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Original Article

RenaGel®, a novel calcium- and aluminium-free phosphate binder, inhibits phosphate absorption in normal volunteers

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Abstract

Background. Available phosphate binders contain aluminium or calcium which can be associated with undesirable effects. RenaGel®, cross-linked poly(allylamine hydrochloride), is a non-absorbed phosphate-binding polymer, free of calcium and aluminium. We conducted this study to examine the safety and phosphate binding efficacy of RenaGel in volunteers.

Methods. During 18 days (days 0–17) at the clinical study unit, 24 subjects consumed a phosphate-controlled diet designed to provide 37.5 mmol (1200 mg) elemental phosphorus per day. From the morning of day 5 to the morning of day 9, urine and faeces were collected. Average baseline urine and faecal phosphorus contents were determined. On days 9–16, the subjects received either RenaGel 1 g, 2.5 g, or 5 g or placebo three times per day immediately prior to the meals. From the morning of day 13 to the morning of day 17, urine and faeces were again collected and phosphorus contents on treatment were determined.

Results. RenaGel inhibited dietary phosphate absorption as measured by a decline in average daily urinary phosphorus excretion and an increase in average daily fecal phosphorus excretion. Average urine phosphorus contents on treatment were 27.2 mmol (870 mg) per day in the placebo group vs 23.8 mmol (762 mg), 19.5 mmol (625 mg), and 16.6 mmol (530 mg) per day in the RenaGel 1-g, 2.5-g, and 5-g groups. Average daily faecal phosphorus content on treatment was markedly higher in the RenaGel 5-g group, 19.1 mmol (611 mg) per day vs 10.7 mmol (342 mg) per day for the placebo group. RenaGel also decreased total serum cholesterol by 0.71 mmol/L (27.5 mg/dl), 0.55 mmol/l (21.3 mg/dl), and 1.08 mmol/l (41.8 mg/dl) for the RenaGel 1-g, 2.5-g, and 5-g groups. RenaGel was well tolerated with adverse events similar to placebo.

Conclusions. RenaGel is a safe, effective, and well tolerated phosphate binder in normal volunteers. The degree of phosphate binding is consistent with its potential use as a phosphate binder in renal failure patients.

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Key words: hyperphosphataemia; poly(allylamine hydrochloride); phosphate binder; renal failure; serum cholesterol

Introduction

In normal man, the serum phosphorus concentration is maintained within a narrow range despite variable dietary phosphorus consumption. The average daily phosphorus content of a western diet is between 31 and 56 mmol (1 and 1.8 g) [1]. Of this amount, 70% is absorbed through the gastrointestinal tract then excreted by the kidneys. In chronic renal failure, the system for maintaining phosphorus balance is disrupted by loss of nephrons. As the glomerular filtration rate falls, there is a renal adaptation characterized by a decline in the renal tubular reabsorption of phosphorus causing an increased phosphaturia in the residual nephrons. Increase in the circulating parathyroid hormone (PTH) level is an important mediator of this adaptation. Beyond a certain point (GFR < 25 ml/min), elevation in PTH levels cannot further increase phosphaturia, and hyperphosphataemia develops [1,2]. Persistent hyperparathyroidism can cause bone disease typified by osteitis fibrosa cystica.

A reduction in phosphorus absorption is crucial to preventing hyperphosphataemia and resulting hyperparathyroidism in patients with decreased functional nephrons. Since phosphorus is absorbed from dietary sources, patients with advanced chronic renal failure are placed on phosphorus-restricted diets. However, dietary phosphate restriction is usually insufficient and most patients use phosphate binders [1]. Aluminium salts are efficacious phosphate binders, but aluminium accumulates in the tissues of renal failure patients and is associated with significant toxicity [3,4]. Calcium salts are also effective as phosphate binders. However, a percentage of the ingested calcium is absorbed, causing hypercalcaemia and increasing the risk of metastatic calcification in some patients [5,6]. Therefore there exists a need for an effective phosphate binder without the side-effects of aluminium or calcium.

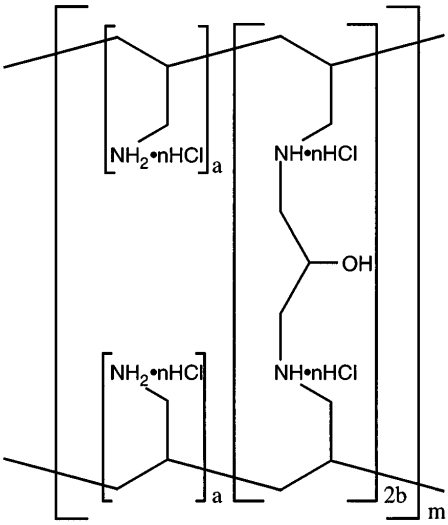

Fig. 1. Structure of RenaGel, cross-linked poly(allylamine) hydrochloride.

RenaGel®, cross-linked poly(allylamine hydrochloride), is an aluminium- and calcium-free phosphate-binding polymer (Figure 1). RenaGel contains multiple amines spaced by one carbon from the polymer backbone. These amines become partially protonated in the intestine and interact with phosphate molecules through charge and hydrogen bonding. Phosphate binding is optimal at pH 7. *In vitro* at pH 7, 1 g of RenaGel binds approximately 2.6 mmol of phosphate at an estimated physiological concentration of 5 mM [7].

RenaGel binds preferentially to trivalent anions, such as phosphate and citrate. RenaGel will also bind bile acids and negatively charged amino-acid conjugates, which like phosphate are abundant in the intestine at mealtimes. RenaGel binding of bile acids leads to increased faecal bile acid excretion and LDL cholesterol lowering (unpublished data). This LDL cholesterol lowering is the primary pharmacological property of RenaGel other than phosphate binding. Absorption studies of radiolabelled RenaGel in rats, dogs, and normal human, have demonstrated that RenaGel is not absorbed (unpublished data).

This first study in man was conducted to assess the safety, tolerance, and phosphate binding efficacy of RenaGel in normal volunteers. Efficacy was assessed by measuring changes in urine and faecal phosphorus content from a baseline period to a RenaGel treatment period. Phosphate binding was anticipated to result in a decrease in urinary phosphorus excretion and an increase in faecal phosphorus excretion. Since the subjects had normal renal function, changes in serum phosphorus were not anticipated.

Subjects and methods

Subjects

Twenty-four healthy male and female volunteers without a history of significant medical disease, not on any regular medication, and between the ages of 18 and 40 years of age were enrolled. The protocol and informed consent form were approved by the Harris Laboratories Institutional Review Board, Lincoln, NE, USA. The study was conducted at Harris Laboratories, Inc. Lincoln, NE, USA.

Study design

On Day 1 the subjects received a single oral dose of RenaGel 1 g, 2.5 g, 5 g, or placebo for the purpose of obtaining single-dose safety and tolerance. From the morning of day 5 to the morning of day 9, urine and faeces were collected at each voiding and pooled in separate containers in 24-h collection intervals for baseline phosphorus content. On days 9–16, the subjects received 1 g, 2.5 g, or 5 g of RenaGel, or placebo three times per day immediately prior to the three main meals. From the morning of day 13 to the morning of day 17, urine and faeces were collected again to determine phosphorus content during treatment with RenaGel or placebo. The subjects were discharged on day 17.

While at the clinical research unit, the subjects consumed a phosphate-controlled diet designed to provide 37.5 mmol (1200 mg) of elemental phosphorus/day (3 meals + 1 snack). The mean phosphorus content of the meals were 12.1 mmol (387 mg), 8.6 mmol (275 mg), 12.0 mmol (416 mg), and 2.6 mmol (83 mg) for breakfast, lunch, dinner, and snack respectively. With breakfast, the majority of the phosphorus was administered in milk. With the other meals phosphorus was primarily administered in solid food. An 8-day menu started on day 1 and continued to day 8 and was repeated from day 9 to day 16. Subjects were required to ingest the entire meal.

The primary objectives of the study were to compare the treatment groups for safety (adverse events, changes in physical examinations, and changes in laboratory safety tests) and efficacy (urinary phosphorus and faecal phosphorus excretion).

Treatment assignment

Qualified subjects were randomly placed, based on order of presentation, into three groups (eight subjects/group). Subjects received numbers from 1 to 24 which identified them throughout the trial. After admission and assignment of a number, subjects were randomly assigned to receive RenaGel (six of the eight subjects per group) or matching placebo (two of the eight subjects per group) using a computer-generated randomization scheme prepared by Clinical Systems, Inc. (Garden City, NY, USA). RenaGel was supplied as hard gelatin capsules containing 500 mg of RenaGel without excipient. Identically appearing placebo capsules contained 350 mg of microcrystalline cellulose. Both RenaGel and placebo capsules were odourless and tasteless. The pharmacist who controlled dosing was the only person to know the identity (RenaGel vs placebo) of the capsules.

Methods

During the two periods of urine and faeces collection (days 5–9 and 13–17), urine and faeces samples were collected at each voiding and pooled in urine or stool collection containers in 24-h intervals. An aliquot of well-mixed urine from each 24-h collection was analysed for elemental phosphorus using standard calorimetric techniques (Miles Technicon Axon). Each 24-h faeces collection was homogenized, then an aliquot was analysed for phosphorus using inductively

coupled plasma atomic emission spectrometry by National Medical Services, Inc., Willow Grove, PA, USA. Mean baseline and treatment phosphorus content and change from baseline were calculated for each subject.

Statistical methods

All subjects completed the study and were included in the analyses. Data from placebo patients were pooled into one group so that four groups were compared (one placebo group and three RenaGel groups). All statistical tests were two-tailed with a P value of 0.05 required for significance. The baseline characteristics of the treatment groups were compared using Fisher's exact test for categorical variables (sex and race) and analysis of variance for continuous variables (age, weight, and height). The overall incidence of all adverse events, adverse events by preferred term and organ class were analysed by Fisher's exact test. Descriptive statistics were prepared for vital signs and laboratory values at each time point. Additionally, intra- and intergroup changes in laboratory values were analysed. For the primary tests of efficacy, change in urine and stool phosphorus, ANOVA was used to detect an overall difference in the treatment groups. If the overall test was significant, pairwise t tests were performed to compare the groups.

Results

Disposition

The 24 subjects enrolled met all inclusion/exclusion criteria. All completed the study and were included in the safety and efficacy analyses. There were no deviations from the protocol.

Demographic characteristics and comparability of treatment groups

Characteristics of the study subjects are summarized in Table 1. There were no statistically significant differences between the groups in terms of sex, race, age, height, and weight.

Safety and tolerance

Each subject received all 25 doses of RenaGel or placebo specified in the protocol. No serious adverse events occurred during the study. There were no statistically significant differences among the four treatment groups in terms of adverse events. There was no evidence that RenaGel treatment was associated with any types of adverse events, including gastrointestinal events. Mean serum phosphorus and calcium on treatment did not change from the baseline value as expected. There were no remarkable changes in the other laboratory tests except for total serum cholesterol, which declined (mean $\pm$ SD) on average 0.71 ± 0.39 mmol/l (28 ± 15 mg/dl), 0.55 ± 0.28 mmol/l (21 ± 11 mg/dl), and 1.08 ± 0.41 mmol/l (42 ± 16 mg/dl) for subjects in the RenaGel 1-g, 2.5-g, and 5-g groups respectively. These changes represent declines in total cholesterol of approximately 15–25% and were highly significant (P values less than 0.01). Mean total serum cholesterol and triglycerides are summarized in Table 2. HDL cholesterol was not measured, and therefore LDL cholesterol could not be calculated.

Efficacy

RenaGel's phosphate-binding efficacy was evaluated by comparing change from baseline in urine and faecal phosphorus excretion, measured as mean daily urine and faecal phosphorus content. Figure 2 displays average total daily urine phosphorus content at baseline and on treatment for the groups. Total daily urine phosphorus content was similar across the groups at baseline, on average 24.6 mmol (787 mg), or approximately 66% of ingested phosphorus. With RenaGel

Table 1. Demographic characteristics of the treatment groups

Parameter	Placebo ($n=6$)	RenaGel 1 g ($n=6$)	RenaGel 2.5 g ($n=6$)	RenaGel 5 g ($n=6$)	P*
Sex					
Male	5 (83%)	4 (67%)	4 (67%)	4 (67%)	1.00
Female	1 (17%)	2 (33%)	2 (33%)	2 (33%)	
Race					
Caucasian	6 (100%)	6 (100%)	3 (50%)	4 (67%)	0.13
African Am.	0 (0%)	0 (0%)	1 (17%)	0 (0%)	
Hispanic	0 (0%)	0 (0%)	1 (17%)	2 (33%)	
Native Am.	0 (0%)	0 (0%)	1 (17%)	0 (0%)	
Age (years)					
Mean $\pm$ SD	27.7 ± 5.5	31.0 ± 8.1	25.2 ± 4.9	28.5 ± 5.1	0.43
Range	24–38	22–39	20–31	25–36	
Height (cm)					
Mean $\pm$ SD	174 ± 7	177 ± 11	177 ± 7	178 ± 10	0.92
Range	165–183	163–193	163–183	168–193	
Weight (kg)					
Mean $\pm$ SD	68 ± 7	75 ± 18	75 ± 9	76 ± 10	0.69
Range	60–75	56–99	61–82	62–86	

*Fisher's exact test for categorical variables and ANOVA for continuous variables.

Table 2. Baseline and end-treatment serum lipid values

Parameter	Placebo ($n=6$)	RenaGel 1 g ($n=6$)	RenaGel 2.5 g ($n=6$)	RenaGel 5 g ($n=6$)
Cholesterol baseline				
mmol/l ± SD	3.70 ± 0.36	4.37 ± 0.62	3.95 ± 0.78	4.39 ± 0.93
(mg/dl ± SD)	(143 ± 14)	(169 ± 24)	(153 ± 30)	(170 ± 36)
Cholesterol treatment				
mmol/l ± SD	3.80 ± 0.41	3.67 ± 0.28*	3.41 ± 0.78*	3.31 ± 0.85*
(mg/dl ± SD)	(147 ± 16)	(142 ± 11)	(132 ± 30)	(128 ± 33)
Triglycerides baseline				
mmol/l ± SD	1.31 ± 0.27	1.72 ± 0.76	1.17 ± 0.47	1.31 ± 0.25
(mg/dl ± SD)	(116 ± 24)	(152 ± 67)	(104 ± 42)	(116 ± 22)
Triglycerides treatment				
mmol/l ± SD	1.26 ± 0.40	2.05 ± 0.82	1.11 ± 0.37	1.32 ± 0.47
(mg/dl ± SD)	(112 ± 35)	(182 ± 73)	(98 ± 33)	(117 ± 42)

*Mean change from baseline $P<0.01$. Pairwise comparisons of mean change from baseline RenaGel groups vs placebo all $P<0.01$.

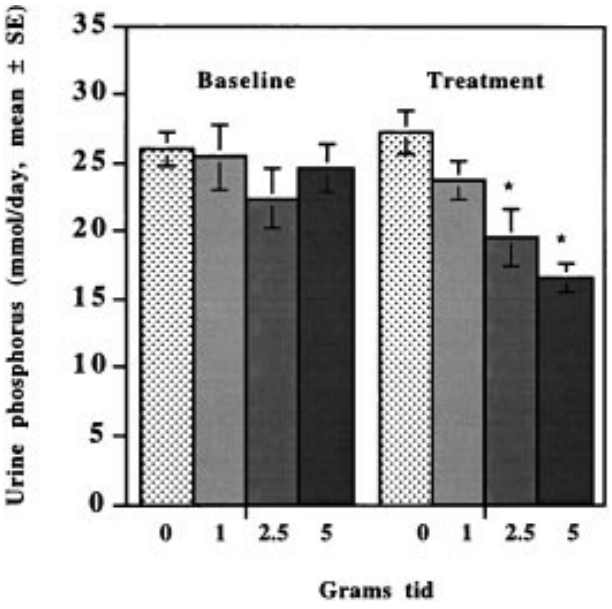

Fig. 2. Average daily urinary phosphorus excretion at baseline and on RenaGel treatment. ANOVA comparing change from baseline for the four treatment groups, $P=0.001$. *Pairwise comparisons vs. placebo, $p<0.01$.

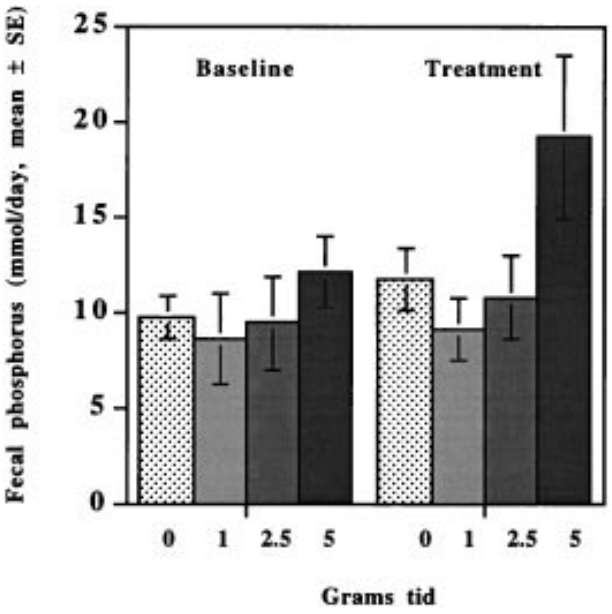

Fig. 3. Average daily faecal phosphorus excretion at baseline and on RenaGel treatment. ANOVA comparing change from baseline for the four treatment groups, $p=0.184$.

treatment, there was a clear dose-dependent decline in urine phosphorus content. Average urinary phosphorus contents were 27.2 ± 3.8 mmol (870 ± 123 mg) per day for placebo vs 23.8 mmol ± 3.4 (762 ± 110 mg), 19.5 ± 5.1 mmol (625 ± 162 mg), and 16.6 ± 2.5 mmol (530 ± 81 mg) per day for the RenaGel 1-g, 2.5-g, and 5-g groups. Pairwise comparisons of mean change from baseline revealed statistically significant differences between placebo and RenaGel 2.5-g groups ($P=0.002$), placebo and RenaGel 5-g groups ($P<0.001$), and between RenaGel 1-g and RenaGel 5-g groups ($P=0.004$).

Figure 3 presents average total daily faecal phosphorus contents at baseline and on treatment. Total faecal phosphorus contents were similar across the treatment groups at baseline. Approximately 26% of ingested phosphorus, 9.9 mmol (317 mg), appeared in the faeces. Average total daily treatment faecal phosphorus content was markedly higher in the RenaGel 5-g group, 19.1 ± 10.6 mmol (611 ± 340 mg), *versus* 11.6 ± 4.0 mmol (371 ± 129 mg), 9.1 ± 4.1 mmol (291 ± 132 mg), and 10.7 ± 5.3 mmol (342 ± 169 mg) for the placebo and RenaGel 1-g and 2.5-g groups. However, due to large variations in the data, the overall intergroup difference was not statistically significant.

Discussion

The primary objective of this study was to assess the safety and tolerance of RenaGel in normal volunteers. RenaGel was very well tolerated, with all subjects consuming the 25 doses prescribed by the protocol. The adverse event profile for RenaGel was not different

than that observed with placebo. Notably, there was no evidence that RenaGel caused gastrointestinal adverse events at doses as high as 15 g/day (5 g t.i.d.). Laboratory safety tests were not significantly altered.

Sequestration of the study subjects allowed for the assessment of phosphate-binding efficacy by measuring changes in urine and faecal phosphorus excretion. In this study, dosing was suboptimal, as the amount of RenaGel was not adjusted to the phosphorus content of the meals and was not given with the evening snack. Despite this, RenaGel was clearly effective in reducing phosphate absorption, as evidenced by the decline in urinary phosphorus excretion. Faecal phosphorus excretion data were more variable, probably because of (1) difficulty in dispersing the insoluble RenaGel and bound phosphate equally throughout the homogenized faeces, and (2) interindividual variations in gastrointestinal transit time. However, there was a strikingly higher mean faecal phosphorus excretion in the highest RenaGel dose group.

The cholesterol-lowering effect of RenaGel is probably caused by bile acid binding noted in previous *in vitro* and *in vivo* experiments (unpublished data). Increased faecal excretion of bile acids leads to LDL receptor upregulation in the liver—the mechanism of action of the lipid-lowering drugs cholestyramine and colestipol. This side-effect may prove to be beneficial in dialysis patients, who may have atherogenic lipid profiles and/or may suffer from atherosclerosis, a major cause of morbidity and mortality in this population. To date, treatment of lipid disorders in dialysis patients has been hampered by a high incidence of side-effects with the commonly used medications [8].

Subsequent to this study, RenaGel was administered to haemodialysis patients in a randomized, placebo-controlled trial. In that study, RenaGel was again well tolerated and safe. RenaGel treatment led to significant reductions in mean serum phosphorus (2.26 mmol/l (7.0 mg/dl) to 1.81 mmol/l (5.6 mg/dl). $P < 0.001$) in 21 hyperphosphataemic patients compared with no change in 11 placebo-treated patients (2.36 mmol/l (7.3 mg/dl) to 2.45 mmol/l (7.6 mg/dl), $P = \text{NS}$) [9,10]. RenaGel treatment also lowered total and LDL cholesterol without effects on HDL cholesterol or triglycerides.

In summary, RenaGel is an effective non-absorbed phosphate-binding polymer free of calcium and aluminium. RenaGel has the additional benefit of lowering serum cholesterol. Longer-term studies with RenaGel will determine the safety and efficacy profile in dialysis patients.

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