Available online on 15.07.2016 at http://jddtonline.info
Journal of Drug Delivery and Therapeutics
An International Peer Reviewed Journal
Open access to Pharmaceutical and Medical research

RESEARCH ARTICLE

EFFICACY AND SAFETY OF SEVELAMER CARBONATE VERSUS CALCIUM ACETATE IN PATIENTS WITH CHRONIC RENAL DISEASE ON DIALYSIS

Akanksha G. William*[1], Jasleen Narula[2], Dinesh K. Badyal[3], Basant Pawar[4]

***Author for correspondence:**

[1]Dr. Akanksha Grace William

Clinical Pharmacologist and Research Associate,

Christian Medical College (CMC) & Hospital, Ludhiana-141008

Phone: 8558827927, Email: akankshawilliam@gmail.com

Contribution: Conceived and carried out the study, followed up the patients, gathered the results, wrote the manuscript and defended the study with Institute Ethics Committee.

Co-Authors Details:

[2]Dr. Jasleen Narula,

Professor, Department of Pharmacology, Christian Medical College (CMC) & Hospital, Ludhiana-141008

Current affiliation:

Dr Jasleen Kaur, Professor and Head, Department of Pharmacology, GGS Medical College, Faridkot, 151203.

Phone: 9814917365, Email: narulajasleen03@gmail.com

Contribution: supervised the study and helped in the preparation of the manuscript.

[3]Dr. Dinesh Badyal,

Professor and Head

Department of Pharmacology, Christian Medical College (CMC) & Hospital, Ludhiana-141008

Phone: +91-9815333776, Email: dineshbadyal@gmail.com

Contribution: supervised the study.

[4]Dr. Basant Pawar,

Professor and Head, Department of Nephrology,

Christian Medical College (CMC) & Hospital, Ludhiana-141008

Phone: +91-9814917365, Email: basant.pawar@gmail.com

Currently affiliation:

Basant Pawar MD, DM, DND, FRACP, FISN., Senior specialist in Renal Medicine

Alice Springs Hospital, Alice Springs NT Australia 0871.

Contribution: supervised the study, helped in planning the study, helped in obtaining consent and patient selection for the study.

Received 04 June 2016; Review Completed 22 June 2016; Accepted 22 June 2016, Available online 15 July 2016

ABSTRACT

Purpose: Powdered sevelamer carbonate is a new phosphate binder with unproven therapeutic benefit in Indian population. Hence, we aimed to compare its efficacy and safety with calcium acetate in patients with Chronic Renal Disease on hemodialysis.
Methods: This was a randomized, prospective, cross over and open labeled study, conducted in the Department of Nephrology, Christian Medical College and Hospital, Ludhiana. Fifty patients were included in data analysis and were randomization into two groups, A & B. Group A patients first received powdered sevelamer carbonate for 4 weeks (n= 25) followed by 1 week of washout and calcium acetate for the next 4 weeks (n=25). Group B: vice-versa. Serum phosphorus, calcium, C-reactive protein (CRP), total cholesterol, triglycerides (TGs) and low density lipoprotein (LDL) levels were performed before and after each drug was administered.
Results: Mean baseline serum phosphorus and calcium phosphorus product in group A, reduced from 6.59 ± 0.31mg/dl & 53.18 ± 2.5mg^2/dl^2 to 5.26± 0.33mg/dl & 44.76mg^2/dl^2 respectively. In group B these reduced from 6.42±0.33 mg/dl & 52.06±2.5 mg^2/dl^2 to 5.44±0.3 mg/dl & 44.5mg^2/dl^2 respectively. The reduction in these values in both groups was statistically significant (p<0.05). Reductions in serum CRP, total cholesterol, triglycerides and low density lipoprotein (LDL) levels were not statistically significant in either group.
Conclusion: Powdered sevelamer carbonate and calcium acetate are equally efficacious with no serious adverse effects. Both the drugs were well tolerated. Hence, powdered sevelamer carbonate can be a useful alternate to calcium based binders in Indian patients.
Keywords: powdered sevelamer carbonate, calcium acetate

 ISSN: 2250-1177 CODEN (USA): JDDTAO

INTRODUCTION:

Hyperphosphatemia is a debilitating consequence of chronic renal disease (CRD). Its long term complications are renal osteodystrophy, hyperparathyroidism, and increased cardiovascular calcification leading to increased mortality and morbidity[1–4]. It can be controlled by restricting phosphorus in the diet, oral phosphate binders (PB) and dialysis. Dietary restriction on phosphate is possible only up to a limit before it adversely affects nitrogen balance. Dialysis can remove up to 70 % of ingested phosphorus[5]. Hence, for long term phosphorus control, patients are prescribed oral PBs. Until recently calcium based PBs were the main stay of treatment but upon including lifetime cost and quality adjusted life-years gained sevelamer may gain approval[6].

Sevelamer carbonate is a non-metal oral PB also used to treat hyperphosphatemia. Its efficacy is proven in western population[6-8]. Unlike metal based oral PB, it is a cross linked polymer containing multiple amine groups. Its powdered form allows it to be sprinkled on food like salt before consumption, and may prove valuable for patients with difficulty swallowing or chewing. It binds to phosphorus in the food, making it unavailable for absorption. It is excreted in the feces. It is also shown to lower serum low density lipoprotein (LDL), triglyceride (TG), C- reactive protein (CRP) and lipids[8,9]. C- reactive protein (CRP) is an acute phase reactant. However, when it is raised for prolonged periods of time it denotes arterial inflammation. Hence, raised CRP is a biomarker for sudden deaths in CRD patients[10–12]. Phosphate binders (PB) are used to control serum phosphorus. Powdered formulation has an advantage of mixing well with food *before* consumption, hence preventing absorption. In Indian population few studies have been done comparing sevelamer with calcium based PBs[13,14]. However, these studies used hydrochloride form that has its own disadvantages. They were done over a short period in small patient population. Furthermore, there has been no study in India that has compared *powdered* form of sevelamer carbonate to calcium acetate. Hence, this study was designed to study the effect of powdered sevelamer carbonate with calcium acetate in patients with chronic renal disease on hemodialysis.

MATERIALS AND METHODS:

This was a prospective, open labeled, cross-over, comparative and randomized study, conducted in patients undergoing maintenance hemodialysis (for ≥6 weeks) in the Department of Nephrology, Christian Medical College (CMC) and Hospital, Ludhiana. The study was conducted after obtaining approval of the Institute Research Committee. The study design was explained to all the patients. All patients were provided with study information and written informed consent was obtained before any intervention.

Patients with chronic renal disease (CRD) of both genders, over 18 years of age, undergoing hemodialysis were included. Those with hypercalcaemia, severe GI disorder, any malignancy, breast feeding women and known hypersensitivity to phosphate binders were excluded.

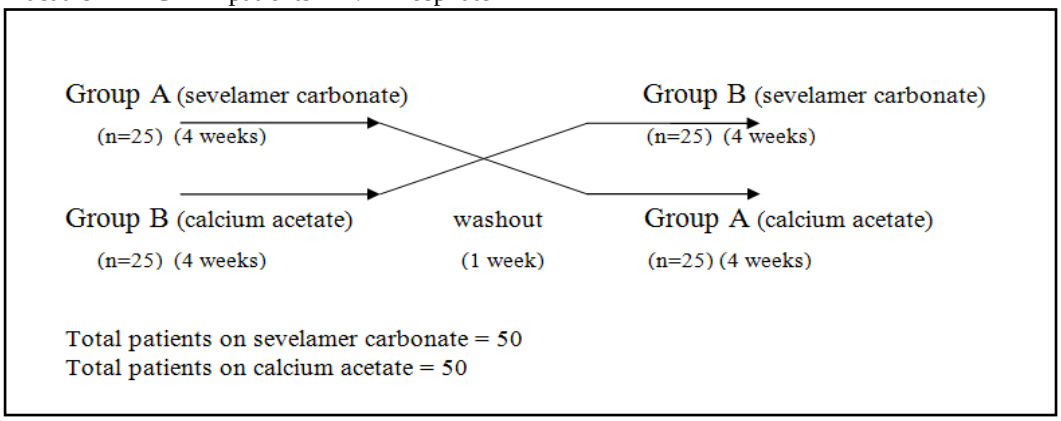


Figure: 1 Study design

All patients were given a washout period of 1 week during which no PB was administered. At the end of 1 week all biochemical parameters were done. If the serum phosphorus level was greater than 4.5 mg/dl the patients was randomized in either group (A or B). Randomization was done according to a computer generated random number table. Group A patients were given powdered sevelamer carbonate in a dose of 400 mgs three times a day for the first 4 weeks (n= 25). They were asked to sprinkle it on food like salt and stir well. At the end of 4 weeks all biochemical parameters were repeated. This was followed by one week of washout period at the end of which all biochemical parameters repeated, followed by tablet calcium acetate (667mgs) three times a day for the next 4 weeks (n=25). At the end of 4 weeks all biochemical parameters were repeated again. The calcium acetate tablets were consumed with food or immediately after finishing the meal. The same procedure was repeated with group B patients but they were given tablet calcium acetate for the first 4 weeks followed by powdered sevelamer carbonate for the next 4 weeks. Figure 1.

 ISSN: 2250-1177 CODEN (USA): JDDTAO

The biochemical parameters included serum phosphorus, calcium, LDL, TG, Cholesterol and CRP. All data was recorded in the patient particular sheet. Unpaired t-test was done to determine if there was a statistically significant difference in the biochemical values after both washouts in the two groups. Since this was insignificant (p=0.711), it was decided to combine pre drug data. At the end of the study, data of 50 patients (25+25) who had taken powdered sevelamer carbonate was collected, and done similarly for patients who had taken calcium acetate. The total duration of the study was 10 weeks. The study design is depicted in Figure1. Consort chart is given in Figure 2.

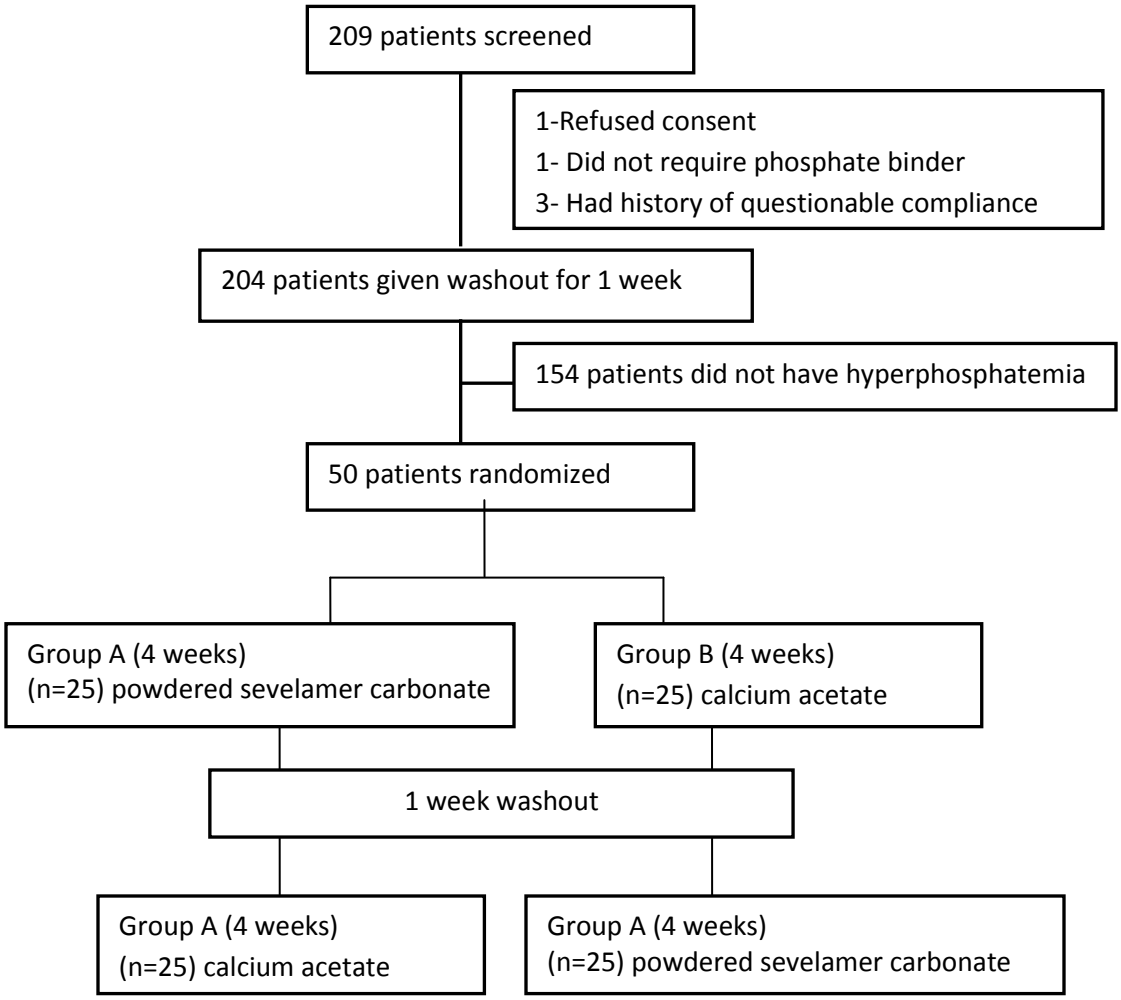


Figure: 2. Consort diagram.

Adverse Drug Reaction (ADR) recording was also done at every follow up and hemodialysis visit for each patient. Both the study drugs (powdered sevelamer carbonate and calcium acetate) along with the investigations were funded by Emcure Pharmaceutical Ltd., Pune, India. The patients did not bear any additional cost by participating in the study. The company had no role in the study design or evaluating the study results or the preparation of this manuscript.

Statistical analysis:

To compare Sevelamer carbonate group with Calcium acetate group, a sample of 100 patients was required (n=50 each group) to achieve 80% power. All statistical tests used for comparisons of the 2 treatment periods were 2 tailed, with probability value of less than 0.05 required for significance. Sample size was calculated using OpenEpi version 3.0.1. The values are expressed as mean ± SD (standard deviation). SPSS 21.0, Armonk NY: IBM corp. was used to analyze the data.

RESULTS

We screened 209 patients, out of which 159 were excluded: 154 due to low serum phosphorus after the washout period, 1 patient refused to participate, 3 patients had history of questionable compliance with medication and 1 patient had no requirement for phosphate binder.

Fifty patients who met the inclusion criteria were included in the study. Out of these 31 were men. The

mean age and demographic profile of patients were comparable between the groups. It is given in Table 1.

Table 1: Baseline demographic characteristics

Baseline characteristics	Group A(n=50)	Group B (n=50)
Age (years)	52.08	47.64
Gender (M/F)	15:10	16:9
Etiology		
Hypertension (mm Hg)	16	17
Diabetes Mellitus	8	8
Polycystic kidney disease (PCKD)	1	0
***p<0.05 as compared to Group A**		

At 0 week, between group A and B, mean serum phosphorus, calcium, calcium phosphorus product, serum cholesterol, TG, LDL and CRP were comparable. At the end of 4 weeks, reduction in serum phosphorus (Figure 3) and calcium phosphorus product (Figure 4) was significant in both the groups when compared to baseline ($p<0.05$). However, this significance was lost when comparison was made in-between the two groups ($p>0.05$). There was no significant change in calcium, LDL, TG, CRP level at 4 weeks and when comparison was made between groups A and B($p>0.05$). The baseline and 4 week values are given in Table 2.

Table 2: Baseline and 4 week biochemical investigations results

Parameter (mg/dl)	Group A		Group B	
	0 week	4 weeks	0 week	4 weeks
Serum Phosphorus	6.65±2.11	5.26±2.22*	6.42±2.35	5.44±2.19*
Serum Calcium	8.1±0.13	8.5±0.13	8.2±0.22	8.2±1.03
Calcium Phosphorus Product (mg^2/dl^2)	54.18±17.23	44.44±18.47*	52.06±17.95	44.54±18.31*
Total Cholesterol	122.89±34.33	122.950±37.64	126.98±39.38	122.62±35.38
LDL	66.81±25.59	56.82±27.67	72.76±33.34	69.50±28.88
TG	124.77±72.16	116.27±57.72	113.02±59.52	117.96±72.67
CRP	2.11±5275	2.49±5.84	2.74±4.85	2.38±3.44

*$p<0.05$ compared to 0 week
# $p<0.05$ compared to group A

Figure 3. Phosphorus level in both groups at 0 and 4 weeks

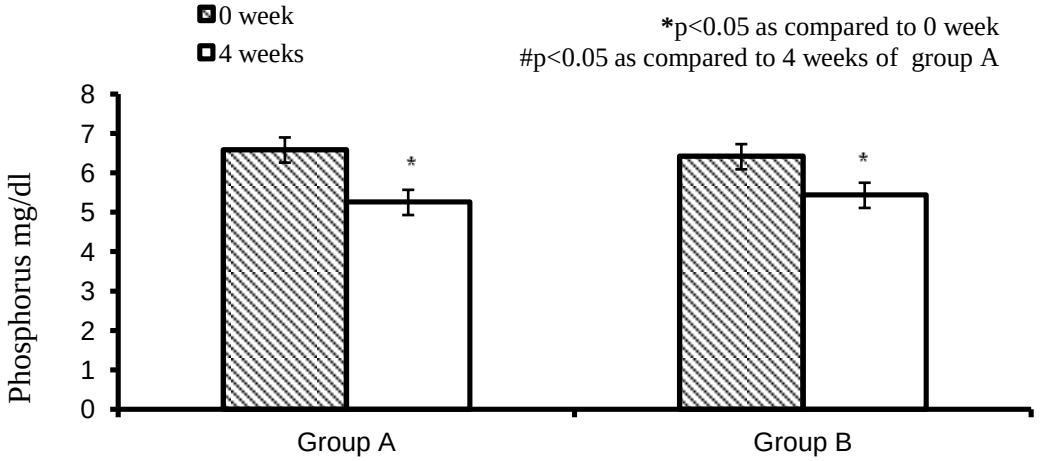
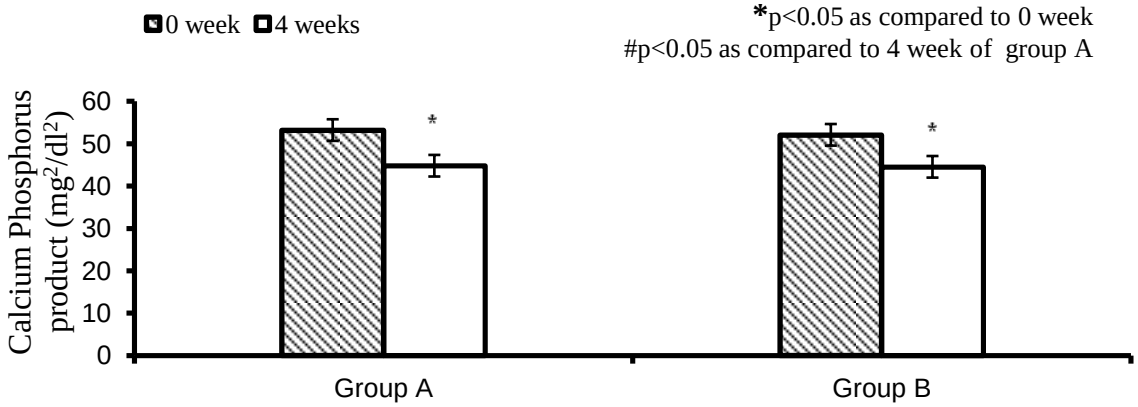


Figure 4. Calcium Phosphorus product in both groups at 0 and 4 weeks



Safety profile

In this study diarrhoea was the only adverse effect reported by two patients in group A. First patient was given de-challenge and a re-challenge. He reported diarrhoea again after re-challenge and was taken off the study. It was 8 on Naranjo's scale. Second patient in the same group also reported diarrhoea which was self-limiting. No adverse effects were reported in group B. In the current study both PB were equally safe since there was no hypercalcaemia seen in calcium acetate arm or hypocalcaemia seen in sevelamer carbonate arm.

DISCUSSION:

Both powdered sevelamer carbonate and calcium acetate were equally efficacious in reducing hyperphosphatemia in patients with chronic renal disease (CRD). Baseline demographic profile; age, gender and aetiology; were comparable in both groups. The mean age of patients in this study was similar to earlier studies done in India but lower than that of USA[11-13]. It strengthens the evidence that CRD affects younger population in India[16,17]. In this study number of men was higher; although this disease is known to affect women more often than men. This trend is also observed in other studies in India[17,18] The most common etiology of CRD reported from India is diabetic nephropathy followed closely by systemic hypertension; although in this study it was systemic hypertension. This data further adds to the need of studies that will elucidate age, gender distribution and etiology of CRD specifically for India.

In this study, serum phosphorus was lowered equally by both PB. There was no statistical difference when phosphorus lowering was compared in between the two groups. Various international studies comparing these PB in adult population have also deduced the findings of this study[19,20] An Indian study also supports this finding although the cohort were pediatric population[13,14].

Reduction in calcium phosphorus product was significant in both groups although this significance was lost in intergroup analysis. This finding is supported by the Indian study done on pediatric age group[14]. It however, had limited sample size and was not done in adults. The same results were reflected in other international studies also done in both pediatric [20] and adult population[21].

Although sevelamer has shown beneficial effects in lowering cholesterol, LDL, TG, current study did not show any significant reduction in either group.[22] It could perhaps be due to the short duration of the study. CRP is an acute phase reactant, elevated CRP levels are associated with increased cardiovascular mortality in CRD[23]. This study did not deduce significant reduction in CRP levels in either group. To the best of our knowledge, no study in Indian setup has compared CRP as primary or secondary outcome.

Safety: Both PBs were well tolerated as seen in other studis[24] although only one case of hypercalcaemia has been reported from a long term study[25]. In this study however, the adverse events were less as compared to these earlier studies. Both sevelamer carbonate and calcium acetate are well tolerated drugs.

CONCLUSION:

Hence, from the data of this study we conclude that powdered sevelamer carbonate does not reduce cholesterol levels significantly when given for 4 weeks (short term). Both powdered sevelamer carbonate and calcium acetate are equally effective in lowering serum phosphorus. Both are well tolerated. Hence, it can be used as an alternative to calcium based PBs in lowering phosphorus levels in Indian population. Moreover, the powdered form has its own advantages with patients who have difficulty chewing and swallowing.

Compliance with Ethical Standards:

This study was performed in accordance with ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. The study was approved by the institute research and ethics committees.

Funding: This study was funded by Emcure Pharmaceuticals Private Limited, Pune, India. The grant

was given to the institute and not to any individual involved in the study.

Conflict of Interest: All authors declares no conflict of interest

REFERENCES

1. Cayir A, Kosan C, Growth hormone therapy in children with chronic renal failure, Eurasian J Med, 2015, 47(1), 62–5.
2. Reddy YN, Sundaram V, Abraham G, Nagarajan P, Reddy YN, Optimal management of hyperphosphatemia in end-stage renal disease: an Indian perspective, Int J Nephrol Renov Dis, 2014,7,391–9.
3. Bureo JC, Arévalo JC, Antón J, Adrados G, Jiménez Morales JL, Robles NR, et al, Prevalence of secondary hyperparathyroidism in patients with stage 3 and 4 chronic kidney disease seen in internal medicine, Endocrinol Nutr, 2015, 62(7):300-5
4. Wang S, Qin L, Wu T, Deng B, Sun Y, Hu D, et al, Elevated cardiac markers in chronic kidney disease as a consequence of hyperphosphatemia-induced cardiac myocyte injury, Med Sci Monit, 2014, 20, 2043–53.
5. Waheed AA, Pedraza F, Lenz O, Isakova T, Phosphate control in end-stage renal disease: barriers and opportunities, Nephrol Dial Transplant, 2013, 28(12), 2961–8.
6. Nguyen HV, Bose S, Finkelstein E, Incremental cost-utility of sevelamer relative to calcium carbonate for treatment of hyperphosphatemia among pre-dialysis chronic kidney disease patients, BMC Nephrol, 2016,17(1), 45.
7. Chen N, Wu X, Ding X, Mei C, Fu P, Jiang G, et al, Sevelamer carbonate lowers serum phosphorus effectively in haemodialysis patients: a randomized, double-blind, placebo-controlled, dose-titration study, Nephrol Dial Transplant, 2014, 29(1), 152–60.
8. Sandler NG, Zhang X, Bosch RJ, Funderburg NT, Choi AI, Robinson JK, et al, Sevelamer does not decrease lipopolysaccharide or soluble CD14 levels but decreases soluble tissue factor, low-density lipoprotein (LDL) cholesterol, and oxidized LDL cholesterol levels in individuals with untreated HIV infection, J Infect Dis, 2014, 210(10),1549–54.
9. Rastogi A, Sevelamer revisited: pleiotropic effects on endothelial and cardiovascular risk factors in chronic kidney disease and end-stage renal disease, Ther Adv Cardiovasc Dis, 2013, 7(6),322–42.
10. Cai C, Hua W, Ding L-G, Wang J, Chen K-P, Yang X-W, et al, High sensitivity C-reactive protein and cardfiac resynchronization therapy in patients with advanced heart failure, J Geriatr Cardiol JGC, 2014 , 11(4), 296–302.
11. Nakata T, Hashimoto A, Moroi M, Tamaki N, Nishimura T, Hasebe N, et al, Sudden death prediction by C-reactive protein, electrocardiographic findings, and myocardial fatty acid uptake in haemodialysis patients: analysis of a multicentre prospective cohort sub-study, Eur Heart J Cardiovasc Imaging, 2015 Dec 27. pii: jev294. [Epub ahead of print]
12. Genovesi S, Valsecchi MG, Rossi E, Pogliani D, Acquistapace I, De Cristofaro V, et al, Sudden death and associated factors in a historical cohort of chronic haemodialysis patients, Nephrol Dial Transplant , 2009 , 24(8):2529–36.
13. Abraham G, Saxena S, Chafekar D, Shetty M, Reddy YNV, Kher V, et al, Sevelamer carbonate experience in Indian end stage renal disease patients, Indian J Nephrol, 2012;22(3):189.
14. Gulati A, Sridhar V, Bose T, Hari P, Bagga A, Short-term efficacy of sevelamer versus calcium acetate in patients with chronic kidney disease stage 3-4, Int Urol Nephrol, 2010, 42(4),1055–62.
15. Foster MC, Hwang S-J, Massaro JM, Jacques PF, Fox CS, Chu AY, Lifestyle Factors and Indices of Kidney Function in the Framingham Heart Study, Am J Nephrol, 2015, 20;41(4–5):267–74.
16. Anupama YJ, Uma G, Prevalence of chronic kidney disease among adults in a rural community in South India: Results from the kidney disease screening (KIDS) project, Indian J Nephrol, 2014;24(4):214–21.
17. Rajapurkar MM, John GT, Kirpalani AL, Abraham G, Agarwal SK, Almeida AF, et al, What do we know about chronic kidney disease in India: first report of the Indian CKD registry, BMC Nephrol, 2012;13:10.
18. Mani MK, Experience with a program for prevention of chronic renal failure in India, Kidney Int Suppl. 2005, (94):S75-78.
19. Evenepoel P, Selgas R, Caputo F, Foggensteiner L, Heaf JG, Ortiz A, et al, Efficacy and safety of sevelamer hydrochloride and calcium acetate in patients on peritoneal dialysis, Nephrol Dial Transplant , 2009, 24(1):278–85.
20. Pieper A-K, Haffner D, Hoppe B, Dittrich K, Offner G, Bonzel K-E, et al, A randomized crossover trial comparing sevelamer with calcium acetate in children with CKD, Am J Kidney Dis, 2006,47(4):625–35.
21. Tonelli M, Wiebe N, Culleton B, Lee H, Klarenbach S, Shrive F, et al, Systematic review of the clinical efficacy and safety of sevelamer in dialysis patients, Nephrol Dial Transplant, 2007, 22(10):2856–66.
22. Silbernagel G, Baumgartner I, Wanner C, März W, Toward individualized cholesterol-lowering treatment in end-stage renal disease, J Ren Nutr, 2014, 24(2):65–71.
23. Li W-J, Chen X-M, Nie X-Y, Zhang J, Cheng Y-J, Lin X-X, et al, Cardiac troponin and C-reactive protein for predicting all-cause and cardiovascular mortality in patients with chronic kidney disease: A meta-analysis. Clin São Paulo Braz, 2015,70(4):301–11.
24. Yusuf AA, Weinhandl ED, St Peter WL, Comparative effectiveness of calcium acetate and sevelamer on clinical outcomes in elderly hemodialysis patients enrolled in Medicare part D, Am J Kidney Dis, 2014, 64(1):95–103.
25. de Francisco ALM, Leidig M, Covic AC, Ketteler M, Benedyk-Lorens E, Mircescu GM, et al, Evaluation of calcium acetate/magnesium carbonate as a phosphate binder compared with sevelamer hydrochloride in haemodialysis patients: a controlled randomized study (CALMAG study) assessing efficacy and tolerability, Nephrol Dial Transplant, 2010, 25(11):3707–17.

How to cite this article:

William AG, Narula J, Badyal DK, Pawar B, Efficacy and safety of Sevelamer carbonate versus Calcium acetate in patients with chronic renal disease on dialysis, Journal of Drug Delivery & Therapeutics. 2016; 6(4):1-6

 ISSN: 2250-1177 CODEN (USA): JDDTAO