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Original Article

Control of hyperphosphatemia in regular hemodialsis (HDx) patients by calcium acetate (CA) versus calcium carbonate (CC). A Double blind crossover prospective study

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Abstract: This study included fourty chronic renal failure patients aged 37 - 83 years (mean 51.3±7) on thrice weekly HDx for 4 - 144 month (Kt/V>1.2).
Acetate dialysate with Calcium concentration of 3 mEq/L was used. All phosphate binders were discontinued for one month.
Patients were divided in two groups. Group I (20 cases) received CA, while group II (20 cases) received CC in equimolar dose (10 m.mol. of either t.i.d.) for one month. Crossover of treatment was done for another month while keeping patients on the same diet.
Serum levels of total calcium (Ca), ionized Ca (iCa), phosphorus (P), alkaline phosphates (AP), urea (U), creatinine (Cr), ALT, AST, total proteins (TP) and albumin (Alb) were estimated before, and at the end of each month of CA and CC treatment.
serum Ca and iCa were significantly lower in group I after CA compared to values after CC ($P<0.01$). Similar results in Ca levels were observed in group II ($P<0.05$).
In group II only serum P was significantly lower after CA compared to its values after CC ($P<0.05$).
There was no significant difference in AP, U, Cr, ALT, AST, TP and Alb before, and at the end of each month of CA and CC treatment ($P>0.05$ in all). We excluded 12.5% of cases due to CA intolerance while non of cases had similar intolerance to CC.

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Conclusion

1) CA is not very superior to CC in control of hyperphosphataemia.
2) CA can be safely increased without the risk of hypercalcemia.
3) Active Vitamin D and high dialysate Ca can be used to suppress parathyroid activity more safely with CA than with CC.
4) Tolerability to CC is superior.

Introduction

Hyperphosphatemia plays a major role in renal osteodystrophy [9]. The management of hyperphosphatemia is rather difficult as poor phosphate diet may interfere with adequate nutrition of chronic renal failure patients.
Moreover, phosphate binders have many drawbacks [16]. The first phosphate binder used was aluminium hydroxide. Constipation is common and more seriously aluminium intoxication in uremic patients receiving this compound for a long time [26, 23]. Calcium carbonate was thus introduced to replace aluminium compounds. It causes heart burn, constipation beside the risk of hypercalcemia. This last side effect may deprive many uremic patients from using active vitamin D, the most potent suppressor of the parathyroid gland [12,22].

More recently calcium acetate was introduced as a phosphate binder [22].

Aim of work

This prospective double blind crossover study was designed to compare equivalent amounts of calcium acetate and calcium carbonate (in terms of elemental calcium) in the control of hyperphosphatemia in chronic renal failure patients maintained on regular hemodialysis.

Materials and methods

Fourty hemodialysis patients were studied. Their age ranged between 37 and 83 years (mean ±SD=51.3±7). They were 31 male and 9 female on thrice weekly hemodialysis for 4 - 144 months using the same type of dialyzer membrane, namely cuprophane, and the time of dialysis session was individualized to keep Kt / V>1.2. All patients had residual creatinine clearance of less than 5ml/ minute. A standard acetate dialysate with a calcium concentration of 3 mEq/L was used. All patients were clinically stable and were kept on oral calcium carbonate in a dose of 10 m.Mol three times/day and 0.25 ug of 1-α calcidol daily. After obtaining consent from every patient calcium carbonate was stopped one month before enrollment in the study and all patients were kept on their usual diet during the study.

Twenty cases (group I) received calcium acetate prepared by Minapharm Pharmaceutical Co. for this research while the other 20 patient (group II) received calcium carbonate in the form of calcimat capsules each of 500 mg [5 mMol] in equimolar dose (10 mMol of either t.i.d.) for one month. Cross over of treatment for another one month was done. Patients were advised to take the calcium treatment during meals.

Weekly personal interviews were conducted with every patient to assess compliance to treatment and possible side effects.

Serum levels of calcium, ionized Calcium, Phosphorus, alkaline phosphates, Urea, Creatinine, Alanine transaminase (ALT), Aspartate transaminase (AST), Total Proteins, and Albumin were estimated before, and at the end of each month of both calcium preparations. Ionized calcium was analyzed using Electrostyl Analyzer (AVL). Beckman Autoanalyzer (Synchron Clinical System CX5) was used for other laboratory parameters.

Statistical analysis of the obtained data was done using the methods described by Armitage and Berry, 1994. The results were tabulated and statistically analyzed on an IBM personal computer using microstat package software.

Results

Five patients (12.5%) did not tolerate calcium acetate because of nausea, vomiting and upper GIT upset. They were excluded as non-compliant patients. Three other patients died during the course of study. The rest of the patients (32, 16 in each group) showed good tolerance for both calcium acetate and calcium carbonate. The results are summarized in tables 1, 2 and Figures 1-3.

Table 1. Different studied parameters before onset and after one month of calcium acetate and another month of calcium carbonate in group I

Item	*Onset* (mean ± SD)	*After 1 month* (mean ± SD)	*After 2 month* (mean ± SD)	*P1*	*P2*	*P3*
S. calcium (mg%)	9.24± 0.99	8.44 ± 0.81	9.5 ± 1.45	<0.001	>0.05	<0.01
S. ionized calcium (mg%)	4.39± 0.46	4.27 ± 0.37	4.71 ± 0.72	>0.05	<0.05	<0.01
S. phosphorus (mg%)	6.64± 1.37	6.33 ± 2.05	6.54 ± 1.26	>0.05	>0.05	>0.05
S. alkaline phosphatase (IU/L)	122.9± 86.4	134.9 ± 114.2	144.88 ± 116.9	>0.05	>0.05	>0.05
S. urea (mg%)	165.2± 18.7	148.6 ± 25.25	159.56 ± 20.98	<0.05	>0.05	>0.05
S. creatinine (mg%)	12.4± 4.4	14.44 ± 3.99	12.93 ± 3.57	<0.05	>0.05	<0.05
S. total protein (gm%)	7.29± 0.76	7.29 ± 0.69	7.32 ± 0.69	>0.05	>0.05	>0.05
S. albumin (gm%)	3.86± 0.28	3.73 ± 0.29	3.67 ± 0.36	<0.05	<0.05	>0.05

P1: Probability values in comparing the studied parameter at onset of study to its value after 1 month of calcium acetate.
P2: Probability values in comparing the studied parameter at onset of study to its value after 1 month of calcium carbonate.
P3: Probability values in comparing the studied parameter after 1 month of calcium acetate to its value after 1 month of calcium carbonate.

Table 2. Different studied parameters before onset and after one month of calcium carbonate and another month of calcium acetate in group II

Item	*Onset* (mean ± SD)	*After 1 month* (mean ± SD)	*After 2 month* (mean ± SD)	*P1*	*P2*	*P3*
S. calcium (mg%)	9.69 ± 0.76	9.46 ± 1.33	8.84 ± 1.09	>0.05	<0.01	<0.05
S. ionized calcium (mg%)	4.43 ± 0.44	4.49 ± 0.39	4.25 ± 0.51	>0.05	>0.05	>0.05
S. phosphorus (mg%)	6.68 ± 2.13	6.38 ± 1.9	5.65 ± 1.77	>0.05	<0.05	<0.05
S. alkaline phosphatase (IU/L)	136.8 ±129.6	153.44 ± 202.47	168.93 ± 240.33	>0.05	>0.05	>0.05
S. urea (mg%)	155.3 ± 17.8	149.88 ± 20.53	152.13 ± 23.999	>0.05	>0.05	>0.05
S. creatinine (mg%)	14.1 ± 2.68	13.71 ± 2.96	12.42 ± 1.39	>0.05	<0.05	>0.05
S. total protein (gm%)	6.98 ± 0.82	6.88 ± 0.70	6.956 ± 0.71	>0.05	>0.05	>0.05
S. albumin (gm%)	3.78 ± 0.43	3.55 ± 0.42	3.51 ± 0.43	<0.05	<0.05	>0.05

P1: Probability values in comparing the studied parameter at onset of study to its value after 1 month of calcium carbonate.
P2: Probability values in comparing the studied parameter at onset of study to its value after 1 month of calcium acetate.
P3: Probability value in comparing the studied parameter after 1 month of calcium carbonate to its value after 1 month of calcium acetate.

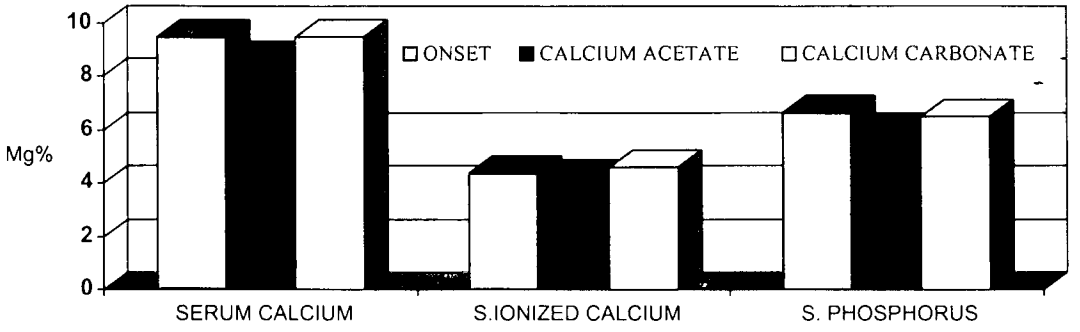

Fig. 1. Effect of calcium acetate vs calcium carbonate on S. calcium, ionized calcium and phosphours

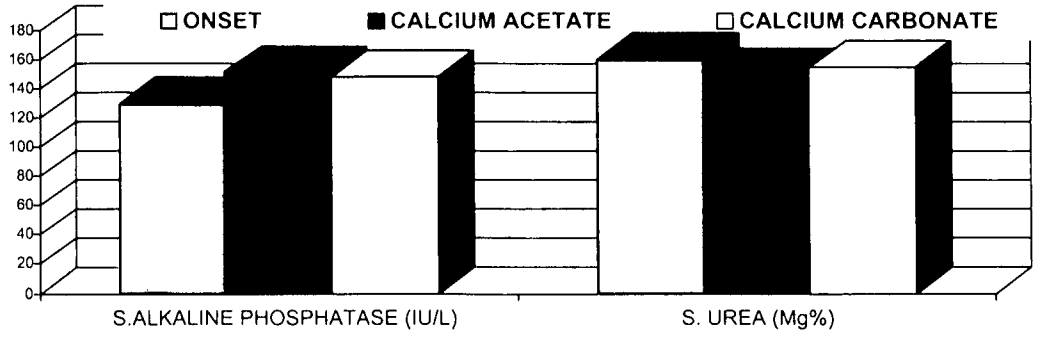

Fig. 2. Serum alkaline phosphate and urea before, after calcium acetate and after calcium carbonate

A significant decrease of serum phosphorus was observed after calcium acetate when compared to values after calcium carbonate (5.98 ± 1.92 vs. 6.46 ± 1.59mg%, $p<0.05$). There is a highly significant decrease of serum total calcium after calcium acetate when compared to values after calcium carbonate (8.63 ± 0.96 vs. 9.47 ± 1.37 mg%, $p < 0.001$) and significant decrease in serum ionized calcium after calcium acetate when compared to values after calcium carbonate (4.25 ± 0.44 vs. 4.6 ± 0.58 mg%, $p<0.01$). The effect of either compound on serum alkaline phosphatase was not significant.

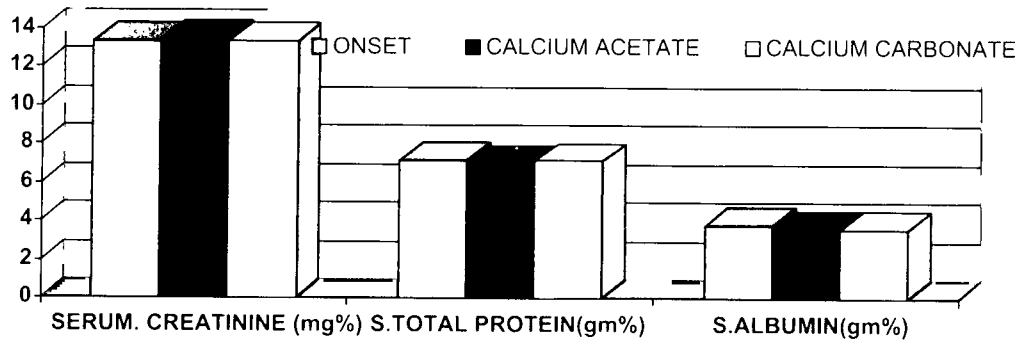

Fig. 3. Serum creatinine, total protein and albumin before and after calcium acetate and calcium carbonate

Discussion

Hyperphospatemia is one of the distressing consequences of C.R.F. It is well known that phosphorus excretion starts to deteriorate early in the course of C.R.F. and phosphate retention start at creatinine clearance less than 30 ml leading to hyperphosphatemia [13]. The rising serum phosphorus lead to decrease in serum calcium, increase PTH secretion and suppression of vitamin D hydroxylation [10]. Retained phosphorus decreases serum calcium through its combination with this calcium either in the bone or in soft tissue [27] Increase PTH secretion in these patients is probably due to the decrease in serum calcium, the increase of serum phosphorus and the decrease of active vit. D_3 level [27]. It is well known that lowering phosphorus level is one of the important stimulators of vitamin D hydroxylation by the kidney [8]. Accordingly, the increase of phosphorus level leads to ineffective activation of vitamin D by the kidney. The skeletal manifestation of hyperphosphatemia include the following [16]:-

- Hyperdynamic bone disease due to hyper-parathyroidism.
- Osteomalacia resulting from negative net calcium balance due to vit. D. dysfunction.

Accordingly, one of the important targets will be trial of normalization of serum phosphorus level in every uremic patient whether before or after initiation of dialysis treatment. This target may be achieved by restriction of phosphorus in the diet [15]. This approach is usually difficult, non-compliant and ineffective. Phosphorus restriction needs severe restriction of most of the high biological value proteins including dairy products, meat, fish, eggs, meat extract, etc. On the other hand, there is increasing tendency to improve the quantity and quality of protein ingested by the uremics to avoid excess morbidity and mortality [4].

In order to control the serum phosphorus in uremic patients on regular dialysis, a highly effective dialyzer with big surface area and membrane with large bore size capable of adequate clearance of phosphorus is usually needed. However, shorte treatment times with these dialyzers may offset the high clearance and thus reduce the net removal of phosphorus. In addition, a higher haematocrite level due to Erythropoietin may decrease phosphorus clearance [7].

Accordingly an effective phosphate binder will be needed by all uremic patients either on conservative treatment or on regular hemodialysis. Such a phosphate binder will allow proper nutrition of uremics without fear of hyperphosphatemia [14].

The first phosphate binder used in these patients was aluminum hydroxide [20]. This compound has many disadvantages mainly constipation and aluminum intoxication [26, 11, 25].

Calcium carbonate was thus introduced as an alternative phosphate binder [6]. Although calcium carbonate will save the patients from aluminum intoxication, yet it causes heart burn, constipation, beside the risk of hypercalcemia. The increase of calcium absorption after calcium carbonate raises the serum calcium and thus deprives most patients from using active vit. D [22]. It is usually needed in these patients, not only to optimize calcium balance, but also to suppress the hyperactive parathyroid gland [12].

Another phosphate binder, the calcium citrate, is not recommended in chronic renal failure patients as it increases the absorption of aluminium traces from the gut [24].

In our study, we tried a new phosphate binder, the calcium acetate, looking for its efficiency in comparison to calcium carbonate together with its effect on serum calcium whether total or ionized. In

addition, we looked for the tolerance of patients to this new compound.

The results of this study showed that calcium acetate was slightly but significantly more effective as a phosphate binder compared to calcium carbonate. This is similar to the findings of Ring et al., 1993. Meanwhile, the administration of equimolar doses of calcium acetate and carbonate showed that calcium acetate was associated with a lower level of either serum calcium or ionized calcium. The highly significant decrease of total serum calcium after calcium acetate compared to values after calcium carbonate and the significant decrease in serum ionized calcium after calcium acetate compared to values after calcium carbonate agree with the results reported by others [21,17, 5, 18]. On the other hand Almirall J, et al., 1994 reported equal effect of either compound on serum calcium. The effect of either compound on serum alkaline phosphatase was not significant as reported by Ben Hamida, 1992. This could be explained by:

1. Duration of treatment was too short to affect alkaline phosphatase level as it is not a sensitive parameter in assessing calcium-phosphorus homeostasis in the short run.
2. The decrease in serum total calcium and ionized calcium may neutralize the suppressing effect of decreased serum phosphorus on parathyroid gland.
3. Patients included in this study had initially normal serum alkaline phosphatase and thus the effect of either compound on this level will not be appreciable.

It can be concluded that calcium acetate is a good alternative to calcium carbonate as phosphate-binder with the following advantages:

It is slightly more effective and is not associated with hypercalcemia. It even decreases the serum calcium level allowing any increase in the dose.

A dialysate containing high calcium concentration (6-7 mg%) can be used without fear of hypercalcemia.

The co-administration of active vitamin D will be possible allowing more effective control of serum calcium and PTH.

However, patients tolerate this compound less than calcium carbonate. Five patients (12.5%) developed nausea, vomiting or GIT upset and discontinued the treatment, a finding reported by Caravaca, 1991 and Pflanz et al., 1994.

Generally, long-term use of this compound is necessary to confirm the speculated advantages of this compound on bone metabolism in uremic patients.

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