Original Article

Effects of Calcium Acetate Versus Calcium Carbonate As Oral Phosphate Binder in CKD Patients

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Summary/Abstract

Hyperphosphatemia and secondary hyperparathyroidism are common complication of CKD lead to significant morbidity.

Dietary restriction of phosphorus is limited by the need to provide adequate protein,estimated at roughly 1.0-1.2g protein per kg body weight in most ambulatory patients[4]. Therefore, most of the patient with CKD require an Exogenous Phosphate binder to prevent hyperphosphatemia.

68 patients of CKD (III - V) not on renal replacement therapy were prospectively evaluated in the department of Nephrology, SSMCH & MH, and Dhaka from Jan 2010 - Dec 2011 to see the effect of calcium acetate & Calcium Carbonate as phosphate binder.

Patients were subdivided into two equal groups, Group A (received calcium acetate, 667 mg BD) Group B (received calcium carbonate, 1250 mg BD). Both the group were matched for age, sex, BMI & renal function.

All patients were withdrawn from any phosphate binder and calcitriol 2 weeks ago & restricted to high protein (0.8 gm/day) & phosphate containing diet.

After a wash out period, group A had taken calcium acetate and group B had taken calcium carbonate. All the biochemical parameters (S. PO_4^-, S. Ca^{++}, S.Creatinine & iPTH) were estimated at 0 month, 1st month, 2nd month & 3rd month.

One month after intervention showed that serum calcium and serum phosphate were significantly reduced in acetate group than those in calcium carbonate group (P=0.03 & P= 0.01).

2nd month after intervention calcium acetate group showed significant reduction of calcium in comparison to calcium carbonate group (P<0.001) & serum phosphate of calcium acetate group decreased further & its difference with calcium carbonate group was significant (P=0.001).

At the end of 3rd month calcium acetate group shows a considerable reduction of serum calcium as such there was significant difference between the groups with respect to the variables (P=<0.001). Serum phosphate of calcium acetate group also decreases faster causing a much wider difference with that of calcium carbonate group (P=0.005).

After end of the study iPTH decreased proportionately in both groups & serum creatinine was not significantly in either group.

Introduction

CKD is defined as either Kidney damage or glomerular filtration rate (GFR) <60 ml/min/1.73 m2 for >3 months. Kidney damage is defined as pathological abnormalities or markers of damage including abnormalities in blood or urine test or imaging studies.

Hyperphosphatemia and secondary hyperparathyroidism are common complication of CKD[4] which can lead to significant morbidity because of pain, bone loss, increased risk of fracture, anaemia, HTN, atherosclerosis vascular disease, pruritus and sexual dysfunction.[3] Dietary phosphate restriction is limited by the need to provide adequate daily protein intake to maintain neural nitrogen balance 4). Therefore, most patients with advanced CKD or ESRD require an exogenous phosphate binder to prevent hyperphosphatemia.

Calcium salts (Usually calcium carbonate/calcium acetate) have become the treatment of choice for

hyperphosphatemia, although provision of calcium can lead to hypercalcaemia and increased risk of metastatic calcification, particularly among patients on Vit-D replacement.[4]

1989 Sheik et al fist demonstrated the superior efficacy of calcium acetate over calcium carbonate as an intestinal phosphate binder[7]; they also showed theoretical as well as experimental evidence of reduced calcium absorption with the acetate salt, offering hope for greatly improved phosphate control.

Subjects and Methods

This clinical trial was performed in the department of Nephrology, SSMCH, Dhaka and investigation were carried out in laboratory, department of SSMC over a period of Jan 2010 to Dec 2011.

Total 68 patients were equally distributed into two groups using a random allocation procedure, one marked with A (for Calcium acetate) & another with B (for Calcium Carbonate).

The daily dose of calcium acetate was 667 mg tab (containing 169 mg of elemental calcium) twice daily after taking meal, while the dose of calcium carbonate was 1250 mg tab (containing 500 mg of elemental calcium) twice daily orally after taking meal.

All patients were withdrawn from a phosphate binder and calcitriol for at least two weeks ago and restricted to high protein (0.8 gm/kg) and phosphate containing drug.

After a washout period of two weeks baseline biochemical markers ($S.PO_4^{--}$, $S.Ca^{++}$, S.Creatinine & iPTH) was measured and then group "A" had taken calcium acetate and group "B" had taken calcium carbonate for 3 months.

Biochemical markers ($S.PO_4^{--}$, $S.Ca^{++}$, S.Creatinine & iPTH) was measured in one month interval for 3 months.

Statistical Method

Data were processed and analyzed using soft SPSS version 11.5. The test statistics used to analyses the data were Chi-square (X2) or fisher exact probability and student's t test.

Results

Mean age of the patients in calcium acetate group was 54.09 ± 9.66 and in calcium carbonate group 53.37 ± 10.42, mean weight was in kg 62.30(± 3.55) in calcium acetate group and 58.20(± 5.96) in calcium carbonate group, mean height (m.) was 1.69(± 0.2) in calcium acetate group and 1.65(± 0.25) in calcium carbonate, BMI in calcium acetate group were 21.78(± 1.95) and 21.32(± 2.22) were in calcium carbonate group.

In the study patients, the baseline level of biochemical variables like S. Calcium, S.Phosphate, S. iPTH & S. Creatinine were almost identical between groups (8.7 ± 1.07 Vs 8.9 ± 0.92 mg/dl, P=0.27, 3.8 ± 1.1 Vs 4.3 ± 1.1 mg/dl, P=0.10, 234.50 ± 42.5 Vs 205 ± 36.2 pg/ml, P = 0.65 & 3.6 ± 1.8 Vs 3.7 ± 2.0 mg/dl P = 0.90 respectively). (Table II)

One month after interventions changes in biochemical variables showed that calcium acetate group responded well than calcium carbonate group with respect to S.Calcium and S.Phosphate (8.5 ± 1.2 Vs 8.9 ± 0.7 mg/dl, P=0.03; 3.5 ± 0.8 Vs 4.1 ± 0.9 mg/dl, P = 0.01). iPTH & S.Creatinine also reduced in both groups but no significant intergroup difference was observed (188.1 ± 35.5 Vs 164 ± 28.4 pg/dl, P = 0.41 and 3.49 ± 1.6 Vs 3.35 ± 1.6 mg/dl, P = 0.52 respectively). (Table III)

Two months after intervention there was significant difference between the group with respect to S.Calcium (8.5 ± 0.97 Vs 9.10 ± 0.38 mg/dl, P =<0.001).

S.PO4 of calcium acetate group decreased further and its difference with Calcium carbonate group was also significant (3.27 ± 0.69 Vs 4.21 ± 1.38 mg/dl, P = 0.001). But there was no significant difference between groups with respect to S.iPTH & S. Calcium. (Table IV)

Three months after intervention of the variable $S.Ca^{++}$ were significantly lower in S.Calcium acetate group than calcium carbonate group (P=<0.001).$S.PO_4$ of calcium acetate group also decreases faster causing a much wider difference with that of calcium carbonate group(p=0.005) No Significant difference between calcium acetate and calcium carbonate group with respect to iPTH and S.Creatinine (P>0.05). (Table V)

Table-1: Demographic characteristics of the study population

Demographic Characteristics	Group		p-value
	Calcium acetate (Group A) (n=33) Mean ± SD	Calcium carbonate (Group B) (n=35) Mean ± SD	
Age in yrs	54.09 ± 9.66	53.37 ± 10.42	0.76
Weigh (kg)	62.30 (± 3.55)	58.20 (± 5.69)	0.005
Height (m.)	1.69 (± 0.2)	1.65 (± 0.25)	0.03
BMI(mean ± SD)	21.78 (± 1.95)	21.32 (± 2.22)	0.39

Data were analyzed using Student's t-Test and were presented as mean ± SD

Table-2: Comparison of baseline values between groups

Baseline variables	Group		p-value
	Calcium acetate (Group A) (n=33)	Calcium carbonate (Group B) (n=35)	
Serum calcium (mg/dl)	8.7 ± 1.07	8.9 ± 0.92	0.27
Serum phosphate (mg/dl)	3.8 ± 1.1	4.3 ± 1.1	0.10
Intact serum PTH (pg/ml)	234.5 ± 42.5	205 ± 36.2	0.65
Serum creatinine (mg/dl)	3.6 ± 1.8	3.7 ± 2.0	0.90

Table-3: Changes of biochemical variables 1 month after intervention

Biochemical variables	Group		p-value
	Calcium acetate (Group A) (n=33)	Calcium carbonate (Group B) (n=35)	
Serum calcium (mg/dl)	8.5 ± 1.2	8.9 ± 0.7	0.03
Serum phosphate (mg/dl)	3.5 ± 0.8	4.1 ± 0.9	0.01
Intact serum PTH (pg/ml)	188.1 ± 35.5	164 ± 28.4	0.41
Serum creatinine (mg/dl)	3.49 ± 1.6	3.35 ± 1.6	0.52

Data were analyzed using Student's t-Test and were presented as mean ± SD

Table-4: Changes of biochemical variables 2 month after intervention

Biochemical variables	Group		p-value
	Calcium acetate (Group A) (n=33)	Calcium carbonate (Group B) (n=35)	
Serum calcium (mg/dl)	8.5 ± 0.97	9.10 ± 0.38	< 0.001
Serum phosphate (mg/dl)	3.27 ± 0.69	4.21 ± 1.38	0.001
Intact serum PTH (pg/ml)	158.5 ± 30.9	153.9 ± 27.7	0.62
Serum creatinine (mg/dl)	3.69 ± 1.87	3.34 ± 1.70	0.25

Data were analyzed using **Student's t-Test** and were presented as **mean ± SD**

Group Statistics

Table-5: Changes of biochemical variables 3 month after intervention

Biochemical variables	Group		p-value
	Calcium acetate (Group A) (n=33)	Calcium carbonate (Group B) (n=35)	
Serum calcium (mg/dl)	8.6 ± 1.06	9.45 ± 0.44	< 0.001
Serum phosphate (mg/dl)	3.13 ± 1.31	3.98 ± 0.67	0.005
Intact serum PTH (pg/ml)	128.1 ± 17.8	148± 36.2	0.64
Serum creatinine (mg/dl)	3.35 ± 1.00	3.48 ± 1.79	0.42

Data were analyzed using **Student's t-Test** and were presented as **mean ± SD**

Table-6: Comparison of changes in serum calcium between the study groups

Group	Mean Serum calcium (mg/dl)				p-value
	0 month	1 month	2 month	3 month	
Calcium Acetate	8.7 ± 1.07	8.5 ± 1.2	8.5 ± 0.97	8.6 ± 1.06	0.003
Calcium Carbonate	8.9 ± 0.92	8.9 ± 0.7	9.10 ± 0.38	9.45 ± 0.44	

Data were analyzed using **Repeated measure ANOVA statistics** and 'p' refers to the overall difference between the groups in terms of changes in serum calcium from baseline to end point of study.

Table-7: Comparison of changes in serum phosphate between the study groups

Group	Mean Serum phosphate (mg/dl)				p-value
	0 month	1 month	2 month	3 month	
Calcium Acetate	3.8 ± 1.1	3.5 ± 0.8	3.27 ± 0.69	3.13 ± 1.31	< 0.001
Calcium Carbonate	4.3 ± 1.1	4.1 ± 0.9	4.21 ± 1.38	3.98 ± 0.67	

Data were analyzed using **Repeated measure ANOVA statistics** and 'p' refers to the overall difference between the groups in terms of changes in serum calcium from baseline to end point of study.

Table-8: Comparison of changes in serum intact PTH between the study groups

Group	Mean Serum PTH (pg/ml)				p-value
	0 month	1 month	2 month	3 month	
Calcium Acetate	234 ± 42.5	188.1 ± 35.5	158.5 ± 30.9	128.1 ± 17.8	< 0.001
Calcium Carbonate	205 ± 36.2	164 ± 28.4	153.9 ± 27.7	148 ± 36.2	

Data were analyzed using **Repeated measure ANOVA statistics** and 'p' refers to the overall difference between the groups in terms of changes in serum calcium from baseline to end point of study.

Table-9: Comparison of changes in serum creatinine between the study groups

Group	Mean Serum creatinine (mg/dl)				p-value
	0 month	1 month	2 month	3 month	
Calcium Acetate	3.6 ± 1.8	3.49 ± 1.6	3.69 ± 1.87	3.35 ± 1.00	0.70
Calcium Carbonate	3.7 ± 2.0	3.35 ± 1.6	3.34 ± 1.70	3.48 ± 1.79	

Data were analyzed using **Repeated measure ANOVA statistics** and 'p' refers to the overall difference between the groups in terms of changes in serum calcium from baseline to end point of study.

Discussion

The present study was under taken to observe the effects of calcium acetate versus calcium carbonate on CKD patients as phosphate binder and also to see the effects of these two drugs on iPTH in CKD patients.

It is generally believed that calcium acetate is better tolerated, binds phosphate efficiently and causes less incidence of hypercalcaemia as compared to calcium carbonate.[11]

In the study of Angel L.M.de Francisco et.ai(2010),mean age of calcium acetate was 59.2±13 and mean age of sevelemer HCL was 55.9±11.75.There was also no significant different between age of the two groups (p=.64).In the same study,BMI of calcium acetate was 27.0±3.8,p=.88,that was nearer to present study.[1o]

In present study serum phosphate level was adequately controlled with both salts. The advantage we observed that this control was achieved using only less than half the amount of elemental calcium with the acetate formulation.

In our study, we used calcium acetate 1.3 gm/day and calcium carbonate 2.5 gm/day without calcitriol. There was significant reduction of serum phosphate (3.13 Vs 3.98) and S.Calcium (8.6 Vs 9.45) in acetate group and significant increase in serum calcium in calcium carbonate group than acetate group.

One author[1] conducted a randomized cross-over study over 24 weeks, in 7 selected hemodialysis patients to compare calcium acetate with calcium carbonate. In acetate form, less elemental calcium was used but there was no difference in phosphate control and the incidence of hypercalcemia was also similar between the two treatments.

Navaneethan &associates[9] noted that there was no significant difference in the serum phosphate level with calcium acetate in comparison to calcium acetate.

At the end of present study, there was significantly higher decrease of Serum phosphate in calcium acetate group compared to calcium carbonate group (3.13 ± 1.31 Vs3.98±0.67),p=.005(Table VII)and calcium acetate group exhibited a considerable reduction of serum calcium (8.6±1.06 vs 9.45±.44) than that of calcium carbonate group and their difference was significant.(Table VI)

Borrego and Collegues[2] compared the efficacy of calcium acetate and calcium carbonate as phosphate binder in 28 patients with CKD. The authors found that both drugs were similarly effective as phosphate binder in lowering phosphate level. Four fold greater dose of elemental calcium was used in calcium carbonate than acetate group and exhibited more hypercalcaemia in carbonate group[2]

IN another study,Ketteler et al showed that sevelamer carbonate is effective in controlling serum phosphorus in CKD patients.[8]

Pflanz et al (1994) performed a randomized cross-over study in 23 patients over 14 weeks. Equimolar doses of calcium acetate and calcium carbonate were used. Serum phosphate was significantly lower with calcium acetate (1.51 Vs 1.80 mmol/l) and iPTH was also lower with calcium acetate (17.8 Vs 25.4 pmol/l). But Serum calcium was significantly higher in the calcium acetate (2.4 Vs 2.32 mmol/l) group than the calcium carbonate group.[6]

Our study also showed that both the drugs were effective as phosphate binder but acetate was more effective than calcium carbonate group. At the end of third month's intervention, calcium carbonate group had significant higher calcium level (Table 7). This can be explained by the use of three fold higher elemental calcium in calcium carbonate group than the acetate group.

Conclusion

Based on the findings of the present study,conclusions of this study is calcium acetate is more effective and safer than calcium carbonate in controlling hyperphosphatemia in patients of chronic kidney diseases (stage 3,4&5) not on maintenance haemodialysis.Apart from its superior phosphate binding activities,it causes less hypercalcemia than calcium carbonate. Both the salts of calcium are equally effective in keeping intact serum PTH to recommended level for CKD patients. Neither of the two drugs was found to produce any more deleterious effect on renal function as evidenced by no change in serum creatinine level during three months treatment.

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