Renagel®: reducing serum phosphorus in haemodialysis patients

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Approximately half of all dialysis patients experience persistent hyperphosphataemia, which causes significant problems. Renagel® is a calcium-free, aluminium-free phosphate binder which reduces serum phosphorus in haemodialysis patients by reducing absorption of dietary phosphorus. This article reviews the management of hyperphosphataemia and presents some Renagel® clinical trial data.

In patients with normal kidney function, calcium and phosphorus balance is maintained through the interaction of parathyroid hormone (PTH) and calcitriol, the active metabolite of vitamin D. The primary function of PTH is to maintain calcium homeostasis. Elevation of serum PTH increases the rate of bone dissolution, which mobilizes calcium and phosphorus from bones into the plasma. PTH also increases renal resorption of calcium and decreases tubular resorption of phosphorus. These actions effectively restore serum calcium levels and maintain serum phosphorus levels.

The mechanisms that maintain phosphorus and calcium balance become compromised as kidney function declines. The kidneys gradually lose their ability to excrete phosphorus, produce calcitriol and maintain calcium balance. As glomerular filtration rate continues to decline, increasingly higher levels of PTH are required to maintain near-normal phosphate concentrations (Delmez and Slatopolsky, 1992).

Hyperphosphataemia confers considerable mortality risk. While the exact mechanisms are unclear, soft tissue calcification caused by high phosphorus levels and elevated calcium x phosphorus product is likely to be important. Soft tissue calcification has been linked to cardiovascular risk, and cardiovascular disease is the cause of death in more than 45% of all dialysis patients (Block et al, 1998; Rostand et al, 1988).

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MANAGING HYPERPHOSPHATAEMIA

Prevention and treatment of hyperphosphataemia is a major treatment goal in the dialysis population (Delmez and Slatopolsky, 1992). The simplest strategy is dietary control of phosphorus. This can be achieved by restricting the intake of foods high in phosphorus. Restriction of phosphorus intake in patients with chronic renal failure has been shown to directly suppress PTH and increase serum calcitriol levels (Combe and Aparicio, 1994; Feinfeld and Sherwood, 1988). Unfortunately, foods that are high in phosphorus are also generally high in protein.

Restricting the dietary intake of phosphorus may lead to a lower protein intake than that required for adequate nutrition. Protein requirements may also be higher in patients on peritoneal dialysis (Blumenkrantz et al, 1982). This is caused by the efflux of proteins into the dialysate. Malnutrition is present in about 50% of patients on dialysis and it is a frequent cause of morbidity and mortality (Pastan and Bailey, 1998). Therefore the benefits of restricting dietary phosphorus intake must be weighed against the risk of malnutrition and resulting increase in morbidity and mortality.

Since there are problems associated with dietary phosphorus restriction and most dialysis treatments cannot clear the amount of phosphorus absorbed from a diet containing adequate amounts of protein, almost all dialysis patients rely on phosphate binders (Delmez and Slatopolsky, 1992; Hsu, 1997).

Phosphate binders reduce the absorption of dietary phosphorus and prevent hyperphosphataemia. Compounds used as phosphate binders include various calcium, aluminium and magnesium preparations. Approximately 90% of dialysis patients use calcium carbonate or calcium acetate binders. Aluminium-based phosphate binders should be used only when other means of managing phosphorus have failed.

Modern management strategies still have limitations, including poor patient compliance with dietary restrictions and binder therapy, lack of

long-term efficacy of binders and the need to withhold calcium, aluminium, or calcitriol therapy as a result of side-effects. Typical problems include the development of aluminium bone disease and other symptoms of aluminium intoxication, hypercalcaemia and soft tissue calcification (Kates and Andress, 1996). Consequently a large proportion (about 60%) of dialysis patients do not achieve adequate control of phosphorus or calcium x phosphorus product, and others continue to have marked elevations of PTH requiring parathyroidectomy (Chertow et al, 1999a).

NEW ALTERNATIVES?

Given the shortcomings of currently available phosphate binders, new alternatives are needed. The ideal phosphate binder would:

- Have a high affinity for phosphate to minimize required dosage
- Not be absorbed
- Be non-toxic with no unwanted side-effects
- Be taken as a solid oral dose so as to not compromise fluid intake levels
- Be palatable to aid compliance
- Not result in hypercalcaemia.

The development of calcium-free, aluminium-free binders that control phosphate without affecting calcium levels are an important advance in the management of hyperphosphataemia and renal osteodystrophy (Malluche and Monier-Faugere, 1999). These binders allow independent control of phosphorus and calcium without contributing to the calcium or aluminium load. Sevelamer (Renagel®, Genzyme BV, Naarden, The Netherlands) is a recently approved calcium-free, aluminium-free phosphate binder. Clinical evaluations have demonstrated that Renagel® reduces the absorption of dietary phosphorus, thereby reducing serum phosphorus in haemodialysis patients.

RENAGEL®

Chemistry

Sevelamer hydrochloride is a non-aluminium, non-calcium-containing hydrogel of cross-linked poly(allylamine hydrochloride) that is resistant to digestive degradation and is not absorbed from the gastrointestinal tract. It is hydrophilic but insoluble in water. The primary amine groups shown in the structure (*Figure 1*) are derived directly from poly(allylamine hydrochloride). The cross-linking groups consist of two secondary amine groups derived from poly(allylamine hydrochloride) and one molecule of epichlorohydrin (Burke et al, 1997).

The mechanism of action relates to the presence of partially protonated amines spaced one carbon from the polymer backbone, which interact with phosphate ions by ionic and hydrogen bonding (*Figure 1*). Sevelamer's preference for phosphate is derived from phosphate's four oxygen atoms that are all capable of interacting with the polymer and the abundance of phosphate in the diet. Sevelamer also binds bile acids; these are also polyanions and are abundant at meal times. Animal studies have shown that sevelamer increases faecal bile acid excretion explaining the lipid-altering effects (D Rosenberg, unpublished data, 1995).

Binding of phosphate to sevelamer is believed to occur primarily in the proximal small intestine at neutral pH. In vitro, sevelamer binds phosphate optimally at pH 7 (Rosenbaum et al, 1997), and thus sevelamer binds phosphate and lowers serum phosphorus in patients using gastric acid-inhibiting drugs (GM Chertow, unpublished data, 1998).

Pharmacokinetics and pharmacology

Animal pharmacology: Several in-vitro assays and animal models were employed to evaluate the activity and efficacy of sevelamer. Administration of sevelamer to normal rats produced 90% and 77% increases in faecal excretion of phosphorus in two experiments. Calcium carbonate produced a 23% increase in faecal phosphorus excretion compared to a 77% increase produced by sevelamer. Decreased urinary phosphorus, indicating decreased absorption of phosphorus, was observed in a dose-dependant manner with sevelamer administration. Animals administered a 0.5% dietary mixture had a 57% decrease in total urinary phosphorus in one experiment, while animals administered 1, 3 and 9% had 66, 88 and 96% decreases in total urinary phosphorus in a separate experiment (Rosenbaum et al, 1997). The

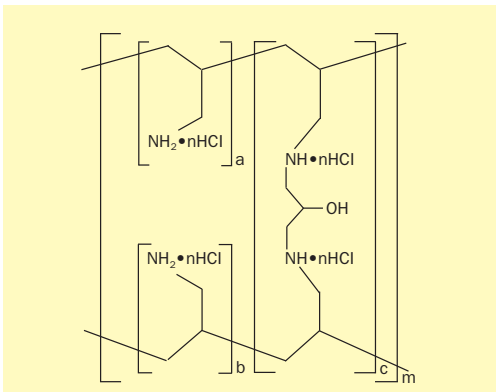

Figure 1. Structural formula of Sevelamer. a, b = number of primary amine groups (a + b = 9), c = number of cross-linking groups (c = 1), n = fraction of protonated amines (n = 0.4), m = large number to indicate extended polymer network.

results from these efficacy studies demonstrate that sevelamer is capable of binding dietary phosphorus in normal animals, preventing gastrointestinal absorption of phosphorus.

Adverse effects: Overall, carcinogenicity studies in rats and mice provide no evidence for potential carcinogenesis of sevelamer. A series of genotoxicity studies were performed to assess sevelamer's mutagenic potential. Sevelamer is considered to be non-mutagenic. Developmental and reproductive toxicity studies have been performed with sevelamer to assess teratogenic potential and effects on fertility. No reproductive toxicity has been observed with sevelamer.

To assess non-clinical toxicity, sevelamer was administered orally to Sprague-Dawley rats acutely and for 1, 3, and 6 months at doses up to 10 g/kg/day, and to beagle dogs acutely and for 1, 3, and 12 months at doses up to 2 g/kg/day. In general, sevelamer caused minimal toxicity. In rats, sevelamer produced a dose-dependent decrease in fat-soluble vitamin E and decreased levels of fat-soluble vitamin D and vitamin K (measured by coagulation time) and folic acid levels at high doses only. Potentially clinically relevant findings (anaemia, focal haemorrhages, and abnormal bone growth) caused by these decreased serum fat-soluble vitamin levels have only been observed in high-dose (4.5–10 g/kg/day) in male rats. These doses are 60 to 140 times the maximum projected human dose of 75 mg/kg/day.

In one study, sevelamer produced an increased incidence of submucosal oedema of the stomach in female rats; the aetiology of this finding is unclear. In dogs, sevelamer produced minimal signs of toxicity. Decreased red blood cell indices and decreased levels of vitamins D and E were observed in animals administered 2 g/kg/day. No overt signs of clinical toxicity and no drug-associated histopathological findings were observed at doses up to 2 g/kg/day.

Drug–drug interactions: Renagel® was studied in human drug–drug interaction studies with digoxin, warfarin, enalapril and metoprolol. Renagel® had no effect on the bioavailability of these medications. However, when administering any other medication where a reduction in the bioavailability of that medication would have a clinically significant effect on safety or efficacy, the physician should consider monitoring blood levels or dosing that medicine apart from Renagel® (at least 1 hour before or 3 hours after Renagel®). Patients taking antiarrhythmic and antiseizure medications were excluded from the clinical trials. Special precautions should be taken when prescribing Renagel® to patients also taking these medications.

Pharmacokinetics: A mass balance study using carbon-14 radiolabelled sevelamer in 16 healthy male and female volunteers demonstrated that sevelamer is not systemically absorbed (S Burke, unpublished data, 1997).

TABLE 1.
Renagel® clinical trials summary

Phase	No of participants	Study design	Objectives
2	36	Randomized, double-blind, placebo controlled	Compare efficacy and safety of Renagel® capsules *vs* placebo
2	48	Open label, dose titration	Investigate safety and efficacy of Renagel® capsules
2	75	Randomized, open label	Investigate safety and efficacy of Renagel® capsules ± evening calcium carbonate supplement
3	83	Randomized, open label, crossover	Compare safety and efficacy of Renagel® capsules *vs* calcium acetate
3	172	Open label, dose titration	Investigate safety and efficacy of Renagel® capsules
3	192	Open label, extended use	Investigate long-term safety and efficacy of Renagel® capsules

Clinical trials

A summary of the clinical trials is shown in *Table 1*. Note that the dose titration studies have aimed to show that Renagel® is at least as efficacious as other available phosphate binders.

Clinical pharmacology

A phase 1 single centre, randomized placebo controlled study to investigate the safety and efficacy of Renagel® hard capsules in 18 normal volunteers showed that Renagel® capsule treatment was safe and well tolerated (Burke et al, 1997). Urine phosphorus decreased in a dose-related manner. The difference was statistically different for all treatment regimens compared to placebo. Total cholesterol decreased significantly for all three Renagel® treatment groups. Analysis of treatment-related adverse events showed that there was no difference between the Renagel® groups and placebo.

Phase 2 and 3: Three phase 2 studies with treatment duration ranging from 2 to 12 weeks and two phase 3 studies with treatment duration of 8 weeks have demonstrated that Renagel® lowers serum phosphorus in patients on haemodialysis.

Comparison of the safety and efficacy of Renagel® with placebo in haemodialysis patients showed that Renagel® significantly reduced serum phosphorus levels (Chertow et al, 1997). In this study, patients continued their regularly prescribed calcium-based phosphate binders during the initial 2 weeks. During the next 2 weeks, patients did not take any phosphate binder. After

the 2-week washout phase, patients were randomized to placebo or Renagel® capsules. Mean serum phosphorus significantly decreased from baseline for Renagel® capsules but increased for placebo (*Figure 2*). Low-density lipoprotein (LDL) cholesterol decreased significantly in patients treated with Renagel® capsules (-17.6 mg/dl), but increased during placebo treatment (+7.3 mg/dl).

A phase 2 dose-titration study has also clearly demonstrated a significant reduction in serum phosphorus and reduction in LDL cholesterol in haemodialysis patients treated with Renagel®. In this study, serum calcium remained within the normal range throughout the 8-week treatment period (Goldberg et al, 1998).

A final phase 2 study looked at the safety and efficacy of Renagel® with an evening calcium supplement in haemodialysis patients (Chertow et al, 1999b). Following a 2-week washout period, patients received Renagel® or Renagel® plus calcium carbonate for 12 weeks. The mean change for serum phosphorus was similar for Renagel® and Renagel® plus calcium carbonate. Similar decreases in calcium x phosphorus product were found in both treatment groups. Serum total and LDL cholesterol also both significantly decreased from baseline in both treatment groups.

A randomized phase 3 crossover study has compared the safety and efficacy of Renagel® with calcium acetate in haemodialysis patients (Bleyer et al, 1999). After a 2-week washout period, patients were randomized to receive either Renagel® or calcium acetate for 8 weeks. Patients were again washed out for 2 weeks and then received the alternative medication for a further 8 weeks. Renagel® and calcium acetate both significantly decreased mean serum phosphorus by about 2 mg/dl (*Figure 3*).

In this phase 3 study, the incidence of hypercalcaemia was significantly lower ($P<0.05$) with Renagel® treatment compared to calcium acetate treatment. During calcium acetate treatment, 22% of patients developed a serum calcium concentration of over 11 mg/dl on at least one occasion, compared with only 5% of patients receiving Renagel®. Mean LDL cholesterol and mean total cholesterol declined significantly in patients receiving Renagel® (–24% and –15% respectively). Neither changed in patients treated with calcium acetate.

A second phase 3 study looked at the effects of Renagel® on phosphorus, calcium and PTH levels in 172 patients (Slatopolsky et al, 1999). Following a 2-week washout period, patients received Renagel® capsules for 8 weeks. Treatment was followed by a 2-week washout period. The results are shown in *Figure 4*. Renagel® significantly reduced serum phosphorus and intact PTH. Calcium did not change significantly over the study period and remained in the normal range. Calcium x phosphorus product declined significantly from 82.1 mg/dl at baseline to 61.4 mg/dl ($P<0.0001$).

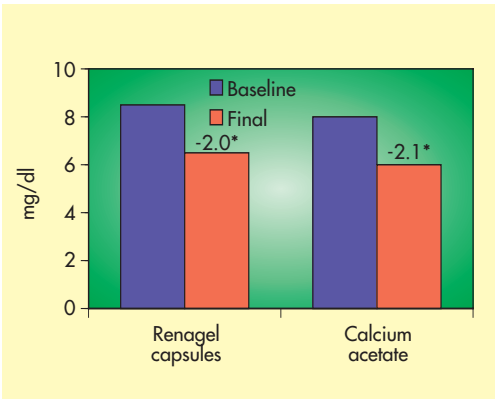

Figure 3. Serum phosphorus (Renagel® vs calcium acetate) phase 3 trial. *P<0.0001 within treatment group comparison.

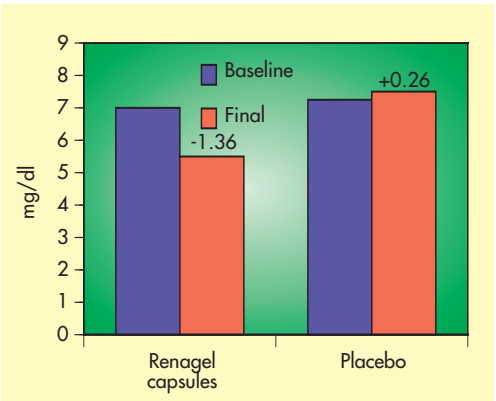

Figure 2. Mean serum phosphorus (placebo vs Renagel®) phase 2 trial.

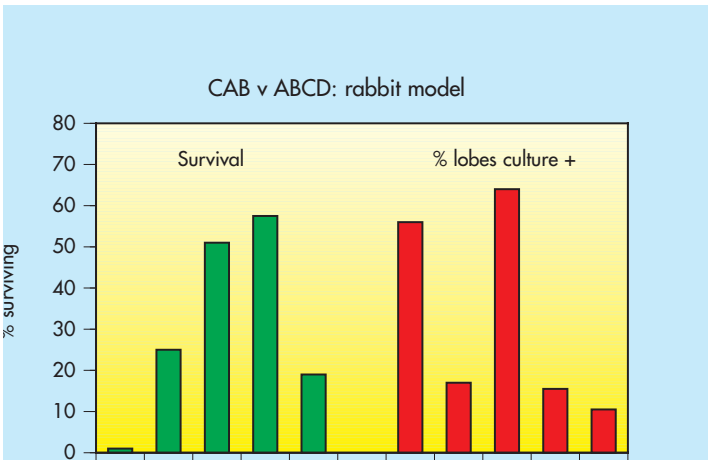

Figure 4. Phosphorus, calcium and parathyroid hormone (PTH) phase 3 trial. P<0.0001 for serum phosphate and PTH.

To investigate the long-term safety and efficacy of Renagel® capsules, a multicentre, open-label, dose titration study has been completed (Chertow et al, 1999b). Following a 2-week washout period, 192 patients were treated with Renagel® for 44 weeks. Compared with baseline, serum phosphorus had declined significantly after 44 weeks (*Figure 5a*). Calcium x phosphorus product was also significantly reduced (*Figure 5b*). Serum total and LDL cholesterol were both significantly reduced. The greatest reduction in LDL cholesterol was in patients with LDL cholesterol levels of greater than 160 mg/dl at baseline. Also after 44 weeks, there was a significant increase in high-density lipoprotein (HDL) cholesterol compared to baseline levels (*Figure 6*).

Data from this 44-week Renagel® trial were used to conduct a case control study (Collins et al, 1999). Of the original 192 Renagel®-treated patients, 152 were unequivocally identified in the United States Renal Data System and matched with 152 control patients from the same haemodialysis centres. Using a Cox regression model, Renagel®-treated patients were found to have:

- A statistically significant 50% reduction in hospitalization
- Non-significant reductions in vascular access complications (30% reduction) and mortality (35%).

These rates were also seen adjusting for race, sex, age, comorbidity and disease severity. In the US this equated to a saving of some $1400 savings per month per patient as determined from Medicare claims data (A Collins et al, unpublished data, 1999). Further prospective studies are required to confirm these findings.

Typical dosage

Dose should be gradually adjusted based on the serum phosphorus concentration. The goal should be to lower serum phosphorus to 6.0 mg/dl or less. In clinical trials, the average dose required was four capsules of Renagel® with each meal (each capsule contains 403 mg of sevelamer hydrochloride). For patients switching from a calcium-based phosphate binder, the conversion should be made on a gram for gram basis, for example a patient taking 3 g of calcium carbonate should be switched to 3 g of Renagel®.

Adverse reactions

The findings from six clinical trials involving approximately 400 patients indicates that Renagel® is well tolerated, with no dose-related increases in treatment-related adverse events. In a placebo-controlled study, adverse events reported during treatment with Renagel® were similar to those reported with placebo.

In a long-term, open label extension trial, adverse events possibly related to Renagel® capsules and which were not dose-related, included nausea (7%), constipation (2%), diarrhoea (4%), flatulence (4%) and dyspepsia (5%).

Note that analysis of adverse events in the dialysis population is complicated by end-stage renal disease-related disturbances in the function of every major organ system and by complications associated with dialysis.

Cardioprotective effects

Since hyperphosphataemia increases morbidity and mortality in dialysis patients, it is critically important to be able to effectively manage phosphate levels. Calcium carbonate is routinely used, but some patients require up to 18 g calcium carbonate each day to control serum phosphate levels. With a typical dosage, patients will retain calcium and will be in constant positive calcium balance (Hsu, 1997). The consequences include calcium phosphate deposition in many body tissues, particularly the vasculature.

Recent studies have shown that typical haemodialysis patients have more coronary artery calcification than patients with coronary artery disease. Further, calcification is present in the mitral and aortic valves of 50–60% of these patients (Braun et al, 1996) and can be associ-

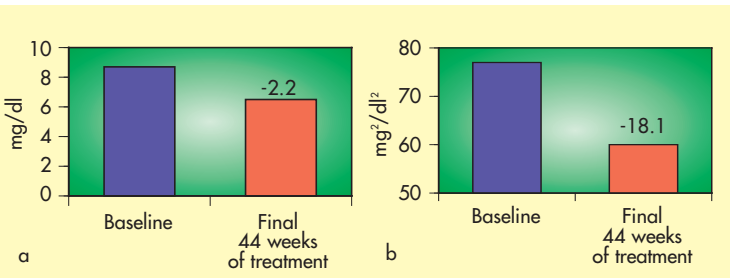

Figure 5. Composite mean serum (a) phosphorus and (b) calcium x phosphorus product. Open label study. ***P<0.0001 for both.***

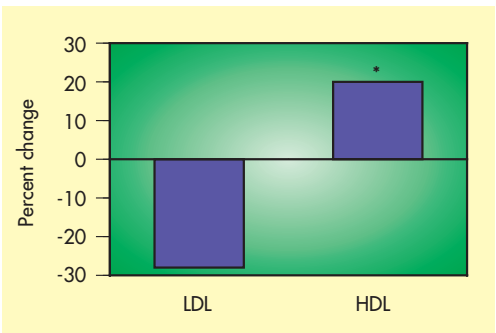

Figure 6. Change in lipid parameters. Open label study. HDL = high-density lipoprotein; LDL = low-density lipoprotein. ***P<0.01.***

ated with disturbance of cardiac conduction (Ribeiro et al, 1998). Coronary artery calcification is present in dialysis patients as young as 20 years of age (Goodman et al, 2000) and is associated with greater intake of calcium-based phosphate binders. The association of calcium dose and vascular calcification has also been seen in the common carotid artery, aorta, and femoral arteries (Guérin et al, 2000). This arterial calcification correlated with deleterious changes in arterial stiffness and left ventricular function. Perhaps most concerning is that calcification increases rapidly in dialysis patients, doubling in many in 1–2 years (Braun et al, 1996; Goodman et al, 2000).

Of considerable interest is the proposition that Renagel® will reduce cardiac calcification in patients on dialysis. Renagel® lowers serum phosphorus without contributing to the positive calcium balance in these patients and further has a beneficial effect of decreasing total and LDL cholesterol and increasing HDL cholesterol (Chertow et al, 1999a). The majority of vascular calcifications in dialysis patients develop in atherosclerotic plaques (Schwarz et al, 2000). In an ongoing study, electron beam computed tomography (EBCT) is being employed to measure the progression of coronary, valvular, and aortic calcification in Renagel® *vs* calcium-based phosphate binder-treated patients. The EBCT technique enables calcification to be accurately imaged and scored. Results of the trial should shed further light on the pathophysiology of this severe complication of end-stage renal disease.

CONCLUSIONS

Renagel® is a novel, non-absorbed polymeric phosphate binder. Clinical trials have clearly shown that Renagel® reduces serum phosphorus and calcium x phosphorus product and has a beneficial effect on the lipid profile without contributing to a positive calcium balance. Whether these features will lead to less vascular calcification needs to be determined by ongoing studies. Early positive data on hospitalization rates should also be confirmed by prospective studies. HM

Conflict of interest: none.

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KEY POINTS

- Renagel® is a calcium-free, aluminum-free, non-absorbed phosphate binder.
- Clinical trials show that Renagel® reduces serum phosphorus and calcium x phosphorus product.
- Renagel® has a beneficial effect on the lipid profile.