Original Article

Effect of RenaGel®, a non-absorbed, calcium- and aluminium-free phosphate binder, on serum phosphorus, calcium, and intact parathyroid hormone in end-stage renal disease patients

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Abstract

Background. Control of dietary phosphate absorption in end-stage renal disease patients is essential to prevent the deleterious sequelae of phosphorus retention. Efficacy of currently available calcium- and aluminium-containing phosphate binders is constrained by the side-effects associated with the absorption of calcium and aluminium. The current study examined the efficacy of RenaGel, a calcium- and aluminium-free, polymeric phosphate binder, in end-stage renal disease patients.

Methods. Administration of calcium- or aluminium-containing phosphate binders ceased during a 2-week washout period. RenaGel, at starting doses of one, two, or three 500-mg capsules three times per day with meals, was administered for 8 weeks. RenaGel dose was titrated up 1 capsule per meal at the end of each 2-week period if necessary to achieve phosphorus control. A second 2-week washout period followed the end of RenaGel treatment.

Results. Mean serum phosphorus rose from a pre-washout level of 6.9 mg/dl (2.23 mmol/l) to 8.1 mg/dl (2.62 mmol/l) at the end of the initial 2-week washout. With RenaGel treatment, serum phosphorus declined and returned to pre-washout levels after 4 weeks. Serum phosphorus reached a nadir of 6.5 mg/dl (2.10 mmol/l) after 7 weeks of RenaGel treatment. Serum phosphorus rose to 8.2 mg/dl (2.65 mmol/l) 2 weeks after cessation of RenaGel treatment. As anticipated, calcium declined during the initial washout period when calcium-based phosphate binders were stopped for the majority of patients. The rise in serum phosphorus and decline in serum calcium during washout resulted in an increase in median intact parathyroid hormone (iPTH) levels from 292 pg/ml to 395 pg/ml. iPTH fell to 283 pg/ml after 6 weeks of RenaGel treatment despite a persistently lower serum calcium. RenaGel treatment also reduced serum total and LDL cholesterol by 25 mg/dl (0.65 mmol/l) and 23 mg/dl (0.59 mmol/l) respectively.

Conclusions. RenaGel appears to be an effective phosphate binder free of calcium and aluminium. Phosphorus control with two to four RenaGel capsules per meal appears to result in comparable phosphorus lowering seen with calcium- or aluminium-based phosphate binders. RenaGel may offer an alternative for the control of phosphorus retention in end-stage renal disease patients.

Key words: hyperphosphataemia; hyperparathyroidism; chronic renal disease; randomized controlled trial; cholesterol

Introduction

Phosphorus retention in patients with advanced renal disease is a major contributor to the development of secondary hyperparathyroidism, osteitis fibrosa and extraosseus calcification of both vascular and non-vascular tissues [1,2]. End-stage renal disease (ESRD) patients are placed on phosphorus-restricted diets. Daily phosphorus intake on restricted diets ranges from 540 mg (17.4 mmol) to 1047 mg (33.8 mmol), depending on the level of protein [3,4]. Despite this, the phosphorus absorbed exceeds the amount of phosphorus removed by dialysis. As a result, ESRD patients are placed on phosphate binders to decrease the absorption of dietary phosphate and control serum phosphorus.

The most commonly used phosphate binders contain

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aluminium or calcium. Aluminium causes neurological, skeletal and haematopoietic toxicities in ESRD patients [5,6], while calcium can lead to hypercalcaemia and soft-tissue calcification [6–8]. Since these toxicities limit utilization of phosphate binders, control of serum phosphorus is less than desirable. As a result, there remains a need for a well-tolerated, aluminium- and calcium-free phosphate binder.

RenaGel is a novel phosphate-binding polymer free of aluminium and calcium (Figure 1). RenaGel, a hydrogel of cross-linked poly(allylamine), is completely resistant to digestive degradation and is not absorbed from the gastrointestinal tract. Partially protonated amines spaced one carbon from the polymer backbone interact with phosphate anions by ionic and hydrogen bonds. The *in vivo* efficacy of RenaGel as a dietary phosphate binder has been demonstrated in rats [9], in normal male and female volunteers [10], and in 21 hyperphosphataemic renal disease patients in a 2-week randomized placebo-controlled study [11]. The current clinical trial was designed to mimic the anticipated clinical use of RenaGel in a larger group of haemodialysis patients over a longer course of treatment. The study was designed to determine: the efficacy of RenaGel in lowering serum phosphorus, the effect of RenaGel on serum intact parathyroid hormone (iPTH), the effect of RenaGel on serum lipid profiles, and the safety and toleration of RenaGel in haemodialysis patients.

Subjects and methods

Patients

Male or female haemodialysis patients 18 years of age or older on three times per week haemodialysis were allowed
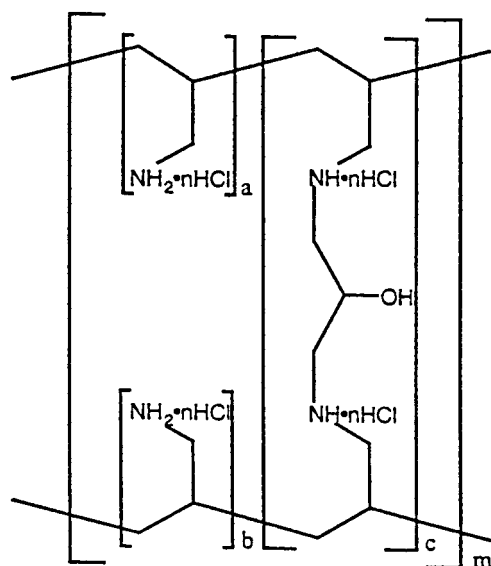
Fig. 1. Structure of RenaGel (sevelamer hydrochloride; poly(allylamine) cross-linked with epichlorohydrin). Primary amines are designated **a** and **b**. Crosslinked amine groups are designated **c**. The extended polymer network is designated by repeated units designated **m**.

to enroll in the study. Inclusion criteria required a stable dose of phosphate binder for at least 1 month prior to the study and, if on vitamin D, a stable dose for at least 1 month. Patients were asked to avoid intentional changes in diet and to refrain from taking aluminium-, calcium-, or magnesium-containing antacids. Eligible patients entered into a 2-week phosphate binder washout period. Those patients with a washout serum phosphorus concentration of greater than 6.0 mg/dl (1.94 mmol/l) qualified to receive RenaGel. Five patients did not qualify for this study based on their serum phosphorus levels. The mean serum phosphorus level of these five patients on their own phosphate binder was 3.9 mg/dl and rose to 4.7 mg/dl after 2 weeks of phosphate binder washout. Table 1 summarizes the clinical characteristics of the 48 patients who received RenaGel.

Study design

Forty-eight patients were eligible for drug treatment. These patients were started on one, two, or three RenaGel 500-mg capsules three times per day with meals based on the degree of hyperphosphataemia experienced during washout (Table 2). At the end of each of three subsequent 2-week periods, RenaGel dose was titrated up by 1 capsule per meal (three capsules per day) if necessary to achieve serum phosphorus control. At the conclusion of the 8-week RenaGel treatment period, patients were washed off RenaGel for 2 weeks then returned to their original phosphate binders.

Collection and handling of blood samples

Blood samples were obtained just prior to dialysis on Mondays for patients on a Monday–Wednesday–Friday schedule and Tuesdays for those on a Tuesday–Thursday–Saturday schedule. Intact parathyroid hormone was measured by an immunoradiometric assay kit (Nichols Institute, San Juan Capistrano, CA, USA) at the Renal Division at Washington University, St Louis, MO. All other biochemical parameters were measured by SmithKline Beecham Clinical Laboratories (Van Nuys, CA, USA).

Record of dietary phosphate intake

A trained interviewer using the 24-h recall method assessed dietary intake. Patients were called on three random days during each of the following periods: the first washout period, the last 2 weeks of the RenaGel treatment period, the second washout period. The calls included one dialysis day, one non-dialysis day, and a weekend day for each of the study periods. If the patient could not be reached for interview, that patient was excluded from the dietary analysis only. The data were analysed using the University of Minnesota Nutrient Data System, version 2.7.

Statistical methods

Changes in serum phosphorus, calcium, calcium–phosphorus product, and iPTH between treatment periods were analysed using paired *t* tests. Differences across dose groups for adverse experiences and changes in safety laboratory tests were examined. To create dosage groups for analysis, patients were ranked by mean actual daily dose during the study and then divided into tertiles to create low, medium, and high dose groups, each containing 16 patients per group. The incidence of adverse experiences among the three dosage groups were

Table 1. Characteristics of end stage renal disease patients entering RenaGel treatment period

Patients (n)	48
Age in years (mean $\pm$ std (range))	52.0 ± 14.6 (20.9–85.8)
Sex (male : female)	30 : 18
Race (Caucasian : African-American : other)	24 : 20 : 4
Weight in kg (mean $\pm$ std (range))	78.0 ± 17.2 (35.8–128.8)
Primary cause of ESRD (diabetes : hypertension : other)	17 : 14 : 17
Previous PO$_4$ binder (calcium acetate : calcium carbonate : aluminium)	24 : 20 : 4
Parathyroidectomy (yes : no)	1 : 47
Vitamin D replacement therapy (yes : no)	29 : 19
Initial calcium dialysate (mEq/l) 2.25 : 2.50 : 3.00 : 3.50	10 : 18 : 9 : 11

Table 2. Serum phosphorus at end of washout and starting RenaGel doses for end-stage renal disease patients

Number of capsules t.i.d.	Washout serum phosphorus mg/dl (mmol/l)	Patients (n)
1	$\geqslant 6.0$ to < 7.0 ($\geqslant 1.94$ to < 2.26)	12
2	$\geqslant 7.0$ to < 8.0 ($\geqslant 2.26$ to < 2.58)	8
3	$\geqslant 8.0$ ($\geqslant 2.58$)	26

analysed using Fisher's exact tests. Safety laboratory changes among the dosage groups were analysed using ANOVA.

The efficacy analyses were based on the intent-to-treat population defined as those patients who received any study treatment and had at least one serum phosphorus measurement on treatment. All hypothesis testing was performed using a two-tailed approach with a 0.05 level of significance. Statistical analyses were conducted using SAS statistical software version 6.11 (SAS Institute, Cary, NC, USA).

Results

Dosage, compliance and dietary intake

The mean actual daily dosage was 8.2 capsules per day, representing 82% compliance with prescribed dosage. Mean daily dietary intakes of phosphorus, calcium, and other nutrients as a function of the RenaGel dosage groups (low, medium, and high) are summarized in Table 3. Intakes of all nutrients increased across the dosage groups. It has previously

Table 3. Mean daily intakes of dietary nutrients during the RenaGel treatment period separated by average daily RenaGel dose

|	Final RenaGel dose level (n)		
	Low (11) Mean $\pm$ SD	Medium (15) Mean $\pm$ SD	High (15) Mean $\pm$ SD
Energy (kcal/day)	1343 ± 420	1501 ± 563	1918 ± 1015
Total fat (g/day)	55 ± 23	59 ± 27	83 ± 51
Total protein (g/day)	49 ± 20	64 ± 26	76 ± 38
Calcium (mg/day)	405 ± 237	538 ± 342	760 ± 394
Phosphorus (mg/day)	711 ± 406	896 ± 424	1097 ± 567
Iron (mg/day)	9.2 ± 3.8	11.1 ± 4.4	16.4 ± 13.0
Sodium (mEq/day)	2279 ± 780	2526 ± 1076	3323 ± 1447
Potassium (mg/day)	1288 ± 624	1847 ± 914	1986 ± 1000

Patients were divided into tertiles to determine low- medium-and high-dose groups.

been reported that the daily dose of dietary phosphate binder required to maintain controlled serum phosphorus levels is determined by a patient's dietary phosphorus ingestion [1]. This was true in the current study, as RenaGel dosage in the low, medium, and high dosage groups was strongly correlated to mean dietary phosphorus intake ($r^2 = 0.98$, $P < 0.001$).

Serum phosphorus, calcium, and iPTH

Figure 2 displays mean serum phosphorus levels in the 48 RenaGel treated patients during the study. Mean serum phosphorus on calcium and aluminium-containing phosphate binders at pre-washout was 6.9 mg/dl (2.23 mmol/l). This high value for pre-washout serum phosphorus levels was the result of excluding patients whose serum phosphorus levels were lower than 6.0 mg/dl. With cessation of phosphate binder therapy during the initial 2-week washout period, there was an abrupt and substantial rise in serum phosphorus to a mean of 8.1 mg/dl (2.62 mmol/l). Mean serum phosphorus declined to 7.3 mg/dl (2.36 mmol/l) during the first 2 weeks of treatment, while patients were on the starting dose of one, two, or three capsules t.i.d. The majority of patients increased their RenaGel dose by one capsule t.i.d. at the study week 4 visit that resulted in a return of mean serum phosphorus levels to pre-washout levels. Additional dose titrations occurred in some patients at study weeks 6 and 8, resulting in a small continued decline in serum phosphorus which reached a nadir of 6.5 mg/dl (2.10 mmol/l) at week 9. The mean serum phosphorus change from baseline (end-washout or week 2) to the end of RenaGel treatment (week 10) was -1.4 mg/dl (0.45 mmol/l), $P = 0.0001$. When RenaGel treatment ceased at week 10, serum phosphorus rose to 8.2 mg/dl (2.65 mmol/l).

Figure 3 displays mean serum calcium over time in the 48 RenaGel treated patients. Mean serum calcium was 9.5 mg/dl (2.37 mmol/l) at pre-washout. As anticipated, mean serum calcium declined slightly when calcium-based phosphate binders were removed during the washout period ($P = 0.1108$). Serum calcium levels remained in the normal range, 8.5 mg/dl to 10.3 mg/dl (2.12 mmol/l to 2.57 mmol/l), and did not return to pre-washout levels at any time. The mean serum calcium level ranged from 9.1 mg/dl to 9.4 mg/dl. There was no statistically significant change in mean serum calcium with RenaGel treatment. One patient who
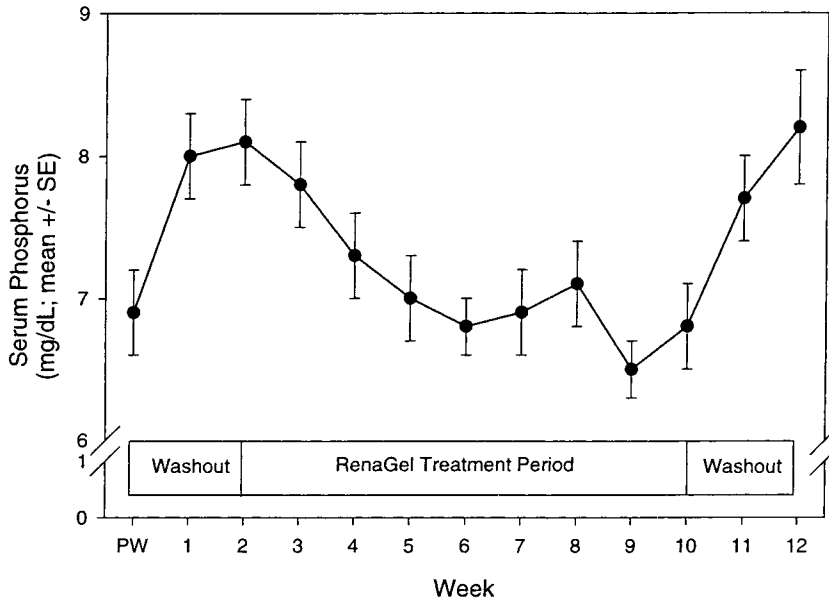
Fig. 2. Mean serum phosphorus ($\pm$SE) during the RenaGel treatment and washout periods. PW indicates the last measurement prior to initiation of the washout period. To convert to mmol/l, divide numbers in mg/dl units by 3.097. The mean per patient change in serum phosphorus from the end of washout to the end of treatment was statistically significant with a *P* value of 0.0001.
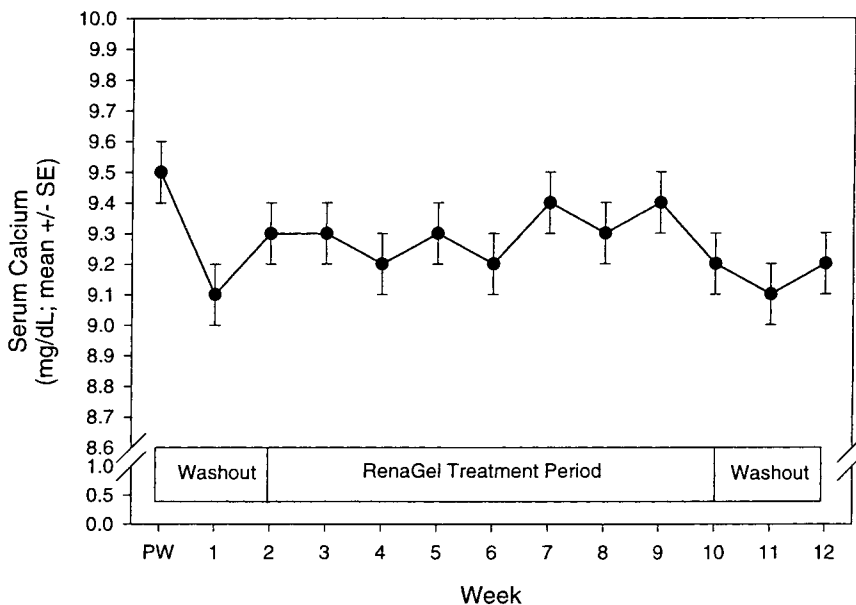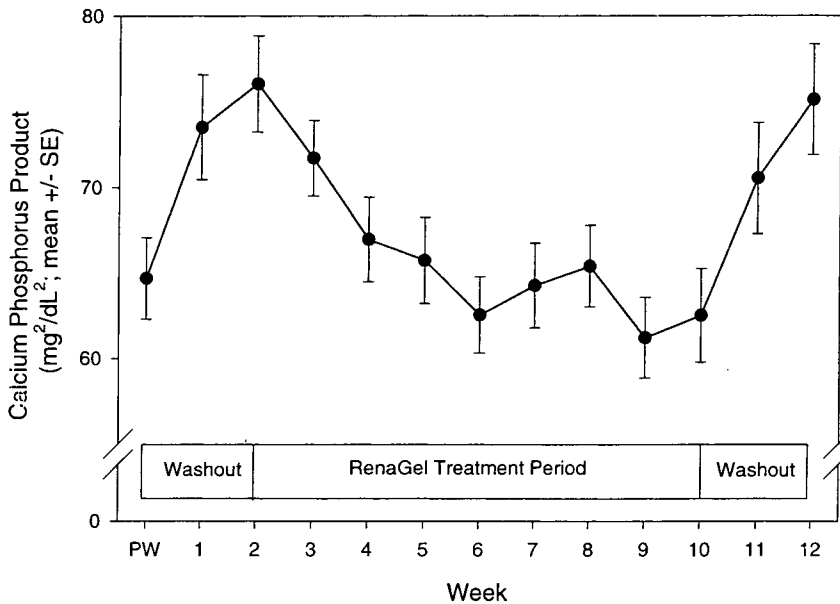

Fig. 3. Mean serum calcium ($\pm$SE) during the RenaGel treatment and washout periods. PW indicates the last measurement prior to initiation of the washout period. To convert to mmol/l, divide numbers in mg/dl units by 4.008. The mean per patient change in serum phosphorus from the end of washout to the end of treatment was not statistically significant with a *P* value of 0.2278.

developed an abnormally low serum calcium received a calcium supplement at bedtime on an empty stomach. No patients initiated vitamin D therapy during this study.

Figure 4 displays mean calcium-phosphorus product over time. Mean calcium-phosphorus product was 65 mg^2/dl^2 at pre-washout. Calcium–phosphorus product rose significantly to 76 mg^2/dl^2 during the initial 2-week washout period ($P = 0.0003$). Calcium–phosphorus product declined to 63 mg^2/dl^2 by the end of RenaGel treatment. The mean serum calcium–

phosphorus product change from baseline (end-washout or week 2) to the end of RenaGel treatment (week 10) was -13.5, $P = 0.0001$. When RenaGel treatment ceased at week 10, calcium–phosphorus product rose to 75 mg^2/dl^2.

Figure 5 displays median serum iPTH during the course of this study. Median was chosen for display since the distribution of iPTH data was skewed by a subset of patients with extreme elevations in iPTH. Median intact PTH rose from 292 pg/ml to 395 pg/ml at week 4. iPTH returned to 283 pg/ml by study week

Fig. 4. Mean calcium–phosphorus product during the RenaGel treatment and washout periods. PW indicates the last measurement prior to initiation of the washout period. The mean per patient change in calcium-phosphorus product from the end of the washout to the end of treatment was statistically significant with a P value of 0.0001.
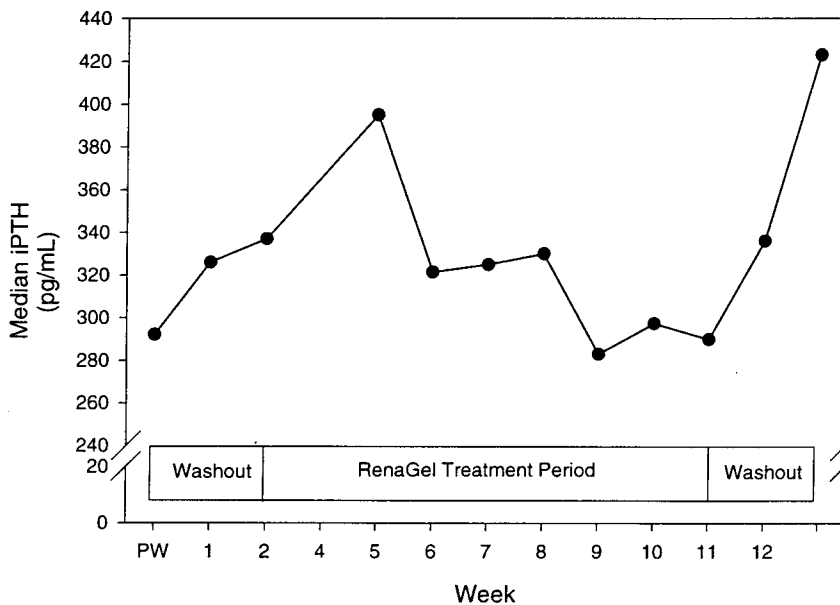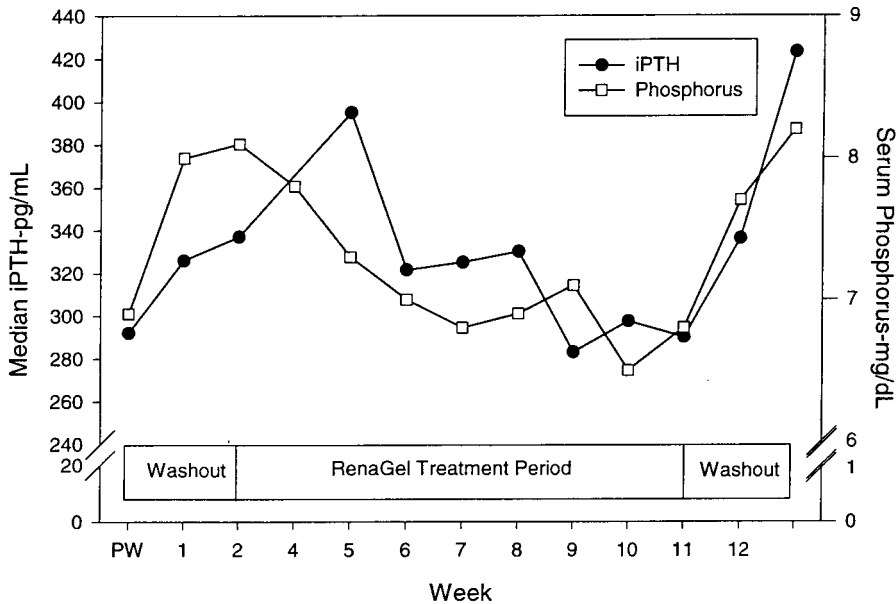

Fig. 5. Median serum intact PTH ($\pm$ IQ range) during the RenaGel treatment and washout periods. PW indicates the last measurement prior to initiation of the washout period.

8 (6 weeks of RenaGel treatment). Once RenaGel treatment ceased, iPTH increased to 423 pg/ml. Changes in iPTH correlated with changes in serum phosphorus ($r = 0.51$, $P < 0.001$) and serum calcium ($r = -0.34$, $P = 0.01$). Figure 6 displays an overlay of mean serum phosphorus and median iPTH.

Serum lipids

Serum lipids at baseline (week 2) and the end of RenaGel treatment and mean changes in serum lipids are summarized in Table 4. Serum total cholesterol decreased from a baseline of 176 mg/dl (4.55 mmol/l) to 149 mg/dl (3.85 mmol/l) at the end of RenaGel treatment. The mean decline in serum total cholesterol of 25 ± 30 mg/dl (0.65 ± 0.77 mmol/l) represented a decline of 14% and was statistically significant ($P = 0.0001$). LDL cholesterol decreased from 98 mg/dl (2.53 mmol/l) at baseline to 73 mg/dl (1.89 mmol/l) at the end of RenaGel treatment. The mean decrease in LDL cholesterol of 23 ± 25 mg/dl (0.59 ± 0.65 mmol/l) represented a decline of 23% ($P =$

Fig. 6. Mean serum phosphorus ($\pm$SE) and median serum iPTH during the RenaGel treatment and washout periods. PW indicates the last measurement prior to initiation of the washout period.

Table 4. Mean baseline, end-treatment serum lipids, and changes in lipids with RenaGel treatment

Lipid parameter	Baseline (Mean $\pm$ SD)	End-treatment (Mean $\pm$ SD)	Change (Mean $\pm$ SD)
Total cholesterol	176.9 $\pm$ 42.2	148.9 $\pm$ 41.2	$-$24.7 $\pm$ 29.7*
LDL cholesterol	97.7 $\pm$ 35.8	72.7 $\pm$ 30.5	$-$23.4 $\pm$ 25.1*
HDL cholesterol	45.4 $\pm$ 21.4	44.2 $\pm$ 19.3	1.0 $\pm$ 10.2
Triglycerides	168.6 $\pm$ 112.9	159.7 $\pm$ 109.5	$-$11.9 $\pm$ 62.8

*P value $<$ 0.0001 for mean per patient change from baseline lipid levels. The change in lipid value is the mean of the individual patient changes. All lipid values are presented in mg/dl (divide by 38.7 to calculate mmol/l).

0.0001). Serum HDL cholesterol and triglyceride levels did not change during RenaGel treatment.

Safety

Of the 48 patients who started RenaGel treatment, 42 completed the treatment period. Five patients discontinued because of serious adverse events unrelated to treatment. A sixth patient developed dizziness which the Investigator felt was unrelated to RenaGel; however, the patient withdrew consent to continue. Adverse events did not increase significantly with increased RenaGel dosage and were probably due to the patients' underlying medical conditions.

There were no clinically significant changes in safety laboratory tests from the end of washout to the end of RenaGel treatment. Tests included a chemistry panel, complete cell blood count, prothrombin time, partial thromboplastin time, vitamins A and E, iron, and iron-binding capacity. There was a statistically significant increase in mean serum chloride concentration from 98.8 mEq/l to 101.8 mEq/l ($P=0.0001$) and

a statistically significant decrease in serum bicarbonate concentration from 18.8 mEq/l to 17.1 mEq/l ($P=0.0001$). There was also a statistically significant increase in mean serum alkaline phosphatase activity from 105.4 U/L to 134.9 U/L ($P=0.0386$). Serum albumin and total serum proteins did not change significantly during the study. Serum prealbumin increased by 2.9 mg/dl ($P=0.02$) from a baseline of 32 mg/dl.

Discussion

In this open-label dose titration study, RenaGel significantly reduced serum phosphorus levels at starting doses of one, two, or three capsules three times per day with meals. A single titration after 2 weeks of treatment returned mean serum phosphorus to pre-washout levels. Based on this study, the anticipated average clinical dose of two to four capsules three times per day with meals will provide serum phosphorus control comparable to that achieved with currently available calcium and/or aluminium based phosphate binders. Individual patients with high or low dietary phosphate intake would probably require more or fewer of capsules with meals.

Serum phosphorus levels between 5.0 mg/dl and 6.5 mg/dl are viewed as acceptable in the ESRD population [1]. We felt that we should only treat patients who would benefit from a phosphate binder, therefore, we excluded patients whose serum phosphorus was less than or equal to 6.0 mg/dl after phosphate binder washout. In this study, pre-washout mean serum phosphorus was 6.9 mg/dl, indicating that more than half of the patients exceeded 'acceptable levels'. There are many possible reasons why most patients do not

achieve desired serum phosphorus control, including non-compliance with both diet and phosphate binder prescriptions. In this study, RenaGel treatment reduced serum phosphorus below pre-washout levels. However, a number of patients did not reach optimal phosphorus control as a result of selecting patients with higher serum phosphorus levels. The onset of RenaGel action was rapid—substantial reductions in serum phosphorus occurred in 2 weeks.

Serum calcium levels declined slightly within the normal range during washout, since calcium acetate and calcium carbonate were discontinued as phosphate binders in all but four patients. A substantial amount of the calcium in these phosphate binders is absorbed [6–8]. Mean dietary calcium intake in these patients was approximately 500 mg/day. Calcium supplements or adjustments to dialysate calcium might be indicated in individual patients to ensure adequate intake of calcium. However, this protocol did not allow for calcium supplements except when a patient's serum calcium level dropped outside the normal range. One patient who developed an abnormally low serum calcium received a calcium supplement at bedtime. No patients initiated vitamin D therapy during this study.

The risk of metastatic calcification increases with increasing serum calcium-phosphorus product. In the present study, serum calcium-phosphorus product was 65 mg^2/dl^2 at baseline and increased to 76 mg^2/dl^2 during the washout period. This increase was anticipated since serum phosphorus rose substantially during this period. As noted previously, serum calcium fell slightly during the initial washout period, thus, the predominant driver of the change in calcium-phosphorus product was the change in serum phosphorus. With RenaGel treatment, mean calcium–phosphorus product declined to levels below pre-washout levels. Therefore use of RenaGel should reduce the risk of metastatic calcification in ESRD patients.

Since serum phosphorus and calcium regulate PTH secretion, a rise in iPTH during the washout periods was predicted [12]. The extent to which the increase in serum phosphorus during the washout period directly stimulated the increase in iPTH is difficult to ascertain. However, the decline in iPTH during the RenaGel treatment period was clearly correlated with the decline in serum phosphorus. Serum calcium remained constant during this period. Evidence for a direct role of serum phosphorus as a regulator of parathyroid gland function has been reported [13–15]. Although human studies have examined the effect of phosphate and/or protein restricted diets on PTH levels, those studies have provided calcium supplementation to maintain serum calcium levels [16,17]. Since RenaGel controls serum phosphorus without contributing calcium and no calcium supplements were given, the current study allows for the examination of the direct effect of phosphorus control on PTH secretion during a period of reduced calcium intake and mildly reduced serum calcium levels. The strong correlation between serum phosphorus levels and iPTH in ESRD patients supports a direct role of serum phosphorus in the regulation of parathyroid gland function in end-stage renal disease.

The mild decrease in serum bicarbonate concentration was probably due to the discontinuation of calcium acetate and carbonate as phosphate binders. Calcium carbonate delivers base in addition to calcium and is known to raise serum bicarbonate [18]. Acetate is absorbed and its metabolism results in bicarbonate production [19]. RenaGel, with a pKa of 9, is a weak base and will accept protons as it passes through the intestinal tract but should not raise serum bicarbonate.

RenaGel treatment decreased total and LDL cholesterol. In the current study, the decline in LDL cholesterol was specific to the activity of RenaGel. Dietary intake of nutrients increased during the study and levels of serum prealbumin, a marker of nutritional status increased during this study. A decrease in LDL cholesterol, may be an additional benefit associated with RenaGel. Cardiovascular diseases, including myocardial infarction, sudden death, and stroke collectively account for approximately 50% of the deaths in ESRD patients [20]. There are multiple abnormalities of the lipid profile of ESRD patients, which may contribute to the high incidence of atherosclerosis [21]. Controlled clinical trials will ultimately demonstrate whether LDL reduction will benefit ESRD patients with atherosclerosis.

Conclusion

RenaGel, a non-absorbed, aluminium- and calcium-free dietary phosphate binder is efficacious and well tolerated in ESRD patients. RenaGel rapidly lowered serum phosphorus in these patients. Lowering serum phosphorus was highly correlated with decreases in iPTH and occurred while serum calcium levels were lower than baseline for the duration of the study. These data support *in vitro* and animal studies indicating that phosphorus has a direct regulatory role on parathyroid gland function. Additional clinical studies with RenaGel in ESRD patients are in progress.

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