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Original Article

Long-term comparison of sevelamer hydrochloride to calcium-containing phosphate binders

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SUMMARY

Aim: In patients with end-stage renal disease (ESRD), hyperphosphataemia and an elevated calcium-phosphorus (Ca-P) product contribute to morbidity and mortality. Suggested target goals for serum phosphorus concentration and calcium-phosphorus product have recently been lowered. As a result, long-term comparative studies of the efficacy of phosphate binders are critical. This study compares the long-term efficacy of sevelamer hydrochloride to calcium-containing binders (CCB).

Methods: A retrospective chart review was conducted in 30 patients receiving sevelamer hydrochloride for >1 years and 25 patients receiving CCB.

Results: Patients on sevelamer hydrochloride had lower serum bicarbonate concentration than those on CCB, 18.6 ± 2.7 versus 20.3 ± 1.8 mmol/L ($P = 0.0017$). Serum phosphorus concentration was higher in patients on sevelamer hydrochloride compared to CCB 2.10 ± 0.87 versus 1.74 ± 0.28 mmol/L ($P = 0.0013$), as was the Ca-P product 4.97 ± 0.94 mmol^2/L^2 (62.1 ± 11.8 mg^2/dL^2) versus 3.97 ± 1.18 mmol^2/L^2 (49.7 ± 14.7 mg^2/dL$^{2)}$, $P = 0.0009$). Only 36% of patients on sevelamer hydrochloride compared with 68% on CCB ($P = 0.015$) met the serum phosphorus goal of ≤1.78 mmol/L.

Conclusion: Patients on sevelamer hydrochloride for >1 years compared to those on CCB had a lower serum bicarbonate concentration, a higher serum phosphorus concentration and a higher Ca-P product. Clinicians should balance the increase in calcium load with CCB versus the cost and effectiveness of sevelamer hydrochloride in choosing a phosphate binder for ESRD patients.

KEY WORDS: **calcium acetate, metabolic acidosis, renal osteodystrophy, serum phosphorus, sevelamer hydrochloride.**

In patients with end-stage renal disease (ESRD), hyperphosphataemia and an elevated calcium-phosphorus product contribute to the development of secondary hyperparathyroidism, metabolic bone disease, and vascular and cardiac calcification.[1] Significant morbidity and mortality may develop in this setting. Hyperphosphataemia and an elevated calcium-phosphorus product are independent predictors of total and cardiovascular mortality in ESRD patients.[2,3] With many patients living years on dialysis and waiting for transplantation, the long-term efficacy of phosphorus binders is an important issue. This study was designed to compare the long-term efficacy of calcium-based phosphorus binders with newer formulations.

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Dietary phosphorus restriction and phosphorus removal on dialysis are often insufficient to maintain neutral phosphorus balance. As a result, the vast majority of ESRD patients require phosphate binders to decrease the gastrointestinal absorption of phosphate in order to maintain the serum phosphorus concentration within an acceptable range.

Calcium-containing phosphate binders are effective in lowering serum phosphorus concentration.[4] They are, however, associated with an increased risk of transient hypercalcaemia[5] and two recent studies showed that calcification in the coronary and peripheral vasculature were related to the prescribed dose of calcium.[6,7] Others argue that vascular calcification is increased in patients with chronic kidney disease prior to dialysis and that vascular calcification was increased in ESRD patients before calcium-containing binders (CCB) were used for serum phosphorus control.[8–12]

A non-calcium containing phosphate binder, sevelamer hydrochloride (Renagel, Genzyme Corporation, Cam-

bridge, MA, USA) was approved in 1998 and is effective at lowering serum phosphorus concentration.[13–17] However, few studies have been published regarding the long-term efficacy of sevelamer hydrochloride compared with CCB. Recently, new target goals for serum phosphorus and calcium-phosphorus product were published.[18] Given these lower target goals, comparative studies of the long-term efficacy of currently available phosphate binders are critical. Therefore, we carried out a retrospective chart analysis designed to compare specifically the long-term efficacy of sevelamer hydrochloride to CCB. Primary outcomes included serum phosphorus concentration, serum calcium-phosphorus product (as described in the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines) serum bicarbonate concentration and the ability of each binder to meet these new target goals.

METHODS

Subjects

Patients were selected from the 160 haemodialysis patients at the Gambro Healthcare Dialysis Center at Yale University School of Medicine (New Haven, Connecticut). Patients were included in the analysis if sevelamer hydrochloride was prescribed for greater than 1 year or they were on CCB (calcium acetate, calcium carbonate or a combination of calcium carbonate and magnesium carbonate) over a similar time period. Patients were excluded if they were prescribed a combination of sevelamer hydrochloride and CCB during this period, or were taking sevelamer hydrochloride for less than 1 year.

Methods

Charts were reviewed and a total of 30 patients on sevelamer hydrochloride met entry criteria. Twenty-five patients on CCB met entry criteria. Of those on CCB, 18 were prescribed calcium acetate (PhosLo, Nabi Pharmaceuticals, Boca Raton, FL, USA). Binder use and compliance was verified by chart review and patient interview. Baseline characteristics of study subjects are shown in Table 1. Serum calcium, phosphorus and bicarbonate concentration were recorded every 2 weeks and mean values determined for three months prior to the time of review. Values for intact-parathyroid hormone (i-PTH), paracalcitol (Zemplar, Abbott Laboratories, Abbott Park, IL, USA) dose, and calcium bath were recorded from the previous month.

Statistical methods

The Mann–Whitney test was used for continuous variables and the Fisher exact test used to analyse categorical variables. Values were considered statistically significant only when the *P*-value was less than 0.05.

RESULTS

No statistically significant differences between patient groups with respect to age, sex, race, dialysis adequacy, diabetes status or nutritional status were observed (Table 1). Both groups were equally well dialysed with mean single pool Kt/V > 1.4. There was a high percentage of African-Americans in both groups indicative of the population of New Haven and the over representation of African-Americans in the ESRD population.[15] There were no known adverse outcomes from either binder.

The sevelamer hydrochloride group had a significantly lower mean serum bicarbonate concentration compared to those prescribed CCB, 18.6 ± 2.7 versus 20.3 ± 1.8 mmol/L, respectively ($P = 0.0017$). Patients on sevelamer hydrochloride were also more likely to have a serum bicarbonate concentration ≤20 mmol/L. Seventy-seven percent of patients on sevelamer hydrochloride had a serum bicarbonate concentration ≤20 mmol/L, versus only 36% of those on CCB ($P = 0.02$).

Patients prescribed sevelamer hydrochloride had a significantly higher mean serum phosphorus concentration than those prescribed CCB, 2.1 ± 0.39 mmol/L versus 1.74 ± 0.48 mmol/L, respectively ($P = 0.0013$). A dot plot of serum phosphorus concentration in the two groups is shown in Figure 1a. Sevelamer hydrochloride-treated patients also had a higher mean calcium-phosphorus product than those in the CCB group: 4.97 ± 0.94 $mmol^2/L^2$ (62.1 ± 11.8 mg^2/dL^2) versus 3.97 ± 1.18 $mmol^2/L^2$ (49.7 ± 14.7 mg^2/dL^2), $P = 0.0009$ (Fig. 1b).

We also compared the ability of sevelamer hydrochloride and CCB to meet currently recommended K/DOQI target goals for serum phosphorus concentration and calcium-phosphorus product. Calcium-containing binders were significantly more effective in meeting target goals; serum phosphorus concentration of ≤1.8 mmol/L and calcium-

Table 1 Patient characteristics

	Sevelamer hydrochloride	Calcium-containing binders	*P*-value
Number	30	25	NS
Sex (% female)	50	56	NS
Race (% African American)	67	64	NS
Age	50.3 ± 12.3	54.9 ± 11.9	NS
DM (% with)	37	40	NS
Weight (kg)	68 ± 19.5	70.5 ± 14.5	NS
Kt/V	1.56 ± 0.21	1.45 ± 0.15	NS
Albumin (g/L)	38.8 ± 0.37	37.8 ± 0.46	NS
Dose (mg/mg elemental Ca)	7800 ± 3463	1359 ± 636	–

DM, diabetes mellitus; NS, not statistically significant.

phosphorus product of ≤4.4 mmol^2/L^2 (55 mg^2/dL^2). In the sevelamer hydrochloride-treated group, only 36% of patients had a serum phosphorus concentration ≤1.8 mmol/L versus 68% in the CCB group ($P = 0.015$). Sixty percent of those treated with CCB had a calcium-phosphorus product ≤4.4 mmol^2/L^2 (55 mg^2/dL^2), versus only 23% in the sevelamer hydrochloride group ($P = 0.005$).

Other relevant mineral metabolism parameters are shown in Table 2. Mean serum calcium concentration was higher in the sevelamer hydrochloride-treated patients compared to CCB patients (2.4 ± 0.17 mmol/L *vs* 2.27 ± 0.15 mmol/L, $P = 0.0190$). PTH concentration was higher in the sevelamer hydrochloride-treated group compared to the calcium-containing binder group but this was not statistically significant. Paracalcitol dose was also higher in the sevelamer hydrochloride-treated patients, 7.7 ± 5.8 μg versus 4.7 ± 5.2 μg ($P = 0.0414$). Dialysate calcium concentration in the two groups was not statistically significantly different.

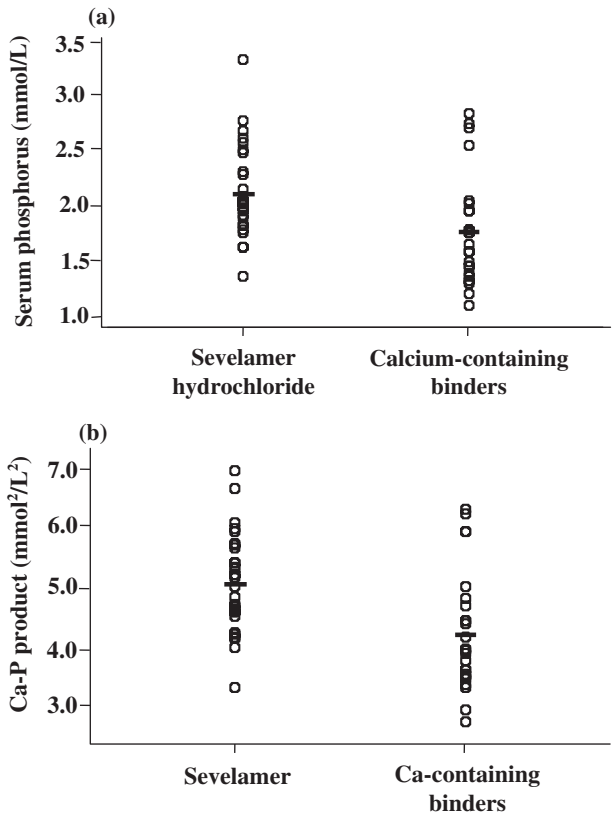

Fig. 1 Dot plot of serum phosphorus concentration (a) and calcium-phosphorus (Ca-P) product values (b) in patients on sevelamer hydrochloride and calcium-containing binders. (a) $P = 0.0013$. (b) $P = 0.0009$.

DISCUSSION

Control of serum calcium and phosphorus concentrations is an important aspect of the management of ESRD patients. A variety of phosphate-binders can be employed to lower the calcium-phosphorus product and serum phosphorus concentration. Sevelamer hydrochloride has been shown to be effective in lowering the serum phosphorus level in patients with ESRD, but little data is available on its long-term efficacy. Given that many patients with ESRD are surviving for years on dialysis, the importance of looking at long-term efficacy of these therapies, and not just short-term trials, is critical. Our study compared the long-term efficacy of sevelamer hydrochloride with CCB in controlling serum phosphorus concentration, calcium-phosphorus product, and the effects of these two medications on serum bicarbonate concentration and PTH. Mean duration of treatment with sevelamer hydrochloride was 23.9 ± 7.7 months. Serum bicarbonate concentration was consistently lower in sevelamer treated patients. Most importantly, calcium-containing binders were more effective at meeting target goals for calcium-phosphorus product and serum phosphorus concentration as will be discussed.

Our study showed a clear difference in serum bicarbonate concentration between groups. Patients on long-term sevelamer hydrochloride had a serum bicarbonate concentration that averaged 1.7 mmol/L lower than those on CCB, as shown in Figure 2.[16–18] This is consistent with previous studies in haemodialysis patients that show a similar decline in serum bicarbonate concentration with sevelamer hydrochloride compared with CCB. The range of serum bicarbonate concentration decrease was 1.7–3.9 mmol/L. The lower serum bicarbonate concentration in patients treated with long-term sevelamer hydrochloride may be of clinical significance in that metabolic acidosis significantly impacts bone disease in patients with chronic kidney disease. Acidosis directly stimulates osteoclasts to resorb bone, inhibits osteoblast function, stimulates parathyroid hormone secretion and suppresses vitamin D synthesis.[19] Excess acid is

Table 2 Other parameters of mineral metabolism

Sevelamer	Sevelamer hydrochloride	Calcium-containing binders	*P*-value
Serum calcium concentration (mmol/L)	2.4 ± 0.18	2.28 ± 0.15	0.02
PTH (pmol/L)	42.6 ± 34	33.8 ± 37.6	NS
Paracalcitol dose (μg)	7.7 ± 5.8	4.7 ± 5.2	0.04
Dialysate calcium concentration (mmol/L)	1.2 ± 0.02	1.25 ± 0.2	NS

PTH, parathyroid hormone; NS, not statistically significant.

buffered in bone and is associated with the release of calcium and phosphorus.[20] Therefore, it is important that normal acid-base balance be achieved in order to optimise bone health.

The mechanism of the lower serum bicarbonate concentration in patients on sevelamer hydrochloride is likely multifactorial. One component may be related to the absence of a bicarbonate equivalent. Also, sevelamer hydrochloride is a protonated amine and its interaction with phosphate releases protons and likely results in an acid load.[21]

There are at least four randomised, short-term, prospective studies in the published work comparing the efficacy of sevelamer hydrochloride to CCB in lowering serum phosphorus concentration that are shown in Table 3.[13,16,21,22] Three concluded that there is no difference in serum phosphorus reduction between the two phosphate binders and one that CCB are more effective in reducing serum phosphorus concentration.

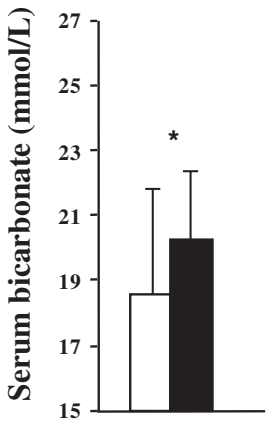

Fig. 2 Serum bicarbonate concentration measurements in haemodialysis patients taking sevelamer hydrochloride (□) were significantly lower compared with those taking calcium-containing binders (■). Data shown from current study. *$P \leq 0.05$.

In our study, both CCB and sevelamer hydrochloride reduced serum phosphorus concentration and the calcium-phosphorus product. Long-term CCB, however, were more effective than long-term sevelamer hydrochloride at meeting target goals for these values in our study. This occurred despite the fact that the mean dose of sevelamer hydrochloride was high (7.8 g) and all patients were receiving the 800 mg tablets during the 3-month period when serum phosphorus concentration was analysed.

The higher serum calcium concentration in the long-term sevelamer hydrochloride-treated patients could have several possible explanations. Patients were not assigned randomly to treatment groups. Those patients on long-term sevelamer hydrochloride may have initially been switched from other phosphate-binding agents due to hypercalcaemia. Alternatively, the sevelamer hydrochloride-treated patients had poorer serum phosphorus control and required higher doses of paracalcitol in order to maintain their PTH values within the target range, as was seen in our patients where the mean paracalcitol dose was 7.4 μg in the sevelamer hydrochloride group and 4.7 μg in the CCB group. The higher dose of the vitamin D analogue may have increased intestinal absorption of calcium and contributed to the slight calcium elevation. The majority (75%) of the increase in the calcium-phosphorus product in the sevelamer hydrochloride-treated patients was a result of an increase in the serum phosphorus concentration.

The choice of the optimal phosphate binder for ESRD patients remains problematic. Several factors must be weighed and there are advantages and disadvantages of both sevelamer hydrochloride and CCB. Sevelamer hydrochloride does not contain calcium. Goodman recently showed that the prescribed dose of CCB is associated with vascular calcification in young dialysis patients.[7] There is increasing concern that positive calcium balance may contribute to vascular calcification in ESRD. Sevelamer hydrochloride also lowers low-density lipoprotein (LDL) cholesterol by 20–25% in a patient population that has a high prevalence of atherosclerotic disease.[13] Sevelamer hydrochloride, however, is expensive. A recent survey of a drug sales website

Table 3 Summary of short-term trials comparing calcium-containing binders (CCB) to sevelamer hydrochloride

Reference	Duration of trial	No. patients	P control result/P result reported
13	8 weeks	84	'Change' in serum P equivalent in two groups Sevelamer: –0.65 ± 0.74 mmol/L (–2.0 ± 2.3 mg/dL) CCB: –0.68 ± 0.61 mmol/L (–2.1 ± 1.9 mg/dL)
16	40 weeks	200	Equivalent P control Sevelamer: 1.65 ± 0.39 mmol/L (5.1 ± 1.2 mg/dL) CCB: 1.65 ± 0.45 mmol/L (5.1 ± 1.4 mg/dL)
22	8 weeks	100	CCB showed improved P control over sevelamer CCB: 1.84 ± 0.65 mmol/L (5.7 ± 2.0 mg/dL) Sevelamer: 2.13 ± 0.55 mmol/L (6.6 ± 1.7 mg/dL)
23	34 weeks	51	Equivalent P control Sevelamer: 1.87 ± 0.33 mmol/L (5.8 ± 1.01 mg/dL) CCB: 1.91 ± 0.48 mmol/L (5.9 ± 1.5 mg/dL)

P, phosphorus.

revealed that the monthly cost for the mean dose prescribed in our study (three 800 mg tablets with each meal) is $US319. The cost for the mean calcium acetate dose prescribed in this study is $US47. Many ESRD patients do not have prescription drug coverage. Calcium acetate, although less expensive, contributes to positive calcium balance and has no effect on LDL cholesterol.

The stimuli for vascular calcification in ESRD are likely multifactorial with hyperphosphataemia, elevated calcium-phosphorus product, cytokines and the inflammatory state, oxidative stress, hypercholesterolaemia and positive calcium balance playing a role. Hyperphosphataemia is a potent stimulus for the expression of osteoblast-specific genes in vascular cells.[23] To the extent that calcium-containing binders result in more effective control of serum phosphorus concentration at a cheaper cost this may counterbalance their exacerbation of positive calcium balance and lack of LDL cholesterol lowering. Both options leave something to be desired and a combination of the two phosphate binders may be the optimal approach until additional agents become available or more definitive trials are carried out. A randomised controlled trial using mortality as the end point would answer the question definitively but would require a large number of patients. For example, if one were to enrol haemodialysis patients with an average survival of 3 years, a study with a two sided *P*-value of 0.05 and a power of 90% that would detect a 25% risk reduction would require 485 patients in each arm. If one were to then assume a drop-in and drop-out rate of 15% that number would increase to 993.

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