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Effectiveness of calcium acetate as a phosphate binder in patients undergoing continuous ambulatory peritoneal dialysis

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We compared the effectiveness of calcium acetate as a phosphate binder with that of calcium carbonate by substituting one for the other in patients undergoing continuous ambulatory peritoneal dialysis. Twenty patients who had been receiving calcium carbonate as a phosphate binder were instead given calcium acetate, initially with two thirds of the previous dose of elemental calcium. The calcium acetate dose was adjusted to achieve adequate calcium-phosphate balance; 65.6% of the previous dose of elemental calcium in calcium carbonate was required. Eighteen of the 20 patients completed the 3-month study. There were no significant differences in the pre-study and study levels of serum phosphate (1.81±0.04 [SEM] versus 1.89±0.06 mmol/L), corrected serum calcium (2.54±0.04 versus 2.57±0.03 mmol/L), calcium phosphate product (4.60±0.15 versus 4.87±0.18), serum alkaline phosphatase (64.75±4.17 versus 69.94±3.77 U/L), and serum parathyroid hormone (122±31 versus 124±27 ng/L). Three patients developed a total of five episodes of hypercalcaemia (corrected calcium level ≥2.85 mmol/L) and four other patients developed gastrointestinal upset. Calcium acetate can thus achieve similar phosphate control to calcium carbonate, using 65.6% of the dose of elemental calcium in calcium carbonate; however, its clinical superiority was not demonstrated in this study.

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Key words: Acetic acids/therapeutic use; Calcium carbonate/therapeutic use; Patient compliance; Peritoneal dialysis, continuous ambulatory; Phosphates/blood

Introduction

In chronic renal failure, phosphate retention contributes significantly to the development of secondary hyperparathyroidism and renal osteodystrophy.[1] Because of the relatively poor dialysis clearance of phosphate and the ubiquitous presence of phosphate in the diet, phosphate binders are needed in 90% to 95% of long-term dialysis patients to achieve a satisfactory phosphate level.[2] Aluminium salts have been efficacious binders of intestinal phosphorus but are now unpopular because of the risk of aluminium toxicity. Calcium carbonate has been widely used as a phosphate binder[3,4]; however, it is only modestly potent in the binding of phosphorus, and the risk of hypercalcaemia has limited the dose one can use to bring the serum phosphate to a satisfactory level. Mai et al compared the effectiveness of calcium acetate and calcium carbonate as phosphate binders in haemodialysis patients using the one-meal gastrointestinal wash-out technique, and found that equivalent doses of calcium acetate bound twice as much phosphorus as calcium carbonate.[5] Clinical studies of haemodialysis patients confirm the effectiveness of calcium acetate as a phosphate binder.[6-8] Nevertheless, studies of calcium acetate as a phosphate binder in peritoneal dialysis patients have rarely been reported. The current study investigates whether calcium acetate has a similar effectiveness to calcium carbonate as phosphate binders in Chinese patients who are undergoing continuous ambulatory peritoneal dialysis (CAPD).

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Subjects and methods

The study included CAPD patients from the divisions of nephrology at the Queen Mary and Tung Wah hospitals who had been on a constant dose of calcium carbonate (Os-Cal chewable tablet; elemental calcium,

500 mg/tablet; Marion Merrell Dow Inc., Cincinnati, Ohio, USA) and who had stable serum biochemistry (with or without the use of low calcium dialysate) 3 months prior to the study, and a serum phosphate level ≥1.44 mmol/L. The dose of elemental calcium given in this form ranged from 500 to 3000 mg/day (1 to 6 tablets/day). The following were excluded from the study: patients who were receiving aluminium hydroxide or sucralfate in addition to calcium carbonate as phosphate binder; patients who required antacids for peptic ulceration; those who were scheduled for a living related transplant or parathyroidectomy within the previous 3 months; those whose calcitriol dose had been adjusted within the previous 3 months; and those with a history of drug non-compliance. Consents were obtained from all patients before the study.

Patients recruited for the study were given calcium acetate (Nephrex; elemental calcium, 152 mg/tablet; Fisons Pharmaceuticals, New South Wales, Australia) in place of calcium carbonate, with an initial dose of two thirds of the previous dose of elemental calcium. The dose chosen was based on the tablet size of the calcium acetate and on studies reporting that the equivalent phosphate binding dose of elemental calcium in calcium acetate in haemodialysis patients is approximately half of that in calcium carbonate.[9,10] The dose of calcium acetate was adjusted to achieve a serum phosphate level between 1.44 and 1.92 mmol/L and serum calcium level between 2.1 and 2.6 mmol/L.[1] The doses of all other drugs given remained the same as before the study, and the diet and frequency of peritoneal exchanges were kept constant. The incidence of hypercalcaemia, defined as a corrected serum calcium level ≥2.85 mmol/L, was noted during the study period. Patients who had persistent hypercalcaemia despite adjusting the dosage of calcium acetate and using low calcium dialysate, and those who could not tolerate either calcium carbonate or calcium acetate were withdrawn from the study.

Patients were followed up every 2 weeks for the first month and then monthly for the next 2 months. The serum urea, creatinine, albumin, calcium, phosphate, and alkaline phosphatase levels were measured each time. The intact parathyroid hormone level was measured before and at the end of the 3-month study. The serum calcium level was corrected for changes in the serum albumin level using the following formula: corrected serum calcium in mmol/L=measured serum calcium level+([41–serum albumin in g/L]x0.025).[11] The incidence of gastrointestinal upset was also noted. Subjective patient acceptance was scaled on a 4-point system: 0=withdrawal from study because of intolerance, 1=preference for previous medication, 2=no preference, 3=preference for study medication. The paired *t* test or the Wilcoxon signed rank test were used where appropriate for statistical comparison. Statistical results with a probability level of $P<0.05$ were considered significant. Data are expressed as mean±standard error of the mean (SEM).

Table 1. Clinical details of the study group

	Patients, n=18 No. (%)
Sex	
male	10 (55.5)
female	8 (44.4)
Type of dialysate received	
normal calcium	12 (66.7)
low calcium	6 (33.3)
No. of dialysis exchanges per day	
3 shifts	16 (88.9)
4 shifts	2 (11.1)
Patients receiving calcitriol	7 (38.9)
Causes of renal disease	
unknown	9 (50.0)
chronic glomerulonephritis	3 (16.7)
systemic lupus erythematosus	2 (11.1)
diabetic nephropathy	2 (11.1)
polycystic kidney disease	2 (11.1)

Results

Twenty CAPD patients were recruited and 18 patients completed the study. One patient withdrew from the study after 2 weeks because of intolerance to calcium acetate. Another patient took the wrong dose of calcium acetate and developed hypercalcaemia. These two patients were excluded from the analysis. The mean age of the 18 patients was 42.7 years (range, 25.1-74.0 years) and the mean duration of CAPD was 44.8 months (range, 2.6-98.1 months). The clinical features of the study population are shown in Table 1.

There were no significant differences between the pre-study and study levels of serum phosphate, corrected serum calcium, serum alkaline phosphatase, or calcium phosphate product (Table 2). There was also no significant difference in the serum parathyroid hormone levels that were measured before the study and at 12 weeks (122±31 versus 124±26 ng/L; P=0.97) [Fig 1]. Three patients developed a total of five episodes of hypercalcaemia during the start of the study and needed a reduction in the dose of calcium acetate. There were no changes in the diet, type of dialysate or dose of calcitriol throughout the study. There were also no significant changes in levels of serum urea (25.8±1.0 versus 27.0±2.4 mmol/L;

Table 2. Plasma parameters after conversion from calcium carbonate to calcium acetate treatment

	Baseline*	2 weeks	4 weeks	8 weeks	12 weeks
Phosphate (mmol/L)	1.81 ±0.04	1.78 ±0.06	1.77 ±0.08	l.81 ±0.07	l.89 ±0.06
Corrected calcium (mmol/L)	2.54 ±0.04	2.49 ±0.04	2.53 ±0.05	2.53 ±0.04	2.57 ±0.03
Calcium phosphate product	4.60 ±0.15	4.45 ±0.99	4.49 ±0.24	4.58 ±0.20	4.87 ±0.18
Alkaline phosphatase (U/L)	64.75 ±4.17	65.72 ±4.86	63.78 ±3.78	65.61 ±4.03	69.94 ±3.77

*Baseline values are at week 0, during calcium carbonate treatment; all values are mean±SEM

P=0.19) and creatinine (1127.6±44.4 versus 1152.4± 39.0 μmol/L; P=0.54) before and during the study.

The dose of elemental calcium in the form of calcium acetate that was needed to achieve similar phosphate control at 3 months was 65.6% of that in calcium carbonate. The mean dose of elemental calcium was 802±83 mg/day in the form of calcium acetate, compared with 1222±147 mg/day in the form of calcium carbonate (Fig 2).

Four (22.2%) of the 18 patients who completed the study developed gastrointestinal upset with the calcium acetate treatment, which included constipation, abdominal discomfort, and dyspepsia. Eight (44.4%) patients expressed a preference for the previous calcium carbonate treatment, eight (44.4%) patients preferred calcium acetate, and two (11.1%) patients had no preference.

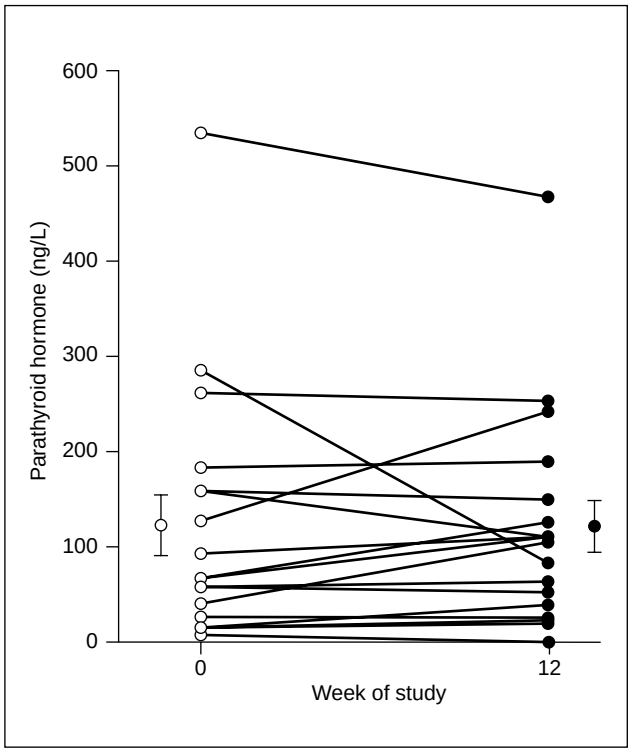

Fig 1. Levels of parathyroid hormone at start of study and after 12 weeks of calcium acetate treatment
The two circles with vertical bars represent the mean±SEM at the two time points. Week 0 represents calcium carbonate treatment; thereafter, calcium acetate was given.

Discussion

This study has shown that calcium acetate is an effective phosphate binder in renal failure patients who are maintained with CAPD. Calcium acetate achieved similar phosphate control to calcium carbonate with 65.6% of the latter's dose of elemental calcium. Despite the lower dose of elemental calcium ingested, however, hypercalcaemia was a problem. While there were no cases of hypercalcaemia before the study, five episodes occurred during the study. This observation contradicts the expectation of a decrease in the incidence of hypercalcaemia as based on

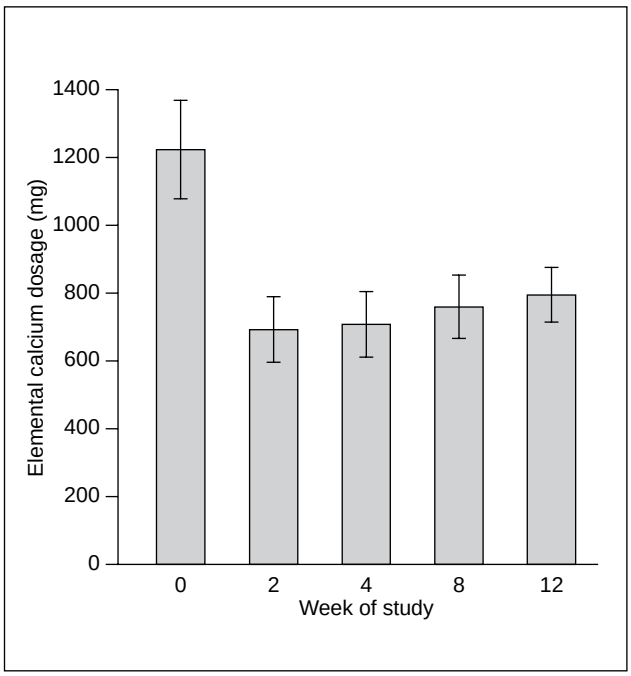

Fig 2. Doses of elemental calcium needed for phosphate control
Bars represent the mean±SEM. Week 0 represents calcium carbonate treatment; thereafter, calcium acetate was given.

calcium absorption data published by Mai et al.[5] Our results concur with those of Moriniere et al[9] and Ben Hamida et al[10] which show that the use of calcium acetate when compared with calcium carbonate does not decrease the incidence of hypercalcaemia in haemodialysis patients. The reason for the conflicting results is not clear. The data from Mai et al[5] are from studies using a gastrointestinal wash-out technique, and extrapolation of the results to an in vivo situation may not be valid. Disagreement between the calculated and actual daily calcium absorption data have also been obtained by Clarkson.[12] Moreover, the higher solubility of calcium acetate at an alkaline pH of the intestine means that more free calcium is available for absorption from calcium acetate than from calcium carbonate.[13] This may explain why there is no decline in the incidence of hypercalcaemia in renal failure patients using calcium acetate. Whether differences between using haemodialysis and CAPD contribute to differential gastrointestinal calcium absorption awaits further studies.

Approximately one quarter of the patients developed gastrointestinal upset; in contrast, all patients tolerated calcium carbonate treatment well. There were no particular preferences for either calcium acetate or calcium carbonate. The preparations of calcium acetate used in this study, however, contained only 152 mg of elemental calcium per tablet; patients needed to take double the number of tablets compared with calcium carbonate to achieve comparable phosphate control. This was an inconvenience and contributed to difficulty in compliance, especially in patients who were already receiving multiple medications. In addition, at the current price the cost of the necessary dose of calcium acetate to achieve equivalent phosphate binding was four times that of calcium carbonate. Thus, the routine use of calcium acetate as a phosphate binder would not be cost-effective.

In conclusion, calcium acetate is an effective phosphate binder in CAPD patients but its clinical superiority over calcium carbonate cannot be demonstrated in this study. Routine use of calcium acetate is therefore not recommended, but it may provide an alternative choice for patients who cannot tolerate calcium carbonate for reasons other than hypercalcaemia.

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