NEW THERAPIES: CALCIMIMETICS, PHOSPHATE BINDERS AND VITAMIN D RECEPTOR ACTIVATORS

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Abstract

At present, new compounds are available to treat secondary hyperparathyroidism, namely calcimimetics, novel phosphorus binders and also novel vitamin D receptor activactors.

Calcimimetics increase the sensitivity of the to parathyroid gland to calcium through spacial configurational changes of the calcium-sensing receptor. In addition experimental studies demonstrated that calcimimetic also upregulate the calcium-sensing receptor and the vitamin D receptor. They are efficacious in children, though the experience in pediatric chronic kidney disease is still limited.

Sevelamer, lanthanum carbonate and magnesium iron hydroxicarbonate are novels phosphorus binders available in the market. Several studies have demonstrated their efficacy and safety though costs are the main limitation for a wider use. Other new salts and polymers are also in development.

New vitamin D receptor activators such as paricalcitol are as effective suppressing PTH as the traditional vitamin D receptor activators used during the last two decades but they have a better and safer profile showing less calcemic and phosphoremic effects while preserving the desirable effects of the vitamin D receptor activators on the cardiovascular system, hypertension, inflammation and fibrosis. The use of them in children with chronic kidney disease demonstrated similar response than in adults.

The novel compounds discussed in this review should facilitate and improve the management of mineral and bone disorders in children with chronic kidney disease.

Introduction

Secondary hyperparathyroidism (SHPT) is a current complication of chronic kidney disease (CKD). The regulatory mechanisms of parathyroid hormone (PTH) synthesis are complex, involving calcium, the calcium-sensing receptor (CaSR), phosphorus, calcitriol and the vitamin D receptor (VDR) [1, 2].

In CKD, the ability of the kidneys to remove phosphorus from circulating plasma is reduced, leading the accumulation of phosphorus. In addition, calcitriol synthesis decreases in direct response to the decline in kidney function, triggering a cascade of events which includes decreased calcium absorption and an increase in PTH production. Elevations in serum PTH concentration are observed early in the development of CKD [3, 4]. Prevention and treatment of SHPT are critical because mineral metabolism imbalances are associated with increased morbidity and mortality in CKD patients [5, 6].

Fortunately, several new compounds are now available that can slow down and/or prevent the progression of SHPT, namely calcimimetics, phosphorus binders and vitamin D receptor activactors (VDRAs).

Serum Calcium, the calcium-sensing receptor (CaSR) and Calcimimetics.

Extracellular calcium is the main parathyroid regulator; low levels of calcium stimulate PTH secretion, while elevated levels inhibit hormone release and favour degradation within the parathyroid gland [7-10]. The parathyroid gland response is sigmoidal; thus, small changes in extracellular calcium cause large PTH variations. The effects of calcium on PTH are mediated by its specific receptor, the CaSR, which belongs to the G-protein-coupled receptors family and is present in the membrane of the parathyroid cells [11]. Any increments in extracellular calcium are sensed by the CaSR, which triggers a cascade of intracellular signalling that results in the inhibition of PTH synthesis and secretion.

It has been demonstrated that in CKD there is a significant reduction in the CaSR expression. As a result, the parathyroid gland is less able to sense the increments of calcium; hence, PTH synthesis and release increase inadequately [1, 2, 12]. The response of the parathyroid gland depends on the rapidity and duration of the hypocalcaemic stress; PTH release in response to calcium occurs within seconds to minutes following signalling through the CaSR [13]. Chronic hypocalcaemia and hyperphosphataemia stimulate PTH gene expression and subsequent PTH synthesis within hours to days [14] and proliferation of parathyroid cells occurs over days to

weeks [15]. The maintained stimulation of the parathyroid gland results in gland enlargement, uncontrolled excess of PTH, and provokes an unwelcome increase of serum Ca which has been consistently associated to an increased risk of mortality [5, 6]. Fortunately, calcimimetics are already available in several countries and offer a great opportunity to improve the management of SHPT in stage 5 CKD patients.

Calcimimetics interact with CaSR at different sites of the molecule than those where calcium binds the CaSR. Calcimimetics change the spacial configuration of CaSR and, as a result, CaSR increases its sensitivity to calcium In addition, experimental studies have demonstrated that calcimimetics upregulate CaSR and VDR, thus, due to both properties they may prevent or attenuate parathyroid hyperplasia [16-18].

Several studies in stage 5 CKD patients have demonstrated a sustained effect of calcimimetics in the parathyroid gland control with concomitant and useful reductions in serum phosphorus and serum calcium [19-21]. By contrast, in stages 3 and 4 CKD patients, calcimimetics should not be used, since it can induce undesirable increments in serum phosphorus by mechanisms not fully understood [22, 23]. On the other hand, cinacalcet can be beneficial in stages 3 and 4 CKD kidney transplant patients in whom the calcimimetic-induced reduction in the "PTH-induced phosphaturia" and the consequent retention of phosphorus may counterbalance the frequently observed PTH-dependent reduction in serum phosphorus due to the persisting parathyroid gland hyperplasia.

Calcimimetics are efficacious in children at stage 5 CKD, though the experience is quite limited and large long-term randomized controlled trials should be conducted [24, 25]. In addition, experimental studies have demonstrated that calcimimetics do not affect growth and promotes weight gain in chronic kidney failure [26].

Impact of high serum phosphorus; experience with novel phosphorus binders

High serum phosphorus levels, a highly prevalent condition in CKD patients, have been associated with the pathogenesis of secondary hyperparathyroidism [5, 6, 27], the

development of vascular calcification [28], vascular stiffness [29], left ventricular hypertrophy [22] and mortality [5, 6]. High serum phosphorus has become an extremely important patogenetic factor in the chronic kidney disease mineral and bone disorders (CKD-MBD) constellation. Furthermore, the reduction of serum phosphorus caused by the use of phosphorus binders has been recently associated with better survival [30, 31]. Even though high serum phosphorus may play a key harmful role in the above-mentioned clinical outcomes, some of its effects can also be partly due to a new phosphorus-related player: the fibroblast growth factor 23 (FGF 23), a phosphatonin which may carry out dependent and independent actions from phosphorus [32].

The kidneys and the bones are the main regulators of phosphorus homeostasis in day-to-day life. While kidney removes phosphorus from circulating plasma, bone acts as a reservoir of phosphorus. As mentioned, the ability of kidneys to remove phosphorus in CKD patients is reduced (stages 3-5), or absent (stage 5D), resulting in high serum phosphorus levels which, in combination with low serum calcium and low calcitriol, stimulate PTH synthesis and secretion. In fact, the most well-known and most studied consequences of high serum phosphorus are the effects on the parathyroid glands, which in turn affect bone metabolism. High serum phosphorus levels impair calcitriol synthesis, increase the skeletal resistance to PTH and also directly increase PTH synthesis. In addition, several studies have shown that high serum phosphorus increases parathyroid cell proliferation and that it can reduce the CaSR expression [33, 34].

The three most important factors in the management of high serum phosphorus are dietary restriction, the use of phosphorus binders, and adequate dialysis. In this review we shall concentrate only on the effect of phosphorus binders. All currently available oral phosphorus binders, the so-called “old and new phosphorus binders”, have limitations.

The “old phosphorus binders”

Aluminium hydroxide was the first phosphorus binder and it has been widely used for many years. It is the most potent phosphorus binder, but also the most toxic one [35]. For this reason, in the 1980`s, it was progressively replaced by the calcium-

containing phosphorus binder. The use of the latter became also widespread, but later on several disadvantages became apparent. It has been proven that the use of calcium salts, especially if exceeding 1.5 grams of calcium daily, increases the risk of vascular calcification -even in children and young adults- [36], and it can also lead to a greater vascular stiffness [37]. Magnesium-containing phosphorus binders have been also used as an alternative, but they are generally less effective. The adverse events have limited the use of the calcium-containing phosphorus-binders and stimulated the synthesis of a new generation of phosphorus binders, including salts and polymers, some of them already available in the market, such as sevelamer and lanthanum carbonate, while others are still being developed [38].

The "new phosphorus binders"

Sevelamer hydrochloride was the first non-aluminum, non-calcium-based phosphorus binder commercially available. Originally, it was developed to lower plasma lipids, but this non-absorbed polymer has been mainly used to reduce phosphorus absorption in stage 5 CKD patients. Several studies have demonstrated that sevelamer is effective in lowering serum phosphorus without inducing increments in serum calcium and, may attenuate coronary and aortic calcification in comparison with calcium-containing phosphorus binders [39]. Other additional beneficial pleiothropic effects of sevelamer have been reported, but they need further confirmation [40, 41]. Despite sevelamer hydrochloride offers several advantages, gastrointestinal disturbances, metabolic acidosis, and a high cost have been limiting factors for a widespread use of this phosphorus binder. A more recent formulation as sevelamer carbonate has been introduced in recent times in order to avoid the mild acidosis observed with the use of sevelamer hydrochloride.

Lanthanum carbonate became available in 2005 in the United States and in 2006 in the European Union. Preclinical animal studies demonstrated that lanthanum carbonate, a non-aluminium, non-calcium-based binder, featured a phosphorus binding capacity closer to that of aluminium with a better safety profile and a low systemic uptake. A minor fraction of the oral dose is absorbed (< 0.0013%), circulates bound to serum proteins and is mainly cleared by biliar excretion after transiting through the liver within lysosomes [42]. The clinical trials using calcium carbonate as comparator demonstrated that lanthanum carbonate was as effective as calcium carbonate, but

induced significantly less hypercalcemia [43]. The relative potency of lanthanum carbonate as a binder allows a reduced pill burden [44]. Despite concerns being raised about potential liver and bone toxicity related with its long-term use [45], recent publications have shown a satisfactory long-term safety profile (up to 6 years of use) [46].

Magnesium iron hydroxycarbonate is another new oral phosphorus binder which has shown promising preliminary results [47]; its use is associated with increased serum magnesium levels. Even though the long-term effects of high serum magnesium has not been specifically assessed, hypermagnesemia has been associated with reductions of vascular calcification [48] and adynamic bone [49].

In summary, we have a few novel phosphorus binders available and others being researched. In addition, in children with stage 5 CKD, there is already a widespread experience with sevelamer hydrochloride, which has shown a similar pattern of response to that observed in adults [50]. Generally speaking, the safety profile of the new phosphorus binders available in the market is safer than that of the old phosphorus binders, their cost being higher, however.

Vitamin D and the new VDR activators (VDRAs)

Vitamin D is a steroid hormone that has long been known for its key role in the regulation of calcium and phosphorus and the mineralization of bone. Calcitriol, the physiological VDRA, is the natural parathyroid gland regulator and exerts its effect on PTH secretion by inhibiting the mRNA synthesis through its action on the VDR, a highly specific receptor which acts as a transcription factor [10]. When calcitriol binds the receptor, it induces the translocation of the calcitriol-VDR complex to the cell nucleus, forming a heterodimer with the retinoid X receptor (RXR). Then, the calcitriol-VDR-RXR complex binds the vitamin D responsive elements present in the PTH gene promoter, blocking its transcription [51]. In addition, calcitriol is able of inhibiting PTH secretion by increasing calcium absorption in the intestine, while also increasing bone resorption and, consequently, calcium release from bone. Contrary to what occurs with

calcium and CaSR, calcitriol regulates the expression of its own receptor (VDR), stimulating its synthesis. The deficit of calcitriol observed in CKD patients is associated with a decrease in VDR levels in the parathyroid gland. Besides its effect on VDR, calcitriol can also regulate the CaSR (7).

Until now, VDRAs have been mainly used in the treatment of SHPT. However, there is new evidence suggesting the use of VDRAs may have other relevant consequences in CKD patients. One of the seminal contributions in this area was the study performed by Teng et al. [52], who showed a better survival in patients treated with paricalcitol compared with calcitriol, supporting the hypothesis that less calcemic and phosphoremic VDRAs may be advantageous for CKD patients. Since then, several papers have concentrated on the likely effects of VDRAs on survival beyond calcium and phosphorus metabolism [53-56].

There is evidence linking VDRAs with the improvement in left ventricular function. Animals lacking the VDR show cardiovascular abnormalities such as hypertension and left ventricular hypertrophy, and cardiomyocytes develop contractile abnormalities [57, 58]. Vitamin D may also influence growth, hypertrophy, collagen deposition, and differentiation of cardiomyocytes [59-61]. Moreover, lower levels of calcidiol has been associated to a higher risk of hypertension, a greater rate of progression to CKD, and mortality [62, 63]. In addition, differential effects among VDRAs has been demonstrated: in fact, hypertensive rats treated with paricalcitol showed a better left ventricular function [64] and a significant renin suppression with less calcemic effect than calcitriol [65].

The presence of VDR on the vascular wall suggests that some of the differential effects of VDRA on the cardiovascular system may be driven by its effects on the vasculature. In fact, high doses of paricalcitol showed almost no vascular calcification, whereas calcitriol induced massive aortic calcifications [66]. The negative effect of calcitriol on the vasculature has been also recently shown in pediatric dialysis patients, in which calcitriol use has been associated with increased vascular calcification [67].

Other beneficial effect of VDRAs on CKD patients may be related to their effects on inflammation and fibrosis. Low vitamin D levels are associated with high C Reactive

protein levels [68] and cardiovascular disease [69]. Similarly, recent studies suggest that paricalcitol may reduce fibrosis, inflammation and proteinuria independently of glomerular filtration rate and blood pressure or angyotensin conversing enzyme inhibitors, though the concomitant use of the latter may improve its performance [70-73].

In summary, the new VDRAs, especially paricalcitol, being the most extensively VDRA studied, have a better and safer profile than classic VDRAs such as calcitriol and alphacalcidol, showing less calcemic and phosphoremic effects while preserving the desirable effects of the VDRAs on the cardiovascular system, hypertension, inflammation and fibrosis. So far, there is experience in children with CKD who present similar responses and characteristics to those of adults [74, 75].

In recent years we have made important advances in the knowledge and understanding of the pathogenic role of calcium, CaSR, phosphorus, VDR and VDRAs in the regulation of the parathyroid function and bone metabolism, but also in other aspects beyond them. All these progresses should allow for a better management of the CKD-MBD, based on a triple combined approach targeting simultaneously, whenever possible, VDR, CaSR and phosphorus, looking for responses not only in the classic bone and mineral parameters, but also in other components of the revisited CKD-MBD constellation [76]

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