oxide	1.5g	Each morning
3	58	M	7	44	Magnesium oxide	1.5g	Each morning
4	57	M	6.1	33	Sennoside Magnesium oxide	24mg 1.5g	Each morning
5	73	F	9.8	15	Sennoside Magnesium oxide	24mg (only HD day) 1.5g	Morning following HD
6	44	F	11.9	8	Sennoside Magnesium oxide	24mg (only HD day) 1.5g	Morning following HD
7	68	M	12.8	6	Sennoside Magnesium oxide	24mg (only HD day) 1.5g	Morning following HD

Magnesium oxide was taken in 3 divided doses, sennoside was taken before bedtime.
HD, hemodialysis.

2. Changes in blood pressure and pulse rate after taking magnesium oxide

The diastolic blood pressure significantly dropped in case number 4 ($P<0.05$). However there were no significant differences between before and after the administration of magnesium oxide in blood pressure and pulse rate (Fig. 2) and no symptoms such as hypotension and bradycardia in the other 5 patients ; case number 7 was excluded due to increased dosage of antihypertensive (amlodipine besilate) during this examination.

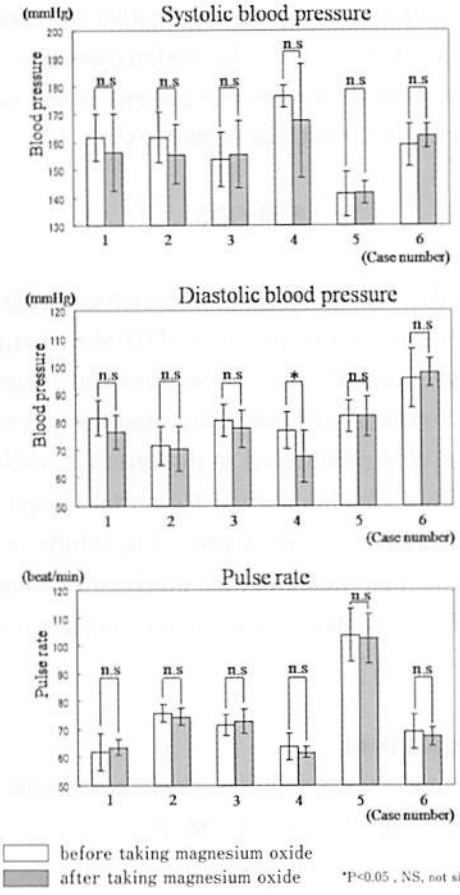


Fig.2 Changes in systolic blood pressure, diastolic blood pressure and pulse rate after taking magnesium oxide.

3. Serum magnesium level and erythrocyte magnesium level

There was no significant difference in the serum magnesium level between N group [2.5~2.7mg/dL (2.59±0.07)] and HD group [2.2~3.1mg/dL(2.59±0.31)]. Whereas, the serum magnesium level in HD-Mg group [3.4~4.3mg/dL(3.79±0.40)] was significantly high compared with those in N group and HD group ($P<0.01$). The erythrocyte magnesium level in HD group [6.4~8.7mg/dL(7.50±0.85)] was significantly high compared with that in N group [5.3~7.8mg/dL (6.49±0.85)] ($P<0.05$). Furthermore, the erythrocyte magnesium level in HD-Mg group [7.8~10.0mg/dL (8.90±0.81)] was significantly high compared with those in N group and HD group ($P<0.01$) (Fig. 3).

Concerning the effect of the duration of magnesium oxide use, the serum magnesium level and erythrocyte magnesium level were not tended to

influence by the duration of drug use in 3 patients (Fig. 4).The other 4 patients dropped out due to decreased dosage of magnesium oxide during this examination.

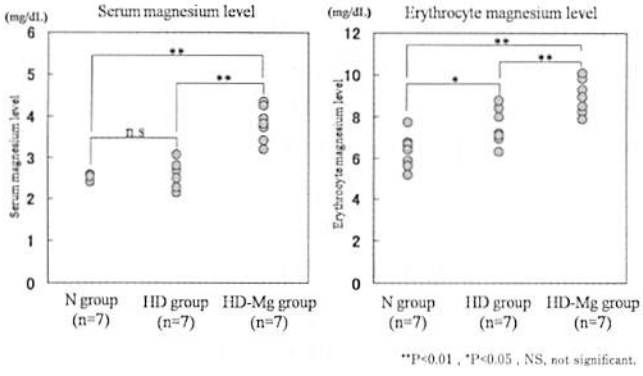
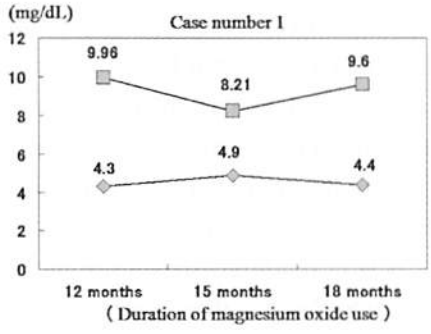
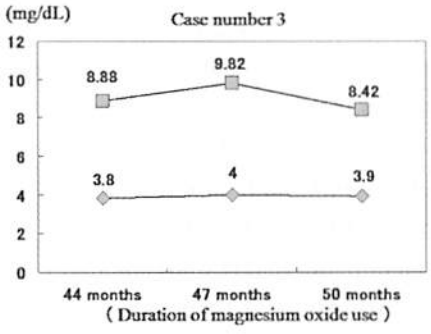


Fig.3 Comparison of N group, HD group and HD-Mg group by serum and erythrocyte magnesium level.





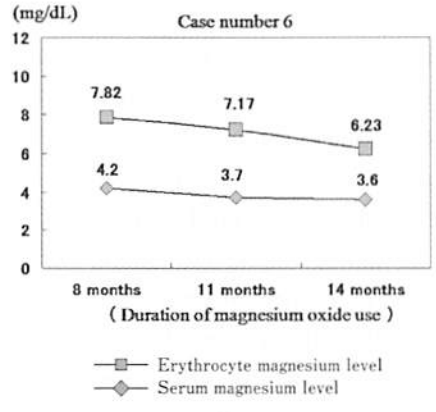


Fig.4 Changes of serum and erythrocyte magnesium level by duration of magnesium oxide use.

4. The ratio of intracellular and extracellular magnesium level

The ratio of intracellular and extracellular magnesium levels in HD group [2.54~3.33(2.92±0.32)] was significantly high compared with that in N group [2.12~2.89(2.50±0.27)] (P<0.05) . Whereas, that in HD-Mg group [1.86~2.88(2.37±0.33)] was significantly low compared with that in HD group (P<0.01), and there was no significant difference in that between N group and HD-Mg group (Fig. 5).

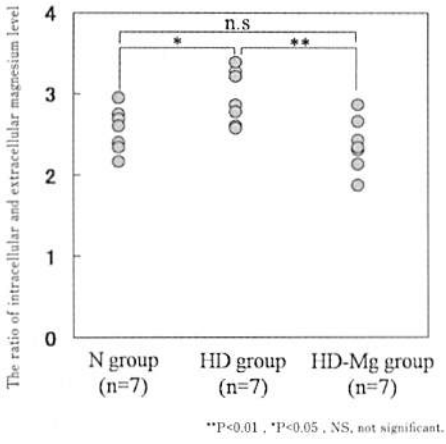


Fig.5 Comparison of N group, HD group and HD-Mg group by the ratio of intracellular and extracellular magnesium level.

5. Changes in serum potassium level after taking magnesium oxide

Serum potassium level was elevated by 0.20~0.81mEq/L (0.49±0.27) in 5 out of 6 patients after taking magnesium oxide, which was significant in 3 of them (P<0.05) (Fig. 6) ; case number 5 was excluded due to increased dosage of potassium adsorbing drug (sodium polystyrene sulfonate) during this examination.

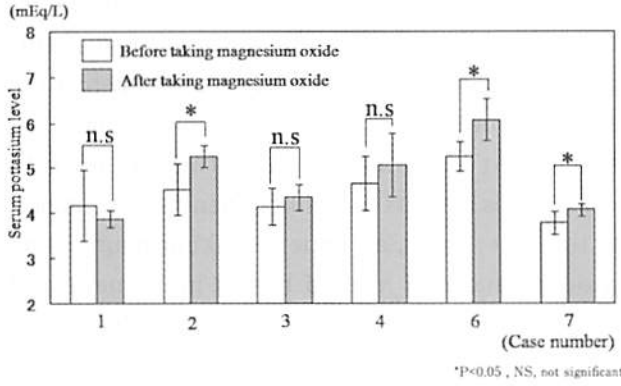


Fig.6 Changes in serum potassium level after taking magnesium oxide.

DISCCUSION

Whereas there was no significant difference in the serum magnesium level between HD group and N group, the erythrocyte magnesium level in HD group was significantly high compared with that in N group. The ratio of intracellular and extracellular magnesium levels in HD group was significantly high compared with that in N group, suggesting that the magnesium retained in the body was taken into the cell since its level was measured pre-hemodialysis. The ratio in HD-Mg group was significantly low compared with that in HD group. This suggests that high-dose administration such as 1.5g of magnesium oxide per day to renal failure patients overflowed from the cell and caused an elevation in the serum magnesium level.

Bulk-forming laxatives and infiltrating laxatives are unsuitable for hemodialysis patients due to fluid restrictions because these laxatives require a large volume of water. Saccharide laxative is cost prohibitive as it is not covered by medical insurance. Because the large intestine stimulant laxative commonly used in hemodialysis patients takes a fair amount of time to the onset of action, the prolonged length of onset of action becomes problem in patients with difficulty of defecation. Hemodialysis patients dislike defecation during hemodialysis due to the necessity to temporarily halt hemodialysis and wean from the hemodialysis machine to go to the restroom, and moreover, defecation is a psychological burden. In fact, more than 60 percent of the hemodialysis patients taking large intestine stimulant laxative admitted that they abstained from taking a laxative on the day before hemodialysis even if they had constipation in order to avoid defecation during hemodialysis[2]. Furthermore, over 30 percent of them answered to be uncertain of bowel movement the following morning even if they take the laxative before bedtime. In addition, while the habitual continued use of this laxative becomes problem, more than 80 percent of them answered to take this laxative habitually[2]. It shows that administration of this laxative to hemodialysis patients may strengthen their habitation. On the other hand, all patients taking magnesium oxide maintained a good bowel movement and magnesium oxide can be taken continuously for long periods because it does not cause habitation. Therefore, these data suggest that administration of magnesium oxide to hemodialysis patients is an effective means in terms of its effectiveness. However, administration of magnesium oxide to hemodialysis patients is limited because it has been reported that its administration to hemodialysis patients causes hypermagnesemia[1]. In this study, while the serum magnesium level and erythrocyte magnesium level were significantly high in HD-Mg group compared with those in HD group and N group, no patients showed symptoms of hypermagnesemia such as hypotension or bradycardia in HD-Mg group. It has been reported that these symptoms appear at a serum magnesium level of more than 4.8 mg/dL[4]. In this study, no patient manifested symptoms of hypermagnesemia because the level was lower than the reported level in most of patients in HD-Mg group. The result suggests that administration of 1.5g of magnesium oxide per day to hemodialysis patients improves bowel movements without symptoms of hypermagnesemia. However, it has been reported that in patients with potassium-depletion hypokalemia, patients taking magnesium sulfate require less potassium replacement for normalizing serum potassium level than patients taking placebo[5]. Therefore, it is considered that administration of magnesium oxide elevates the serum potassium level. In this study, the serum potassium level was tended to elevate in 5 out of 6 patients after taking magnesium oxide. Since serum potassium level elevation is a serious problem for the hemodialysis patients tending to manifest hyperkalemia, magnesium oxide should be carefully administered to hemodialysis patients.

The Ministry of Health, Labour and Welfare (MHLW) alerted the possibility of occurrence of hypermagnesemia due to magnesium oxide in Pharmaceuticals and Medical Devices Safety Information. MHLW indicated that the relevant pharmaceutical companies must add new sections "Important Precautions" and "Clinically Significant Adverse Reactions" in the PRECAUTIONS section of the package inserts[3]. In this study, however, the serum potassium level was elevated by 0.20 ~ 0.81mEq/L after 1.5g of taking magnesium oxide. Furthermore, while there is range between normal range (1.8~2.6mg/dL) and the level resulting in fatal arrhythmia (12mg/dL) in serum magnesium level, there is a narrow range between the two levels in the serum potassium level (normal range : 3.7~4.8mEq/L,

level resulting in fatal arrhythmia : 7.0mEq/L). Therefore, it is necessary to measure not only the serum magnesium level but also the serum potassium level when magnesium oxide is administered.

CONCLUSIONS

In conclusion, the results suggest that administration of 1.5g of magnesium oxide per day to hemodialysis patients dialyzed by dialysate with 1.2mg/dL magnesium maintain bowel movement control without symptoms of hypermagnesemia. However, because there is a possibility that it induces hyperkalemia resulting in fatal arrhythmia, vague administration of magnesium oxide to hemodialysis patients should be avoided and the serum potassium level should be monitored when magnesium oxide is administered to hemodialysis patients.

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