Serum Phosphate Control: New Developments

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Phosphorus control remains a challenge for the nephrologist since hyperphosphatemia has obvious clinical importance. Consequences of inadequately controlled serum phosphorus are metastatic calcifications and renal bone disease both responsible for a significant morbidity (1,2).

To prevent hyperphosphatemia, most patients with end-stage renal failure require an exogenous phosphate binder. In the past, aluminium-containing phosphate binding agents were most widely used. The systemic absorption of aluminium over time (0.04% - 0.2%) (3) however, may lead to the development of the so-called aluminum-related bone diseases (either osteomalacia or adynamic bone), dementia, and more subtle disorders at the level of the parathyroid gland, hematopoiesis, and myopathy (4,5).

In the 1980s and 1990s calcium- (mainly the carbonate form) and to a less extent magnesium salts (6) largely replaced the aluminium-based phosphate binders. Being less effective than aluminium however, large daily doses of calcium are often required leading to a positive calcium balance and hypercalcaemia, concerns that recently have been justified by the observation that in dialysis patients both coronary (7) and aortic calcifications (8) are, amongst others, related to the total calcium dose (9). Patients receiving vitamin d replacement in combination with calcium, and others having low bone turn-over rates (adynamic bone disease) have been shown to be at increased risk for metastatic calcifications (7,10,11). Based on these observations the abandonnement of calcium-containing phosphate binders has been advocated by several members of the renal community. Others (12) however, be circumspect of the putative, isolated role of calcium salts in the pathobiology of coronary artery calcification stating that several issues impugn the interpretation of the associations, such as (i) a flawed causal pathway linking calcium ingestion to intimal calcification. Here the dialysate should be scrutinized as well, (ii) the occurrence of coronary artery calcifications in patients not exposed to calcium binders. In this respect should other prevalent and severe atherogenic abnormalities in end stage renal failure (e.g. Oxidative damage to the endothelium, lipoprotein abnormalities and/or hyperhomocysteinaemia) be considerd as well, (iii) reported discrepancies between changes in divalent ion concentrations, pth level and degree of intimal calcifications. Indeed excessive cardiovascular mortality was observed decades before the introduction of calcium salts. At that time many patients received aluminium-containing phosphate binders and had hyperphosphatemia, and secondary hyperparathyroidism with hypocalcemia (13), (iv) limitations of study design. The preponderance of studies examining the relationship between calium binders and coronary artery calcifications are cross-sectional and observational.

Aiming to avoid side effects during phosphate control, alternative phosphate binders have been developed in recent years.

Recently, the potential use of polynuclear iron preparations generated substantial interest. Indeed, the solubility product of iron and phosphate is extremely low, the compound is well tolerated and effective but is still in the early stages of clinical development (14).

Polyallylamine-hydrochloride (sevelamer, renagel®) is a non-absorbed cationic, calcium- and aluminium-free polymer that binds phosphate anions through ion exchange and hydrogen binding. This class of compounds was originally developed to lower plasma lipids, and this effect is still seen with sevelamer (15). Both the compound's ability to improve lipid profiles and the fact that, in contrast to calcium-based binders, therapeutic administration of the compound does not promote elevations in serum calcium and ca x p may have contributed to the attenuation in the progression of coronary and aortic calcifications recently reported in both experimental studies and hemodialysis patients receiving sevelamer (16,17). These findings may also put the issue on the mechanisms underlying the enhancement of vascular calcifications in an new perspective. Indeed, these are still largely unknown as are the underlying etiologic and modulating factors. Classically, the disturbance of calcium and phosphorus balance in chronic renal failure patients, with secondary hyperparathyroidism, and resulting in an increased calcium-phosphorus ion product, were held responsible. To which extent the relative contribution of the well-known lipid-lowering effect of sevelamer might have played a role in the observed decrease in calcification is an intruiging question which needs further investigation. It should also be noticed that, as a lipid-binding compound, sevelamer has the ability to sequester fat soluble vitamins and nutrient compounds also (18). Although no problems in this respect have emerged so far, more information on long-term safety is required. Also is the efficacy of sevelamer in lowering phosphate levels still a matter of debate as the target serum phosphate level of 5.5mg/dl cannot be reached in the majority of patients especially when the compound is used as monotherapy (9).

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More recently, lanthanum carbonate has been introduced as an alternative phosphate binder. Lanthanum, discovered in 1839 by mosander, is a naturally occurring rare element (mw: 139 da). As a trivalent hard acid cation it has a high affinity for phosphate and thus is regarded an attractive candidate for use as phosphate binding agent. Indeed, in vitro studies have shown the element to have as a phosphate binding capacity of > 97% at ph 3-5 (19). Furthermore, an extensive programme of (pre-)clinical trials suggest lanthanum to possess a low toxic potential and provide evidence that lanthanum carbonate at lanthanum doses up to 3000 mg/day is an effective and well-tolerated agent in patients with end-stage renal disease (20). Lanthanum carbonate thus offers potential as a non-calcium, non-aluminium agent to control serum phosphorus without adding to calcium burden.

Having a phosphate binding capacity comparable that of aluminum, concerns have been raised, as to which extent lanthanum might possess similar side-effects to this element also. Compared to aluminum, the gastrointestinal absorption of lanthanum however is low and in humans has been predicted 0.00003% (20) i.e. 1300 to 6600 times less the most recent values reported for aluminium (0.04% - 0.2%) (3). Inherent to this minimal absorption an increase in plasma lanthanum levels over baseline up to values that rarely exceed 1µg/l, was noticed in clinical studies in dialysis patients receiving lanthanum carbonate at doses up to 2250 mg/day (20,21). It should be mentioned that these values did not further increase with continuing treatment as a plateau was already reached after 2 – 3 weeks of treatment. Nevertheless this raises the question to which extent lanthanum accumulates in bone and tissues. In this context should it be noted that, in contrast to aluminum, biliary excretion is the major excretion route of lanthanum. Hence, one may reasonably expect that, once equilibrium between bone/tissue and plasma lanthanum concentrations is achieved, the element will be removed from the body via this pathway thus minimizing the potential for tissue accumulation (20). The important biliary excretion of lanthanum also implies that, in contrast to aluminum which is mainly excreted by the kidney, end-stage renal failure/dialysis patients are not at an increased risk for accumulation of the element in comparison to subjects with normal renal function.

During animal studies with lanthanum carbonate, no adverse histopathology was identified in bone of animals with normal renal function in any repeat-dose toxicity study. In an experimental study assessing the possible effects of lanthanum on bone in rats with chronic renal failure (5/6 nephrectomy) receiving various doses of lanthanum carbonate (0, 100, 500, 1000 mg/kg) during 12 weeks, an impaired mineralisation was seen in some animals receiving the highest dose whilst rats with normal renal function receiving the same dose presented with a normal bone histology (22). Bone lanthanum levels were dose-dependently increased from baseline with slightly higher concentrations in the renal failure group reaching a median value of 1.5 µg/g wet weight in the highest dose group. In contrast to rats with normal renal function, lanthanum dosing in chronic renal failure rats went along with a dose-dependent decrease in phosphaturia and reduced 25-(oh)-vitd$_3$ ((not 1,25--(oh)$_2$-vitd$_3$). Moreover, in these rats the bone lanthanum concentration did not correlate with histomorphometric bone parameters, neither did lanthanum affect osteoblastic activity (23). These findings allow to suggest that in contrast to aluminium, the observed mineralization defect was not the direct consequence of lanthanum accumulation in bone but resulted from the high phosphate binding capacity of the compound in combination with reduced vitamin d levels inherent to the chronic renal failure. This statement is further corraborated by the data of subsequent studies in which (i) the effects of lanthanum on bone were compared to these of sevelamer. When given at the same doses (1000 mg/kg) to chronic renal failure rats, this organic metal free compound induced a mineralisation defect similar to that observed for lanthanum (24) (ii) non-dietary repletion of phosphorus to lanthanum treated rats reversed the mineralisation defect (25). Preliminary results from an ongoing experimental study furthermore indicate that in lanthanum loaded rats bone mineralisation improves already after a 2 weeks washout period whilst bone lanthanum levels had not changed.

Given the past tragic experience with aluminium and in order to further substantiate the issue of bone lanthanum accumulation/toxicity in humans, a 'bone-biopsy based" open-label multicentre (n=12) study was set up in which for the first time paired bone biospies (baseline and after 1-year follow up) were taken in 63 dialysis patients and the effects of lanthanum carbonate (n =33) versus calcium carbonate (n=30) were compared (21). Serum phosphate levels were well controlled in both groups and lanthanum carbonate was well tolerated thereby confirming efficacy and safety data published previously (20). Patients receiving calcium carbonate had a much higher incidence (49%) of hypercalcemia (serum calcium level > 2.65 mmol/l) as compared to the lanthanum group (6%). Bone histomorphometric data revealed that after 1 year of lanthanum treatment 5 of 7 patients with baseline low bone turn-over (either adynamic bone or osteomalacia) and 4 out of 5 patients with hyperparathyroidism, had evolved towards a normalisation of their bone turn-over. Only 1 (3%) lanthanum-treated patient evolved toward adynamic bone compared with 6 (20%) patients in the calcium carbonate group. Furthermore in the lanthanum group the number of patients having either adynamic bone, osteomalacia, or hyperpara decreased overall from 12 (36%) at baseline to 6 (18%), while in the calcium group, the number of patients with these types of rod increased from 13 (43%) to 16 (53%). Overall, lanthanum treatment led to a considerably better outcome than treatment with calcium and, even more importantly, did not possess any of the adverse bone effects previously reported for aluminium hydroxide.

Moreover, as data of the present and various other preclinical and clinical studies indicate lanthanum carbonate treatment to (i) effectively reduce the calcium x phosphorus product, (ii) have a beneficial effect on bone turn-over; i.e.

Conserves the capacity of bone to buffer serum calcium levels, (iii) be less likely to cause oversuppression of pth (as compared to calcium carbonate), further investigations on the compound's effect on the progression and development of metastatic calcification are worthwhile to be performed. As in contrast to sevelamer, there is no evidence for lanthanum to affect the serum lipid profile, a set up comparing the effects of both compounds would enable us to distinguish between the role of either a reduced calcium x phosphorus product or lipid lowering in the development of vascular calcifications. Moreover it may shed some light on the disputable role of calcium salts in this issue (12,26).

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