

The treatment of mineral metabolism disorders: a recent approach with new compounds and a proposed algorithm

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■ INTRODUCTION

During the last few years there have been major developments in the management of bone and mineral disorders in chronic kidney disease (CKD) stage 5 haemodialysis patients. The knowledge that these bone and mineral abnormalities impact heavily on morbidity and mortality means the practicing nephrologist must pay major attention to control these alterations. In addition, new compounds have been developed for the control of hyperphosphataemia and for the treatment of secondary hyperparathyroidism (SHPT). Many practical questions have been raised by nephrologists on the use of non-calcium containing phosphate binders. Furthermore, the use of the new calcimimetic agent, cinacalcet, that suppresses PTH secretion and, in contrast with the effect of active vitamin D, lowers calcium and phosphorus serum levels, brings new questions and concerns to the mind of the clinical nephrologists taking care of dialysis patients. For these reasons and due to the interactions seen with the treatment of secondary hyperparathyroidism and the control of hyperphosphataemia and *vice versa*, this editorial reviews the recent major developments in the treatment of hyperphosphataemia and secondary hyperparathyroidism. Based on published data and recommendations, a practical treatment algorithm will be proposed which combines the treatment of hyperphosphataemia and secondary

hyperparathyroidism and highlights synergies between different compounds such as sevelamer, cinacalcet and active vitamin D.

■ CONTROL OF HYPERPHOSPHATAEMIA

In recent years it has become clear that the presence of elevated serum phosphorus levels in CKD stage 5 patients is positively associated with increased mortality^{1,2}. Hyperphosphataemia and elevated calcium-phosphorus product (Ca x P) are associated with cardiovascular calcification^{3,4}; the latter an independent predictor of mortality. Several authors have now reported a strong positive association between the presence and extent of vascular calcification and cardiovascular and all cause mortality⁵⁻⁷. Raggi *et al.*⁸ reported that previous myocardial infarction, angina and known coronary artery disease were all more common in CKD stage 5 patients with extensive calcification.

Patients with stage 5 CKD have a high prevalence of hyperphosphataemia. The clinical consequences of hyperphosphataemia include SHPT with the consequent renal bone disease, extra-osseous calcification and increased mortality.

Therapeutic strategies to control phosphorus levels include dietary restrictions, dialysis and the use

of phosphate binding agents. The dietary restriction with reduction of phosphate intake is often difficult for patients to achieve and is also limited by the associated protein restriction since all proteins contain phosphate. Phosphate is also difficult to remove by dialysis. Increased dialysis length or frequency may be effective, but it is often difficult to implement due to logistical problems and poor patient acceptance. Until recently, the phosphate binders available were only aluminium or calcium based compounds. These compounds were efficacious but also associated with significant side effects. The use of aluminium-containing phosphate binders is associated with aluminium bone disease and haematological and central nervous system toxicity. The use of calcium-containing phosphate binders is associated with increased risk of hypercalcaemia and cardiovascular calcification^{3,4,6,9}. It is now known that serum calcium levels are not accurate in predicting calcium balance and burden. The excessive amount of calcium ingested from the diet and from calcium-containing binders has been associated with cardiovascular calcifications, even in the presence of normal calcium serum levels^{3,4,6,9}. The new non-calcium containing, non-metal containing and non-absorbed phosphate binder, sevelamer hydrochloride, has provided an effective way to bind phosphorus in the gut without the risks of hypercalcaemia, soft tissue or vascular calcifications, or heavy metal accumulation.

Sevelamer hydrochloride has been widely studied and shown to be effective in reducing phosphorus levels and Ca x P without causing hypercalcaemia and soft tissue calcification in the stage 5 CKD population on haemodialysis. Moreover, sevelamer induces a reduction in total cholesterol and low density lipoprotein (LDL) cholesterol. This compound is very well tolerated with very few side effects. The more frequently reported adverse effects are diarrhoea, constipation, dyspepsia, nausea and vomiting.

Chertow *et al.*⁹ reported the results of a randomised parallel design clinical trial comparing sevelamer with the calcium-based phosphorus binders in 200 haemodialysis patients. Sevelamer and calcium-based compounds provided similar control of serum phosphorus and Ca x P. Adherence to the prescribed dose of binder in the sevelamer and the calcium-containing binders groups was similar; 86 vs. 80%, respectively. The group treated with sevelamer received an average binder dose of 6.5 ± 2.9 g per day

and the group treated with calcium based binders 4.3 ± 1.9 g per day (4.6 g and 3.9 g per day of calcium acetate or calcium carbonate, respectively). The calcium-based group had more frequent episodes of hypercalcaemia than the sevelamer group; 43% and 17%, respectively. Suppression of intact parathyroid hormone secretion (iPTH) below the 150 to 300 pg/ml range was more common at the end of the study in the calcium-based binders group; 57 vs. 30%, despite the protocol specified reduction or cessation of vitamin D for iPTH below 150 pg/ml. Twelve percent of subjects in the calcium group required rescue therapy with aluminium containing binders for a calcium-phosphorus product above $72 \text{ mg}_2/\text{dL}^2$, compared to 4% of the patients in the sevelamer group. The total cholesterol and LDL cholesterol decreased significantly in the sevelamer treated group compared to a non change in the calcium binders group. Of relevance, the electron beam computerised tomography (EBCT) performed at the beginning of the study detected a prevalence of coronary artery calcification of 83% and aortic calcification of 80% of the study patients. There was a significant progression of the coronary artery and aortic calcification EBCT score, at week 26 and 52, in the calcium-containing binders treated group, despite the use of an average dose of calcium carbonate of only 3.9 g per day (1.56 g of elemental calcium) in fact, the actual K/DOQI recommended upper limit. There was no significant progression in the sevelamer treated group.

The high prevalence of vascular calcification seen in the dialysis population in the Chertow study⁹ has been confirmed by other reports and is of major concern due to the positive association between the presence and severity of calcification and mortality in this population. There is also some evidence that most of the patients develop vascular calcifications while on haemodialysis treatment. In fact, a report from Spiegel *et al.*¹⁰ revealed that only 34% of patients with advanced chronic kidney disease starting dialysis had coronary artery calcifications scores that placed them above the 90th percentile for age and sex. In this same population of patients initiating dialysis, 109 patients underwent baseline and at least one additional measurement of coronary artery calcification¹¹. At baseline, 37% of the patients that underwent treatment with sevelamer and 31% of the patients that underwent treatment with calcium-based binders had no evidence of calcification. The authors report that no patients with a zero coronary calcium

score progressed to a coronary artery calcium score > 30 , using EBCT, in a 18 months period of time. Patients already having a coronary artery calcium score > 30 at baseline progressed during the time of the study in both arms. The patients treated with calcium-based binders showed a more rapid and severe progression than those receiving sevelamer. The authors conclude that patients new to dialysis with no evidence of coronary calcification showed little evidence of disease development over a period of 18 months independent of the phosphate binder used. While patients with even little evidence of coronary calcification progress with both binders, the group treated with calcium-based binders has a much more severe progression than the patients treated with sevelamer¹¹. This study confirms without a doubt the importance of the National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines for bone metabolism and disease in chronic kidney disease, recommending that calcium based binders should be avoided in patients with evidence of severe calcification.

A three-year trial involving more than 2,100 patients compared the difference in mortality and morbidity outcomes for patients receiving sevelamer and those receiving calcium-containing phosphate binders¹². This was the largest outcomes study ever conducted in the haemodialysis population. This study showed that the patients treated with sevelamer experienced a reduction of 9% in the risk of death from all causes when compared to the patients treated with calcium-based phosphate binders, statistically not significant ($p=0.3$). The patients aged 65 years old or more were 22% less likely to die when treated with sevelamer compared to treatment with calcium-based binders ($p=0.03$). Also, patients treated with sevelamer for more than two years had a 34% reduction of the mortality risk for all causes compared to those treated with calcium-containing binders ($p=0.02$). However pre-established analysis of patients age 65 years old or more who were treated with sevelamer for more than two years presented a mortality risk reduction of 54% when compared to those treated with calcium-containing compounds ($p=0.0009$).

In a prospective, open label study¹³ Block GA *et al.* found that in 127 patients incident to dialysis treatment, randomised into treatment with sevelamer or calcium-containing binders, the mortality was lower

for those treated with sevelamer after a median 44 months of follow-up. The survival benefit observed with sevelamer treatment persisted after full multivariate adjustment.

The current K/DOQI clinical practice guidelines for bone metabolism and disease state that the clinical use of sevelamer is recommended as an important first-line treatment option for the control of hyperphosphatemia and/or an elevated Ca x P product in stage 5 CKD patients¹⁴. The use of calcium-containing phosphate binders is limited to a maximum of 1.5 g per day of elemental calcium to achieve control of hyperphosphataemia. Patients with hypercalcaemia (corrected serum calcium > 10.2 mg/dL), or with plasma iPTH levels below 150 pg/mL on two consecutive measurements, or with severe vascular calcification and/or other soft tissue calcification, should be treated with sevelamer.

■ TREATMENT OF SECONDARY HYPERPARATHYROIDISM

The use of calcitriol and other active vitamin D analogues has been very helpful for the treatment of secondary hyperparathyroidism, suppressing the secretion of parathyroid hormone (PTH). Frequent secondary side effects and morbidity has been associated with active vitamin D treatment. Failure to control properly SHPT is frequent due to this narrow therapeutic window. The most common secondary effects are hypercalcaemia, hyperphosphatemia, increased Ca x P and the development of soft tissue calcifications.

The new compound cinacalcet is a calcimimetic agent that modulates the calcium sensing receptor increasing its sensitivity to circulating ionized calcium and therefore making it more responsive to the calcium suppressive effect on PTH secretion. In clinical trials involving SHPT patients, cinacalcet has been shown to efficiently decrease PTH levels but also to have the beneficial effect of decreasing the calcium and phosphorus serum levels with a concomitant decrease in the Ca x P.

Block GA *et al.* presented the combined results of two identical, randomised, multicentre, double blind, placebo controlled studies¹⁵. Haemodialysis patients

with SHPT not controlled despite conventional treatment with vitamin D analogues were randomised into 26 weeks of cinacalcet treatment ($n = 371$) or placebo ($n = 370$) in addition to conventional treatment. Of note is that 66% and 67% of the patients were being treated with vitamin D in the cinacalcet group and placebo group, respectively, suggesting that these patients were not controlled despite conventional therapy. The initial dose of cinacalcet was 30 mg a day titrated up to 180 mg a day in order to obtain suppression of iPTH to values ≤ 250 pg/ml. The basal levels of iPTH were 643 ± 18 pg/ml in the cinacalcet group and 642 ± 19 pg/ml in the placebo group. In 40% of the cinacalcet treated patients there was a suppression of the iPTH levels to a mean value below 250 pg/ml compared to 5% of the placebo group. During the maintenance phase there was a decrease in the iPTH levels of 43% from the baseline compared to an increase of 9% in the patients taking placebo. The treatment with cinacalcet was associated with a reduction of calcium and phosphorus serum levels 6.4% and 8.4%, respectively, with no change in the placebo group. The mean dose of phosphate binders and vitamin D was not different between groups.

The cinacalcet treatment safety was well evident in this study. The adverse events more frequently reported in the cinacalcet compared to placebo treated patients were nausea (32% vs. 19%, respectively) and vomiting (30% vs. 16%, respectively). These gastrointestinal adverse events were usually mild to moderate and of limited duration. Less than 5% of the patients on cinacalcet and less than 1% on placebo were withdrawn from the study due to nausea and vomiting. The incidence of hypocalcaemia defined as a corrected serum calcium level of less than 7.5 mg/dl at least in two consecutive measurements occurred in 5% of cinacalcet treated patients and in 1% of the placebo patients. The hypocalcaemic episodes were transient, rarely associated with symptoms and resolved with management of phosphate binders and/or vitamin D analogues.

The same efficacy and safety have now been documented also in long-term studies up to 4 years¹⁶⁻¹⁸.

A *post hoc* analysis of the combined results of three 26-week, placebo-controlled, phase III studies evaluating the efficacy and safety of a once-daily dose of cinacalcet for the treatment of SHPT demonstrat-

ed the efficacy of therapy was independent of disease severity evaluated by PTH levels¹⁹.

Treatment with cinacalcet not only improved the ability of patients to achieve their K/DOQI targets but also their ability to maintain these targets²⁰. Seventy-one percent of cinacalcet-treated patients were able to achieve their iPTH target after 6 months of cinacalcet treatment. Of the group who achieved their target at 6 months, 82% also maintained their iPTH target after 1 year. In contrast, in the standard care group, 12% of patients achieved their iPTH target, with 53% of this group maintaining their iPTH within the target range after 1 year.

A study compared a cinacalcet-based regimen with the best unrestricted conventional care (vitamin D and phosphate binders) for achieving the stringent targets proposed by the K/DOQI²¹. In this "Open-Label, Randomized Study Using Cinacalcet To Improve Achievement of K/DOQI Targets in Patients with ESRD" (OPTIMA), haemodialysis patients with poorly controlled SHPT were randomised to receive conventional care ($n=184$) or a cinacalcet based regimen ($n=368$) that includes vitamin D and phosphate binders, in which the doses of cinacalcet, vitamin D sterols, and phosphate binders were subsequently adjusted during a 16 week dose-optimisation phase, using an algorithm proposal. The theory behind this algorithm was to allow cinacalcet to be administered with lower doses of active vitamin D maintaining the same suppression of iPTH secretion but with an optimal effect in the reduction of the phosphorus serum levels and Ca x P. The cinacalcet-based regimen was significantly more effective than conventional care in bringing patients to target for PTH (71% vs. 22%; $p<0.001$, respectively), Ca x P (77% vs. 58%; $p<0.001$), calcium (76% vs. 33%; $p<0.001$), phosphorus (63% vs. 50%; $p<0.002$), and the combined target PTH and Ca x P (59% vs. 16%, $p<0.001$). The effect on phosphorus levels of cinacalcet is only due to a reduction of bone turnover in patients with secondary hyperparathyroidism and not in phosphorus intestinal absorption, therefore these patients still require effective phosphate binding therapy. In patients receiving active vitamin D at baseline there was a 22% reduction in the dosage administered. Achievement of targets was greatest in patients with less severe disease (iPTH range 300 to 500 pg/mL) who required lower cinacalcet doses (median=30 mg/day).

This study definitely validated the rationale, the value and usefulness of the part of the algorithm dealing with SHPT proposed in this editorial and adapted from a previous publication by Cunningham *et al.*²².

In a *post hoc* analysis the data on the incidence of parathyroidectomy, fracture, hospitalisation and mortality were analysed in a population of CKD stage 5 haemodialysis patients with SHPT treated with cinacalcet in addition to conventional therapy with vitamin D and phosphate binders (n=697) compared to treatment with placebo and conventional therapy (n=487)²³. There was a significant risk reduction in parathyroidectomy, fracture and hospitalisation due to cardiovascular disease for the patients in the cinacalcet group as compared to the placebo group.

The calcimimetic agent cinacalcet, in synergy with phosphate binders and eventually Vitamin D, is a very new and innovative compound that meets a previous therapeutic need for the CKD stage 5 dialysis patients with secondary hyperparathyroidism.

CONCLUSION

In view of the presented data, arguments and previously published recommendations for the treatment of bone and mineral disorders I propose the use of the following therapeutic algorithm (Figure 1) to control two common disorders seen in stage 5 CKD dialysis patients: hyperphosphataemia and secondary hyperparathyroidism.

The optimisation of synergies observed with the combined use of cinacalcet and sevelamer will certainly be very helpful in controlling the mineral and bone disorders seen in this population and improving outcomes.

Conflict of interest statement.

Prof. Frazão is a scientific consultant for Amgen (Portugal) and a member of the Cinacalcet European Advisory Board. He is also a scientific consultant for Genzyme (Portugal) and a member of the Hectero Global Advisory Board. He has also served as a member of the Abbott International Advisory Board.

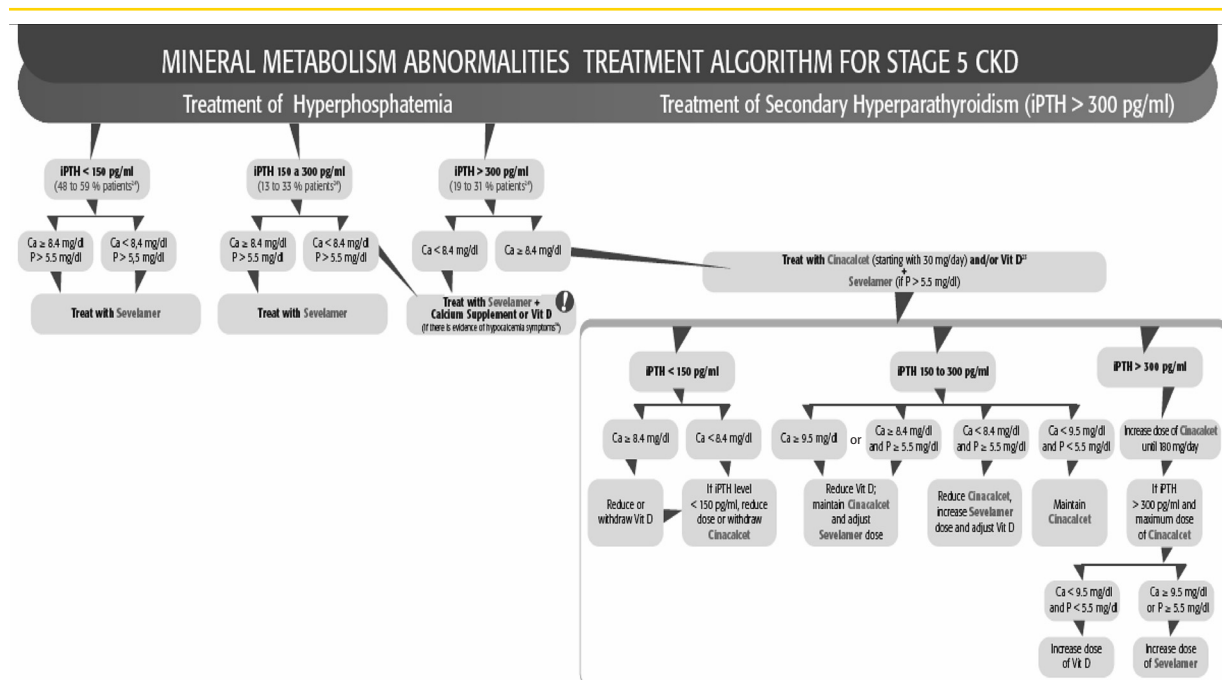


Figure 1

Treatment algorithm combining the treatment of hyperphosphataemia and secondary hyperparathyroidism. Corrected calcium values should be considered. According to K/DOQI guidelines the dose of elemental calcium administered as phosphate binders should not be superior to 1.5 g/day¹⁴.

⚠ Doses of elemental calcium under 1.5 g/day were associated with vascular and soft tissue calcification risk⁹.

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