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Original Article

Long-term effects of sevelamer hydrochloride on the calcium × phosphate product and lipid profile of haemodialysis patients*

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Abstract

Background. Short-term studies have suggested that sevelamer hydrochloride, a non-aluminium- and non-calcium-containing hydrogel, is an effective phosphate binder in haemodialysis patients, and may produce favourable changes in the lipid profile.

Methods. To determine the long-term effectiveness of sevelamer hydrochloride, we performed an open-label clinical trial in 192 adult patients with end-stage renal disease on haemodialysis. Drug-related changes in the concentrations of serum phosphorus, calcium, calcium × phosphate product, parathyroid hormone, and low- and high-density lipoprotein cholesterol concentrations were the major outcomes of interest.

Results. Treatment with sevelamer was associated with a mean change in serum phosphorus of -0.71 ± 0.77 mmol/l, serum calcium of 0.08 ± 0.22 mmol/l, and calcium × phosphate product of -1.46 ± 1.78 mmol/l ($P < 0.0001$ for all comparisons). There were no significant overall treatment-related changes in parathyroid hormone. Serum levels of LDL cholesterol decreased by 0.81 ± 0.75 mmol/l (mean -30%, $P < 0.0001$) and HDL cholesterol increased by a mean of 0.15 ± 0.29 mmol/l (mean $+18\%$, $P < 0.0001$). Drug-related adverse events were infrequent and most were of mild intensity.

Conclusion. Sevelamer is a safe and effective phosphate binder that leads to significant improvements in the calcium × phosphate product and lipid profile of haemodialysis patients.

Key words: end-stage renal disease; hyperphosphataemia; hyperparathyroidism; haemodialysis; cholesterol; phosphate; calcium

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Introduction

Hyperphosphataemia and secondary hyperparathyroidism are common complications of advanced chronic renal insufficiency and end-stage renal disease (ESRD) [1]. Untreated, secondary hyperparathyroidism can lead to significant morbidity because of pain, bone loss, increased risk of fractures and anaemia [2–5], and has been postulated to contribute to hypertension, atherosclerotic vascular disease, pruritus, and sexual dysfunction [5–9]. Modern treatment of hyperphosphataemia and secondary hyperparathyroidism consists of dietary phosphorus restriction, provision of aluminum or calcium salts to bind dietary phosphorus, and often, the oral or intravenous administration of vitamin D metabolites (e.g. 1, 25-OH vitamin D3, calcitriol). To date, medical management of these conditions has been less than optimal, as a large fraction ($\sim 60\%$) of patients do not achieve adequate control of serum phosphorus and the calcium × phosphate product, and others continue to have marked elevations of parathyroid hormone (PTH) or require parathyroidectomy. It is noteworthy that hyperphosphataemia is an independent determinant of hyperparathyroidism, rendering the parathyroid gland less sensitive to the suppressive effects of calcium and vitamin D [10].

Dietary restriction of phosphorus is limited by the need to provide adequate daily protein intake to maintain neutral nitrogen balance, estimated at roughly 1.0–1.2 g protein per kg body weight in most ambulatory patients. Therefore, most patients with advanced chronic renal failure or ESRD require an exogenous phosphate binder to prevent hyperphosphataemia. This stands in contrast to patients with renal insufficiency who may maintain normal or near normal levels of

serum phosphorus as a consequence of hyperparathyroidism, due to the effect of PTH in augmenting renal phosphorus excretion. Aluminum hydroxide is effective at binding intestinal phosphorus, although its systemic absorption over time can lead to a microcytic, hypochromic anaemia, osteomalacia, myopathy, and rarely, dementia [11–13]. Calcium salts (usually carbonate or acetate) have become the treatment of choice for hyperphosphatemia [14,15], although the provision of calcium can lead to hypercalcaemia and increase the risk of metastatic calcification in a substantial fraction of patients, particularly among patients on vitamin D replacement, and others with low bone turnover rates (adynamic bone disease) evidenced by low levels of PTH, serum osteocalcin, and alkaline phosphatase [16].

Sevelamer hydrochloride (herein referred to as sevelamer) is a non-aluminum, non-calcium-containing hydrogel of cross-linked poly [allylamine hydrochloride] that is resistant to digestive degradation and is not absorbed from the gastrointestinal tract. Its mechanism of action relates to the presence of partially protonated amines spaced one carbon from the polymer backbone (Figure 1), which interact with phosphate ions by ionic and hydrogen bonding. Several short-term clinical studies in patients with ESRD have established that sevelamer is as efficacious as calcium carbonate or acetate at lowering serum phosphorus, and is well-tolerated [17–19]. Furthermore, short-term control of hyperparathyroidism has proved to be adequate, with maintenance of normal serum calcium concentrations, and significant decreases in the calcium × phosphate product. In addition, short-term favourable effects on the lipid profile have been observed, with a 20–30% decrease in low density lipoprotein (LDL) cholesterol, and a 5–15% increase in high density lipoprotein (HDL) cholesterol concentrations, presumably related to the binding of bile acids by the compound.

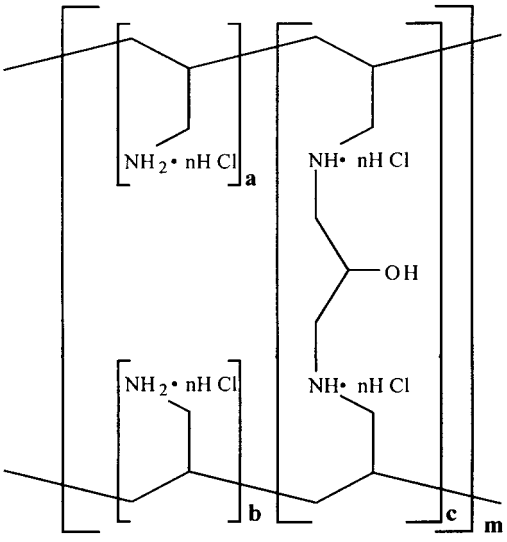

Fig. 1. Structure of sevelamer hydrochloride.

The current study was undertaken to evaluate the long-term safety and effectiveness of sevelamer at controlling hyperphosphataemia, allowing investigators the flexibility to utilize vitamin D metabolites, supplemental calcium, or other therapies in concert with sevelamer, as would practitioners in a non-clinical trial setting. We also sought to determine whether favourable changes in the lipid profile seen over 2–12 week study periods would be sustained over time.

Methods

Subjects

One hundred and ninety-two subjects participated in this study, 185 (96%) of whom were prior participants in shorter-term studies using sevelamer [17–19]. Inclusion criteria for these studies included: age 18 years or above, the provision of thrice weekly haemodialysis for at least 3 months, and the regular administration of aluminium- and/or calcium-based phosphate binders, with or without vitamin D metabolite replacement therapy at stable doses for at least 1 month. Subjects with the following history were excluded: serious gastrointestinal disease (including dysphagia, vomiting, motility disorder, major intestinal surgery, markedly irregular bowel function), ethanol or drug dependence or abuse, active malignancy, HIV infection, vasculitis, or poorly controlled diabetes mellitus or hypertension.

Protocol

Subjects who completed a dose titration study with sevelamer were eligible to continue on sevelamer longer-term. Written informed consent was obtained from all subjects, after consultation with their primary nephrologist. Following screening, when medical history, physical examination, and laboratory studies were reviewed, there were 2 weeks of 'pre-treatment' washout, when all phosphate binders were discontinued. The investigator determined the initial sevelamer dose based on the subject's previous experience, the estimated dietary phosphorus intake, and overall clinical judgment. Phosphorus and calcium levels were monitored every 4 weeks during the treatment period; levels of PTH, cholesterol, and other laboratory tests were monitored at weeks 2, 10, 18, 26, 34, and 46. Laboratory tests were drawn before the mid-week dialysis session, timed in accordance with the subject's dialysis schedule. Therefore, some subjects had laboratory tests performed at night, others in the morning, although the timing was uniform within subject. The dose of sevelamer was titrated monthly if necessary. There were no protocols in place or restrictions enforced on the provision of vitamin D metabolites, supplemental calcium, or other conventional or alternative drug therapies during the course of the study. Dialysate calcium concentration was chosen by the primary nephrologist, as were other details of the dialysis prescription. This approach allowed the physician a degree of flexibility that simulated a non-clinical trial setting. A second 2-week washout ('post-treatment') followed the treatment period, and constituted study completion.

Statistical analysis

Continuous variables, expressed as mean ± SD or median when the data were highly skewed, were compared with

Student's *t*-test, the Wilcoxon signed rank test, or the Kruskal–Wallis test, where appropriate. Categorical variables were compared with Fisher's Exact test. The effect of treatment was analysed using the change from the end of the initial washout to the end of the treatment period. In the event of study withdrawal, the final value obtained was carried forward. The dose-response was tested by linear regression, using change in the laboratory parameter of interest as the dependent variable, and sevelamer dose as a continuous independent variable.

Primary analyses were based on the entire study sample. Pre-specified subgroup analyses categorized by the average prescribed daily sevelamer dose (low <5.0 g, medium 5.0–6.75 g, high >6.75 g, a proxy for the severity of hyperphosphataemia) were performed for the phosphorus, calcium, calcium $\times$ phosphate product, and PTH determinations. Serum lipids were evaluated among pre-specified subgroups based on the initial LDL cholesterol concentration (LDL <2.58, LDL 2.58–3.33, LDL 3.36–4.11, LDL $\geqslant 4.13$ mmol/l). Post-hoc analyses of phosphorus, calcium, calcium $\times$ phosphate product, and PTH were performed based on whether subjects had been prescribed an increase (i.e. new start or increase in dose) in vitamin D metabolite therapy ($n=66$, 34%) over the course of the study. Additional analyses were restricted to subjects who completed the study protocol ($n=123$, 64%). Because of multiple comparisons, two-tailed probability values <0.01 were considered significant.

Table 1. Baseline characteristics of study sample

Age (years)	56.1 ± 14.6
Gender (%) female)	38%
Race/ethnicity (%)	
African American	54%
Caucasian	35%
Hispanic	7%
Asian	2%
Other	1%
Primary renal disease[a]	
Hypertension	34%
Diabetes mellitus	30%
Glomerulonephritis	14%
Polycystic kidney disease	3%
Other	20%
Duration of dialysis (years)	3.8 ± 3.7 median 3.0, range <1 to 21
Previous kidney transplant	10%
Partial parathyroidectomy	7%
Kt/V[b]	1.5 ± 0.2
Vitamin D metabolite use	
None	26%
Oral	8%
Intravenous	66%
Increase in vitamin D during study	34%
Dialysate calcium (mmol/l)	
<1.25	7%
1.25	64%
1.50	12%
1.75	16%

[a]per physician report.
[b]an index of dialysis intensity, the clearance-time product divided by the volume of distribution of urea.

Results

One hundred and ninety-five subjects entered the study; three patients were excluded before the start of the treatment period (one withdrew consent, one violated the study protocol, and one was lost to follow-up). Figure 2 outlines the reasons for study withdrawal, including 12 (6%) deaths, and 25 (13%) adverse events, which included kidney transplantation and prolonged hospitalization or referral to an institution where careful study monitoring could not take place. None of the serious adverse events were attributable to the study drug.

The mean age of study subjects was 56.1 ± 14.6 years (range 19–86 years). Seventy-two (38%) subjects were female, 104 (54%) were African American, 68 (35%) Caucasian, 14 (7%) Hispanic, 4 (2%) Asian, and 2 (1%) were of other race or ethnicity. Table 1 outlines the baseline clinical characteristics of the study sample.

All subjects were taking phosphate binders before entering the study. One hundred and one (53%) subjects proceeded directly from a previous sevelamer study into the current one following the 2-week washout. Of the remaining 91 subjects, 36 (19%) were taking calcium acetate, 24 (13%) calcium carbonate, and 27 (14%) other calcium preparations or a combination thereof. Four (2%) subjects were taking aluminium hydroxide with or without calcium before entering the study.

Subjects were categorized by the mean prescribed daily sevelamer dose (low, $n=57$, medium, $n=48$, high, $n=87$). The mean prescribed daily dose was 6.3 g. The average adherence with therapy (determined by pill counts) was 84%. Therefore, the mean actual daily dose consumed was 5.3 g. Age was inversely correlated with sevelamer dose (mean age 61.7 *vs* 56.2 *vs* 52.3 years in low-, medium-, and high-dose groups, respectively, $P=0.0008$). Mean weight was directly correlated with dose (mean weight 77.9 *vs* 79.3 *vs* 83.0 kg in corresponding groups) although the difference among the three sevelamer dose groups was not statistically significant. Other demographic and clinical characteristics were not different across the three sevelamer dose groups. There was a trend toward less frequent use of vitamin D metabolites among subjects who required higher sevelamer doses (84% *vs* 79% *vs* 66% in the low-, medium- and high-dose groups, $P=0.03$).

Phosphorus

The mean serum phosphorus after pre-treatment washout was 2.81 ± 0.71 mmol/l and at the end of treatment was 2.06 ± 0.61 mmol/l, corresponding to a mean change of -0.71 ± 0.77 mmol/l ($P<0.0001$). After 2 weeks of post-treatment washout, the mean serum phosphorus increased by 0.55 ± 0.61 mmol/l ($P<0.0001$). The reduction in serum phosphorus was most pronounced in the high-dose group. The mean change in serum phosphorus was -0.61, -0.52, and -0.87 mmol/l, in the low-, medium-, and high-dose groups, respectively. The mean pre-treatment serum phosphorus levels were 2.42, 2.74, and 3.06 mmol/l

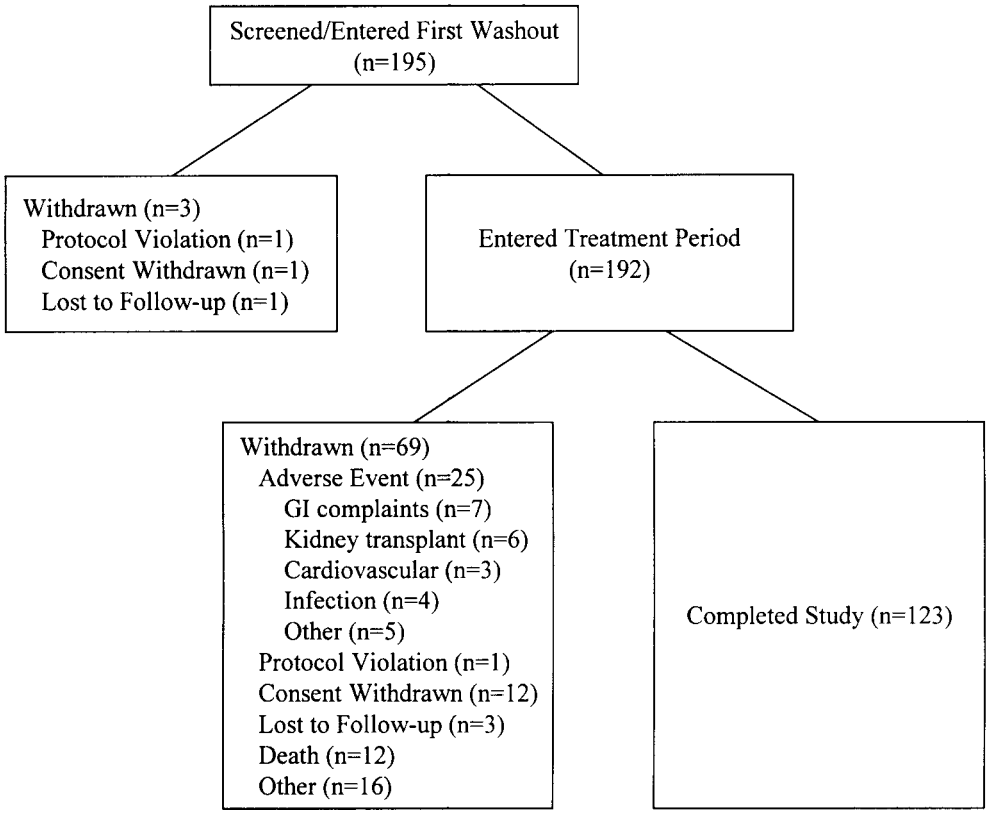

Fig. 2. Flow of study subjects and reasons for withdrawal.

with corresponding end of treatment values of 1.77, 2.23, and 2.19 mmol/l. Sevelamer lowered serum phosphorus whether or not an increase in vitamin D metabolite therapy was prescribed. The mean change in serum phosphorus among patients who increased vitamin D was -0.55 ± 0.65 mmol/l and -0.81 ± 0.81 mmol/l among patients with no change or a decrease in vitamin D dosage ($P < 0.001$ for both comparisons). For those subjects who were not withdrawn from the study prematurely, the mean serum phosphorus at study completion was 1.97 mmol/l (median 1.87 mmol/l, corresponding to 5.79 mg/dl).

Calcium

The mean serum calcium after pre-treatment washout was 2.28 ± 0.20 mmol/l and after treatment 2.35 ± 0.20 mmol/l, corresponding to a mean change in serum calcium of 0.08 ± 0.22 mmol/l ($P < 0.0001$). There was no significant change in serum calcium concentration from the end of treatment to the end of the post-treatment washout. The small but significant increase in serum calcium was evident across sevelamer dose groups, with no apparent dose effect. The magnitude of the increase in serum calcium was not dependent on whether vitamin D dosage was increased (mean increase 0.12 ± 0.20 *vs* 0.05 ± 0.22 mmol/l in patients with an increase, and patients with no change or a decrease in vitamin D dosage, respectively). The average incidence of hypercalcaemia (serum calcium $\geqslant 2.75$ mmol/l) was $<2\%$, confirming prior reports that sevelamer does not promote hypercalcaemia.

Calcium × phosphate product

The mean calcium × phosphate product after the pre-treatment washout was 6.32 ± 1.60 mmol/l, and at the end of treatment was 4.86 ± 1.45 mmol/l, corresponding to a mean change of -1.46 ± 1.78 mmol/l ($P < 0.0001$). After 2 weeks of post-treatment washout, the calcium × phosphate product increased by 1.24 ± 1.31 mg/dl ($P < 0.0001$). The reduction in the calcium × phosphate product was most pronounced in the high-dose sevelamer group (mean change -1.20, -1.10, -1.82 mmol/l in the low-, medium-, and high-dose groups, respectively), mirroring the trend observed for the serum phosphorus concentration. The mean pre-treatment levels of the calcium × phosphate product were 5.45, 6.37, and 6.86 mmol/l in the low-, medium-, and high-dose groups, respectively, and the corresponding end of treatment values were 4.25, 5.26, and 5.05 mmol/l. The calcium × phosphate product was reduced in subjects whether or not they were prescribed an increase in vitamin D dosage, although the reduction was more pronounced in those subjects whose vitamin D dosage was not increased (-1.73 ± 1.82 *vs* -0.94 ± 1.60 mmol/l). For those subjects who were not withdrawn from the study prematurely, the mean calcium × phosphate product at study completion was 4.67 ± 1.36 mmol/l (median 4.41 mmol/l, correspond-

Table 2. Phosphorus, calcium, and $Ca \times PO_4$ product over time, mean ± SD (median)

Weeks on treatment	*N*	Phosphorus	Calcium	Calcium × phosphorus	Intact PTH
Washout	192	2.81 ± 0.71 (2.71)	2.28 ± 0.20 (2.28)	6.33 ± 1.61 (6.27)	401 ± 378 (287)
3	187	2.32 ± 0.61 (2.32)	2.30 ± 0.18 (2.33)	5.36 ± 1.39 (5.41)	
4	177	2.20 ± 0.58 (2.16)	2.30 ± 0.20 (2.30)	5.04 ± 1.27 (4.92)	
6	179	2.13 ± 0.61 (2.07)	2.30 ± 0.18 (2.33)	4.87 ± 1.33 (4.74)	
10	175	2.07 ± 0.55 (2.00)	2.33 ± 0.18 (2.33)	4.82 ± 1.26 (4.59)	397 ± 411 (263)
14	170	2.16 ± 0.65 (2.07)	2.30 ± 0.18 (2.30)	4.96 ± 1.52 (4.64)	
18	161	2.07 ± 0.58 (1.97)	2.33 ± 0.20 (2.33)	4.78 ± 1.36 (4.71)	363 ± 390 (231)
22	152	2.07 ± 0.58 (2.00)	2.33 ± 0.20 (2.30)	4.77 ± 1.34 (4.71)	
26	146	2.13 ± 0.61 (2.07)	2.35 ± 0.18 (2.33)	5.01 ± 1.45 (4.79)	400 ± 432 (253)
30	142	2.10 ± 0.68 (2.03)	2.33 ± 0.20 (2.35)	4.89 ± 1.58 (4.78)	
34	134	2.10 ± 0.61 (2.10)	2.35 ± 0.20 (2.33)	4.93 ± 1.50 (4.96)	377 ± 386 (235)
38	124	2.03 ± 0.61 (1.94)	2.33 ± 0.20 (2.33)	4.77 ± 1.49 (4.50)	
42	124	2.00 ± 0.58 (1.94)	2.33 ± 0.25 (2.33)	4.62 ± 1.38 (4.65)	
46	111	1.97 ± 0.58 (1.87)	2.35 ± 0.18 (2.38)	4.67 ± 1.36 (4.41)	387 ± 471 (225)

For phosphorus, to convert to mg/dl, divide by 0.3229.
For calcium, to convert to mg/dl, divide by 0.25.

ing to 54.6 mg/dl). Figure 3 depicts the trends over time in phosphorus, calcium, and calcium × phosphate product for all subjects throughout the study period.

Parathyroid hormone

The median PTH after the pre-treatment washout was 287 pg/ml. Overall, there was no significant change in PTH over the treatment period (median change −18.0 pg/ml, $P = 0.40$). There was a significant interaction between the change in PTH and sevelamer dose, a proxy for the severity of hyperphosphataemia (median change −55.0, −16.5, and +10.0 pg/ml in the low-, medium-, and high-dose groups, respectively, $P = 0.003$). This trend was present whether or not an increase in vitamin D dosage was prescribed. The median PTH of subjects who completed the study was 225 pg/ml. It is noteworthy that the PTH was controlled without induction of hypercalcaemia.

LDL and HDL cholesterol

The mean change in LDL cholesterol with treatment was −0.82 ± 0.74 mmol/l ($P < 0.0001$), corresponding to an average decrease of 30% from baseline. The mean change in HDL cholesterol was 0.15 ± 0.29 mmol/l ($P < 0.0001$), corresponding to an average increase of 18% from baseline. Triglyceride levels were not significantly changed (median change −0.07 mmol/l). Changes in LDL and HDL cholesterol were dependent on the starting LDL cholesterol concentration (Table 3). Subjects with higher baseline LDL concentrations experienced more pronounced changes in the lipid profile after treatment with sevelamer (Figure 4).

Other laboratory values

Magnesium was significantly increased (mean change 0.04 ± 0.12 mmol/l, $P = 0.0007$). Uric acid was significantly decreased (mean change −47.6 ± 77.3 μmol/l, $P < 0.0001$). There were increases in the serum chloride (mean change 1.3 ± 4.2 mmol/l, $P < 0.0001$) and bicarbonate (mean change 1.3 ± 4.8 mmol/l, $P = 0.0003$) that were statistically significant, but extremely small in magnitude and of questionable clinical significance. There were no changes in levels of serum albumin or total protein, liver enzymes, or bilirubin. There was a significant increase in the alkaline phosphatase (mean 32.3 ± 72.6 U/l, $P < 0.0001$) as had been observed in previous studies [17–19]. There was no change in the serum levels of the fat-soluble vitamins A and E.

Discussion

This long-term study confirms and extends prior reports that sevelamer is effective at lowering serum

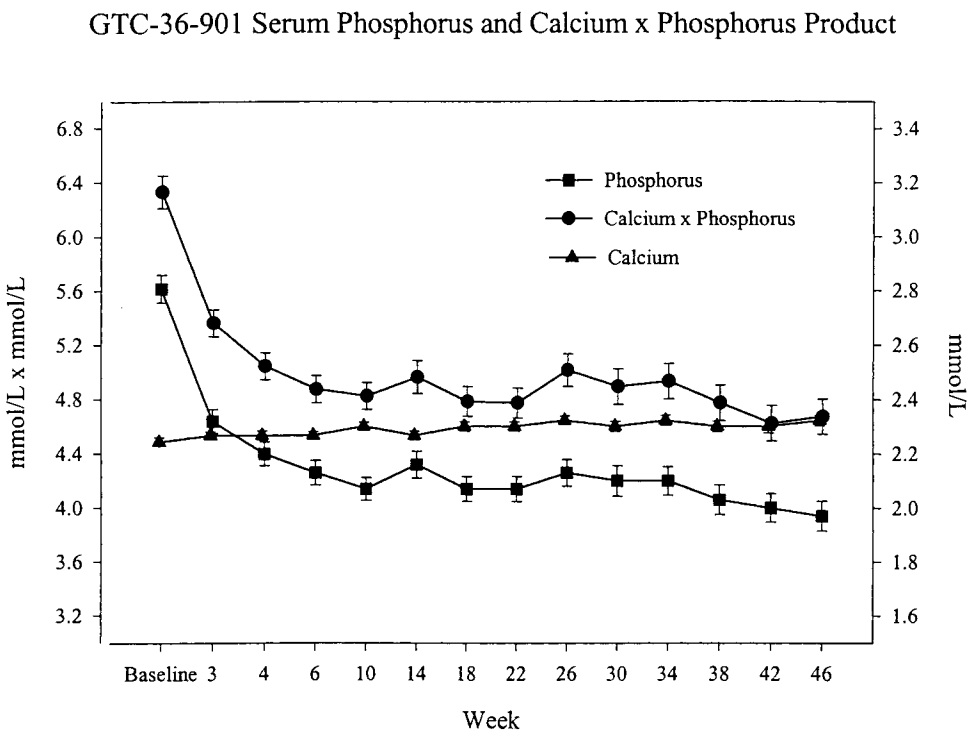

Fig. 3. Trends in phosphorus, calcium, and calcium × phosphate product.

Table 3. Lipid levels stratified by initial LDL cholesterol

		<2.58	2.58–3.33	3.36–4.11	⩾4.13
LDL-C	Baseline	2.06	2.93	3.68	4.82
	Final	1.54	2.05	2.53	2.85
HDL-C	Baseline	0.95	0.93	0.95	0.93
	Final	1.07	1.07	1.17	1.19
TG	Baseline	1.34	1.63	1.60	2.22
	Final	1.21	1.49	1.46	1.84

LDL-C = low density lipoprotein cholesterol, HDL-C = high density lipoprotein cholesterol, TG = triglycerides (presented as median), all units in mmol/l.

phosphorus in haemodialysis patients. Serum phosphorus was significantly reduced by sevelamer treatment, with a corresponding reduction in the calcium × phosphate product. The beneficial effect of sevelamer on serum phosphorus and the calcium × phosphate product was sustained over time.

Serum calcium was slightly but significantly increased, even among patients with no change or a decrease in their vitamin D dosage. There are two likely explanations for this phenomenon. First, since sevelamer competes with dietary calcium for phosphate binding, more free calcium may be absorbed with sevelamer treatment. Second, with reduction in the serum phosphorus concentration and the calcium × phosphate product induced by sevelamer, there may be less deposition of calcium phosphate crystals in tissue, thereby raising the calcium concentration in serum.

The slight increase in bicarbonate concentration confirms the fact that sevelamer does not promote metabolic acidosis, either directly or secondary to the loss of base (carbonate or acetate with calcium). The mild hypouricaemic effect of sevelamer has not been previously observed, and may relate to the competitive binding of urate, another organic anion. The increase in alkaline phosphatase has been previously observed, and most likely relates to the effect of sevelamer on bile acid metabolism. Similar laboratory changes have been observed in studies of cholestyramine and other bile acid sequestrants, without any clinically apparent hepatic or systemic effects over time [20–22]. It is noteworthy that there was no change in the serum albumin concentration over time, suggesting no adverse effect on nutritional status or the inflammatory response.

The reduction in the calcium × phosphate product may prove to be among the most important of sevelamer's benefits. A recent study by Block *et al.* [23] utilized laboratory data collected on two representative cohorts of US haemodialysis patients. With a calcium × phosphate product of 3.47–4.19 mmol/l as a referent category (quintile 2 of 5), there was a steady increase in the relative risk (RR) of death with higher levels of calcium × phosphate product (unadjusted RR 1.08, 1.13, and 1.34 for 4.27–4.84, 4.92–5.81, and 5.89–10.65 mmol/l, respectively). These and other authors have hypothesized that higher levels of the calcium × phosphate product might promote vascular calcification, and lead to decreased survival related to cardiovascular disease. While the mechanism remains

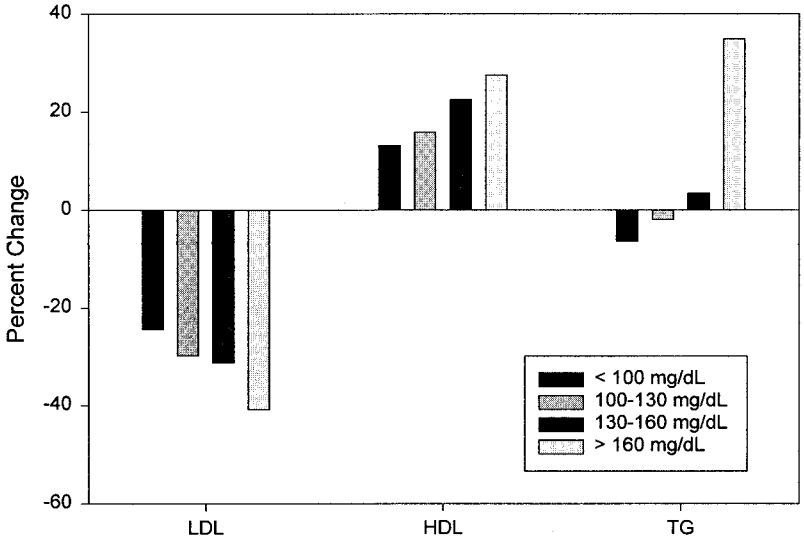

Fig. 4. Percent change in LDL cholesterol, HDL cholesterol, and triglyceride values in groups stratified by initial LDL cholesterol concentration.

to be proved, a relative reduction in the calcium × phosphate product of as little as 0.4–0.8 mmol/l might appreciably improve survival in this population.

The relative benefits of modifying the lipid profile in haemodialysis patients are also unknown. Although large cohort studies have shown that patients with total cholesterol levels in the 5.17–6.46 mmol/l range experience the lowest all-cause mortality rates [24], these and other studies of cholesterol and mortality are confounded by malnutrition, hepatic, and inflammatory diseases [25]. The risk of myocardial ischaemia and infarction is increased by more than an order of magnitude in patients with ESRD compared with non-uraemic age- and sex-matched individuals [26] and elevated serum cholesterol concentrations have been shown to predict cardiac death in patients with ESRD and diabetes [27]. As might be expected, patients with ESRD have been excluded from large clinical trials of HMG-CoA reductase inhibitors and other lipid profile-modifying agents. Nevertheless, changes in LDL and HDL cholesterol of the magnitude induced by sevelamer in this study would be expected to reduce the rate of cardiovascular disease, and potentially increase survival in this population. Prevention may be a particularly effective strategy in this setting, given that survival rates for patients with ESRD and acute myocardial infarction are less than 50% at 1 year [28]. Whether there might be an additive or synergistic effect of modifying the lipid profile and lowering calcium × phosphate product is unknown. Evaluation of the cost-effectiveness of sevelamer is another important area of inquiry. Finally, although control of phosphorus was similar to that observed in other clinical trials of phosphate binders, levels in the range of 2 mmol/l should not be considered 'optimal'. More intensive dose titrations, more aggressive management of hyperparathyroidism (to limit the contribution to hyperphosphataemia of endogenous, non-dietary phosphorus), and alternative analytic techniques (note that the 'last value carried forward' method biases toward nil effect) might highlight the efficacy of sevelamer and other phosphate binders in future clinical investigations.

In summary, a 1-year, open-label trial of the non-aluminum-and non-calcium-containing phosphate binder sevelamer in haemodialysis patients demonstrated sustained reductions in serum phosphorus, and adequate control of hyperparathyroidism without promoting hypercalcaemia. Treatment with sevelamer resulted in sustained, favourable changes in the calcium × phosphate product and lipid profile. Further experience with this agent will help to define its ultimate role in the management of hyperphosphataemia and other metabolic complications of ESRD.

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References

1. Slatopolsky E, Lopez-Hilker, Delmez J, Dusso A, Brown A, Martin KJ. The parathyroid-calcitriol axis in health and chronic renal failure. *Kidney Int Suppl* 1990; 29: S41–S47
2. Gonzalez EA, Martin KJ. Renal osteodystrophy: pathogenesis and management. *Nephrol Dial Transplant* 1995; 3: 13–21
3. Piraino B, Chen T, Cooperstein L, Segre G, Puschett J. Fractures and vertebral bone mineral density in patients with renal osteodystrophy. *Clin Nephrol* 1988; 30: 57–62
4. Rao DS, Shih MS, Mohini R. Effect of serum parathyroid hormone and bone marrow fibrosis on the response to erythropoetin in uremia. *N Engl J Med* 1993; 328: 171–175
5. Massry SG, Goldstein DA. Role of parathyroid hormone in uremic toxicity. *Kidney Int Suppl* 1978; 8: S39–S42
6. Bogicevic M, Stefanovic V. Relationship between parathyroid hormone and pituitary-testicular axis in patients on maintenance hemodialysis. *Exp Clin Endocrinol* 1988; 92: 357–362
7. Bro S, Olgaard K. Effects of excess PTH on nonclassical target organs. *Am J Kidney Dis* 1997; 30: 606–620
8. Fliser D, Franek E, Fode P, Stefanski A, Schmitt CP, Lyons M, Ritz E. Subacute infusion of physiologic doses of parathyroid

hormone raises blood pressure in humans. *Nephrol Dial Transplant* 1997; 12: 933–938
9. Nishizawa Y, Shoji T, Kawagishi T, Morii H. Atheroslcerosis in uremia: possible roles of hyperparathyroidism and intermediate density lipoprotein accumulation. *Kidney Int Suppl* 1997; 62: S90–S92
10. Slatopolsky E, Finch J, Denda M, Ritter C, Zhong M, Dusso A, MacDonald PN, Brown AJ. Phosphorus restriction prevents parathyroid gland growth: High phosphorus directly stimulates PTH secretion *in vitro*. *J Clin Invest* 1996; 97: 2534–2540
11. Goodman WG. Bone disease and aluminum: pathogenic considerations. *Am J Kidney Dis* 1985; 6: 330–335
12. Drueke TB, Lacour B, Touam M, Jacquel JP, Plachot JJ, Cournot-Witmer G, Galle P. Effect of aluminum on hematopoesis. *Kidney Int Suppl* 1986; 18: S45–S48
13. Arieff AI. Aluminum and the pathogenesis of dialysis encephalopathy. *Am J Kidney Dis* 1985; 6: 317–321
14. Slatopolsky EA, Weerts C, Lopez-Hilker S, Norwood K, Zink M, Windus D, Delmez JA. Calcium carbonate as a phosphate binder in patients with chronic renal failure undergoing dialysis. *N Engl J Med* 1986; 315: 157–161
15. Mai ML, Emmet M, Sheikh MS, Santa Ana CA, Schiller L, Fordtran JS. Calcium acetate, and effective phosphorus binder in patients with renal failure. *Kidney Int* 1989; 36: 690–695
16. Meric F, Yap P, Bia MJ. Etiology of hypercalcemia in hemodialysis patients on calcium carbonate therapy. *Am J Kidney Dis* 1990; 16: 459–464
17. Chertow GM, Burke SK, Lazarus JM, Stenzel KH, Wombolt D, Goldberg D, Bonventre JV, Slatopolsky E. Poly[allylamine hydrochloride] (RenaGel): a non-calcemic phosphate binder for the treatment of hyperphosphatemia in chronic renal failure. *Am J Kidney Dis* 1997; 29: 66–71
18. Bleyer AJ, Garrett B, Kant KS, Lynch D, Rahman N, Schoenfeld P, Teitelbaum I, Zeig S, Slatopolsky E. An open-label, cross-over study of the new phosphate binder RenaGel in the management of hyperphosphatemia in ESRD patients. *Am J Kidney Dis* 1999; 33: 694–701
19. Chertow GM, Dillon M, Burke SK *et al.* A randomized trial of sevelamer hydrochloride (RenaGel) with and without supplemental calcium: strategies for the control of hyperphosphatemia and hyperparathyroidism in hemodialysis patients. *Clin Nephrol* 1999; 51: 18–26
20. Molgaard H, von Schenck H, Olsson AG. Comparative effects of simvastatin and cholestyramine in treatment of patients with hypercholesterolemia. *Eur J Clin Pharmacol* 1989; 36: 455–460
21. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial Results. I. Reduction in incidence of coronary heart disease. *JAMA* 1984; 251: 351–364
22. Probstfield JL, Statland BE, Gorman L, Hunninghake DB. Alterations in human serum alkaline phosphatase and its isoenzymes by hypolipidemia agents: colestipol and clofibrate. *Metabolism* 1983; 818–821
23. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium × phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis* 1998; 31: 607–617
24. Lowrie EG, Lew NL. Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis* 1990; 15: 458–482
25. Owen WF, Lowrie EG. C-reactive protein as an outcome predictor for maintenance hemodialysis patients. *Kidney Int* 1998; 54: 627–636
26. Ma KW, Greene EL, Raji L. Cardiovascular risk factors in chronic renal failure and hemodialysis populations. *Am J Kidney Dis* 1992; 19: 505–513
27. Tschope W, Koch M, Thomas B, Ritz E, and the German Study Group Diabetes and Uremia. Serum lipids predict cardiac death in diabetic patients on maintenance hemodialysis. *Nephron* 1993; 64: 354–358
28. Herzog CA, Ma JZ, Collins AJ. Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. *N Engl J Med* 1998; 339: 799–805

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