Calcium Acetate as a Phosphorus Binder in Hemodialysis Patients

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ABSTRACT

Much interest is currently centered on the use of calcium acetate as a phosphorus binder in patients with renal failure. Therefore, this compound in subjects previously stable on calcium carbonate and undergoing high-efficiency hemodialysis with a dialysate calcium of 2.5 mEq/L was evaluated. Twenty subjects were switched from generic calcium carbonate to a single calcium carbonate preparation for a period of 2 months. This was followed by a phase (1 month) in which calcium acetate was substituted for calcium carbonate at a dose containing half the amount of elemental calcium. Subjects then continued calcium acetate for 6 months. It was found that calcium acetate allowed comparable control of immunoreactive parathyroid hormone, calcium, and phosphorus levels compared with calcium carbonate. This occurred with half the amount of elemental calcium ingested in the form of calcium acetate (349 ± 25 versus 699 ± 75 mmol/day; P < 0.001). With this lower dose, the overall incidence of hypercalcemia was the same with each formulation. In the eight subjects concurrently receiving i.v. calcitriol, the incidence of hypercalcemia was significantly higher during the first month of calcium acetate compared with those not receiving this compound (P < 0.05). Of those four subjects receiving the high dose of calcitriol (2 µg thrice weekly), all required either reduction in the dose or discontinuation of the drug.

Thus, mineral metabolism could be controlled adequately with calcium acetate despite using half as much elemental calcium compared with calcium carbonate. This, however, did not result in a lower incidence of hypercalcemia, particularly in those receiving i.v. calcitriol.

Key Words: Calcium acetate, calcium carbonate, phosphorus, parathyroid, calcitriol, osteodystrophy

Central to the treatment of hyperparathyroidism in chronic renal failure is the maintenance of optimal serum calcium and phosphorus levels. Traditionally, aluminum-containing phosphorus binders were used to bind phosphorus in the gut. However, it subsequently became known that significant amounts of the oral aluminum were absorbed. This led to the clinical manifestations of dementia, osteomalacia, and microcytic anemia (1–9). Following the lead of Clarkson et al. (10), many investigators have shown that calcium carbonate is an effective phosphorus binder (11–15). However, the use of calcium carbonate, in conjunction with a dialysate calcium concentration of 3.25 to 3.5 mEq/L, may lead to hypercalcemia and metastatic calcification. We have previously shown that control of calcium and phosphorus levels could be attained with the use of calcium carbonate and a 3.25-mEq/L calcium dialysate (14). However, almost one third of the patients developed hypercalcemia, requiring the continued use of aluminum-containing phosphorus binders. This led us (16) and others (17,18) to investigate the effect of dialysate containing lower concentrations of calcium. Using dialysate containing 2.5 mEq/L of calcium, we recently found that phosphorus levels could be adequately controlled with calcium carbonate alone with few episodes of hypercalcemia. Nonetheless, it is likely that patients who require large doses of calcium carbonate or who are treated with vitamin D preparations are at risk for the development of hypercalcemia. A more effective phosphorus binder would be highly advantageous. Calcium acetate has been shown to bind phosphorus better than calcium carbonate in vitro and in normal subjects (19). Mal et al. (20), using the one-meal gastrointestinal washout technique in six hemodialysis patients, found that calcium acetate bound more than twice the amount of phosphorus per amount of calcium ab-
sorbed compared with calcium carbonate. We, therefore, evaluated the efficacy of calcium acetate in a group of hemodialysis patients.

METHODS

Protocol

Subjects, whose phosphorus was controlled primarily with the use of calcium carbonate, were enrolled in the study. To ensure adequate bioavailability of calcium carbonate (21,22), subjects were switched from generic brands to Os-Cal (Marion Laboratories, Kansas City, MO). The protocol is summarized in Figure 1. During this induction phase (phase I), the dose of calcium carbonate was adjusted weekly to attain a target calcium of 2.2 to 2.7 mmol/L and phosphorus of 1.3 to 1.9 mmol/L (9 to 11 mg/dL and 4 to 6 mg/dL, respectively). Upon successful completion of the induction phase at a constant dose of calcium carbonate, the subjects entered the maintenance phase (phase II), in which the amount of calcium carbonate did not change unless hypercalcemia (calcium >2.75 mmol/L) developed. The duration of this phase was 4 wk. The subjects were then switched to calcium acetate (Phos Lo; Braintree Laboratories, Braintree, MA) at a dose containing half the elemental calcium ingested during phase II. During this titration phase (phase III), the dose of calcium acetate was adjusted weekly to attain the same target values for calcium and phosphorus as those during phases I and II. The subjects then entered the maintenance phase (phase IV), lasting 6 months. Laboratory values were obtained weekly during phases I through III and monthly during phase IV. Three-day dietary histories were conducted during phases I, III, and IV. The quantities of calcium and phosphorus ingested were calculated by the method described by Adams (23). Compliance was assessed by weekly pill counts.

After the successful completion of the protocol, subjects were switched back to calcium carbonate at the doses used in phase II. Weekly immunoreactive parathyroid hormone (iPTH), calcium, and phosphorus levels were monitored for 1 month.

Subjects

Twenty-three subjects were recruited. All were treated with a stable calcium carbonate regimen and had been on chronic hemodialysis for more than 3 months. Three withdrew before receiving calcium acetate. One was transplanted, and two were found to be noncompliant. Thus, 20 subjects were evaluated whose duration of dialysis was 71 ± 11 months (range, 6 to 156) and whose mean age was 55 ± 3 yr (range 27 to 70). The causes of renal failure were hypertension (eight patients), chronic glomerulonephritis (three patients), diabetes (two patients), atheroemboli (two patients), and one patient each of the following: Wegener’s granulomatosis, systemic lupus, obstruction, polycystic kidney disease, and unknown. Eight of the 20 were also receiving long-term i.v. calcitriol beginning 4.5 ± 0.4 months before entering the study. The dose (0.5 to 2.0 μg thrice weekly) was not changed unless hypercalcemia developed. Seventeen subjects participated in the follow-up phase, having switched back to calcium carbonate. Three subjects had prior partial parathyroidectomies more than 3 years before the study. No subjects were on other medications known to affect mineral metabolism. The KT/V was maintained between 1.0 and 1.2 in all subjects with either Cilrins T175 (Terumo, Tokyo, Japan) or Hemoflow F8 (Seratronics, Concord, CA) dialyzers. The blood flow was 400 mL/min, and the dialysate flow was between 500 and 800 mL/min with Fresenius 2008 (Seratronics, Concord, CA) dialysis machines with bicarbonate dialysate. The dialysate calcium was 2.5 mEq/L in all patients. There was no change in the mean hematocrit during the study. All patients had a normal serum albumin (≥3.6 g/dL). Written consent was obtained from all patients, and the studies were approved by the Human Research Committee of Washington University.

Measurements

The concentration of total calcium was determined by atomic absorption spectroscopy (Model 503: Perkin-Elmer, Norwalk, CT). Phosphorus was measured by the Technicon Autoanalyzer (Technicon Instruments, Tarrytown, NY). Serum levels of immunoreactive parathyroid hormone (PTH) were assessed by the CH9 antibody that recognizes the intact, midregion, and C-terminal portion of the hormone. The method has been previously described in detail (24).

Statistics

Statistical analysis included t test for paired and unpaired data, Wilcoxon signed rank test for nonparametric data, one-way and repeated measures analysis of variance (ANOVA), and two-tailed Fisher’s ex-
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RESULTS

The amounts of dietary phosphorus and calcium remained constant throughout the study (Figure 2). The phosphorus intake during phase I was 257 ± 14 mmol/day (797 ± 45 mg/day), and the amount of dietary calcium was 89 ± 9 mmol/day (359 ± 37 mg/day). There were no statistical differences in the amounts of calcium or phosphorus ingested during the subsequent phases (ANOVA).

The dose of elemental calcium necessary to achieve the target calcium and phosphorus in each case was dependent upon the form of calcium (Figure 3). During calcium carbonate ingestion (phases I and II), the required amount for maintenance of Ca and P was 699 ± 75 mmol/day (2.8 ± 0.3 g/day). With calcium acetate (phases III and IV), the dose of elemental calcium fell by half to 349 ± 25 mmol/day (1.4 ± 0.1 g/day; P < 0.001). The calcium and phosphorus levels at each time point in the study were well controlled with either calcium carbonate or calcium acetate (Figure 4). ANOVA failed to show differences in calcium or phosphorus levels in the four study phases, although there was a tendency for phosphorus levels to be slightly higher with calcium acetate.

The absolute levels of iPTH and percent iPTH compared with baseline are depicted in Figure 5. The baseline iPTH level of 303 ± 59 μL Eq/mL did not change during either calcium carbonate or calcium acetate treatment. Similarly, the alkaline phosphatase levels were no different before and after 7 months of calcium acetate (124 ± 17 versus 93 ± 10 IU/L, respectively; normal range, 38 to 126 IU/L).

The mean level of iPTH during the calcium carbo-

ate follow-up phase was 403 ± 80 μL Eq/mL. This was not different from that of phase IV (354 ± 74 μL Eq/ 
ml; P = not significant; Wilcoxon signed rank). The serum calcium and phosphorus levels were also not different (2.34 ± 0.05 versus 2.42 ± 0.05 mmol/L and 1.58 ± 0.06 versus 1.7 ± 0.06 mmol/L or 9.4 ± 0.2 versus 9.7 ± 0.2 mg/dL and 4.9 ± 0.2 versus 5.3 ± 0.2 mg/dL, respectively).

The mean calcium and phosphorus values of each subject during phases II, III, and IV were assessed. By paired analysis, phosphorus levels were higher in the calcium acetate phases (Table 1). When the subjects were divided into groups either receiving or not receiving calcitriol, only the former had higher phosphorus levels with calcium acetate. The calcium lev-

els of those receiving calcitriol were slightly higher than those not receiving calcitriol in phase III (P < 0.05; ANOVA).

The overall incidence of hypercalcemia (calcium >2.75 mmol/L) per measurement was 8.7% during treatment with calcium carbonate (phases I and II) and 8.3% during treatment with calcium acetate (phases III and IV) (P = not significant). This occurred
Figure 5. Monthly absolute mean ± SE iPTH values and percent iPTH levels compared with baseline during the protocol.

TABLE 1. The effects of calcitriol on calcium and phosphorus levels during treatment with calcium carbonate (phase II) and calcium acetate (phases III and IV)*

<table>
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<th>Phases</th>
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<tr>
<td></td>
<td>II</td>
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<tr>
<td>All Patients (N = 20)</td>
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<tr>
<td>Ca</td>
<td>2.54 ± 0.02</td>
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<tr>
<td>P</td>
<td>1.52 ± 0.06</td>
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<tr>
<td>No Calcitriol (N = 12)</td>
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<tr>
<td>Ca</td>
<td>2.52 ± 0.05</td>
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<tr>
<td>P</td>
<td>1.58 ± 0.06</td>
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<tr>
<td>On Calcitriol (N = 8)</td>
<td></td>
</tr>
<tr>
<td>Ca</td>
<td>2.57 ± 0.02</td>
</tr>
<tr>
<td>P</td>
<td>1.42 ± 0.06</td>
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* Values for Ca and P are in millimoles per liter.
* P < 0.05 compared with phosphorus levels during phase II.
* P < 0.05 compared with calcium levels in subjects not treated with calcitriol during phase II.

Despite the lower dose of elemental calcium ingested at the time of hypercalcemia in the acetate phases (P < 0.001; Table 2). The peak calcium levels during hypercalcemia were the same with calcium carbonate and calcium acetate. Because of concern that monitoring laboratory data on a monthly basis during the calcium acetate maintenance phase (phase IV) might not allow a valid comparison with phases I and II, wherein data were assessed weekly, the incidence of hypercalcemia during only the calcium acetate titration phase (phase III) was assessed. The incidence of hypercalcemia (6.2%) was no different with calcium acetate in this phase compared with that in phases I and II where calcium carbonate was used (Fisher’s exact test). Similarly, the number of patients who experienced one or more episodes of hypercalcemia during the calcium acetate titration phase (3) was not statistically different from that of phase I (5) or phase II (7).

The effect of i.v. calcitriol on the development of hypercalcemia was assessed during the calcium acetate titration phase. When calcium acetate was introduced, there was a very high incidence of hypercalcemia with calcitriol (22% of measurements) compared with none in those not receiving the metabolite (P < 0.001; Fisher’s exact test). During the calcium acetate maintenance phase (phase IV), the incidence of hypercalcemia was not different in the two groups. Interestingly, of the four subjects receiving the highest dose of i.v. calcitriol (2 μg thrice weekly), all required a dose reduction (two patients) or discontinuation.
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uation (two patients) of the drug because of hypercalcemia while being treated with calcium acetate. A short questionnaire was filled out by the subjects at the end of phase III concerning binder preference. Seven preferred calcium carbonate because of ease in swallowing and the fewer number of pills. Six preferred calcium acetate because of the smaller size of the pills. The remainder lacked a preference.

**DISCUSSION**

This long-term study confirms the prediction of Mai et al. (20) that phosphorus could be controlled with calcium acetate with approximately half the amount of elemental calcium needed during treatment with calcium carbonate. In this study, control of phosphorus with calcium acetate was achieved without changes in serum Ca or iPTH levels. In addition, the incidence and severity of hypercalcemia were not different with calcium acetate compared with calcium carbonate. These results were surprising. If half the amount of calcium were absorbed per amount of phosphorus bound, then one would predict worsening of hyperparathyroidism and a decreased incidence of hypercalcemia. Because neither of these occurred, other possibilities should be considered. Serum calcium levels could have been maintained by the efflux of calcium from bone. This is unlikely because the iPTH and alkaline phosphatase levels did not change. Alternatively, it is possible that the long-term administration of calcium acetate was associated with an increase in the amount of calcium available for absorption per amount ingested compared with calcium carbonate. Finally, it is possible that the use of calcium acetate allowed the mobilization of calcium from nonosseous tissues. Because none of the subjects had radiographic evidence of soft-tissue calcification before the study, this hypothesis could not be answered by this study.

Recently, Emmett et al. (25) reported that calcium acetate was superior to placebo in controlling calcium and phosphorus levels in hemodialysis patients. However, no direct comparison of calcium acetate with calcium carbonate was made. Interestingly, the amount of elemental calcium necessary to control phosphorus (586 mg/meal) in their study was very close to our mean dose of 1.4 g/day, assuming three meals per day. To our knowledge, the only study directly comparing calcium acetate with calcium carbonate was by Schaefer et al. (26). It was found that similar control of calcium, phosphorus, and PTH could be achieved with treatment for 7 wk with calcium acetate and calcium carbonate. This was achieved with slightly more than half the elemental calcium in the form of calcium acetate (1.02 g/day) compared with calcium carbonate (1.88 g/day). The episodes of hypercalcemia or the need to discontinue calcitriol did not appear to be statistically different comparing calcium acetate and calcium carbonate phases.

Conceivably, the reduced intake of calcium with calcium acetate could lead to a decrease in the extent of metastatic calcification. It should be noted, however, that Moriniere et al. (27) could not detect a progression of metastatic calcification with the long-term use of calcium carbonate.

Currently, the control of serum phosphorus in dialysis patients includes the restriction of dietary phosphorus within the confines of an adequate protein intake, the avoidance of aluminum-containing phosphorus binders, and the use of calcium carbonate to bind intestinal phosphorus. The amount of calcium prescribed should be proportional to the amount of phosphorus ingested with each meal. If hypercalcemia develops with this strategy, then lowering the dialysate calcium from 3.0 to 3.5 mEq/L to 2.5 mEq/L may be sufficient to avoid future hypercalcemia. The difficult clinical situation occurs when these maneuvers are not sufficient to control hyperphosphatemia without concomitant hypercalcemia. It was anticipated that the use of calcium acetate, under these circumstances, might be of value. Unfortunately, the incidence of hypercalcemia was the same with calcium acetate as with calcium carbonate. Hence, calcium acetate may be of limited value in this situation.

We (28) and others (29,30) have shown that i.v. calcitriol is efficacious in suppressing secondary hyperparathyroidism. In part, its effects are due to the direct suppression of PTH secretion by the gland (31,32). The concurrent use of i.v. calcitriol and calcium carbonate may increase the risk for hypercalcemia. By giving half the amount of elemental calcium during calcium acetate treatment, it was hoped that the incidence and severity of hypercalcemia would be decreased. Unfortunately, this was not so. Overall, there were no differences with calcium acetate or calcium carbonate. Moreover, when patients were started on calcium acetate (phase III), there was higher incidence of hypercalcemia in those patients receiving calcitriol than in those who did not. In addition, all patients receiving 2 µg of calcitriol thrice weekly during the calcium carbonate phases required either a dose reduction or discontinuation during treatment with calcium acetate.

In summary, calcium acetate is an alternative to calcium carbonate in the control of hyperphosphatemia and hyperparathyroidism in hemodialysis patients. Its main advantage is that phosphorus control can be achieved by administering half the amount of elemental calcium. This, however, did not result in a decrease in the incidence and severity of hypercalcemia. This was particularly evident in those receiving calcitriol and recently switched to calcium ace-
tate. More studies are necessary to define the role of calcium acetate as a phosphorus binder in chronic renal failure.

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REFERENCES


