SEVELAMER HYDROCHLORIDE IN PERITONEAL DIALYSIS PATIENTS: RESULTS OF A MULTICENTER CROSS-SECTIONAL STUDY

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Background: Sevelamer hydrochloride is a phosphate binder widely employed in hemodialysis patients. Until now, information about its efficacy and safety in peritoneal dialysis patients has been scarce.

Methods: In September 2005 a cross-sectional study of demographic, biochemical, and therapeutic information about its efficacy and safety in peritoneal dialysis patients has been conducted.

Results: We analyzed data from 228 patients. At the time of the study, 128 patients (56%) were receiving sevelamer. Patients receiving sevelamer were younger (p < 0.01), showed a longer period of time on dialysis (p < 0.01), and had a lower Charlson Comorbidity Index (p < 0.01). Serum calcium and intact parathyroid hormone levels were not different between the two groups, while phosphate levels <5.5 mg/dL were observed more frequently in patients not receiving sevelamer (79% vs 61%, p < 0.01). Serum total cholesterol (167 ± 41 vs 189 ± 42 mg/dL, p < 0.01) and low density lipoprotein (LDL) cholesterol (90 ± 34 vs 109 ± 34 mg/dL, p < 0.01), but not high density lipoprotein cholesterol or triglycerides, were lower in sevelamer-treated patients. Moreover, sevelamer-treated patients displayed a higher serum albumin (38 ± 5 vs 36 ± 4 g/L, p < 0.01) and a lower C-reactive protein (4.9 ± 12.8 vs 8.8 ± 15.7 mg/L, p < 0.01). Blood bicarbonate levels <22 mmol/L were observed more frequently in patients receiving sevelamer (22% vs 5%, p < 0.01). Logistic regression analysis adjusting by confounding variables confirmed that sevelamer therapy was associated with serum total cholesterol <200 mg/dL (relative risk (RR): 2.77, 95% confidence interval (CI): 1.44 – 5.26, p = 0.002) and blood bicarbonate <22 mmol/L (RR: 8.5, 95% CI: 2.6 – 27.0, p < 0.001), but not with serum phosphate >5.5 mg/dL, calcium–phosphate product >55 mg²/dL², serum albumin <35 g/L, or C-reactive protein >5 mg/L.

Conclusions: This uncontrolled cross-sectional study in peritoneal dialysis patients showed that sevelamer hydrochloride treatment allows an adequate serum phosphate level in about 60% of patients and significantly reduces total and LDL-cholesterol levels. Since this treatment is associated with metabolic acidosis in 22% of patients, we recommend close monitoring of bicarbonate levels in this group of patients until the clinical significance of this result is clarified.


KEY WORDS: Sevelamer hydrochloride; phosphate binders.

Elevated serum phosphate is a common complication in chronic renal failure and contributes to the high morbidity and mortality observed in these patients (1). Patients with serum phosphate levels above 6.5 mg/dL have a 27% higher risk of death compared to those with a serum phosphate between 2.4 and 6.5 mg/dL (2). For this reason, one of the main goals in end-stage renal disease patients is to maintain serum phosphate in the range recommended in different guidelines for dialysis patients. The latest version of K/DOQI guidelines as well as European Best Practice Guidelines recommend maintaining serum phosphate between 3.5 and 5.5 mg/dL (3).

In order to maintain serum phosphate in the desired range, patients on dialysis need to reduce not only phosphate intake but also intestinal phosphate absorption by the utilization of different phosphate binders. The phosphate binders most often used in the past were aluminum-based but their relations with neurological,
hematological, and bone complications nowadays limit their use. On the other hand, the most widely used calcium-based phosphate binders could facilitate the progression of soft tissue and vascular calcifications (4).

Sevelamer hydrochloride is an ion exchange resin, nonabsorbable, and the first phosphate binder that is not a source of aluminum or calcium. Since its appearance, several studies have demonstrated the efficacy and safety of this product in hemodialysis (HD) patients (5–7). Major adverse events related to sevelamer therapy are gastrointestinal intolerance and metabolic acidosis (8,9). However, information on the efficacy and safety of sevelamer hydrochloride in peritoneal dialysis (PD) patients is scarce (10–12). For these reasons, we conducted a multicenter cross-sectional study in a large group of PD patients to evaluate the prevalence of sevelamer use and its efficacy and safety.

PATIENTS AND METHODS

STUDY DESIGN

In September 2005, a cross-sectional study was conducted in 10 PD units in Catalonia and the Balearic Islands. The purpose of the present study was to evaluate the prevalence, efficacy, and safety of sevelamer hydrochloride treatment in these patients. Serum calcium, phosphate, intact parathyroid hormone (iPTH), and total cholesterol were considered as efficacy variables, while safety was evaluated according to blood bicarbonate levels. Patients were divided as treated or not treated with sevelamer hydrochloride independently of whether or not they were receiving other phosphate binders.

VARIABLES

Demographic, clinical, biochemical and therapeutic data from all patients were recorded. Comorbidity of patients was evaluated by the Charlson Comorbidity Index (13). At the time of the study, levels of serum calcium, phosphate, iPTH, total cholesterol, low (LDL)- and high density lipoprotein (HDL)-cholesterol, triglycerides, albumin, and C-reactive protein, blood bicarbonate, and residual renal function were collected. Serum calcium, phosphate, and cholesterol were measured using standard automated analyzers (Hitachi 747; Boehringer Mannheim, Germany). In all centers, iPTH was measured using an immunoradiometric assay and bicarbonate was measured by means of blood gas analysis. Total weekly dialysis dose (Kt/V), dialysate calcium concentration, and therapy with statins and calcium-based phosphate binders were also documented.

STATISTICS

Results are expressed as mean ± standard deviation. Comparison between categorical data was done by chi-square and comparison between means of normally distributed quantitative data was done by Student’s t-test. Logistic-regression analysis adjusting for confounding variables was employed to analyze the relationship between sevelamer treatment and biochemical data. A two-tailed p value less than 0.05 was considered significant.

RESULTS

Data from 228 patients controlled in 10 PD units were available. At the time of the study, 128 patients (56%) were receiving sevelamer hydrochloride treatment. Demographic and clinical data are shown in Table 1. Noticeably, patients receiving sevelamer were younger, showed a longer period of time on dialysis, and had a lower comorbidity index. Serum calcium and iPTH levels were not different between groups, while patients receiving sevelamer displayed higher phosphate levels and calcium–phosphate product (Ca×P) (Table 2). Calcium levels >9.5 mg/dL were observed in 51 sevelamer-treated patients and in 29 patients not receiving sevelamer (40% vs 29%, p = NS). Phosphate levels <5.5 mg/dL were observed in 78 sevelamer-treated patients and in 79 patients not receiving sevelamer (61% vs 79%, p < 0.01). Similarly, Ca×P <55 mg²/dL² was observed less frequently in sevelamer-treated patients (70% vs 80%, p = 0.03). Calcium-based phosphate binders were employed in 75 sevelamer-treated patients and in 67 patients not

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sevelamer (n=128)</th>
<th>No sevelamer (n=100)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52±14</td>
<td>60±14</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>92/36</td>
<td>61/39</td>
<td>NS</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.78±0.20</td>
<td>1.74±0.19</td>
<td>NS</td>
</tr>
<tr>
<td>Primary renal disease (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomerular</td>
<td>26</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Interstitial</td>
<td>27</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Polycystic kidneys</td>
<td>12</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>30</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>30</td>
<td>24</td>
<td>NS</td>
</tr>
<tr>
<td>Months on dialysis (%)</td>
<td>26±22</td>
<td>17±17</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CCI</td>
<td>4.9±2.4</td>
<td>6.0±2.6</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

CCI = Charlson Comorbidity Index; NS = not significant.
receiving sevelamer (59% vs 67%, \( p = \text{NS} \)). The majority of patients in both groups used a dialysate calcium of 3.5 mEq/L (82% & 81%, \( p = \text{NS} \)). Total weekly dialysis dose was not different between groups (2.5 ± 0.5 vs 2.6 ± 0.6, \( p = \text{NS} \)). Residual renal function was higher in patients not receiving sevelamer (0.91 ± 0.74 vs 0.68 ± 0.62, \( p = 0.01 \)).

Serum total cholesterol and LDL-cholesterol, but not HDL-cholesterol or triglycerides, were lower in sevelamer-treated patients (Table 2). Statins were employed in 45 sevelamer-treated patients and in 44 patients not receiving sevelamer (35% vs 44%, \( p = \text{NS} \)). Moreover, sevelamer-treated patients displayed a higher serum albumin (38 ± 5 vs 36 ± 4 g/L, \( p < 0.01 \)) and a lower C-reactive protein (4.9 ± 12.8 vs 8.8 ± 15.7 mg/L, \( p < 0.01 \)). However, normalized protein catabolic rate was not different between the two groups: 1.11 ± 0.39 g/kg body weight/day in the sevelamer group and 1.02 ± 0.23 g/kg body weight/day in the non-sevelamer group (\( p = \text{NS} \)).

Blood bicarbonate levels were lower in patients receiving sevelamer treatment (24.0 ± 3.2 vs 26.7 ± 3.2 mmol/L, \( p < 0.01 \)). This means that 22% of patients receiving sevelamer showed a blood bicarbonate level <22 mmol/L, while this result was observed in only 5% of patients not receiving sevelamer. The proportion of patients using a bicarbonate/lactate dialysate (Physiome; Baxter Healthcare, Castlebar, Ireland) was not different in patients receiving sevelamer versus the non-sevelamer group (16% vs 21%, \( p = \text{NS} \)). In patients on sevelamer treatment, blood bicarbonate levels were not different among patients receiving or not receiving calcium salts (24.1 ± 3.4 vs 24.0 ± 2.9 mmol/L, \( p = \text{NS} \)).

Sevelamer treatment was available without restrictions in all units. Phosphate binders were used and doses adjusted according to goals of K/DOQI guidelines. Mean dose of calcium acetate was 1.7 ± 0.7 g/day, mean dose of calcium carbonate was 1.9 ± 0.9 g/day, and mean dose of sevelamer hydrochloride was 3.7 ± 1.7 g/day. Only 7% of evaluated patients had mild gastrointestinal symptoms possibly related with phosphate binder therapy and, in any patient, phosphate binder regime was modified for this reason. These adverse effects were present in 4% of non sevelamer-treated patients and in 8% of sevelamer-treated patients (\( p = \text{NS} \)).

In order to analyze the relationship between sevelamer treatment and biochemical data, a logistic regression analysis adjusting by confounding variables was done. Sevelamer treatment was associated with serum total cholesterol levels <200 mg/dL (relative risk (RR): 2.77, 95% confidence interval (95% CI): 1.44 – 5.26, \( p = 0.002 \)) and blood bicarbonate levels <22 mmol/L (RR: 8.5, 95% CI: 2.6 – 27.0, \( p < 0.001 \)), but not with serum phosphate levels >5.5 mg/dL (RR: 1.83, 95% CI: 0.96 – 3.48, \( p = 0.066 \)), Ca×P >55 mg\(^2\)/dL\(^2\) (RR: 1.45, 95% CI: 0.75 – 2.82, \( p = \text{NS} \)), serum albumin <35 g/L (RR: 0.60, 95% CI: 0.31 – 1.17, \( p = \text{NS} \)), or C-reactive protein >5 mg/L (RR: 0.72, 95% CI: 0.39 – 1.31, \( p = \text{NS} \)) adjusting by patient age, months on dialysis, and Charlson Comorbidity Index.

**DISCUSSION**

Several clinical studies have been conducted in HD patients to establish that sevelamer hydrochloride is as efficacious as calcium-based phosphate binders in reducing serum phosphate levels. Moreover, in these studies it was also observed that sevelamer allows for good control of Ca×P, with less vascular and soft-tissue calcification (4–7). However, the efficacy and safety of sevelamer hydrochloride has not been properly evaluated by prospective controlled clinical trials in PD patients. In the present cross-sectional study, we showed that 56% of patients were receiving this drug in our area. For the purpose of the analysis, patients were divided according to whether they were receiving sevelamer treatment or not, and we observed that the groups were not comparable with respect to main clinical data. As expected, younger patients being longer on dialysis and with less comorbidity were more prone to show hyperphosphatemia and to be treated with sevelamer. Furthermore, patients treated with sevelamer had a lower residual renal function, which may have contributed to lower urinary calcium excretion and reduced intake of calcium salt binders. Taking into consideration the

### TABLE 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sevelamer (n=128)</th>
<th>No sevelamer (n=100)</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mg/dL)</td>
<td>9.5±0.7</td>
<td>9.4±0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Phosphate (mg/dL)</td>
<td>5.3±1.5</td>
<td>4.6±1.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ca×P (mg(^2)/dL(^2))</td>
<td>50±15</td>
<td>43±12</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>iPTH (pg/mL)</td>
<td>227±252</td>
<td>205±288</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>167±41</td>
<td>189±42</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>50±15</td>
<td>52±16</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>90±34</td>
<td>109±34</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>151±108</td>
<td>153±86</td>
<td>NS</td>
</tr>
</tbody>
</table>

Ca×P = calcium–phosphate product; iPTH = intact parathyroid hormone; HDL = high density lipoprotein; LDL = low density lipoprotein; NS = not significant.
limitations of our study, we explored in a nonclinical trial setting the utility and safety of sevelamer therapy in PD patients.

According to clinical guidelines for dialysis patients (3), 61% of our patients treated with sevelamer showed adequate control of serum phosphate, and 70% of patients also showed an adequate Ca×P. The proportion of patients with calcium levels over the target range is relevant in our study (29% for the group not receiving sevelamer and 39% for patients receiving sevelamer) possibly in relation to the high dialysate calcium levels used in our area. Whether lower dialysate calcium levels will overcome the risk of hypercalcemia and allow increases in the oral dose of calcium salt binders deserves further studies. However, this approach will favor the progression of secondary hyperparathyroidism.

In HD patients treated with sevelamer, serum phosphate is adequately controlled in 50% – 60% of patients, while Ca×P is controlled in 70% – 80% of patients (2,14,15). However, less experience is available in PD patients. In a Canadian study evaluating 12 sevelamer-treated PD patients, mean serum phosphate was 6 mg/dL, indicating that more than 50% of patients were out of the desired range. In a 1-year longitudinal study conducted in a Spanish center, 14 patients treated with sevelamer reached a serum phosphate level of about 5 mg/dL and a Ca×P of about 50 mg²/dL² (10). Taken together, these results suggest that treatment with sevelamer is as efficacious in PD patients as in HD patients but, despite its combination with calcium-based phosphate binders, about 40% of patients will still be out of range.

Since its first use, favorable effects on the lipid profile have been observed in patients treated with sevelamer. A decrease of 20% – 30% in LDL-cholesterol levels and an increase of 5% – 15% in HDL-cholesterol has been reported in HD patients. In a randomized crossover study conducted in 30 PD patients, sevelamer decreased total cholesterol by 10% and LDL-cholesterol by 20% in comparison to aluminum-based phosphate binders (12). In our study, we also observed that sevelamer-treated patients showed a significant decrease in total cholesterol and LDL-cholesterol in comparison to patients not receiving sevelamer. Regression logistic analysis confirmed that this result is independent of other confounding variables.

Adverse gastrointestinal events potentially related to sevelamer treatment included nausea, constipation, diarrhea, flatulence, and dyspepsia (5). In our patients, only mild adverse gastrointestinal effects were observed. Our patients received 1.7 g/day calcium acetate, 1.9 g/day calcium carbonate, and 3.7 g/day sevelamer, while the average dose reported by Chertow et al. was 4.6 g/day calcium acetate, 3.9 g/day calcium carbonate, and 6.5 g/day sevelamer (14). In another Spanish PD study (10), sevelamer doses were 2.76 g/day and mild adverse gastrointestinal effects were also reported. These doses are significantly lower compared to doses employed in other HD studies (14). These significant differences in phosphate binder doses might be related to the dialysis technique, residual renal function, or dietetic habits in different countries. Despite proposals that adverse gastrointestinal effects are not dose dependent, few studies have been conducted to confirm this hypothesis and, in our sample, we did not have sufficient statistical power for its evaluation.

Sevelamer treatment has been associated with metabolic acidosis since it is an acidic agent and replaces calcium-based phosphate binders. In HD patients, K/DOQI guidelines recommend maintaining predialysis bicarbonate levels above 22 mmol/L in order to avoid excess protein catabolism. However, sevelamer treatment has been associated with metabolic acidosis in a high proportion of HD patients (16). Less information on PD patients has been available until now. A short report evaluating PD patients observed a bicarbonate level lower than 24 mmol/L in only 1 of 12 patients, and this proportion is similar to that observed in PD patients not receiving sevelamer (10). On the other hand, a longitudinal study evaluating 14 PD patients treated with sevelamer showed nonsignificant changes in bicarbonate levels during 1 year of follow-up. On the contrary, the appearance of mild metabolic acidosis was shown in 11 PD patients treated with sevelamer; those patients using standard calcium dialysate without calcium-based phosphate binders being at higher risk (17). In our study, 22% of patients treated with sevelamer showed a blood bicarbonate level lower than 22 mmol/L and, in these patients, bicarbonate levels were not related to the use of calcium salt treatment. On the other hand, the protein catabolic rate was slightly higher in the younger group of patients receiving sevelamer but this difference did not reach statistical significance. Moreover, the proportion of patients with mild metabolic acidosis was significantly higher than the 5% of patients not receiving sevelamer, and multivariate analysis confirmed that this degree of metabolic acidosis seemed to be related to sevelamer therapy. The clinical significance of this result in PD patients will require further studies for clarification. Classically, metabolic acidosis in chronic renal failure is suggested to be an important factor responsible for protein and caloric malnutrition. Nevertheless, the effect of metabolic acidosis on the nutritional status of HD patients has not been completely clarified.
Recently, predialysis midweek bicarbonate levels in the range 19 – 22 mmol/L have not been associated with increased morbidity and mortality in comparison to serum bicarbonate levels higher than 22 mmol/L (18). These results suggest that mild predialysis acidosis may even be beneficial for HD patients.

In summary, sevelamer hydrochloride treatment in PD patients seems to be as efficacious as in HD patients in maintaining serum phosphate and calcium–phosphate product within the target range. However, sevelamer hydrochloride may be associated with mild metabolic acidosis in some patients. Thus, we recommend close monitoring of bicarbonate levels in this group of patients until the clinical significance of this result can be clarified.

REFERENCES