NEPHROLOGY 2004; **9**, 406–413

Original Article

Efficacy and side-effect profile of sevelamer hydrochloride used in combination with conventional phosphate binders

JOANNA M STURTEVANT, CARMEL M HAWLEY, KYLIE REIGER, DAVID W JOHNSON, SCOTT B CAMPBELL, JOHN R BURKE, ANDREW BOFINGER and NICOLE M ISBEL

Department of Nephrology, Princess Alexandra Hospital, Brisbane, Queensland, Australia

SUMMARY:

Background: Poor phosphate control is common among patients with end-stage renal disease. Sevelamer hydrochloride has been demonstrated to be a safe and effective phosphate binder when used as a monotherapy. However, cost limits its usefulness in many countries. Data assessing its effectiveness and safety in combination with conventional phosphate binders are lacking.

Methods: Dialysis patients meeting the following inclusion criteria participated in this study: (i) hyperphosphataemia >1.8 mmol/L (5.6 mg/dL); and (ii) an inability to tolerate currently available binders. The trial was conducted in three phases each lasting 3 months: (i) an observation phase (patients continued on their regular phosphate binders); (ii) a titration phase (sevelamer was added at a dose of 403 mg three times daily with meals, titrated to a maximum of 1209 mg three times daily); and (iii) a maintenance phase.

Results: Twenty-five patients were recruited into the study. Eighteen patients completed all three trial phases. Mean serum phosphate dropped from 2.11 ± 0.06 mmol/L (6.6 ± 0.2 mg/dL) during the observation period to 1.91 ± 0.01 mmol/L (5.9 ± 0.003 mg/dL) during the maintenance phase ($P = 0.02$). Calcium × phosphate product fell from 5.49 ± 0.17 $mmol^2/L^2$ (68.64 ± 2.11 $mg^2\ dL^2$) to 4.89 ± 0.27 $mmol^2/L^2$ (61.36 ± 3.35 $mg^2\ dL^2$) ($P = 0.02$). There was no significant change in serum calcium or parathyroid hormone. Total serum cholesterol fell from 3.8 mmol/L (3.4–4.37) 147 mg/dL (131–169) to 3.55 mmol/L (2.97–4.2) 137 mg/dL (115–162) ($P = 0.02$). Serum low-density lipoprotein cholesterol also fell significantly from 1.67 ± 0.10 mmol/L (65 ± 4 mg/dL) to 1.52 ± 0.11 mmol/L (59 ± 4 mg/dL) ($P = 0.04$). The average prescribed dose of sevelamer was 2.4 g/day. Elemental calcium dropped from 3.4 g/day (1.4 to 4.6) to 1.2 g/day (0.6–2.4) ($P = 0.04$). Seventy-two per cent of patients reported mild flatulence, nausea and indigestion. Three patients discontinued treatment because of adverse effects.

Conclusions: Sevelamer in combination with conventional phosphate binders is effective in lowering serum phosphate and calcium-phosphate product in patients with refractory hyperphosphataemia. Beneficial effects on lipid profile were also observed. Mild gastrointestinal upset is common.

KEY WORDS: **calcium × phosphate product, calcium, dialysis, parathyroid hormone, phosphate, sevelamer hydrochloride.**

INTRODUCTION

It has been well established that hyperphosphataemia plays a key role in the pathogenesis of bone disease in patients with renal impairment. Recent data demonstrating an association between hyperphosphataemia and mortality has, however, shifted the focus from the role of hyperphosphataemia in renal bone disease to the role of disturbed mineral metabolism in the pathogenesis of cardiovascular disease.

Cardiovascular mortality accounts for the deaths of approximately 50% of all dialysis patients, a figure that is dramatically higher than that of the general population. In a large observational study, serum phosphate (P) and calcium-phosphate product (Ca × P) were shown to be

Correspondence: Ms Joanna M Sturtevant, Department of Pharmacy, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Brisbane, Qld 4102, Australia.
Email: jo_sturtevant@health.qld.gov.au

Accepted for publication 26 August 2004.

independent risk factors for mortality in dialysis patients. A serum P level greater than 2.1 mmol/L (6.5 mg/dL) is associated with a 27% increase in mortality compared with a serum P of between 1.42 mmol/L (4.4 mg/dL) and 1.78 mmol/L (5.5 mg/dL). Patients with a Ca × P greater than 5.8 $mmol^2/L^2$ (72.5 mg^2 dL^2) have a 34% higher risk of death than those patients with a product between 3.38 and 4.19 $mmol^2/L^2$ (42.25 and 52.38 mg^2 dL^2).[1] Furthermore, there is increasing evidence that the high prevalence of vascular, cardiac and visceral calcification and an associated reduction in arterial compliance in dialysis-dependent patients is rising.

Thus, increasing recognition is being given to the role of abnormal mineral metabolism and secondary hyperparathryoidism in the morbidity and mortality of end-stage renal disease (ESRD), particularly cardiovascular disease. Moreover, attention is being redirected to the critical importance of controlling serum P to improve outcomes in ESRD patients. Recent recommendations suggest a target serum of P <1.75 mmol/L (5.4 mg/dL).[2]

The recommended targets for serum P and Ca × P are frequently difficult to achieve with conventional phosphate binders. Calcium, aluminium and magnesium salts, the mainstays of therapy for many years, are associated with significant problems including the absorption of free cations. Aluminium administration is associated with dementia, bone disease and anaemia. The large doses of calcium salts required for phosphate binding limit their utility because of the associated symptomatic hypercalcaemia and constipation. Furthermore, recent evidence supports a role for calcium-containing P binders in the pathogenesis of cardiovascular disease.[3] Magnesium-containing P binders have poor efficacy and may induce hypermagnesaemia.

Alternative novel phosphate binders have been developed. Sevelamer hydrochloride is a non-absorbed phosphate binding polymer.[4] Previous studies have shown sevelamer monotherapy to be effective in reducing serum phosphate levels.[5–10] Beneficial effects on lipid profiles have also been reported,[5–9,11] as well as evidence consistent with less aortic and coronary calcification compared with calcium acetate.[12] However, the major problems with the use of sevelamer as a single agent have been that target P concentrations are difficult to meet and, not to be understated, this agent is significantly more expensive than other P binders, which limits its availability in many countries.[13,14]

We postulated that sevelamer might be best used in combination with other available P binders, thereby optimizing P control and limiting cost. There is a paucity of information in the literature examining the combination of sevelamer with conventional P binders to achieve desired targets. One study examined the use of sevelamer in combination therapy with the aim of decreasing calcium carbonate binders rather than to treat a target serum P. [15]

Therefore, we designed a study to explore the efficacy of combinations of aluminium hydroxide, calcium carbonate and magnesium salts with sevelamer hydrochloride in dialysis patients with refractory hyperphosphataemia. Our primary aim was to achieve a decrease in predialysis serum P to 0.2 mmol/L (0.6 mg/dL). Our secondary aims were to achieve an average serum P of <1.8 mmol/L (5.6 mg/dL), to explore the side-effect profile, particularly gastrointestinal tract (GIT) disturbance, lipid effects, serum bicarbonate levels, effect on vitamin K and liver function tests and to assess the cost of sevelamer when used in this manner.

METHODS

Patients

All 280 patients receiving dialysis (43% peritoneal dialysis and 57% haemodialysis) at Princess Alexandra Hospital at the commencement of the study (March 2001) were eligible provided that they met the following inclusion criteria: (i) hyperphosphataemia >1.8 mmol/L; and (ii) an inability to tolerate a higher dose of conventional binders because of hypercalcaemia, a serum aluminium of >2 mmol/L or other dose-limiting side-effects. One hundred and sixteen of the 280 dialysis patients (41%) in our department were eligible on the basis of a serum P level >1.8 mmol/L. From this group we chose 25 patients who were willing to consent to the study and who were unable to tolerate higher doses of conventional binders. All patients in the study met the usual minimum standard for dialysis adequacy. Haemodialysis patients had an equilibrated Kt/V of >1.0 and were dialysed three times per week for between 4 h and 5 h per session. Patients on peritoneal dialysis had a creatinine clearance per week of >60 L/week/1.73 m^2. Informed consent was obtained from all patients prior to their participation in the trial and the study protocol was reviewed and approved by the Princess Alexandra Hospital Research Ethics Committee.

Study protocol

This study followed a prospective, interventional design whereby patients acted as their own controls. The trial was conducted in three phases: (i) an observation phase where patients continued on their regular phosphate binders; (ii) a titration phase where patients were commenced on 403 mg sevelamer hydrochloride (Renagel, Genzyme BV, Naarden, The Netherlands) three times a day with meals, titrated up to a maximum of 1209 mg (three capsules) three times a day, with the aim of achieving a P level <1.8 mmol/L (5.6 mg/dL) based on a P level carried out monthly; and (iii) a maintenance phase. Each phase lasted 3 months. Patients were instructed to take the capsules with meals.

Sevelamer hydrochloride was added to the patients' current phosphate-binding therapy, which included any combination of calcium carbonate, aluminium hydroxide and magnesium trisilicate. Treating physicians were able to alter the dose of the P binders other than sevelamer if clinically appropriate. Dialysate calcium concentration was stable throughout the period of the study, with the majority of patients using a dialysate calcium of 1.3 mmol/L (5.2 mg/dL). Elemental calcium dose was estimated only from the content of the P binder. Dietary calcium intake was not formally estimated. No specific dietary advice or additional education was given to patients in the trial other than the

standard practice of our unit. Patients' lipid-lowering therapy could not be altered throughout the study. There were no other restrictions on the provision of vitamin D metabolites or other conventional or alternative drug therapies during the course of the study. However, prescribed calcitirol doses and changes throughout the study were analysed.

Blood samples were collected at monthly intervals during the study for the determination of serum phosphate, calcium, calcium × phosphate product, serum magnesium, serum bicarbonate and liver function tests. Serum aluminium, intact parathyroid hormone, international normalized ratio (INR) and serum lipids were monitored every 3 months. All haemodialysis patients had their blood tests collected immediately prior to the dialysis session.

Adverse gastrointestinal events such as nausea, constipation, diarrhoea, flatulence and indigestion were recorded at monthly intervals. Patients documented all adverse effects on an event form, which was collected at each clinic visit. Compliance with phosphate binders was assessed by checking pharmacy dispensing records.

Statistical analysis

Results are expressed as mean ± SEM or median and interquartile range for continuous data depending on the data distribution, and as frequencies and percentages for categorical data. Paired *t*-tests were used for analysis of parametric variables and the Wilcoxon rank sum test for non-parametric data. In the primary analyses, the mean of the three values obtained during the observation period was compared with the mean of the three values obtained during the maintenance phase for all parameters. Repeated measures analysis used the method of generalized estimating equation (GEE),[16] which uses changes in the above parameters over the entire study (i.e. all values during the observation, titration and maintenance periods were included in the repeated measures analysis). Sex, diabetic status and the type of dialysis were included as explanatory variables in the multivariate analysis of change in serum P and Ca × P. A *P*-value of <0.05 was considered significant.

Power calculations indicated that a minimum of 20 patients would be required to have 80% power of detecting a difference of 0.2 mmol/L (0.6 mg/dL) in serum P over the course of the study, assuming a SD of 0.3 mmol/L (0.9 mg/dL) and setting alpha at 0.05. Allowing for an attrition rate of approximately 33% (for death, renal transplantation, withdrawal from the study), 25 patients were enrolled in the study. Data analysis was carried out using STATA Version 8, Stata Corporation (College Station, TX, USA).

RESULTS

Patients

Twenty-five patients were recruited into the study. Patient characteristics as depicted in Table 1 include: Caucasoid (84%), majority on haemodialysis (80%) rather than peritoneal dialysis, diabetic (25%), male (64%), median duration of dialysis 1.75 years (1.1–2.8) and mean age 47.7 ± 2.64 years. All patients in the study were on a combination of P binders. Twenty-eight per cent of patients were taking three different P binding agents and 60% of patients were taking calcitriol. Ninety-two per cent of patients were taking statins. Seven patients did not complete the study because of renal transplantation ($n = 2$), parathyroidectomy ($n = 1$), death ($n = 1$) or patient-requested withdrawal because of adverse effects ($n = 3$). Our 25 patients were representative of the 116 dialysis patients with serum P >1.8 mmol/L at the time of patient selection with respect to sex (64% of patients were male vs 72%), race (84% Caucasoid *vs* 90%), dialysis modality (80% on haemodialysis *vs* 72%), duration of ESRD (median 1.75 *vs* 2.5 years, $P = 0.3$) and diabetic status (25% were diabetic *vs* 40%). However, the study patients were younger (47.7 ± 2.6 *vs* 57.6 ± 15.12 years, $P = 0.007$) and had a lower serum P (2.11 ± 0.30 *vs* 2.29 ± 0.46, $P = 0.03$) compared to patients with serum P >1.8 mmol/L that did not participate in the study.

Serum phosphate control

Changes in serum phosphate over time are shown in Table 2 and Figure 1. Serum phosphate improved significantly over the course of the study (mean serum phosphate 2.11 ± 0.06 mmol/L (6.6 ± 0.2 mg/dL) during the observation period versus 1.91 ± 0.01 mmol/L (5.9 ± 0.003 mg/dL) during the maintenance period ($P = 0.02$). Using repeated measures analysis (GEE) the change in serum phosphate levels between the observation period and the maintenance period was highly significant ($P = 0.001$). Seven of the 18 patients (38%) who completed the study reached the target serum phosphate of <1.8 mmol/L (5.6 mg/dL). Age, diabetic status, sex and dialysis type were not predictive of phosphate changes in response to sevelamer in the multivariate analysis.

Table 1 Baseline patient characteristics of the study population

n	25
Age (years)	47.7 ± 2.6
Sex (%male)	64
Caucasoid (%)	84
Diabetes (%)	25
Duration of end-stage renal disease (year)	1.75 (1.1–2.8)
Dialysis modality: haemodialysis (%)	80
Phosphate binders:	
Aluminium hydroxide and calcium carbonate (%)	56
Aluminium hydroxide and magnesium trisilicate (%)	12
Calcium carbonate + aluminium hydroxide + magnesium trisilicate (%)	28
Calcium carbonate + magnesium trisilicate (%)	4
Usage of vitamin D analogue (%)	60
Taking statins (%)	92

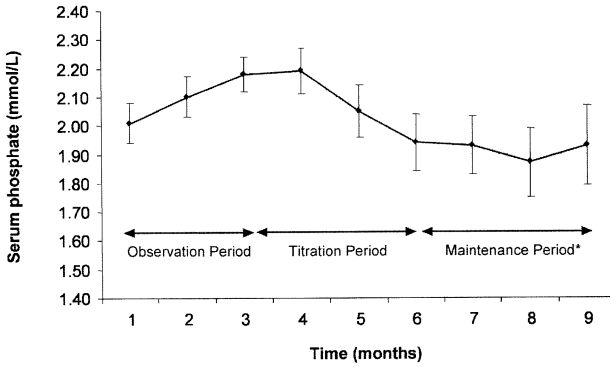

Fig. 1 Serum phosphate (mmol/L) during the three consecutive periods of the trial, the observation period (3 months), the titration period (3 months) and the maintenance period (3 months). $n = 25$; $^*P = 0.02$ versus observation period.

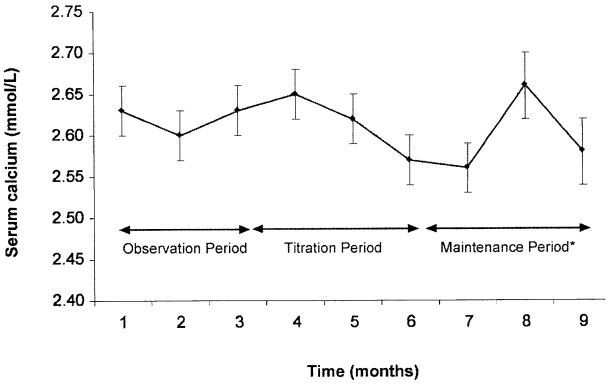

Fig. 2 Serum calcium (mmol/L) during the three consecutive periods of the trial, the observation period (3 months), the titration period (3 months) and the maintenance period (3 months) ($n = 25$). No statistically significant differences were observed.

Calcium × phosphate, serum calcium and intact PTH

Changes in serum calcium and in the Ca × P are shown in Table 2 and in Figures 2 and 3, respectively. There was a significant difference in Ca × P in the observation and maintenance phases, 5.49 ± 0.17 mmol^2/L^2 (68.64 ± 2.11 mg^2 dL^2) versus 4.89 ± 0.27 mmol^2/L^2 (61.36 ± 3.35 mg^2 dL^2) ($P = 0.02$). Using repeated measures analysis (GEE) the change in Ca × P between the observation and maintenance periods was highly significant ($P = 0.000$). Age, diabetic status, sex and dialysis type were not predictive of the change in Ca × P in response to sevelamer in the multivariate analysis.

There was no significant change in serum calcium during the study (serum calcium 2.6 ± 0.03 mmol/L (10.5 mg/dL ± 0.1) compared with 2.6 ± 0.03 mmol/L (10.4 mg/dL ± 0.1) for the observation and maintenance periods, respectively, $P = 0.38$). Serum intact PTH did not change during the course of the study, 25.5 pmol/L (13–75) 242.17 pg/mL (123.46–712.25) compared with 25.5 pmol/L (12–49) 242.17 pg/mL (113.96–465.34) in the observation and maintenance periods, respectively ($P = 0.22$).

Dose of phosphate binders and vitamin D during the trial

During the maintenance phase the average dose of sevelamer was 2418 mg/day (two sevelamer 403 mg capsules with each meal). The lowest sevelamer dose taken was one capsule with each meal. Seven patients were taking the maximum dose of nine capsules per day (total daily dose 3627 mg).

During the maintenance phase of the study there was a non-statistically significant trend towards patients taking a greater total number of phosphate-binding tablets (9.6 compared with 11 tablets per day).

Elemental calcium dose dropped significantly from 3.4 g/day (1.4–4.6) to 1.3 g/day (0.3–3.0), $P = 0.002$, over the course of the study. A statistically significant fall was also observed in the aluminium hydroxide dose from 2.0 g/day (1.6–3.2) to 1.2 g/day (0.6–2.4), $P = 0.04$. There was no significant change in the dose of magnesium trisilicate or calcitriol (Table 2).

Lipid effects

Total serum cholesterol fell during the study from 3.80 mmol/L (3.4–4.37) 147 mg/dL (131–169) to 3.55 mmol/L (2.97–4.2) 137 mg/dL (115–162) during the observation and maintenance periods, respectively ($P = 0.02$). Serum LDL also fell significantly from 1.67 ± 0.10 mmol/L (65 ± 4 mg/dL) to 1.52 ± 0.11 mmol/L (59 ± 4 mg/dL) ($P = 0.04$). There was a non-statistically significant trend towards a reduction in serum high-density lipoprotein cholesterol (HDL) during the study.

There was no significant change in serum triglycerides over the study period (Table 2).

International normalized ratio, serum bicarbonate, magnesium and aluminium levels and liver function tests

International normalized ratio, serum bicarbonate, magnesium and aluminium did not change significantly over the course of the study. No patients developed abnormal liver function tests during the study (Table 2).

Adverse events

During the observation period 39% of patients reported mild gastrointestinal symptoms. Following commence-

ment of sevelamer 38% of patients reported new symptoms of mild flatulence, nausea and indigestion, and a further 28% reported worsening in their baseline symptoms. Three patients ceased sevelamer because of intolerable gastrointestinal side-effects, including nausea, diarrhoea and abdominal cramping. One death occurred during the study, which was related to ischaemic bowel. This death was not judged by the investigators to be related to the treatment.

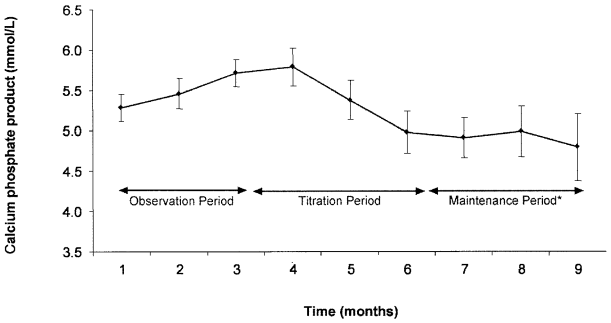

Fig. 3 Calcium × phosphate product ($mmol^2/L^2$) during the three consecutive periods of the trial, the observation period (3 months), the titration period (3 months) and the maintenance period (3 months). $n = 25$; $*P = 0.02$ versus observation period.

Costs

At the commencement of the study the average daily cost of conventional phosphate binders totalled $0.57 (AUD). The addition of sevelamer increased the average daily cost of phosphate-binding therapy to $6.31 (AUD).

DISCUSSION

The results of the present study demonstrate that sevelamer used in combination with conventional phosphate binders is effective at lowering serum P and Ca × P. To our knowledge this is the first prospective study to have used sevelamer in combination with conventional phosphate binders with the prime purpose of obtaining additional P-binding potential in patients with refractory hyperphosphataemia. The vast majority of previous work investigates the usefulness of sevelamer as a sole agent in reducing serum phosphate.[5–11]

The power calculation outlined in this study was based on our primary aim of achieving a 0.2 mmol/L fall in serum phosphate during the course of the study. Although we suffered a reduction in our calculated power (76% rather than 80%) because 18 rather than 20 patients completed the study, this is a positive study because we achieved the 0.2 mmol/L reduction in serum

Table 2 Primary and secondary outcome analyses

Variable	Observation period	Maintenance period	*P*
Serum phosphate mmol/L (mg/dL)	2.11 ± 0.06 (6.5 ± 0.2)	1.91 ± 0.10 (5.9 ± 0.3)	0.02
Serum calcium mmol/L (mg/dL)	2.61 ± 0.03 (10.5 ± 0.1)	2.60 ± 0.03 (10.4 ± 0.1)	0.38
Calcium × phosphate product $mmol^2/L^2$ (mg^2/dL^2)	5.49 ± 0.17 (68.25 ± 2.11)	4.89 ± 0.27 (61.36 ± 3.35)	0.02
PTH pmol/L (pg/mL)	25.5 (13–75) 242.17 (123.46–712.25)	25.5 (12–49) 242.17 (113.96–465.34)	0.22
Serum aluminium μmol/L (mg/L)	0.78 (0.7–1.4) 2.1 (1.89–3.77)	1.00 (0.7–1.3) 2.7 (1.89–3.51)	0.35
Serum magnesium mmol/L (mg/dL)	1.00 ± 0.05 2.4 ± 0.1	1.11 ± 0.05 2.7 ± 0.1	1.0
Serum bicarbonate mmol/L or mEq/L	24.08 ± 0.67	23.47 ± 0.72	0.2
Serum total cholesterol mmol/L (mg/dL)	3.80 (3.4–4.37) 147 (131–169)	3.55 (2.97–4.2) 137 (115–162)	0.02
Serum LDL cholesterol mmol/L (mg/dL)	1.67 ± 0.10 65 ± 4	1.52 ± 0.11 59 ± 4	0.04
Serum triglycerides mmol/L (mg/dL)	1.93 (1.33–2.50) 171 (118–221)	2.17 (1.57–2.40) 192 (139–213)	0.35
Serum HDL cholesterol mmol/L (mg/dL)	1.13 (0.93–1.2) 43.7 (35.96–46.4)	1.10 (1.0–1.2) 42.54 (38.67–46.4)	0.07
Calcitriol dose (mcg per day p.o.)	0.57 (0–1.3)	0.20 (0–1.0)	0.21
Elemental calcium dose (g/day)	3.4 (1.4–4.6)	1.3 (0.3–3.0)	0.002
Magnesium trisilicate (g/day)	1.8 (0–5.5)	0 (0–5.5)	0.8
Aluminium hydroxide dose (g/day)	2.0 (1.6–3.2)	1.2 (0.6–2.4)	0.04
INR	1.10 (1.00–1.15)	1.10 (1.00–1.15)	0.44

The values for the variables are the mean ± SEM or median and interquartile range for the three values for each variable taken during the observation and maintenance phases of the study. Comparisons were made by using either paired *t*-tests or Wilcoxon rank sum tests. HDL, high-density lipoprotein cholesterol; INR, international normalized ratio; LDL, low-density lipoprotein cholesterol; PTH, parathyroid hormone.

phosphate that we planned. However, we did not achieve the arguably more clinically relevant secondary aim of a reduction in mean serum phosphate to <1.8 mmol/L (5.6 mg/dL). Our patients achieved a mean serum phosphate of 1.91 mmol/L (5.9 mg/dL) and only seven of 18 (38%) patients reached the secondary endpoint of a serum phosphate level of <1.8 mmol/L (5.6 mg/dL) during the maintenance phase.

A previous study by McIntyre *et al.*[15] reported on the strategy of combining sevelamer with a reduced dose of calcium-containing phosphate binder with the express purpose of limiting hypercalcaemia. After 8 weeks of follow up, serum calcium significantly fell without a significant change in serum phosphate. Eighty-three per cent of patients in this study had a phosphate level of <2 mmol/L (6.2 mg/dL) at commencement. The absence of a fall in serum calcium in our study is consistent with many other studies including a meta-analysis.[7] Although McIntyre *et al.*[15] did record a fall in serum calcium their patients, unlike ours, were hypercalcaemic at baseline and their main aim was to reduce serum calcium and control P.

The magnitude of the effect of sevelamer in our study was a fall in serum P of 0.2 mmol/L (0.6 mg/dL) and a fall in Ca × P of 0.6 $mmol^2/L^2$ (7.5 mg^2/dL^2). In our study intact parathyroid hormone (iPTH) did not fall. Other published studies have shown a fall in P of between 0.39 and 1.45 mmol/L (1.2–4.5 mg/dL), a fall in Ca × P of 1.33–2.84 $mmol^2/L^2$ (16.63–35.5 mg^2/dL^2), and a fall in iPTH of 0–9.2 pmol/L (0–87.37 pg/mL).[5,6,8,9,11] A recent meta-analysis of 17 core studies using sevelamer in dialysis patients showed an inverse variance weighted mean fall in the following parameters: serum P of 0.69 mmol/L (2.1 mg/dL), Ca × P 1.27 $mmol^2/L^2$ (15.88 mg^2/dL^2) and iPTH of 3.6 pmol/L (34 pg/mL). As in our study, no significant change was observed in serum calcium.[7]

It is not surprising that sevelamer had a smaller magnitude of effect in our study compared to previous studies (i.e. a smaller fall in serum P and Ca × P than in previous studies and no fall in iPTH compared to modest falls in published studies). First, in our study sevelamer was being added to other P-binding agents compared with other studies in which other P binders had been withdrawn, thus the studies were starting from a higher baseline P. Second, we were dealing with a group of refractory patients with an average serum P at the commencement of the study of 2.1 mmol/L (6.5 mg/dL). Third, the dose we used in this study was lower than in previously published studies. In addition to these factors, the duration of our study was relatively short (6 months on study drug) and iPTH at baseline in this group was not particularly high (25.5 (13–75) pmol/L), which may explain why no change in PTH was recorded in our study.

In the present study we recorded a significant fall both in the elemental calcium dose related to calcium carbonate binder dose reduction and in the aluminium hydroxide dose while still achieving the planned improvement in serum phosphate. This supports our claim that the fall in serum P is related to the addition of sevelamer rather than to the administration of other P binders.

Sevelamer binds bile acids and results in increased faecal bile acid excretion and a lowering of low density lipoprotein cholesterol, which may potentially have a positive impact on the cardiovascular risk profile of the dialysis population.[9] We documented a fall in total cholesterol of 0.25 mmol/L (10 mg/dL), a fall in LDL cholesterol of 0.15 mmol/L (6 mg/dL) and no significant change in HDL cholesterol despite the low cholesterol at baseline and the continuation of a statin agent throughout the study. These changes can be compared with a fall in total cholesterol of 0.79 mmol/L (31 mg/dL), a fall in LDL cholesterol of 0.81 mmol/L (31 mg/dL) and a significant increase in HDL cholesterol of 0.11 mmol/L (4.25 mg/dL) documented in the meta-analysis.[7] The lower dose of sevelamer coupled with the fact that the majority of our study population were receiving statins, resulting in cholesterol being tightly controlled prior to study commencement, are likely factors explaining the difference between our study and previous studies.

In our study we did not witness the changes in serum bicarbonate observed in other studies, particularly a fall in serum bicarbonate. However, in our study 92% of patients stayed on calcium carbonate throughout the study. In previous publications the fall in serum bicarbonate has primarily been ascribed to the withdrawal of calcium carbonate.[10,17–19] Although serum calcium did not change, the doses of calcium and aluminium salts fell significantly during the study. These doses were altered at the discretion of individual treating physicians. The ability to lower the doses of calcium carbonate and aluminium hydroxide, while at the same time achieving better serum P control when sevelamer was added (even in the low doses used in this study), is a major advantage of the addition of this novel agent.

Previous studies,[5,6,8] with the exception of Bleyer *et al.* who reported a 34% incidence of gastrointestinal intolerance,[11] have suggested that sevelamer is well tolerated as a monotherapy. Gastrointestinal intolerance was also common in our study with a 66% incidence of this adverse event. This may appear surprising because we were using sevelamer doses approximately two to threefold less. McIntyre *et al.* who used sevelamer in combination with calcium carbonate reported a 30% incidence of gastrointestinal intolerance with an 8% withdrawal rate and commented that the use of combination treatment might be implicated.[15] Sadek *et al.*[10] reported a significant dropout rate because of gastrointestinal disturbance, which was attributed to the use of 400 mg capsules. The use of 403 mg capsule formulation and the fact that all patients were taking sevelamer in combination with at least one other phosphate binder may explain the high rate of gastrointestinal intolerance in our study. Our study is the only study published to date that uses sevelamer combined with aluminium and calcium salts

and this may have contributed to the particularly high incidence of gastrointestinal side-effects. This may be a limiting factor in the use of combination P binders and it may be worth studying combination P binders with an 800 mg formulation, which may have a lower incidence of gastrointestinal side-effects.

Because of sevelamer's bile acid binding property there has been concern regarding its potential interference with the absorption of fat-soluble vitamins, such as vitamin K. However, in our study there was no change in INR throughout the study period.

Our study does have limitations. The study was short (only 6 months on the study drug) and only looked at a low dose of sevelamer. In our study, as in other trials involving phosphate binders, there is a tendency to reduce and/or not maximize the dose of binders when the serum phosphate is approaching the target level. A trial design aimed at achieving a serum phosphate below that of a minimum requirement (i.e. aim for a target of 1.6 mmol/L (5.0 mg/dL) to try to have the majority of participants reach a target of <1.8 mmol/L (5.6 mg/dL) may have led to greater efficacy of the combination therapy by resulting in more modest reductions in the doses of conventional binders. In addition, although pharmacy dispensing records suggested excellent compliance, it is impossible to be certain that patients actually took the medication that was dispensed.

We selected only patients with the most refractory hyperphosphataemia who may be more resistant to treatment than the average patient for multiple reasons. It is possible that sevelamer may have been more effective in less refractory patients and thus more cost effective in this group. In addition, participation bias may have been a confounding factor in this study because our patients had a lower P and were younger than all the patients in the unit with poor P control. Furthermore, the study was not placebo controlled, which could have led to over-reporting of gastrointestinal side-effects.

In our study, sevelamer was used with aluminium hydroxide as well as calcium carbonate, whereas most clinicians will be primarily interested in the combination of calcium salts with sevelamer without the use of aluminium hydroxide. However, in the majority of our patients, calcium carbonate was the major P binder used prior to the introduction of sevelamer and the dose of aluminium hydroxide was low (patients were taking an average of three tablets containing 600 mg aluminium hydroxide at the commencement of the study). We were also only able to use the 403 mg galenic preparation rather than the perhaps better-tolerated 800 mg tablet formulation.

One of the major concerns regarding the use of sevelamer is its cost. Sevelamer is approximately 10-fold the cost of conventional phosphate binders and is currently not funded on the pharmaceutical benefits scheme in Australia. Thus, the use of sevelamer in combination has an added advantage from a financial viewpoint. The average daily dose of sevelamer used in this study, 2.4 g, was significantly lower than that used in other studies (5.6 g/day).[5,6,9,11] Even in the present study, which used low-dose sevelamer, the cost of P binders rose from $AUD 0.57 to 6.31 per patient per day when sevelamer was added. It is questionable whether this extra cost is justified given the modest fall in P and Ca × P recorded. However, the cost of the drug could potentially be offset by decreased hospitalization[20] and by potentially lowering the risk of outcomes such as cardiovascular disease, uraemic calcific arteriolopathy (UCA), bone disease and by reducing the need for parathyroidectomy.

In summary, we have shown that sevelamer in combination with conventional phosphate binders is effective in lowering serum phosphate and calcium × phosphate product in a group of patients with poorly controlled hyperphosphataemia. Combination therapy has the major advantages of being less expensive and it may lead to more effective P control than is currently achieved with sevelamer alone. However, the GIT side-effects and compliance are significant problems with such an approach. We need to continue to explore the possibilities of combining P binders, particularly the combination of sevelamer and calcium carbonate, to determine whether such approaches are safe and effective in the long term.

ACKNOWLEDGEMENTS

We thank the nursing staff in the dialysis unit for their help during the conduct of this trial. There have been no external financial grants or funding for this study.

REFERENCES

1. 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**: 607–17.
2. Block GA, Port FK. Re-evaluation of risks associated with hyperphosphatemia and hyperparathyroidism in dialysis patients: recommendations for a change in management. *Am. J. Kidney Dis*. 2000; **35**: 1226–37.
3. Llach F. Calcific uremic arteriolopathy (calciphylaxis): an evolving entity? *Am. J. Kidney Dis*. 1998; **32**: 514–18.
4. Plone MA, Petersen JS, Rosenbaum DP, Burke SK. Sevelamer, a phosphate-binding polymer, is a non-absorbed compound. *Clin. Pharmacokinet*. 2002; **41**: 517–23.
5. Wilkes BM, Reiner D, Kern M, Burke S. Simultaneous lowering of serum phosphate and LDL-cholesterol by sevelamer hydrochloride (RenaGel) in dialysis patients. *Clin. Nephrol*. 1998; **50**: 381–6.
6. Slatopolsky EA, Burke SK, Dillon MA. RenaGel, a nonabsorbed calcium- and aluminum-free phosphate binder, lowers serum phosphorus and parathyroid hormone. The RenaGel Study Group. *Kidney Int*. 1999; **55**: 299–307.

7. Burke SK, Dillon MA, Hemken DE, Rezabek MS, Balwit JM. Meta-analysis of the effect of sevelamer on phosphorus, calcium, PTH, and serum lipids in dialysis patients. *Adv. Ren. Replace. Ther.* 2003; **10**: 133–45.
8. Chertow GM, Burke SK, Lazarus JM *et al.* Poly[allylamine hydrochloride] (RenaGel): a noncalcemic phosphate binder for the treatment of hyperphosphatemia in chronic renal failure. *Am. J. Kidney Dis.* 1997; **29**: 66–71.
9. Chertow GM, Burke SK, Dillon MA, Slatopolsky E. Long-term effects of sevelamer hydrochloride on the calcium × phosphate product and lipid profile of haemodialysis patients. *Nephrol. Dial. Transplant.* 1999; **14**: 2907–14.
10. Sadek T, Mazouz H, Bahloul H *et al.* Sevelamer hydrochloride with or without alphacalcidol or higher dialysate calcium vs calcium carbonate in dialysis patients: an open-label, randomized study. *Nephrol. Dial. Transplant.* 2003; **18**: 582–8.
11. Bleyer AJ, Burke SK, Dillon M *et al.* A comparison of the calcium-free phosphate binder sevelamer hydrochloride with calcium acetate in the treatment of hyperphosphatemia in hemodialysis patients. *Am. J. Kidney Dis.* 1999; **33**: 694–701.
12. Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int.* 2002; **62**: 245–52.
13. Hergesell O, Ritz E. Phosphate binders in uraemia: pharmacodynamics, pharmacoeconomics, pharmacoethics. *Nephrol. Dial. Transplant.* 2002; **17**: 14–17.
14. Cizman B. Hyperphosphataemia and treatment with sevelamer in haemodialysis patients. *Nephrol. Dial. Transplant.* 2003; **18** (Suppl. 5): v47–9.
15. McIntyre CW, Patel V, Taylor GS, Fluck RJ. A prospective study of combination therapy for hyperphosphataemia with calcium-containing phosphate binders and sevelamer in hypercalcaemic haemodialysis patients. *Nephrol. Dial. Transplant.* 2002; **17**: 1643–8.
16. Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. *Biometrics* 1988; **44**: 1049–60.
17. Borras M, Marco MP, Fernandez E. Treatment with sevelamer decreases bicarbonate levels in peritoneal dialysis patients. *Perit. Dial. Int.* 2002; **22**: 737–8.
18. Marco MP, Muray S, Betriu A *et al.* Treatment with sevelamer decreases bicarbonate levels in hemodialysis patients. *Nephron* 2002; **92**: 499–500.
19. Gallieni M, Cozzolino M, Brancaccio D. Transient decrease of serum bicarbonate levels with Sevelamer hydrochloride as the phosphate binder. *Kidney Int.* 2000; **57**: 1776–7.
20. Collins AJ, St Peter WL, Dalleska FW, Ebben JP, Ma JZ. Hospitalization risks between Renagel phosphate binder treated and non-Renagel treated patients. *Clin. Nephrol.* 2000; **54**: 334–41.