COMPARISON OF CALCIUM ACETATE WITH CALCIUM CARBONATE AS PHOSPHATE BINDER IN PATIENTS ON MAINTENANCE HAEMODIALYSIS

Imran Saif, Abdul Halim, Ashfaq Altaf, Mohsin Saif, Muhammad Khalid, Dilshad Ahmad, Humera Imran

Department of Nephrology, Department of Medicine, Military Hospital Rawalpindi, Department of Pathology, Army Medical College Rawalpindi

Background: Hyperphosphatemia is common in end-stage renal disease patients. Objective of this study is to compare the hypercalcaemic effect and phosphate binding power of calcium acetate and calcium carbonate in end-stage renal disease patients on maintenance haemodialysis.

Methods: This randomised control trial was conducted in four phases with calcium acetate or calcium carbonate. Sixty-four patients on haemodialysis were randomly divided into 2 groups. After a washout period of 2 weeks, each group was given calcium acetate or calcium carbonate for 2 months. After another washout period the patients were crossed over and again received these drugs for 2 months. Serum Calcium, phosphate, and albumin were analysed on Selectra E auto analyser at completion of each phase of study. Hypercalcaemic effect was defined as serum calcium >2.54 mmol/l, and phosphate binding power as serum phosphate <1.61 mmol/l.

Results: Forty-one patients completed the study. Though lower dose of calcium acetate was used, it resulted in equally good control of hyperphosphatemia as compared with calcium carbonate therapy [1.37 mmol/l (SD 0.33) vs. 1.46 mmol/l (SD 0.34), p=0.16]. Incidence of hypercalcaemia was higher with calcium carbonate therapy (2.73±0.67 mmol/l vs. 2.32±0.28 mmol/l, p<0.01). Both drugs were well tolerated, but patients more frequently complained of muscle cramps while taking calcium acetate. Conclusions: It is concluded that calcium acetate has similar effect on serum phosphate levels as compared to calcium carbonate in patients on maintenance haemodialysis. However, calcium acetate results in lesser frequency of hypercalcaemia compared to calcium carbonate. Tolerance to both drugs was similar, though patients complained of more muscle cramps while taking calcium acetate.

KEY WORDS: Calcium acetate, Calcium carbonate, Hyperphosphatemia

INTRODUCTION

In the steady state, the serum phosphate (PO₄) concentration is primarily determined by the ability of the kidneys to excrete dietary PO₄. Renal excretion is so efficient in normal subjects that the balance can be maintained with only a minimal rise in serum PO₄ concentration even if intake is increased to as much as 4000 mg/day (130 mmol/day).

Hyperphosphatemia has an important role in the development of secondary hyperparathyroidism and bone disease in patients with end-stage renal disease (ESRD). Hyperparathyroidism is a major cause for concern, because the high circulating levels of parathyroid hormone (PTH) play an important role in the development of renal osteodystrophy and possibly in other uremic complications as well. Many such patients are also treated with calcitriol or a vitamin D analog in an attempt to suppress PTH release. However, these drugs also increase intestinal PO₄ absorption and can exacerbate the hyperphosphatemia unless bone remodelling is reduced due to inhibition of PTH secretion. A sustained elevation in serum PO₄ among patients with end-stage renal failure is also associated with increased mortality.

Differences among various PO₄ binders may be due to variations in formulation (disintegration and dissolution), the nature of the chemical reaction between the binder and phosphorus and its modification by the changing pH of the gastrointestinal tract. Other factors can be the presence or absence of other anions that compete with phosphorus for binding sites, and the intrinsic transport characteristics of the small intestine.

Aluminium hydroxide had previously been a well-established PO₄ binder, but its use was associated with neurologic and bone toxicity. The problems with aluminium led to the preferential administration of calcium salts to bind intestinal PO₄. In addition to lowering the serum PO₄ concentration, absorption of some of the calcium (Ca) can also raise the serum Ca concentration, providing an additional mechanism by which PTH secretion might be reduced.

Ca salts are widely used in Pakistan these days as oral phosphorus binders to control hyperphosphatemia in patients on maintenance haemodialysis. The most commonly used, calcium carbonate (CaCO₃) is not the ideal binding agent, primarily because of its hypercalcaemic effect. In this regard, calcium acetate (CaAc) has been
reported to have at least a similar phosphorus binding efficiency, and a less pronounced hypercalcaemic effect.5

No such local published studies were available for our ESRD population to compare the efficacy of these two calcium salts. This study was designed to compare their efficiency, and to establish whether CaAc was a more effective phosphorus binder than CaCO3, and if its use reduced the incidence of hypercalcaemia.

MATERIAL AND METHODS

The study was carried out at the Haemodialysis Centre, Nephrology Department, Military Hospital Rawalpindi. Sixty-four consecutive patients of ESRD, who were on maintenance haemodialysis for at least 3 months, were recruited. These included both males and females age 12 and above. Phosphate binding power was defined as ability of these drugs to maintain serum PO4 levels with in normal range (<1.61 mmol/l),6,7 which is a desired effect in ESRD patients. Hypercalcaemic effect was determined by increased serum Ca levels (> 2.54 mmol/l),8 an unwanted effect in patients of ESRD. Patients with previous para-thyroideectomy and advanced malignancy/ metastasis were excluded from the study. Haemodialysis was done twice or thrice a week. All other medications that the patients were taking were continued and no changes were made to their usual diet.

The randomised control trial was conducted in four phases with calcium acetate or calcium carbonate. In phase 1, CaCO3/CaAc were withdrawn from both groups for a period of 2 weeks (washout period). Baseline tests were taken after the washout period. In phase 2, group A was initiated on 4.002 g/day (1.014 g elemental calcium) of CaAc, and group B on 5.625 g/day (2.25 g elemental calcium) of CaCO3 for 4 weeks. This was followed by a washout period of 2 weeks (phase 3), in which no PO4 binder was given to either group. After this period, patients were crossed over in phase 4. In this phase, patients in group A were given CaCO3, and patients in group B were given CaAc for 4 weeks. All of them were instructed to take the medication with meals. Serum urea and Creatinine, Ca, albumin, and PO4 were measured during each phase of study.

RESULTS

Forty-one patients completed the study (Table-1). Age ranged between 14 and 75 years. There were 24 (58.5%) male and 17 (41.5%) female patients. Duration on maintenance haemodialysis varied between 3 and 66 months.

<table>
<thead>
<tr>
<th>Table-1: Data of Study Cases, (n=41)</th>
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<tbody>
<tr>
<td><strong>Frequency</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
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<table>
<thead>
<tr>
<th><strong>Mean</strong></th>
<th><strong>SD</strong></th>
<th><strong>SEM</strong></th>
<th><strong>p value</strong></th>
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</thead>
<tbody>
<tr>
<td>Ca (CaAc)</td>
<td>2.32</td>
<td>0.28</td>
<td>4.39</td>
</tr>
<tr>
<td>Ca (CaCO3)</td>
<td>2.73</td>
<td>0.67</td>
<td>0.10</td>
</tr>
<tr>
<td>PA4 (CaAc)</td>
<td>1.37</td>
<td>0.33</td>
<td>5.09</td>
</tr>
<tr>
<td>PA4 (CaCO3)</td>
<td>1.46</td>
<td>0.34</td>
<td>5.24</td>
</tr>
<tr>
<td>Albumin (phase 2)</td>
<td>36.43</td>
<td>3.30</td>
<td>0.52</td>
</tr>
<tr>
<td>Albumin (phase 4)</td>
<td>34.37</td>
<td>4.99</td>
<td>0.78</td>
</tr>
</tbody>
</table>

Though lower dose of CaAc (based on elemental calcium) was used, it resulted in equally good control of hyperphosphatemia as compared with CaCO3 therapy (Figure-1).

Figure-1: Drop-line graph showing differences in Ca level while giving CaAc (red), and CaCO3 (green). PO4 levels are while taking CaAc. (n=41)

Serum PO4 levels with CaAc were 0.81±2.72 mmol/l vs 0.77±2.72 mmol/l on CaCO3, (p>0.10). Serum Ca levels (Mean±SD) while taking CaCO3 were 2.73±0.67 mmol/l (range 1.56-4.36), and were 2.32±0.28 mmol/l (Range: 1.89-3.24) while taking CaAc, making the difference statistically significant (p<0.01). Both drugs were well tolerated, but patients more frequently complained of muscle cramps and abdominal discomfort while taking CaAc. During the study period, serum albumin levels of the patients declined from 36.43±3.30 g/l to 34.36±4.99 g/l (p<0.05).

DISCUSSION

It is generally believed that CaAc is better tolerated, binds phosphate more effectively, and causes less incidence of hypercalcaemia as compared to CaCO3.7,9 In this study, serum PO4 levels were adequately controlled with both salts. The advantage
we observed was that this control was achieved using only half the amount of elemental calcium with the acetate formulation.

Both drugs were tolerated equally well, though some patients did complain of more frequent episodes of muscle cramps while taking CaAc. A recently published Iranian study also interestingly reports exact same problems with CaAc use.\textsuperscript{10} Though this and some other international studies do claim that it is a better phosphate binder, but we did not find CaAc to be superior to CaCO\textsubscript{3} in this regard.

A statistically significant increase in Ca levels was seen while patients were taking CaCO\textsubscript{3}. This finding could simply be accounted for by the higher amount of elemental Ca given during CaCO\textsubscript{3} treatment because of study design. Many studies done internationally denied the lesser hypercalcaemic effect of CaAc,\textsuperscript{11,12} but interestingly, the only prospective double-blind crossover comparison in literature favours a high frequency of hypercalcaemia with CaAc.\textsuperscript{13} There were however, some relative differences in the design of that study that may explain the discrepancies. First of all, the dose of elemental Ca was kept the same with both salts, and secondly, there was no washout period in between treatments.

Currently, the control of serum phosphate levels in patients on haemodialysis requires the restriction of dietary PO\textsubscript{4} intake. The dose of PO\textsubscript{4} binders ideally should be proportional to the amount of phosphorous ingested with each meal. But this is not practical for our dialysis population, most of whom are neither well-educated, nor have easy access to a dietician. The acetate salt is significantly expensive compared to carbonate. As the phosphate dosing is reduced, if hypercalcaemia develops with this strategy, then lowering the dialysate Ca from 3.0 to 2.5 mmol/l may be effective in avoiding hypercalcaemia.\textsuperscript{14} A practical problem occurs when such manoeuvre is not sufficient to control hyperphosphataemia without concomitant hypercalcaemia, and CaAc may be valuable in this situation.

To summarize, CaAc should be used in patients who develop significant hypercalcaemia with CaCO\textsubscript{3}. Otherwise, with our population it may be possible to achieve the desired effects with a lesser dose of CaCO\textsubscript{3}, while also keeping the treatment costs low.

REFERENCES


Address for Correspondence:
Dr. Imran Saif, Nephrologist, House No. 4, Street 40, Sector F-7/1, Islamabad-44000. Tel: +92-51-9206600.
E-mail: imransaif@hotmail.com