

Treatment of hyperphosphatemia in hemodialysis patients: The Calcium Acetate Renegel Evaluation (CARE Study)

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Treatment of hyperphosphatemia in hemodialysis patients: The Calcium Acetate Renegel Evaluation (CARE Study).

Background. Hyperphosphatemia underlies development of hyperparathyroidism, osteodystrophy, extraosseous calcification, and is associated with increased mortality in hemodialysis patients.

Methods. To determine whether calcium acetate or sevelamer hydrochloride best achieves recently recommended treatment goals of phosphorus ≤ 5.5 mg/dL and Ca \times P product ≤ 55 mg²/dL², we conducted an 8-week randomized, double-blind study in 100 hemodialysis patients.

Results. Comparisons of time-averaged concentrations (weeks 1 to 8) demonstrated that calcium acetate recipients had lower serum phosphorus (1.08 mg/dL difference, $P = 0.0006$), higher serum calcium (0.63 mg/dL difference, $P < 0.0001$), and lower Ca \times P (6.1 mg²/dL² difference, $P = 0.022$) than sevelamer recipients. At each week, calcium acetate recipients were 20% to 24% more likely to attain goal phosphorus [odds ratio (OR) 2.37, 95% CI 1.28–4.37, $P = 0.0058$], and 15% to 20% more likely to attain goal Ca \times P (OR 2.16, 95% CI 1.20–3.86, $P = 0.0097$). Transient hypercalcemia occurred in 8 of 48 (16.7%) calcium acetate recipients, all of whom received concomitant intravenous vitamin D. By regression analysis hypercalcemia was more likely with calcium acetate (OR 6.1, 95% CI 2.8–13.3, $P < 0.0001$). Week 8 intact PTH levels were not significantly different. Serum bicarbonate levels were significantly lower with sevelamer hydrochloride treatment ($P < 0.0001$).

Conclusion. Calcium acetate controls serum phosphorus and calcium-phosphate product more effectively than sevelamer hydrochloride. Cost-benefit analysis indicates that in the absence of hypercalcemia, calcium acetate should remain the treatment of choice for hyperphosphatemia in hemodialysis patients.

Hyperphosphatemia is associated with increased mortality in hemodialysis patients and plays a key role in the

Key words: calcium acetate, sevelamer hydrochloride, hyperphosphatemia, hypercalcemia, hypocalcemia, metabolic acidosis.

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development of hyperparathyroidism, renal osteodystrophy, and extraosseous calcification. Serum phosphorus exceeding 5.5 mg/dL, and calcium phosphate product (Ca \times P) over 52 mg²/dL² each correlate with increased mortality risk in dialysis patients [1]. These findings have led to recent recommendations for more rigorous control of serum phosphorus to between 2.5 and 5.5 mg/dL, while maintaining Ca \times P product less than 55 mg²/dL² [2].

Because dietary phosphorus restriction and hemodialysis often fail to adequately control serum phosphorus, phosphate binders are routinely prescribed to reduce intestinal absorption of phosphate. Although effective, aluminum-containing binders have largely been abandoned because of risks of aluminum intoxication [3]. Calcium acetate is the most commonly prescribed calcium-containing phosphate binder in the United States. Sevelamer hydrochloride is a recently introduced phosphate binder that is a quaternary amine anion exchange resin that contains no calcium or aluminum [4]. Various open-label studies have shown that both calcium acetate and sevelamer reduce serum phosphorus levels in hemodialysis patients [4–8]. However, in most of these studies, hyperphosphatemic dialysis patients treated with sevelamer have not reliably achieved the newly recommended treatment goal for serum phosphorus. Control of serum phosphorus to normal levels is clearly important for prevention and treatment of secondary hyperparathyroidism, and has the potential to reduce cardiovascular risk in dialysis patients. We, therefore, conducted a randomized double-blind study to compare the efficacy of calcium acetate and sevelamer hydrochloride for serum phosphorus control in patients with end-stage renal disease (ESRD) on maintenance hemodialysis.

METHODS

Study design

The Calcium Acetate Renegel Evaluation (CARE Study) was a prospective, multicenter, randomized,

double-blind study comparing the efficacy of calcium acetate and sevelamer hydrochloride for the treatment of hyperphosphatemia in patients with ESRD on hemodialysis. The study was conducted at six outpatient clinics associated with two study centers: the University of Texas Health Sciences Center at San Antonio (San Antonio, TX, USA), and the Austin Diagnostic Clinic (Austin, TX, USA). The protocol was approved by the respective Institutional Review Boards. Enrolled patients consisted of 100 adults receiving maintenance hemodialysis for at least 3 months, receiving a stable dose of phosphate binder and intravenous vitamin D for at least one month. Main exclusion criteria were intact parathyroid hormone (iPTH) level over 1000 pg/mL, or a history of previous parathyroidectomy. Patients whose serum phosphorus was ≥ 6.0 mg/dL after 1 to 3 weeks of binder withdrawal were randomized to 8-week treatment with either calcium acetate (PhosLo[®] 667 mg capsules; Braintree Laboratories, Braintree, MA, USA) or sevelamer hydrochloride (Renagel[®] 403 mg capsules; Genzyme Corporation, Cambridge, MA, USA). Study blinding was maintained by packaging calcium acetate in hard gelatin capsules identical to the sevelamer hydrochloride capsules. The starting dose of study medication was based on package insert recommendations indexed to serum phosphorus at the end of washout as follows: ≥ 6 mg/dL and < 7.5 mg/dL, 2 capsules thrice daily; ≥ 7.5 mg/dL and < 9.0 mg/dL, 3 capsules thrice daily; ≥ 9.0 mg/dL, 4 capsules thrice daily. Study drug was administered with meals, with one half the dose immediately before, and the other half immediately after the meal. Each week the dosage of study drug was increased 1 to 2 capsules per meal as needed to achieve a goal serum phosphorus ≤ 5.5 mg/dL. Dosage adjustment was based only on the serum phosphorus without regard to the Ca \times P product. If the serum calcium level exceeded 11.0 mg/dL, binder dose was decreased by one capsule per meal. Dialysate calcium concentration (2.5 mEq/L) and prestudy intravenous vitamin D dosage were held constant during the study. At enrollment, patients were counseled with regard to a phosphorus-restricted diet, and instructed to maintain that diet throughout the course of the study. Except as outlined above, patients were prohibited from consuming calcium supplements or antacids containing aluminum, magnesium, or calcium. Study drug compliance was assessed by weekly pill counts. Each week, subjects graded their subjective symptoms of constipation, nausea, vomiting, diarrhea, and abdominal pain on a scale of 0 (none) to 10 (severe). Predialysis blood samples were obtained weekly for determination of phosphorus, calcium, and bicarbonate. At weeks 0 (baseline), 4, and 8, intact parathyroid hormone (iPTH) levels were measured. Laboratory analyses were performed at a central reference laboratory. Projected annual costs of phosphate binder treatment were calculated

based on the mean binder dose at week 8 and average wholesale prices.

Statistical methods

Weekly serum phosphorus, serum calcium, and calcium \times phosphorus product (Ca \times P) were described by their mean values, as well as by a binary treatment outcome of “goal attained or not.” For serum calcium, a three-level outcome (hypocalcemia, normal serum calcium, and hypercalcemia) was also used. Primary analyses were repeated measures regressions, a logistic model for binary outcomes, and a proportional odds model for the three-level, repeated ordinal outcome. These models were implemented in SAS/STAT software PROC GENMOD (version 8.2, SAS Institute, Cary, NC, USA). Treatment effects were assessed by their odds ratio (OR), but simpler percentage differences were also given because they were roughly constant over time for serum phosphorus and Ca \times P product. Each week’s serum phosphorus level was coded as “goal attained” for $P \leq 5.5$ mg/dL, and similarly for serum calcium, but with the goal of 8.5 mg/dL $\leq Ca \leq 11$ mg/dL. A three-level ordinal outcome for serum calcium was also defined by the same limits. For Ca \times P product to be coded as “goal attained,” the product had to be ≤ 55 mg²/dL², and the binary goals for serum phosphorus and serum calcium also had to be attained. Repeated measures models included linear and quadratic terms in time (the latter to allow for curved trajectories), a binary indicator for treatment (calcium acetate vs. sevelamer hydrochloride), and baseline values of the quantitative outcome and of iPTH level, weight, age, gender, and study center. Interactions among treatment, time, and center were also examined. Autoregressive correlation structure was assumed. All subjects and observations were included (intention-to-treat analysis). Time was included in models as 1, 2, ..., 8 weeks, except for a set of models that omitted the first four weeks of outcomes in order to focus on longer-term responses after the initial four weeks of study drug titration. No imputation was used but sensitivity analyses examined the impact of setting all missing values to “goal attained,” or all to “goal not attained,” and also included compliance as defined by weekly percent of pills taken. Significant treatment effects were defined by likelihood ratio *P* values of 0.05 or less for treatment main effects, or, as appropriate, combined main effects and interactions of treatment with time. Similar repeated measures models were used to analyze continuous and binary serum bicarbonate outcomes. Time to first attainment of treatment goals was described by Kaplan-Meier curves, and compared between treatment groups by log-rank test (SAS Institute). Additional analyses of each outcome concerned the proportion of eight study weeks with the goal attained. Failure was assumed in weeks with missing data. Treatments were

Table 1. Demographics and baseline laboratory parameters^a

Parameter	Calcium acetate	Sevelamer HCl	<i>P</i> value ^c
Number of patients	48	50	
Age years	53.9 ± 13.3	52.3 ± 14.7	0.57
Predialysis weight kg	76.8 ± 18.7	85.5 ± 22.5	0.040
Gender			0.82
Male	28 (58%)	28 (56%)	
Female	20 (42%)	22 (44%)	
Race			0.74
Hispanic	26 (54%)	24 (48%)	
Black	15 (31%)	14 (28%)	
White	7 (15%)	12 (24%)	
Years on dialysis	3.7 ± 2.7	4.8 ± 6.5	0.28
Vitamin D therapy	31 (65%)	30 (60%)	0.64
Prestudy binder			0.079
Calcium-based alone	33 (69%)	26 (52%)	
Sevelamer alone	5 (10%)	6 (12%)	
More than one binder	10 (21%)	18 (36%)	
Baseline laboratory data ^b			
Serum phosphorus mg/dL	7.7 ± 1.8	7.7 ± 2.0	0.99
Serum calcium mg/dL	8.9 ± 0.9	8.9 ± 0.7	0.84
Ca × P product mg ² /dL ²	69.0 ± 17.3	69.5 ± 19.4	0.91
Intact PTH pg/mL	257.3 ± 160.6	206.1 ± 125.7	0.15 ^d
Serum bicarbonate mEq/L	19.6 ± 2.5	20.5 ± 3.0	0.11

^aPlus minus values are mean ± SD.

^bBaseline laboratory data were obtained at the end of 1- to 3-week washout period off all phosphate binders.

^cThe Cochran-Mantel-Haenszel chi-square was used to assess treatment group differences for categorical data. Student *t* test was used to compare means.

^d*P* value obtained from comparison of log₁₀-transformed values.

compared by exact Cochran-Mantel-Haenszel test, and also by proportional odds regression (SAS Institute), with the same baseline covariates as for the repeated measures model. To summarize weekly means for serum phosphorus, calcium, and Ca × P product, each subject's quantitative outcomes were averaged to produce three values of C_{avg} , computed by trapezoidal rule area-under-the-curve, excluding baseline, divided by follow-up time. Between-treatment comparisons of C_{avg} were by linear regression (SAS Institute), again with the same baseline covariates. Similar linear models were used for iPTH outcomes.

RESULTS

Demographics and baseline laboratory comparisons

A total of 128 patients with ESRD on maintenance hemodialysis were screened for enrollment. There were 28 potential subjects who failed screening for the following reasons: 16 had serum phosphorus less than 6.0 mg/dL after a 3-week washout period off of phosphate binders; 4 patients refused study participation; 3 had a history of questionable compliance with medications; 4 had previous parathyroidectomy; and 1 patient had no requirement for binder therapy for phosphorus control. One hundred patients were enrolled; however, two patients in the calcium acetate group were dropped from the study because they inadvertently resumed their prestudy phosphate binder. Forty-eight patients were randomized to calcium acetate, and 50 to sevelamer hydrochloride, with 96% and 90% completing the study with no missing

postbaseline visit (*P* value 0.44 by Fisher exact test). Each study center had 49 patients who were included in the analysis. Patient demographics and baseline laboratory comparisons are shown in Table 1. Although a statistically significant between-group difference in weight was identified, this difference had no effect on the primary "goal attained" outcomes (Table 2). No baseline laboratory measures differed significantly between treatment groups. Bicarbonate was also analyzed as an outcome. Baseline iPTH (after log₁₀ transformation) was also included as a covariate for all outcomes in the repeated measures logistic regression model (Table 2).

Weekly means and average concentrations (C_{avg}) for serum phosphorus, serum calcium, and Ca × P product

Weekly mean values for the three outcomes are displayed in Figures 1A, Figures 2A, and Figures 3A. Calcium acetate-treated subjects had significantly lower mean serum phosphorus (Fig. 1A), higher mean serum calcium (Fig. 2A), and lower mean Ca × P product (Fig. 3A). Summarizing these weekly values, average concentrations were computed for each patient. Means and standard deviations of C_{avg} by outcome and treatment group are shown in Table 3, both for weeks 1 to 8 and weeks 5 to 8. Covariate-adjusted comparisons of C_{avg} between treatment groups show that, during weeks 1 to 8, in the calcium acetate group, mean serum phosphorus was lower (1.08 mg/dL difference, *P* value 0.0006), mean serum calcium was higher (0.63 mg/dL difference, *P* value < 0.0001), and mean Ca × P product was lower (6.1 mg²/dL² difference, *P* value 0.022). During weeks 5 to 8, treatment effects on C_{avg} for phosphorus and calcium were significant and similar to the effects for weeks 1 to 8, but there was no significant treatment effect on Ca × P.

Attainment of binary treatment goals over weeks 1 to 8 and 5 to 8

In both treatment groups, median times to first attainment of the binary treatment goals were two weeks for serum phosphorus, less than one week for serum calcium, and 3 to 4 weeks for Ca × P product, with no significant treatment effects. Repeated measures regression models for weeks 1 to 8 and, separately, for weeks 5 to 8 agreed well with the observed weekly proportions of "goal attained" for serum phosphorus and Ca × P product, but less well for serum calcium (Table 2, Figs. 1B, 2B, and 3B). Beginning one week after the start of treatment, in each week's observation, calcium acetate recipients were 20% to 24% more likely to attain the serum phosphorus goal (weeks 1 to 8: summary OR 2.37, 95% CI 1.28–4.37, treatment *P* value 0.0058; weeks 5 to 8: treatment *P* value 0.016) (Fig. 1B). An alternative, less stringent goal for serum phosphorus was defined by a threshold of 6.5 mg/dL. At each postbaseline week,

Table 2. Details of repeated measures logistic regression models for primary “goal attained” outcomes

Covariates	Phosphorus ^a		Calcium ^b		Ca × P product ^c	
	Parameter estimate	P value	Parameter estimate	P value	Parameter estimate	P value
Main effects						
Intercept	-0.886	0.64	-4.585	0.21	-1.600	0.39
Drug: calcium acetate	0.862	0.0058	0.791	0.31	0.769	0.0097
Week	0.563	0.0005	-0.244	0.34	0.399	0.012
Week-squared	-0.051	0.0020	0.044	0.14	-0.034	0.044
Baseline outcome	-0.367	0.0004	0.732	0.010	-0.033	0.0014
Baseline iPTH (log ₁₀)	1.126	0.11	-0.053	0.94	1.005	0.11
Age	0.016	0.24	-0.004	0.76	0.008	0.50
Gender: female	-0.269	0.42	-0.174	0.62	-0.201	0.53
Weight	-0.009	0.26	-0.002	0.76	-0.004	0.55
Center	-0.589	0.076	0.007	0.98	-0.319	0.32
Interaction ^d between drug (calcium acetate) and Week			0.165	0.66		
Week-squared			-0.043	0.31		

^aGoal serum phosphorus ≤5.5 mg/dL.

^bGoal serum calcium equals 8.5–11 mg/dL.

^cGoal serum calcium × phosphorus product ≤55 mg²/dL².

^dAlthough individual interaction term was not significant, the combined interaction effect of two terms was significant at P value of 0.019.

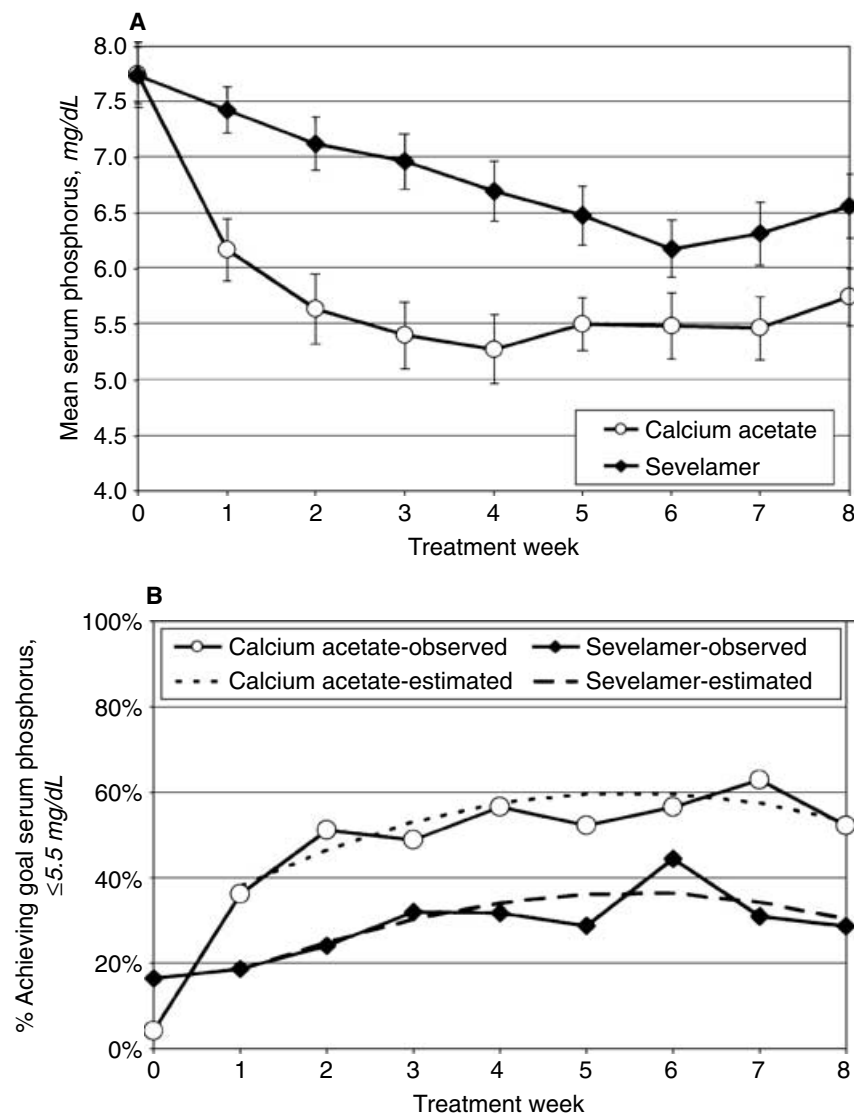


Fig. 1. Serum phosphorus control with calcium acetate or sevelamer hydrochloride. Mean (±SE) serum phosphorus levels at baseline and weekly during treatment with either calcium acetate (open circles) or sevelamer hydrochloride (closed diamonds) (A). At baseline, mean serum phosphorus levels were not significantly different between the two groups ($P = 0.99$). Calcium acetate reduced mean serum phosphorus below the target level of 5.5 mg/dL by the third week of treatment, and maintained serum phosphorus below the target level until week 8. In the sevelamer hydrochloride treatment group, mean serum phosphorus never fell below the target level throughout the 8-week treatment period. Overall, serum phosphorus levels were significantly lower during treatment with calcium acetate than during treatment with sevelamer hydrochloride (1.08 mg/dL difference in C_{avg} during weeks 1 to 8, P value 0.0006 by covariate-adjusted regression). To convert values for phosphorus to millimoles per liter, multiply by 0.32. Observed and model-estimated percent of subjects achieving goal serum phosphorus level (≤ 5.5 mg/dL) by treatment group and week (B). Main treatment effect $P = 0.0058$ (all weeks), and 0.016 for weeks 5 to 8 only.

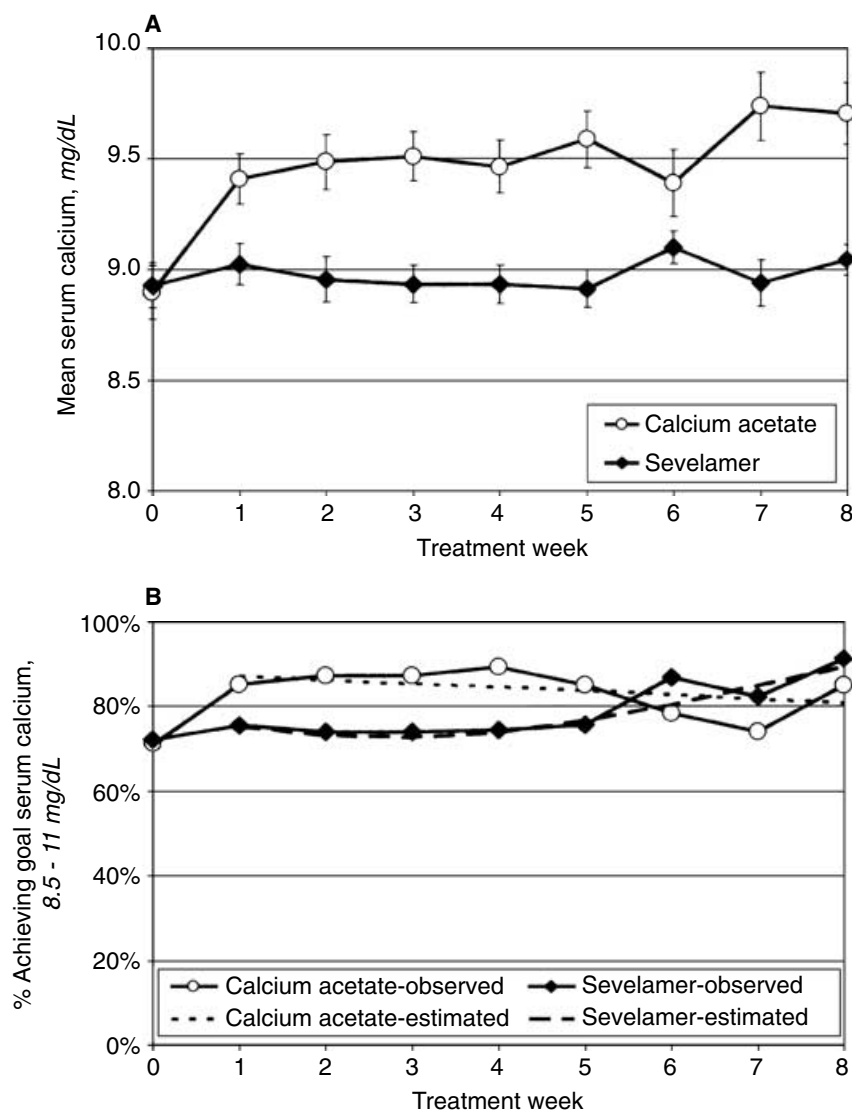


Fig. 2. Serum calcium levels during treatment with calcium acetate or sevelamer hydrochloride. Mean (\pm SE) serum calcium levels at baseline and weekly during treatment with either calcium acetate (open circles) or sevelamer hydrochloride (closed diamonds) (A). At baseline, mean serum calcium was not significantly different between the two groups ($P = 0.84$). Overall, serum calcium levels were significantly higher during treatment with calcium acetate than with sevelamer hydrochloride (0.63 mg/dL difference in C_{avg} during weeks 1 to 8, P value < 0.0001 by covariate-adjusted regression). During treatment with either binder, mean serum calcium levels remained within the normal range of 8.5 to 11 mg/dL. To convert values for calcium to millimoles per liter, multiply by 0.25. Observed and model-estimated percent of subjects achieving goal serum calcium level (between 8.5 to 11 mg/dL) by treatment group and week (B). Main treatment effects: P value = 0.16 (all weeks), 0.79 (weeks 5 to 8 only). Combined treatment-by-week interaction: P value = 0.019.

calcium acetate recipients were 10% to 30% more likely to be below the threshold than sevelamer recipients, yielding a figure (not shown) similar to Figure 1B, but 10% to 20% higher in each week. A repeated measures model, adjusted for the baseline variables previously cited, showed a significant benefit for calcium acetate (main effect P value 0.0043, no significant treatment by time interaction). Calcium acetate recipients were 15% to 20% more likely to attain the Ca \times P goal in each week (weeks 1 to 8: summary OR 2.16, 95% CI 1.20–3.86, treatment P value 0.0097, weeks 5 to 8: treatment P value 0.054) (Fig. 3B). Results for calcium were more complex because with the binary goal, there was a significant treatment by time interaction (likelihood ratio P value 0.019) (Fig. 2B). Main effects of treatment were not significant for the serum calcium goal, but proportions attaining the serum calcium goal were higher in weeks 1 to 5 for calcium acetate recipients, and higher in weeks 6 to 8 for sevelamer hydrochloride recipients (weeks 1 to 8

and 5 to 8: treatment main effect P values 0.16 and 0.79). All treatment comparisons were adjusted for age, gender, weight, and baseline iPTH, but these were never significant (Table 2). With two study centers, there was a nearly significant center effect for phosphorus (center effect OR 1.80, 95% CI 0.94–3.46, P value 0.076, not adjusted for compliance), but there were no significant treatment-by-center interactions for any outcome. Analyses for missing values had no significant impact upon treatment results.

Analysis of total number of weeks with treatment goals attained

The number of subjects by treatment group attaining the treatment goals for a given number of weeks is shown in Table 4. For example, 8 calcium acetate recipients and 18 sevelamer hydrochloride recipients attained the treatment goal for serum phosphorus for 0 weeks (i.e., never attained serum phosphorus less than 5.5 mg/dL). An

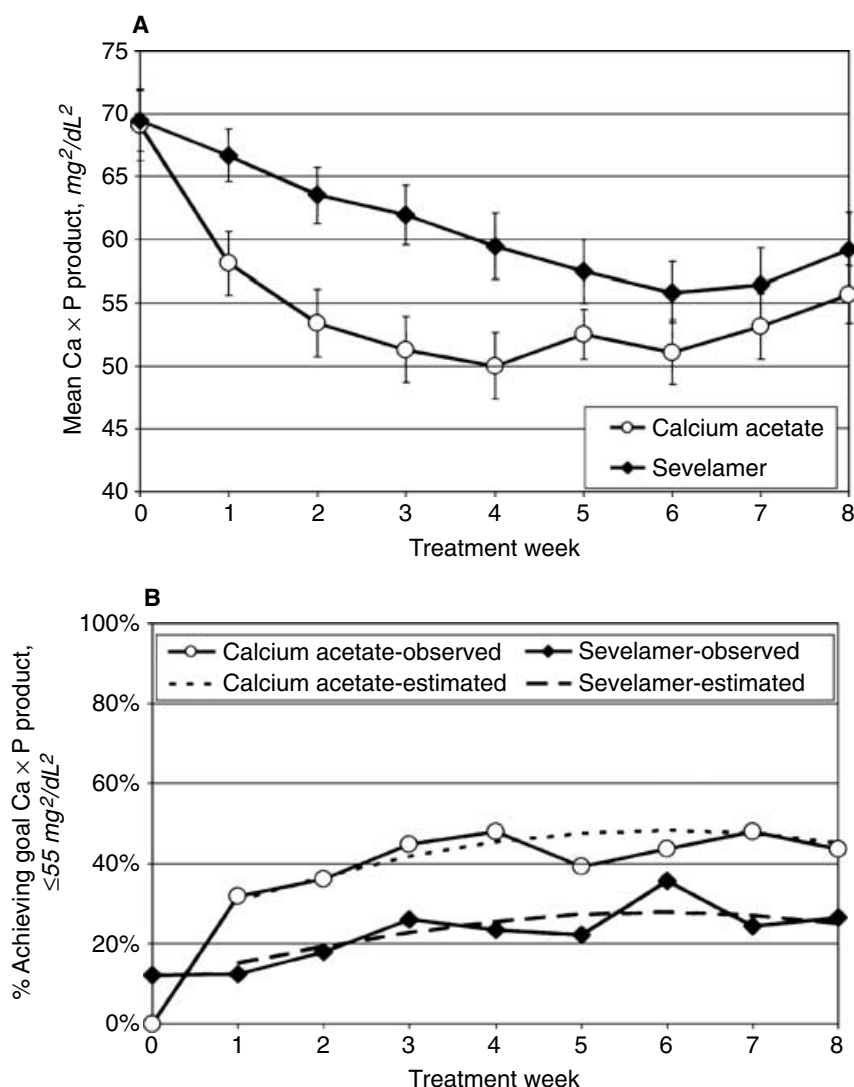


Fig. 3. Calcium × phosphorus products during treatment with calcium acetate or sevelamer hydrochloride. Mean serum calcium × phosphorus product at baseline and weekly during treatment with either calcium acetate (open circles) or sevelamer hydrochloride (closed diamonds) (A). At baseline, Ca × P product was not significantly different between the two groups ($P = 0.91$). However, Ca × P product was significantly lower during treatment with calcium acetate than with sevelamer hydrochloride ($6.1 \text{ mg}^2/\text{dL}^2$ difference in C_{avg} during weeks 1 to 8, P value < 0.0001 by covariate-adjusted regression). To convert from units of mg^2/dL^2 to mmol^2/L^2 , multiply by 0.08. Observed and model-estimated percent of subjects achieving goal Ca × P product ($\leq 55 \text{ mg}^2/\text{dL}^2$, as well as individual goals for serum phosphorus and serum calcium) by treatment group and week (B). Main treatment effect: P value = 0.010 (all weeks), 0.054 (weeks 5 to 8 only).

exact Cochran-Mantel-Haenszel trend test significantly favored calcium acetate for both serum phosphorus goal and Ca × P product goal, but was not significant for serum calcium goal. A post hoc observation is that nearly 4 of 5 of the calcium acetate recipients attained the phosphorus goal rarely (0 to 1 weeks) or almost always (6 to 8 weeks). Among the 37 calcium acetate recipients in these extreme groups, significant or nearly significant predictors of successful serum phosphorus control were greater compliance and center (logistic regression OR for summary percent compliance: 1.07, CI 1.01–1.14, P value 0.035; OR for center: 2.84, CI 0.88–9.14, P value 0.080). Age, baseline phosphorus, and baseline iPTH did not predict successful calcium acetate control of serum phosphorus levels. During eight weeks of follow-up, median numbers of weeks with the serum phosphorus goal attained were 5 weeks for calcium acetate, and 1 week for sevelamer hydrochloride. Median numbers of weeks of goal attainment were 7 and 7 for the serum calcium goal, and 4 and

Table 3. Average values (C_{avg}) during weeks 1 to 8 and weeks 5 to 8 by treatment group

Time frame	Treatment group	Mean ± standard deviation		
		Phosphorus	Calcium	Ca × P
Weeks 1 to 8	Calcium acetate	5.5 ± 1.5	9.5 ± 0.7	52.7 ± 14.2
	Sevelamer HCl	6.8 ± 1.6	8.9 ± 0.5	60.4 ± 14.1
	P value ^a	0.0006	<0.0001	0.022
Weeks 5 to 8	Calcium acetate	5.5 ± 1.7	9.6 ± 0.8	52.7 ± 16.5
	Sevelamer HCl	6.4 ± 1.6	9.0 ± 0.4	57.3 ± 13.9
	P value ^a	0.038	<0.0001	0.42

^aFrom linear regression model. [Units: serum phosphorus (mg/dL), serum calcium (mg/dL), Ca × P product (mg²/dL²); to convert values for phosphorus to millimoles per liter, multiply by 0.32; to convert values for calcium to millimoles per liter, multiply by 0.25; to convert values for Ca × P to mmol²/L² multiply by 0.08].

1 for Ca × P product goal, respectively. Treatment comparisons by ordinal logistic regression, adjusted for age, baseline serum phosphorus, baseline iPTH, and other covariates were similar to the unadjusted results shown in Table 4 (adjusted P values of 0.0023, 0.13, and 0.011 for

Table 4. Number of subjects by treatment group attaining the treatment goal for a given number of weeks

Outcome	Treatment	Number of weeks goal attained ^a								P value ^b	
		0 ^c	1	2	3	4	5	6	7		8
Phosphorus	Calcium acetate	8	8	2	3	1	4	6	8	7	0.0012
	Sevelamer HCl	18	8	2	6	7	4	2	2	1	
Calcium	Calcium acetate	0	1	2	1	2	4	5	11	21	0.12
	Sevelamer HCl	1	2	2	5	4	3	3	13	17	
Ca × P	Calcium acetate	11	7	4	1	7	5	4	4	4	0.0023
	Sevelamer HCl	19	9	6	6	6	1	1	2	0	

^aOnly study weeks 1 to 8 are counted. Failure was assumed in weeks with missing data.

^bP value from exact Cochran-Mantel-Haenszel test for trend.

^cOne calcium acetate recipient had no follow-up and is excluded.

phosphorus, calcium, and Ca × P product, respectively), favoring calcium acetate for both phosphorus and Ca × P product.

Analysis of hypercalcemia and hypocalcemia

Calcium acetate recipients generally had a higher probability of postbaseline hypercalcemia and a lower probability of hypocalcemia than did sevelamer recipients (Table 5). Varying among postbaseline weeks 1 to 8, but with no evident time trend, 2% to 9% of calcium acetate recipients were hypercalcemic, while 2% to 13% were hypocalcemic. These proportions compare with 0% hypercalcemic and 7% to 24% hypocalcemic among sevelamer hydrochloride recipients. Regression analysis confirmed that hypercalcemia was significantly more likely in the calcium acetate group (summary OR 6.1, 95% CI 2.8–13.3, treatment P value < 0.0001 in a nine-level repeated measures ordinal logistic regression, with the same baseline covariates outlined above). Overall, transient hypercalcemia developed in 8 of 48 (16.7%) calcium acetate-treated subjects. All 8 patients who experienced hypercalcemia were receiving concomitant intravenous vitamin D therapy. The overall results of the analysis of calcium data were unchanged when calcium was corrected for serum albumin levels.

Binder dosage

The mean daily binder dose at each week is shown in Figure 4. By week 8, the average daily dose was 10.7 ± 7.5 capsules (7.1 ± 5.0 g/d) in the calcium acetate group compared with 17.2 ± 9.0 capsules (6.9 ± 3.6 g/d) in the sevelamer hydrochloride group. In repeated measures regression models, calcium acetate recipients received a significantly fewer pills each day (P value 0.0017) with the difference increasing over time (P value for the two d.f. treatment-by-time interaction < 0.0001).

Impact of compliance on treatment effects

Compliance was defined by weekly pill counts. Summary compliance during the entire follow-up period (per-

cent of all prescribed pills not returned by the patient) was also examined. Weekly mean compliance varied only from 66% to 76% over the eight weeks with no time trend, and little difference between the calcium acetate group and the sevelamer hydrochloride group. However, individual patient compliance varied substantially, with patients' average compliance over the eight weeks 69% ± 22% (mean ± SD) in the calcium acetate group, and 71% ± 19% in the sevelamer hydrochloride group. Compliance was reported only for 83% of all patient weeks, and this analysis omitted weeks with a missing report. Estimated treatment effects were nearly the same whether the subset with compliance data or all patients were included. With "goal attained" as the outcome, compliance terms were then included in regression models. For both serum phosphorus and the Ca × P product, higher levels of either time-varying or average compliance significantly increased the probability of attaining the goals. However, compliance did not significantly affect the probability of attaining the serum calcium goal. In other models with the "goal attained" outcome, the interaction of compliance and treatment was never significant, implying that the observed differences in outcomes between calcium acetate- and sevelamer-treated subjects were unaffected by issues of compliance. Compliance was also examined as a predictor of the number of weeks with goal attained, and had qualitatively the same results as above: better compliance predicted a larger number of successful weeks, but had little impact upon the highly significant treatment effect that favored calcium acetate.

iPTH levels

Intact PTH levels were measured at baseline, weeks 4 and 8. For analysis, iPTH values were log₁₀-transformed. Baseline values did not differ significantly (*t* test P value 0.15) and, as an adjustment variable for the primary "goal attained" outcomes, baseline iPTH was never statistically significant (Table 2). In the calcium acetate group, geometric mean (GM) iPTH declined 37% from baseline to week 4, but only 6% more in weeks 4 to 8. In the sevelamer group, GM iPTH declined 6% from baseline to week 4, and 11% in weeks 4 to 8. Separately at 4 and 8 weeks, linear regression was used to compare GM iPTH between calcium acetate and sevelamer recipients. There was a significant treatment effect on iPTH only at 4 weeks (week 4 GM values: 131 pg/mL and 158 pg/mL for calcium acetate and sevelamer, respectively; covariate-adjusted P value 0.0034). There was no significant difference in GM iPTH levels between the two groups at week 8. Adjustment for average compliance had no impact upon these results. Individual patient data for iPTH levels at baseline and week 8 are shown in Figure 5.

Table 5. Number and percent of subjects with hypocalcemia, normal serum calcium, and hypercalcemia by treatment group and week

Week	Calcium acetate			Sevelamer HCl		
	Hypo-calcemia	Normal	Hyper-calcemia	Hypo-calcemia	Normal	Hyper-calcemia
0	11 (22.9%)	37 (77.1%)	0 (0.0%)	12 (24.0%)	38 (76.0%)	0 (0.0%)
1	4 (8.5%)	42 (89.4%)	1 (2.1%)	9 (18.4%)	40 (81.6%)	0 (0.0%)
2	3 (6.4%)	42 (89.4%)	2 (4.3%)	12 (24.0%)	38 (76.0%)	0 (0.0%)
3	2 (4.3%)	44 (93.6%)	1 (2.1%)	9 (18.0%)	41 (82.0%)	0 (0.0%)
4	2 (4.3%)	41 (89.1%)	3 (6.5%)	9 (19.1%)	38 (80.9%)	0 (0.0%)
5	4 (8.7%)	40 (87.0%)	2 (4.3%)	9 (20.0%)	36 (80.0%)	0 (0.0%)
6	6 (13.0%)	38 (82.6%)	2 (4.3%)	5 (11.1%)	40 (88.9%)	0 (0.0%)
7	4 (8.7%)	38 (82.6%)	4 (8.7%)	8 (17.8%)	37 (82.2%)	0 (0.0%)
8	1 (2.2%)	42 (91.3%)	3 (6.5%)	3 (6.7%)	42 (93.3%)	0 (0.0%)

Serum bicarbonate

Weekly serum bicarbonate data were analyzed as mean concentrations (Fig. 6A), and also as “alert level attained” when values were below a threshold of 17 mEq/L or a more stringent lower limit of 22 mEq/L (Fig. 6B). During weeks 1 to 8, mean serum bicarbonate levels were 20.4 to 21.9 mEq/L with calcium acetate and 19.2 to 20.2 with sevelamer hydrochloride. By the end of the 8 weeks, the serum bicarbonate level increased to 21.0 ± 2.6 mEq/L (mean ± SD) with calcium acetate, while it decreased to 19.3 ± 2.7 with sevelamer hydrochloride. Baseline proportions of patients below 17 mEq/L were 14.9% for calcium acetate and 16.0% for sevelamer. In weeks 2 to 8, these proportions were 14.9% to 22.2% for sevelamer, but only 0 to 8.5% for calcium acetate. Baseline proportions below 22 mEq/L were 72.3% and 80.0% for calcium acetate and sevelamer. In weeks 2 to 8, these proportions were 72.3% to 86.7% for sevelamer compared with 45.7% to 65.2% for calcium acetate. Thus, during treatment, relatively few subjects reached the lowest threshold of 17 mEq/L for serum bicarbonate, but this was more likely with sevelamer. Subjects in both treatment groups often had serum bicarbonate below 22 mEq/L, but this was much more common with sevelamer. Moreover, mean serum bicarbonate levels were always higher with calcium acetate. In repeated measures regression models, main effects showed significantly better results for calcium acetate (*P* values < 0.0001 for all three serum bicarbonate outcomes).

Adverse events

There were no significant differences between the two treatment groups in the overall incidence of adverse events or serious adverse events. None of the serious adverse events was related to treatment with study drug. Moreover, there was no significant difference between the groups in the overall incidence or subjective symptom scores for gastrointestinal side effects.

DISCUSSION

CARE is the first study to compare the efficacy of calcium acetate and sevelamer in a randomized, double-blind fashion in hyperphosphatemic hemodialysis

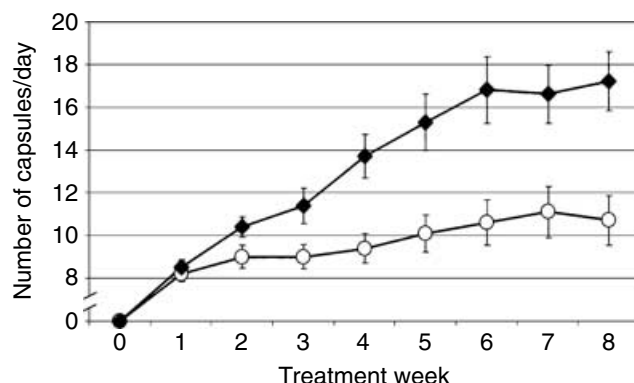


Fig. 4. Mean daily binder dose at each treatment week. Daily binder dose (mean ± SE) during each treatment week for calcium acetate (open circles) and sevelamer hydrochloride (closed diamonds). By repeated measures regression models, the prescribed number of capsules per day was significantly higher for the sevelamer hydrochloride group than for calcium acetate group (*P* value 0.0017). The mean daily dose of sevelamer hydrochloride was significantly higher than the preceding week at each treatment week except week 7. In contrast, the mean daily dose of calcium acetate did not increase significantly between weeks after week 2.

patients. Calcium acetate was significantly more effective than sevelamer in controlling serum phosphorus and Ca × P product. In the calcium acetate group mean serum phosphorus was at or below 5.5 mg/dL after only three weeks of treatment, while the mean serum phosphorus in the sevelamer group never reached the target level, despite steady dose escalation. We chose to use the 403-mg size sevelamer capsules rather than 800-mg pills because use of the former was required for performance of a double-blind study (calcium acetate pills were placed in hard gelatin capsules identical to the sevelamer capsules). The starting dose of sevelamer was defined according to the manufacturer recommendations for patients not currently receiving phosphate binders (i.e., our study patients at the end of the washout phase). Moreover, the daily prescribed dose of sevelamer hydrochloride at week 8 (6.9 ± 3.6 g/d) is comparable to doses employed in long-term binder trials [9]. Our results contrast with a previous open-label study, which suggested that, despite a higher mean serum phosphorus in sevelamer-treated patients,

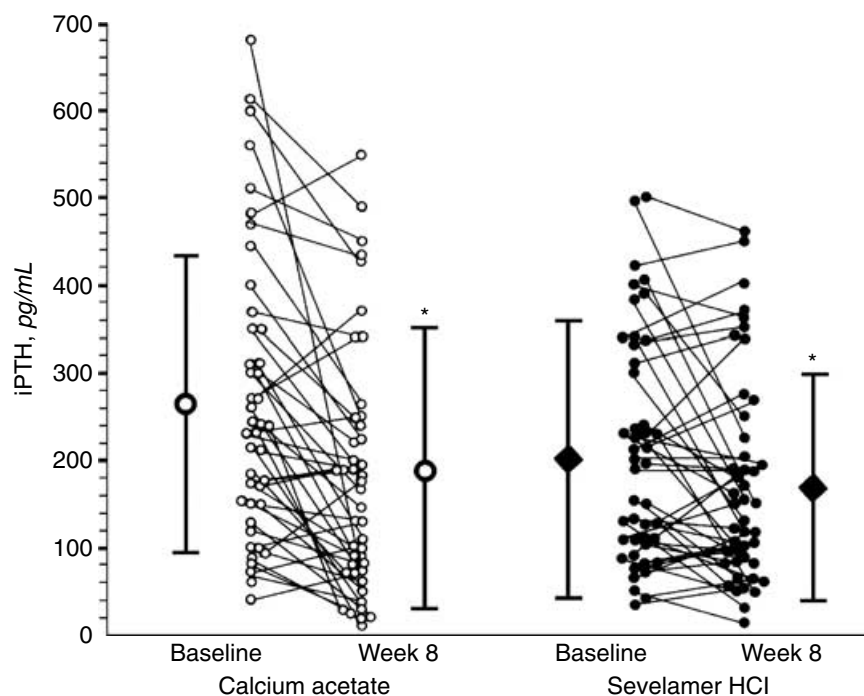


Fig. 5. Parathyroid hormone levels at baseline and during treatment with calcium acetate or sevelamer hydrochloride. Scatter plots of the intact parathyroid hormone (iPTH) levels at baseline and at week 8 during treatment with either calcium acetate (open circles) or sevelamer (closed circles). Diagonal lines connect the baseline and week 8 values for individual subjects. The vertical line adjacent to each scatter plot displays the mean \pm SD. At baseline, the mean iPTH level was not significantly different between the calcium acetate group and the sevelamer group (P value 0.15). Treatment with either binder resulted in a significant decrease in iPTH levels at week 8 compared with the respective baseline values ($*P$ value < 0.01). However, there was no significant difference between the two groups with regard to mean iPTH levels at week 8 (P value 0.12) in a covariate-adjusted generalized linear model. To convert serum iPTH to picomoles/liter, multiply by 0.1.

both binders were equally efficacious [5]. In our study, inadequate phosphorus control in the sevelamer group could not be explained by differences in compliance with binder therapy as measured by pill counts. In the absence of a formal balance study it is not possible to definitively state that calcium acetate is a more efficacious phosphate binder than sevelamer. Better control of serum phosphorus in the calcium acetate group might also be explained by a decrement in the release of phosphorus from bone as the result of better correction of metabolic acidosis [10].

Data were also analyzed using serum calcium corrected for albumin concentration. The findings were essentially unchanged with regard to the incidence of hypercalcemia, hypocalcemia, as well as the $\text{Ca} \times \text{P}$ product results. This finding is in accord with a recent study that recommended abandonment of correction formulas in favor of the use of uncorrected calcium, because none of the published formulas for albumin correction better predict ionized calcium in dialysis patients compared with simply utilizing the total serum calcium values [12].

In the CARE Study, hypercalcemia occurred only in calcium acetate-treated patients. Transient hypercalcemic episodes tended to occur at relatively low doses of calcium acetate, and only in patients treated with intravenous vitamin D. It is possible that more judicious use of intravenous vitamin D preparations may lead to a reduction in the incidence of hypercalcemia associated with calcium acetate treatment. Some investigators have raised concerns about the potential risk of hypercalcemia and cardiovascular calcification with calcium-containing binders [5, 9, 13, 14]. Although these hypotheses remain unsubstantiated [15], they are based on observational

studies, which suggest a correlation between vascular calcification or arterial stiffness and the prescribed dose of calcium-containing binder [13, 14]. However, it is possible that observed correlations between arterial calcification and prescribed binder dose are the result of refractory hyperphosphatemia rather than a complication of treatment with calcium-containing phosphate binders per se. Indeed, because compliance with phosphate binder therapy is often poor in hyperphosphatemic dialysis patients, the findings in the studies are difficult to interpret given that the prescribed dose may not be an accurate measure of consumed binder dose [16]. In the CARE Study, although weekly mean serum calcium levels were significantly higher during calcium acetate treatment, they consistently remained well within the usual normal range. The frequency of hypercalcemia in the CARE Study was much lower than previously reported. This observation may be explained by the fact that, unlike previous studies [7, 17], we maintained the dialysate calcium level at 2.5 mEq/L throughout the treatment period. Our finding that hypercalcemia developed only in patients receiving concomitant therapy with calcium acetate and intravenous vitamin D analogs suggests that the higher prevalence of hypercalcemia in other studies may be the result of inappropriate use of these drugs. In this regard, in the Treat-to-Goal study most of the calcium-containing binder treated patients received calcitriol therapy, despite the presence of only mild hyperparathyroidism at baseline [9]. In order to achieve the therapeutic goals for iPTH and serum phosphorus with avoidance of hypercalcemia, a more logical treatment regimen would have been the use of escalating doses of calcium-containing phosphate binder

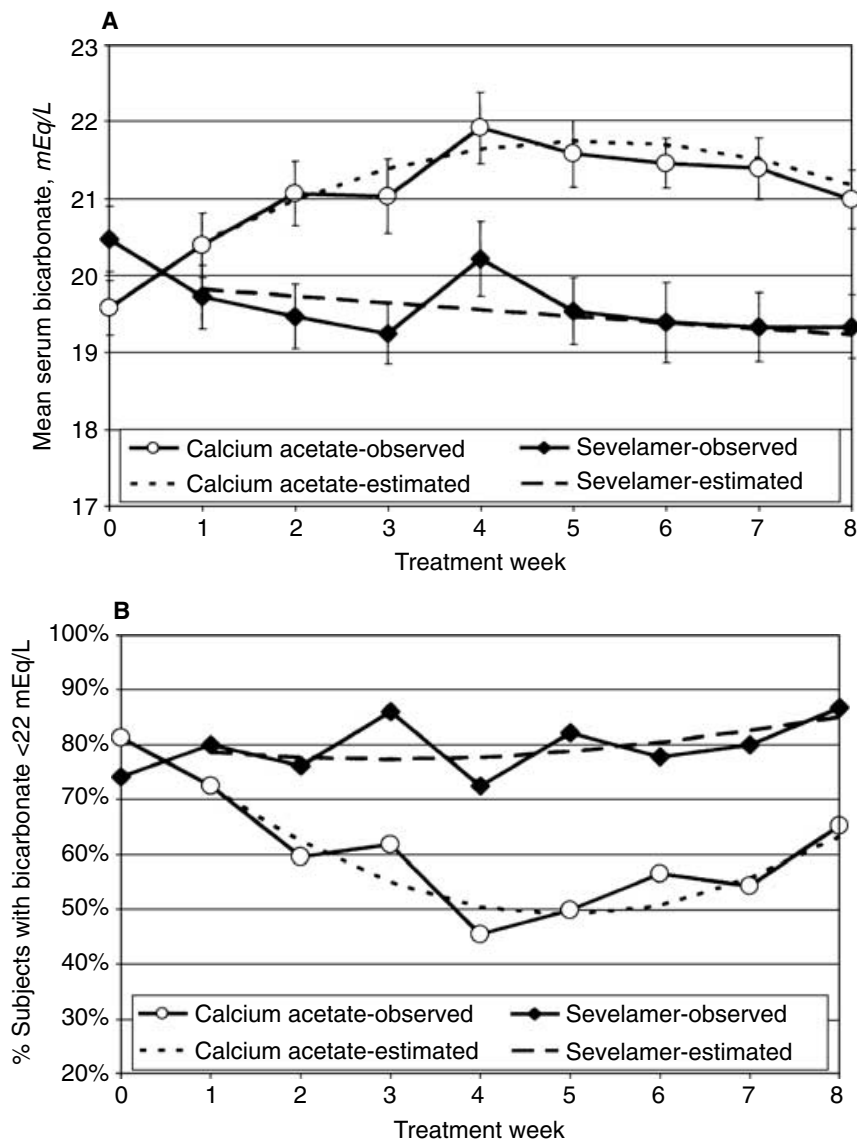


Fig. 6. Serum bicarbonate levels during treatment with calcium acetate or sevelamer hydrochloride. Mean serum bicarbonate levels at baseline and weekly during treatment with either calcium acetate (open circles) or sevelamer hydrochloride (closed diamonds) (A). At baseline, serum bicarbonate was not significantly different between the calcium acetate and sevelamer hydrochloride groups (*P* value 0.11). However, during treatment mean serum bicarbonate levels were significantly lower in the sevelamer group than in the calcium acetate group (*P* value < 0.0001 by covariate-adjusted repeated measures regression). Observed and model-estimated percent of subjects with serum bicarbonate <22 mEq/L by treatment group and week (B). Main treatment effect: *P* value < 0.0001.

without exogenous vitamin D therapy, because this approach has been shown to result in adequate control of both serum phosphorus and iPTH in most patients [18]. Administration of calcitriol in the setting of moderate hyperparathyroidism might also adversely impact phosphorus control by increasing intestinal absorption of calcium and phosphate [19].

The potential risks of hypercalcemia associated with calcium-containing phosphate binders may have been overemphasized since virtually all studies have failed to find a correlation between elevated calcium levels per se and increased mortality in the dialysis population [1, 20]; unless the serum calcium is chronically elevated to levels exceeding 11 mg/dL [abstract; Chertow et al, *J Am Soc Nephrol* 11: 560A, 2000]. In a recent study of hemodialysis patients, mortality risk was found to increase with each 1 mg/dL increase in serum calcium level [21]. However, the strength of the association was weak and

became nonsignificant after adjustment for confounding variables such as serum phosphorus [abstract; Klassen et al, *JAMA* 288:695–696, 2002]. A recent analysis of over 70,000 hemodialysis patients found that the risk of cardiovascular disease was actually reduced in patients in the highest quintile of serum calcium compared with those in the lowest quintile [abstract; Mazess et al, *J Am Soc Nephrol* 13:387A, 2002].

In contrast, increased Ca × P product has been independently associated with increased risk of death in dialysis patients [1]. In this regard, it should be noted that in the CARE Study, despite somewhat higher mean serum calcium levels, calcium acetate-treated patients had consistently lower Ca × P products than sevelamer-treated patients. Even among the subgroup of patients with baseline Ca × P products exceeding 70 mg²/dL², treatment with calcium acetate resulted in a more rapid reduction of the Ca × P product than treatment with sevelamer (data

not shown). Moreover, fewer calcium acetate-treated patients experienced an increase in $\text{Ca} \times \text{P}$ product above the baseline value during the first month of therapy (data not shown).

In the CARE Study, hypocalcemia occurred significantly more often during sevelamer treatment. The pathogenesis of sevelamer-induced hypocalcemia has not been carefully studied. Because dialysate calcium of 2.5 mEq/L results in no net calcium flux [22], and dialysis patients have reduced intestinal absorption of dietary calcium [23], although formal balance studies were not performed, it is possible that simple withdrawal of calcium-containing phosphate binders was sufficient to cause a net negative calcium balance and hypocalcemia in 50% of sevelamer-treated patients. In this regard, decreasing dialysate calcium from 3.0 to 2.5 mEq/L for a one-year period has been shown to result in an average 100 pg/mL increase in iPTH levels [24]. The long-term sequelae of chronic hypocalcemia in sevelamer-treated patients are currently unknown. Nonetheless, hypocalcemia should probably be avoided since an independent association between chronic hypocalcemia and increased mortality in dialysis patients has been reported [20, 25]. In dialysis patients with serum calcium less than 8.8 mg/dL, relative risk of death increased three-fold [20]. Accordingly, it has been recommended that patients treated with sevelamer receive a nighttime supplement of 1 g of elemental calcium to prevent hypocalcemia [26]. When calcium carbonate is given on an empty stomach, as much as 40% of the calcium may be absorbed [27]. In contrast, only about 15% to 20% of the elemental calcium is absorbed when calcium acetate is taken with meals [28]. Thus, patients taking sevelamer with supplemental calcium carbonate at night are likely to absorb as much calcium as patients taking calcium acetate with meals as a phosphate binder. The rationale for treatment of patients on sevelamer with a nighttime calcium supplement is not entirely clear. It would be more logical to administer required calcium supplements with meals as part of an overall phosphate-binding regimen.

We found no evidence of oversuppression of iPTH in calcium acetate-treated patients because the PTH levels at week 8 were not significantly different in sevelamer-treated patients. Baseline iPTH was not significantly different between the two groups and inclusion of baseline iPTH as covariate in the repeated measures logistic regression model had no effect on the observed benefit of treatment with calcium acetate with regard to better control of serum phosphorus or $\text{Ca} \times \text{P}$ product.

Calcium acetate and sevelamer hydrochloride were both well tolerated, and gastrointestinal side effects were similar. However, we confirmed previous reports that treatment with sevelamer leads to reduction in serum bicarbonate levels [7, 9, 29]. Analysis of the proposed phosphate-binding mechanism for sevelamer hydrochloride

indicates that one molecule of hydrochloric acid is released in exchange for every molecule of phosphate bound. Data from our laboratory suggest that treatment with sevelamer hydrochloride results in a significant increase in the daily acid load. Normal rats fed a diet containing sevelamer hydrochloride develop a significant decrease in urine pH and a significant increase in urinary ammonium excretion as measured by ion-specific electrode (unpublished observation). Acidemia should clearly be avoided in patients with chronic renal failure because it has two major systemic consequences [30]. Metabolic acidosis has several effects on bone, causing physiochemical dissolution of bone and cell-mediated bone resorption (inhibition of osteoblast and stimulation of osteoclast function) [10, 30]. Chronic metabolic acidosis also induces a net-negative nitrogen and total body protein balance, which improve following bicarbonate supplementation [30, 31, 32]. The data suggest that metabolic acidosis is both catabolic and antianabolic [30]. These considerations underscore the urgent need for further studies of acid-base balance during long-term treatment with sevelamer hydrochloride.

One of the limitations of this study is the relatively short 8-week treatment period. However, the doses of calcium acetate and sevelamer used in the CARE Study were similar to those employed in longer-term phosphate binder studies [9]. Moreover, a recent cross-sectional study of hemodialysis patients treated with sevelamer hydrochloride for longer than one year (mean 23 months, range 13 to 40 months), revealed that in comparison to patients treated with calcium-containing phosphate binders, sevelamer-treated patients had higher serum phosphorus levels (6.5 ± 1.2 vs. 5.4 ± 1.5 mg/dL; $P < 0.05$), higher $\text{Ca} \times \text{P}$ products (62.1 ± 16 vs. 49.7 ± 14.6 mg²/dL²; $P < 0.05$), and lower serum bicarbonate levels (18.6 ± 2.7 vs. 20.3 ± 1.8 mEq/L; $P < 0.05$) [abstract; Ciampi MA et al, *J Am Soc Nephrol* 13:586A, 2002]. Very similar findings were reported in another cross-sectional study comparing hemodialysis patients treated with either sevelamer or calcium-containing binders [abstract; Block GA, *J Am Soc Nephrol* 12:761A, 2001].

The recently published Treat-to-Goal Study, an open-label comparison of calcium salts to sevelamer, suggested that calcium salt usage may be associated with progression of vascular calcification in dialysis patients [9]. However, information was not provided regarding the use of nighttime calcium supplements in the sevelamer group or the dialysate calcium concentrations employed in the two treatment groups. The fact that 17% of sevelamer-treated patients in this study developed hypercalcemia suggests that they may have been treated with higher dialysate calcium or received dietary calcium supplements. If calcium supplements were prescribed to sevelamer-treated patients to prevent hypocalcemia as in other studies by these investigators [26], it would be difficult to draw any

firm conclusions regarding the possible pathogenic role of calcium loading from calcium salts in the progression of cardiovascular calcification. Furthermore, calcium loading from the use of calcium-containing binders is only one possible explanation for the slower progression of cardiovascular calcification observed in sevelamer-treated patients. This finding might also be explained by the marked difference in total and low-density lipoprotein (LDL) cholesterol levels between the two treatment groups, whereby the calcium-containing binder group had mean LDL cholesterol levels nearly twice as high as the sevelamer group. Sevelamer is a bile acid sequestrant which, when given in large doses, can significantly reduce cholesterol levels [8]. It is quite possible that the beneficial effect of sevelamer on the progression of cardiovascular calcification in the Treat to Goal Study [9] was the result of better lipid control because LDL cholesterol has been implicated as an important contributing factor in the progression of cardiovascular disease in the general population. Moreover, lowering the LDL level with HMG-CoA reductase inhibitors have been shown to significantly reduce coronary calcification after only one year of treatment [33, 34]. Thus, the important issue of increased cardiovascular calcification in dialysis patients can only be addressed by well-designed, double-blind studies which control for not only the type of phosphate binder, but also for the myriad risk factors potentially associated with vascular calcification, including dialysate calcium level, vitamin D usage, and treatment of hyperlipidemia [15].

CONCLUSION

The cost of phosphate binder therapy remains an important issue. Based on week 8 doses and average wholesale prices for PhosLo[®] and Renagel[®] [35], the projected annual per patient cost for treatment with calcium acetate would be \$732 compared to \$4,283 for sevelamer. Thus, if sevelamer were to be adopted as the first-line phosphate binder, the cost for treatment of the roughly 270,000 dialysis patients in the United States would increase by over 1 billion dollars per year. Although the lipid-lowering effect of sevelamer may have a beneficial role in slowing the progression of cardiovascular calcification in dialysis patients [9], cost-benefit analysis reveals that combined treatment with an HMG-CoA reductase inhibitor and calcium-containing phosphate binders would be a far more cost-effective alternative. Given the superior efficacy of calcium acetate for control of serum phosphorus and Ca × P product, it appears to be the more cost-effective choice as first-line treatment for hyperphosphatemia in patients with ESRD on maintenance dialysis. Nevertheless, in the occasional patient who develops persistent hypercalcemia during calcium acetate treatment despite appropriate reduction in vitamin D

dosage, it may be prudent to reduce the dose of calcium acetate and add a non-calcium-containing binder such as sevelamer hydrochloride [36].

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