INTRODUCTION

Normal kidneys filter large amounts of organic phosphate of which about 98% is handled by the proximal tubules. Early stages of renal dysfunction do not alter serum phosphate levels as the filtered load and degree of reabsorption decrease proportionately. With failure of this homeostatic mechanism there is progressive hyperphosphatemia.

Phosphate is now regarded as a uremic toxin according to many studies and the statistical association between serum phosphorus and all-cause mortality has transformed phosphate into a ‘dialysis enemy’. Inspite of all this, phosphate control in CKD patients continues to be poor. Various factors have been implicated such as difficulty in adhering to a low phosphate diet, efficacy, cost and palatability of the phosphate binder.

Untreated hyperphosphatemia leads to secondary hyperparathyroidism, renal bone disease and increased vascular/soft tissue calcification all of which contribute to increased mortality and morbidity in CKD patients. Thus phosphate control is an important therapeutic option in CKD patients with an aim to reduce cardiovascular mortality and morbidity. Buschinsky et al makes the point that a prudent clinician cannot dismiss evidence that serum phosphorus correlates with cardiovascular morbidity and consequently the addition of phosphorus to the list of cardiovascular risk factors in CKD.

The three key elements in the management of elevated serum phosphorus levels are dietary restriction, drug treatment using phosphate binders and adequate hemodialysis. Dietary phosphorus restriction always carries a risk of severe protein malnutrition and thus phosphate binders play a pivotal role in the management of stage 3-5 CKD.

Effect Of Lanthanum Carbonate vs Calcium Acetate As A Phosphate Binder In Stage 3-4 CKD- ‘Treat To Goal Study’

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Abstract

Context: Hyperphosphatemia is a common in stage 3-4 CKD and influences the progression and prognosis in CKD patients. The efficacy and tolerability of non-calcium phosphate binders has not been studied in any open-label RCT. This study tried to compare the efficacy of lanthanum carbonate with conventional calcium-based phosphate binders such as calcium acetate.

Aim: 1. Compare the efficacy of lanthanum carbonate vs calcium acetate as a phosphate binder
2. Compare the propensity of the above two drugs in producing/preventing hypercalcemia
3. Economic comparison between the two drugs
4. Setting and Design: ‘Treat to Goal’ open-labeled randomized cross-over comparison study

Methods and Materials: Seventeen patients were randomized to receive either lanthanum carbonate or calcium acetate for 8 weeks. After a washout period of 2 weeks, patients were crossed to receive alternate drug for 8 weeks. For patients whose phosphorus was still not in target range, combination of the two drugs were given for 8 weeks. Serum calcium, serum phosphorus, Ca X P product and serum creatinine were estimated at frequent intervals. Paired ‘T’ test was used to compare the means of the two groups.

Results: In the 15 patients who completed the study both lanthanum and calcium acetate were equally good phosphate binders. Although rise in calcium and Ca X P product was more with calcium acetate, it was not statistically significant.

Conclusion: Both lanthanum carbonate and calcium acetate are equally effective phosphate binders and reduce phosphorus levels to a similar extent. Serum calcium and Ca X P products showed a rising trend with calcium acetate but it was not statistically significant. The cost of lanthanum carbonate was 17 times more than that of calcium acetate which is an important consideration in a developing country like ours.

Key-words: Hyperphosphatemia, phosphate binders, randomized cross over study, lanthanum carbonate, calcium acetate

Key messages: Although lanthanum carbonate was as effective as calcium acetate in lowering serum phosphorus levels, it was 17 times costlier than the latter.
and no RCT has shown one is superior to another. Table 1 summarizes the oral phosphate binders.

Table 1: Comparison of oral phosphate binders

<table>
<thead>
<tr>
<th>Phosphate Binder</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum salts</td>
<td>High efficacy independent of pH</td>
<td>Toxicty</td>
</tr>
<tr>
<td></td>
<td>Inexpensive</td>
<td>No definite safe dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Frequent monitoring</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>Aluminum free</td>
<td>Efficacy influenced by pH</td>
</tr>
<tr>
<td></td>
<td>Moderately effective</td>
<td>Unpalatable</td>
</tr>
<tr>
<td></td>
<td>Moderate pill burden</td>
<td>Hypercalcemia</td>
</tr>
<tr>
<td></td>
<td>Inexpensive</td>
<td>GI side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Possible ectopic calcification</td>
</tr>
<tr>
<td>Calcium acetate</td>
<td>Aluminum free</td>
<td>Large tablets</td>
</tr>
<tr>
<td></td>
<td>pH dependent efficacy</td>
<td>Hypercalcemia</td>
</tr>
<tr>
<td></td>
<td>Fairly inexpensive</td>
<td>GI side effects</td>
</tr>
<tr>
<td></td>
<td>Lower calcium load than calcium carbonate</td>
<td>Possible ectopic calcification</td>
</tr>
<tr>
<td>Lanthanum carbonate</td>
<td>Calcium and aluminum free</td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td>Chewed, not swallowed whole</td>
<td>GI side effects</td>
</tr>
<tr>
<td></td>
<td>High efficacy, regardless of pH</td>
<td>Minimal gastrointestinal absorption</td>
</tr>
<tr>
<td></td>
<td>Low pill burden</td>
<td></td>
</tr>
</tbody>
</table>

The study had the following aims

1. To compare the efficacy of lanthanum carbonate and calcium acetate in reducing phosphorus levels in stage 3-4 CKD.
2. To compare the changes in serum calcium and Ca X P product of the patients while taking lanthanum carbonate or calcium acetate.
3. To find mean effective dose of these two drugs, to obtain levels of serum phosphorus, serum calcium and Ca X P product.
4. To find out whether fixed dose combination of these drugs is superior than maximum tolerated dose of either.
### TABLE 3: LABORATORY PARAMETERS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drug</th>
<th>N</th>
<th>Pre-drug mean(SD)</th>
<th>Post drug mean(SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Phosphorus (mg/dl)</td>
<td>Lanthanum carbonate</td>
<td>15</td>
<td>6.50 (0.27)</td>
<td>4.93 (0.97)</td>
</tr>
<tr>
<td></td>
<td>Calcium acetate</td>
<td>15</td>
<td>6.87 (1.34)</td>
<td>5.40 (1.00)</td>
</tr>
<tr>
<td></td>
<td>Combination</td>
<td>7</td>
<td>6.45 (1.17)</td>
<td>5.00 (0.47)</td>
</tr>
<tr>
<td>Serum Calcium (mg/dl)</td>
<td>Lanthanum carbonate</td>
<td>15</td>
<td>8.21 (0.70)</td>
<td>7.80 (1.29)</td>
</tr>
<tr>
<td></td>
<td>Calcium acetate</td>
<td>15</td>
<td>8.00 (0.68)</td>
<td>8.22 (1.03)</td>
</tr>
<tr>
<td></td>
<td>Combination</td>
<td>7</td>
<td>7.56 (1.44)</td>
<td>7.76 (0.84)</td>
</tr>
<tr>
<td>Calcium X Phosphorus (mg²/dl²)</td>
<td>Lanthanum carbonate</td>
<td>15</td>
<td>45.48 (1.68)</td>
<td>38.07 (1.73)</td>
</tr>
<tr>
<td></td>
<td>Calcium acetate</td>
<td>15</td>
<td>52.42 (10.32)</td>
<td>48.63 (11.63)</td>
</tr>
<tr>
<td></td>
<td>Combination</td>
<td>7</td>
<td>48.18 (1.51)</td>
<td>38.81 (1.23)</td>
</tr>
</tbody>
</table>

### SUBJECTS AND METHODS

An open-labeled randomized two-group crossover study was performed to evaluate the efficacy and safety of lanthanum carbonate vs calcium acetate at the Department of Nephrology, Medical College Hospital, Trivandrum. The study design is shown in Figure 1.

**Figure 1: Study design**

**Inclusion criteria:**
1. Age between 18 and 80 years
2. Stage 3-4 CKD
3. Serum phosphorus >5.5mg/dl at the time of recruitment
4. Serum calcium <10.5mg/dl at the time of recruitment

**Exclusion criteria:**
1. End stage renal disease requiring dialysis
2. Acute worsening of chronic renal failure
3. Massive edema and hypoproteinemia
4. Allergy and distressing symptoms to any of the medications
5. Women who are pregnant or lactating or not using appropriate birth control measures
6. Any life threatening malignancy
7. Any exposure to other investigational drugs within 30 days prior to the start of the study.

The total duration of the study for each patient was 18 weeks, which was divided into 2 stages of 8 weeks each with 2 weeks washout period in between. The patients were randomly allocated into two groups to receive either lanthanum carbonate or calcium acetate for 8 weeks. At the end of the first stage the respective drug was stopped and the patient entered a 2 week drug free washout period. After the 2 week washout period, the patients were crossed over to receive the alternate drug for 8 weeks. The patients served as their own controls. The patients were assessed at 2 weekly intervals. At the time of entry into the study and during each visit, a detailed history was taken. Physical examination including general examination, vital signs and relevant systemic examination were also carried out at baseline and during each visit. Serum phosphorus, serum calcium, serum alkaline phosphate and serum creatinine were the biochemical parameters that were estimated at baseline and at each visit. The doses of phosphate binders given were:

- Calcium acetate: 1 tablet containing 667mg of calcium acetate thrice daily. The tablet was swallowed along with the meals. Dose of calcium acetate was titrated by adding one tablet during each visit if target serum phosphorus is not achieved up to a maximum of 2 tablets three times daily.
- Lanthanum carbonate: 1 tablet containing 500mg of lanthanum carbonate thrice daily. The tablet was chewed along with the meals. Dose of lanthanum carbonate was titrated by adding one tablet during each visit if target serum phosphorus is not achieved up to a maximum of 2 tablets three times daily.

All the data collected were recorded in a specific case record form designed for this study. Compliance was estimated by pill count. The incidence of drug related adverse effects during the study period also were noted in the proforma. The costs of the 8-week treatments with lanthanum carbonate and calcium acetate were calculated from the MRP labels on the respective packages.

**Statistical analyses**

Data were fed into the statistical package 70 of Microsoft Excel and checked for data entry errors. The distribution of variables was noted. Data from the patients who completed the study was analyzed using SPSS software. For comparison of the means between the groups paired ‘t’ test was used. The level of significance was fixed at 5%.

**Adverse effects**
All adverse effects that occurred during the study were documented in the case record form. A Serious Adverse Event (SAE) was defined as any reaction requiring hospitalization.

RESULTS

A total of 17 patients who satisfied the inclusion criteria were enrolled for the study after obtaining written informed consent. Out of these, 15 patients completed the study. Out of 2 patients who did not complete the study, 1 patient was withdrawn during the phase 1 (pre-washout), due to worsening of their renal status while on lanthanum carbonate; 1 patient was withdrawn in phase 2 (post-washout) due to worsening of their renal status while on calcium acetate. The compliance of the patients during the study was found to be more than 90%. The demographic features of the treated patients are shown in Table 2. The important laboratory parameters are shown in Table 3.

Table 2: Demographic features of treated patients

Table 3: Laboratory parameters

**Serum phosphorus**

The mean serum phosphorus concentrations
showed a declining trend during the period in which the phosphate binders were taken. The mean serum phosphorus levels during the intake of lanthanum carbonate decreased from 6.50±0.27mg/dl to 4.93±0.97mg/dl, while the mean serum phosphorus levels during calcium acetate decreased from 6.87±1.34mg/dl to 5.40±1.00mg/dl and combination of both reduced mean serum phosphorus level from 6.45±1.17 to 5.00±0.47. The reduction in serum phosphorus produced by lanthanum carbonate and calcium acetate was similar. The reduction in serum phosphorus produced by lanthanum carbonate and calcium acetate was similar to the reduction in serum phosphorus produced by fixed dose combination of both drugs. The trends in serum phosphorus in the 3 groups are shown in Figure 2.

Figure 2: Trends in serum phosphorus in 3 groups

Serum calcium

The changes in mean serum calcium concentrations during treatment with lanthanum carbonate and calcium acetate showed opposing trends. Serum calcium decreased from 8.00±0.68 to 7.80±1.29mg/dl with lanthanum carbonate. Fixed dose combination of both also produced trend towards hypercalcemia (7.56±1.44 to 7.76±0.84mg/dl). Changes in serum calcium produced by these drugs were not statistically significant. The trends in serum calcium in the 3 groups are shown in Figure 3.

Figure 3: Trends in serum calcium in 3 groups

Ca X P product

The mean calcium X phosphorus product showed a declining trend during treatment with both the phosphate binders. The mean Ca X P product during treatment with lanthanum carbonate decreased from 45.48±1.68 to 38.07±1.73mg2/dl2 and during treatment with calcium acetate decreased from 52.42±10.32 to 48.63±11.63mg2/dl2 and with fixed dose combination of both the figures were 48.18±1.51mg2/dl2 and 38.81±1.23mg2/dl2 pre drug and post drug respectively. A statistically significant difference was not seen while comparing the reduction in Ca X P product produced by lanthanum carbonate and calcium acetate. When fixed dose combination of both were compared with optimum dose of either, reduction in Ca X P product was not statistically significant. The trends in Ca X P in the 3 groups are shown in Figure 4.

Figure 4: Trends in Ca X P product in 3 groups

Serum creatinine

Mean creatinine levels were stable throughout the course of treatment.

Dose

Mean dose required for achieving target serum phosphorus concentration and Ca X P product was 2000mg for lanthanum carbonate and 2668mg for calcium acetate.

Adverse events

Over the entire course of the study, adverse events were reported by 3 out of 17 of our enrolled patients. All these adverse events occurred while the patient was on lan-
thanum carbonate. All these three had abdominal discomfort and burning sensation all over the body. No adverse event was reported during the intake of calcium acetate.

**Comparative cost of treatment**

An 8 week treatment with lanthanum carbonate (Fosbait) 500mg 4 tablets a day (mean dose) costs Rs 3584. One 500mg tablet costs Rs 16. A total of 4 X 56 = 224 tablets are needed for 8 weeks of treatment. So total cost was 16 X 224 = Rs 3584. When compared to this, treatment with calcium acetate (Hypophos) 667mg 4 tablets daily (mean dose) is cheaper. One 667mg tablet costs only Rs 0.95. A total of 4 X 56 = 224 tablets are needed for 8 weeks of treatment. So total cost was 0.95 X 84 = Rs 212.8. Fixed dose combination of both costs Rs 2847.6. Total cost of treatment with lanthanum carbonate is 17 times more than treatment with the conventional drug ie calcium acetate.

**DISCUSSION**

Our study attempted to compare the efficacy and tolerability of a calcium based phosphate binder such as calcium acetate with a non calcium containing phosphate binder like lanthanum carbonate. It was seen that both the drugs were equally good phosphate binders and lowered phosphorus levels to a similar extent. It is observed that adequate control of phosphorus levels may be achieved by using considerably lower doses of calcium acetate than prescribed for Western population.

The target serum calcium levels and Ca X P product in CKD patients is 9-10mg/dl and 55mg2/dl2. A high calcium level directly correlates with degree of vascular and cardiac calcification10. We found out that calcium acetate use was associated with a statistically insignificant rise in serum calcium levels. Even though Ca X P product showed a falling trend with lanthanum, the difference in fall between the two drugs was not statistically significant.

The steady creatinine values observed during the study confirmed the stable condition of the 20 patients who completed the study. In a study by Hutchinson et al it was shown that lanthanum was superior in reducing Ca X P product and the incidence of hypercalcemia is less with the drug11. This was similar to our study but we could also infer that rise in serum calcium with calcium acetate is not statistically significant.

There were no adverse effects with calcium acetate, but with lanthanum carbonate 3 patients had adverse gastrointestinal side effects. It could not be purely attributed to lanthanum as patients were on other drugs as well. In a resource limited setting like ours where cost is an important consideration, a drug like lanthanum carbonate was found to be 17 times costlier than calcium acetate. The high cost of lanthanum takes it out of reach of majority of our patients.

**Limitations**

Dietary phosphorus intake is different in different groups and hence the lack of conformity in diet was a major issue. Sample size was also small and not adequate for achieving power of 80%. Observation period in each arm should desirably be longer to substantiate results. Further studies are required to establish whether there is a statistically significant decrease in efficacy between the two phosphate binders.

**CONCLUSION**

Lanthanum carbonate and calcium acetate are equally good phosphate binders with comparable efficacy in reducing phosphorus levels. Though lanthanum carbonate produced a falling trend in Ca X P product as well as serum calcium, the rise in above two parameters with calcium acetate was not significant either. This is very important in a resource limited setting like ours as lanthanum carbonate is 17 times costlier than calcium acetate. More studies are required in future to establish if there is any difference in efficacy between the two phosphate binders.

**REFERENCES**


ACKNOWLEDGEMENTS
Nil.