Effect of Histamine H2-Receptor Antagonist on the Phosphorus-Binding Abilities of Calcium Carbonate and Calcium Lactate in Hemodialysis Patients

NORIHIRO TAKAHASHI,* TETSUO SHOJI,* KEISUKE MATSUBARA,* HIROFUMI HITOMI,* MAYUKO HASHIMOTO,* HIDEYASU KIYOMOTO,* KOICHI UCHIDA,* SHIGEHIRO MIKI,* MAMORU HIROHATA,† TSUTOMU ISHIZU,† KENJI AKIYAMA,† KATSUFUMI MIZUSHIGE,* HIROHIDE MatsuO,* and SHIGEKAZU YUASA*

*Second Department of Internal Medicine, Kagawa Medical University, and † Mitoyo General Hospital, Kagawa, Japan.

Abstract. The effect of histamine H2-receptor antagonist (famotidine) on the phosphorus-binding abilities of calcium carbonate and calcium lactate were examined in 13 chronic hemodialysis patients. In seven patients receiving calcium carbonate, famotidine (20 mg/d) was given because of gastroduodenal disorders, and calcium carbonate was replaced with calcium lactate as a phosphorus binder after 4 wk of treatment with famotidine. With the 4-wk administration of famotidine accompanied by calcium carbonate, the serum phosphorus level increased from 6.3 ± 0.9 to 7.1 ± 0.5 mg/dl (∗P < 0.05). However, with the substitution of calcium lactate, the serum phosphorus level decreased significantly when compared to that before substitution (6.3 ± 0.2 and 6.0 ± 0.9 mg/dl after 4 and 8 wk of substitution, respectively), despite continued administration of famotidine. Serum calcium, creatinine, alkaline phosphatase, high sensitive parathyroid hormone, blood urea nitrogen, arterial blood pH, and bicarbonate were not significantly altered during the trial period. In six control patients treated with calcium carbonate alone, there were no statistical changes in serum calcium and phosphorus levels after substitution of calcium lactate for calcium carbonate. These results suggest that famotidine significantly affects the phosphorus-binding ability of calcium carbonate, but not that of calcium lactate. A careful observation of changes in the serum phosphorus level should be required in hemodialysis patients receiving calcium carbonate and histamine H2-receptor antagonists. Calcium lactate may be useful as a phosphorus binder in such hemodialysis patients.

In hemodialysis patients, hyperphosphatemia plays a major role in the development of secondary hyperparathyroidism (1–6). To correct hyperphosphatemia in hemodialysis patients presenting with diminished urinary phosphorus excretion, it is necessary to restrict oral phosphorus intake and use phosphorus binders (7,8). In the past, an aluminum-containing agent was commonly used as a phosphorus binder. However, in recent years aluminum toxicity, clinically manifested as dementia, osteomalacia, and anemia, has been demonstrated (9–11). To avoid aluminum toxicity, calcium-containing phosphorus binders are used increasingly, and calcium carbonate is the most principal agent presently used.

It has been demonstrated that the phosphorus-binding ability of calcium carbonate is affected by the presence of acid (12). However, in vitro, the dramatic fall in phosphorus binding by calcium carbonate at higher pH (6–8) has also been shown (13). Moreover, it has been reported that calcium carbonate is ineffective as a phosphorus binder in hemodialysis patients that have undergone gastrectomy. Previously, we have reported that histamine H2-receptor antagonists significantly affect the phosphorus-binding ability of calcium carbonate in hemodialysis patients because of a rise in pH of the gastric juice (14). The in vitro study has indicated that calcium lactate did bind phosphorus more effectively compared with calcium carbonate in the neutral pH range.

To compare the effect of histamine H2-receptor antagonist on the phosphorus-binding abilities of calcium carbonate and calcium lactate, we investigated prospectively changes of serum phosphorus levels in hemodialysis patients receiving histamine H2-receptor antagonist accompanied by calcium carbonate, and substituted calcium lactate for calcium carbonate.

Materials and Methods

Thirteen patients undergoing maintenance hemodialysis (six men and seven women) were selected for the study; informed consent was obtained from each patient. All were receiving a stable dose (3 g/d) of...
calcium carbonate as a phosphorus binder. They were divided into two groups: (1) a trial group of seven patients receiving the histamine H2-receptor antagonist famotidine (20 mg/d) accompanied by calcium carbonate; and (2) a control group of six patients treated with calcium carbonate alone. Patients’ characteristics are summarized in Table 1. There were no significant differences in age and duration of dialysis between the two groups. Basal serum calcium and phosphorus levels in the trial group were similar to those of the control group.

Over 12 wk of the study, famotidine (20 mg/d) was given in the trial group because of gastroduodenal disorders. After the initial 4 wk, calcium carbonate was replaced with calcium lactate (3 g/d) as the phosphorus binder in both groups. Furthermore, the dose of calcium lactate was increased to 6 g/d (an approximately equivalent dose of elemental calcium compared with 3 g/d of calcium carbonate) after an 8-wk period of the study. Serum calcium, phosphorus, creatinine, and blood urea nitrogen (BUN) were measured every 4 wk during the study. Arterial blood pH and bicarbonate, serum alkaline phosphatase (ALP), and high sensitive parathyroid hormone (HS-PTH) were measured at both the start and the end of the 12-wk study period. HS-PTH was assayed using RIA.

Dosages of 1α-hydroxyvitamin D₃ or 1α, 25-dehydroxyvitamin D₃ were not altered during the study period. All patients underwent dialysis 3 times a week for 4 h. During the study, dialysate calcium concentration (3.5 mEq/L) was not changed. Blood flow and dialysate flow were 200 and 500 ml/min, respectively.

Statistical Analyses

All data are expressed as mean ± SD. Data analysis was assessed using the Wilcoxon signed rank test (nonparametrical method), and a P value <0.05 was used as a level of significance.

Results

The changes of serum calcium and phosphorus levels in the trial group are shown in Figure 1. The change of serum calcium level was not statistically significant throughout the study. With the 4-wk administration of famotidine accompanied by calcium carbonate, the serum phosphorus level increased significantly compared with the basal level (from 6.3 ± 0.9 to 7.1 ± 0.5 mg/dl, P < 0.05). However, the increment in serum phosphorus level was completely abolished by the substitution of calcium lactate, and the serum phosphorus levels at the 8- and 12-wk period of the study were restored to levels no different from the basal level, despite continued administration of famotidine (6.3 ± 0.2 and 6.0 ± 0.9 mg/dl, respectively).

The dramatic fall in phosphorus-binding abilities of calcium-containing compounds at low pH has been assumed to be due mainly to the fact that the high hydrogen ion concentration competes with calcium for phosphorus, so the binding ability of calcium-containing salts is generally increased in the neutral pH range. However, the in vitro study showed that calcium carbonate bound far less phosphorus than theoretical equilibrium values at high pH (13). This probably can be attributed to its extreme insolubility and slow dissolution. Thus, calcium carbonate cannot be converted into the highly soluble salt calcium chloride as the pH rises. On the other hand, calcium lactate is a more readily soluble salt compared with calcium carbonate.

In this study, we investigated changes of the serum phosphorus level in hemodialysis patients receiving famotidine accompanied by calcium carbonate, and substituted calcium lactate for calcium carbonate.

In the trial group with the 4-wk administration of famotidine accompanied by calcium carbonate, the serum phosphorus level increased significantly. However, this increment in serum phosphorus level was completely abolished by the substitution of calcium lactate for calcium carbonate, despite continued administration of famotidine. We did not perform dietary history to determine the amount of phosphorus ingested during the

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Trial Group (n = 7)</th>
<th>Control Group (n = 6)</th>
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<tbody>
<tr>
<td>Mean age (range)</td>
<td>60.0 ± 4.7 (36 to 65)</td>
<td>58.2 ± 7.1 (43 to 69)</td>
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<td>Underlying disease</td>
<td>Chronic glomerulonephritis, 5; Diabetic nephropathy, 2</td>
<td>Chronic glomerulonephritis, 4; Diabetic nephropathy, 1; Polycystic kidney, 1</td>
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<td>Duration of dialysis (range)</td>
<td>161.5 ± 43.4 mo (110 to 211)</td>
<td>133.0 ± 93.1 mo (11 to 276)</td>
</tr>
<tr>
<td>Dose of drugs</td>
<td>Calcium carbonate 3 g/d; Famotidine 20 mg/d; Alfacalcidol (0.5 μg/d), 3</td>
<td>Calcium carbonate 3 g/d; Calcitriol (0.5 μg/d), 3</td>
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</tbody>
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*Table 1. Patients’ profile*

*Trial group, patients treated with famotidine and calcium carbonate; control group, patients treated with calcium carbonate alone. n = number of patients. Values are expressed as mean ± SD.*
study. However, we provide an indirect proof that there was no significant change in phosphorus intake during the study, since dialysis dose remained constant and the changes of BUN in the trial group were not statistically significant during the study. In the control group, changes of the serum phosphorus level during the study period were not statistically significant. These results suggest that famotidine significantly affects the phosphorus-binding ability of calcium carbonate, but not that of calcium lactate. Although the exact mechanism remains obscure, one possible explanation might be the rise in pH of gastric juice. It has been generally accepted that calcium carbonate is converted into the highly soluble salt calcium chloride in the stomach, and that dissolved calcium ions can effectively bind phosphorus in the small intestine as the pH rises. In the absence of gastric hydrochloride acid, the solubilization of calcium carbonate in the stomach is reduced, and hence many

![Figure 1. Changes in serum calcium and phosphorus levels during treatment with famotidine in hemodialysis patients receiving calcium carbonate initially, later substituted with calcium lactate. Each symbol shows the same patient. —4W, point of administration of famotidine; 0W, point of substitution with calcium lactate for calcium carbonate; 4W, point of increasing dose of calcium lactate; 8W, end of the study. W, week.](image)

<table>
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<tr>
<th>Parameter</th>
<th>−4W</th>
<th>0W</th>
<th>4W</th>
<th>8W</th>
<th>P Value</th>
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<tr>
<td>BUN (mg/dl)</td>
<td>68.6 ± 11.0</td>
<td>72.6 ± 8.2</td>
<td>71.6 ± 8.4</td>
<td>68.6 ± 8.7</td>
<td>NS</td>
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<tr>
<td>Cr (mg/dl)</td>
<td>11.3 ± 1.6</td>
<td>11.3 ± 1.9</td>
<td>10.9 ± 1.8</td>
<td>10.7 ± 1.9</td>
<td>NS</td>
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<tr>
<td>pH</td>
<td>7.32 ± 0.01</td>
<td>7.32 ± 0.01</td>
<td>7.32 ± 0.01</td>
<td>7.32 ± 0.01</td>
<td>NS</td>
</tr>
<tr>
<td>HCO₃ (mEq/L)</td>
<td>20.1 ± 1.1</td>
<td>20.1 ± 1.1</td>
<td>20.1 ± 1.1</td>
<td>20.1 ± 1.1</td>
<td>NS</td>
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<tr>
<td>ALP (IU/L)</td>
<td>212.2 ± 88.2</td>
<td>212.2 ± 88.2</td>
<td>212.2 ± 88.2</td>
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<td>NS</td>
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<tr>
<td>HS-PTH (pg/ml)</td>
<td>8600 ± 4515</td>
<td>9416 ± 4886</td>
<td>9416 ± 4886</td>
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*a* −4W, point of administration of famotidine; OW, point of substitution with calcium lactate for calcium carbonate; 4W, point of increasing dose of calcium lactate; 8W, end of the study. BUN, blood urea nitrogen; Cr, serum creatinine; pH, arterial blood pH; HCO₃, arterial blood bicarbonate; ALP, serum alkaline phosphatase; HS-PTH, high sensitive parathyroid hormone. Values are expressed as mean ± SD.
less calcium ions are delivered to the small intestine where they are available for phosphorus binding. The in vitro study has also demonstrated that calcium lactate is a more readily soluble salt compared with calcium carbonate in the neutral pH range, so calcium lactate is expected to be a more effective phosphorus binder when administered with the histamine H2-receptor antagonist. Although we did not examine the effect of famotidine on the phosphorus-binding ability of calcium acetate, calcium acetate may be another effective phosphorus binder in patients with a rise in gastric acidity. Because calcium acetate is readily soluble in both acid and alkaline environments, its phosphorus-binding ability may not be affected by histamine H2-receptor antagonist. In Japan, however, the clinical trial of calcium acetate has not been performed yet, so calcium acetate is not approved for use as a drug. However, we intend to investigate the phosphorus-binding ability of calcium acetate, as it may eventually be made available for clinical use.

It has also been demonstrated that in regular hemodialysis patients, the advantage of calcium acetate might disappear if calcium carbonate is taken on an empty stomach, a few minutes before meals (15). In this study, each subject ingested calcium salts immediately after meals, and the patients in the trial group were instructed to take famotidine immediately after breakfast. Because we did not investigate the acidity of gastric juice in each subject, the precise extent to which famotidine influences the acidity of an empty stomach is unclear. We also did not assess the effect of famotidine on phosphorus absorption in the absence of calcium carbonate or calcium lactate. However, it is unlikely that inhibition of gastric acid secretion has a direct effect on intestinal phosphorus absorption from our previous findings (14).

The results of this study indicate that a careful observation of changes in the serum phosphorus level should be required in hemodialysis patients receiving calcium carbonate and histamine H2-receptor antagonists. Calcium lactate may be useful as a phosphorus binder in such hemodialysis patients.

References
5. Portale AA, Booth BE, Halloran BP, Morris RC: Effect of dietary phosphorus on circulating concentrations of 1,25-dihydroxyvitamin D and immunoreactive parathyroid hormone in...


