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A new paradigm for the treatment of secondary hyperparathyroidism

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Abstract

The global rise in chronic kidney disease makes secondary hyperparathyroidism (SHPT) a growing medical concern. Conventional therapies for treating SHPT are limited and include calcium-based and calcium-free phosphate binders for reducing serum phosphorus and vitamin D or its analogues for simultaneous stimulation of calcium absorption and suppression of parathyroid hormone (PTH) gene expression. Control of SHPT using these therapies has typically been poor. Recent studies have demonstrated that use of calcimimetics that reduce PTH secretion by increasing the sensitivity of the parathyroid gland calcium-sensing receptor to circulating calcium allow improved control of serum PTH, calcium, phosphorus and calcium–phosphorus product. This review describes experimental data and the clinical rationale supporting novel strategies for the integration of calcimimetics with conventional therapies to improve control of SHPT.

Keywords: calcium-sensing receptor; chronic kidney disease; cinacalcet; parathyroid hormone; secondary hyperparathyroidism

Introduction

Until recently, therapeutic options for management of secondary hyperparathyroidism (SHPT) had been limited to the use of phosphate binders (reducing serum phosphorus reduces parathyroid hormone [PTH] secretion) [1], calcium [1] and vitamin D or its analogues [1,2]. Although phosphate binders may help normalize serum phosphorus and, consequently, also help normalize PTH, there are compliance problems [3] associated with high doses, and for some treatments, high daily tablet burdens [4] are required for successful control of serum phosphorus. There is a separate set of concerns regarding the use of vitamin D therapy for SHPT, because vitamin D, although frequently successful as an initial therapy, may give rise to hypercalcaemia and hyperphosphataemia [5], and patients may become refractory to the effects of vitamin D as SHPT progresses [6,7]. Similarly, the use of supplemental calcium and calcium-based

phosphate binders poses a potential risk for hypercalcaemia [8].

It has long been recognized that serum calcium plays a pivotal role in the regulation of PTH secretion [9]. Following the discovery of the calcium-sensing receptor (CaR) as a primary regulator of PTH synthesis and secretion in the parathyroid gland [10–12], it was recognized that modulation of the activity of the receptor might represent an effective new treatment modality for SHPT [13]. Recently, allosteric modulators of the CaR (termed type II calcimimetics) have been shown to be safe and effective treatments for SHPT [14]. Here we review traditional approaches to the treatment of SHPT and also the new experimental findings that may form the basis of treatments that can halt progression and ultimately stabilize this chronic, progressive disease.

Current treatment options for SHPT

As noted, there are serious limitations associated with the conventional best standard of care for SHPT patients, and treatment targets are not being adequately achieved. The optimal serum PTH range for patients with stage 5 chronic kidney disease (CKD) is 150–300 pg/mL, according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI™) guidelines [1]. A study of 17 236 haemodialysis patients in the United States, Europe and Japan between 1996 and 2001 indicated that 51% of patients fell below this range and 27% were above this range for PTH [15]. PTH levels were associated with all-cause and cardiovascular mortality, consistent with previous reports of a positive correlation between elevated PTH and increased mortality risk in CKD patients [16]. Similarly, a study of 1312 haemodialysis patients in Spain found that the percentage of patients not achieving their KDOQI™ targets was 77% for PTH, 50% for calcium, 46% for phosphorus and 33% for calcium–phosphorus product (Ca × P) [17]. These data suggest that conventional treatment modalities for SHPT are not sufficient to effectively manage PTH levels on a long-term basis in CKD patients.

Phosphate binders

The management of CKD patients in advanced stages of renal failure generally includes the prescription of oral

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phosphate binder medication to keep serum phosphorus levels under control. Although the use of aluminium-based phosphate binders has largely been discontinued owing to toxicity in bone [18] and the central nervous system [19], calcium salts are still frequently used to treat hyperphosphataemic CKD patients. Calcium effectively decreases serum phosphorus and PTH but increases the risk of hypercalcaemia [8] and calciphylaxis [20]. Increased rates of vascular calcification have also been observed in CKD patients taking high doses of calcium salts [21,22].

Calcium-free phosphate binders, such as sevelamer and lanthanum carbonate, effectively decrease serum phosphorus with little or no concomitant effect on serum calcium [23–26]. Compared with calcium-based phosphate binders, sevelamer significantly slows the progression of vascular calcification [27]. Although these calcium-free binders effectively lower serum phosphorus and may consequently help control increase in circulating PTH, they do not significantly lower PTH levels [23–26]. Furthermore, sevelamer is less effective in lowering serum phosphorus compared with calcium salts in the long-term management of CKD patients [28]. Also, sevelamer has been shown to reduce serum bicarbonate, thereby increasing the risk for metabolic acidosis [29]. In patients with advanced SHPT and parathyroid hyperplasia, the response of parathyroid cells to normalization of mineral balance is diminished, and therapies for controlling PTH release become less effective. Therefore, even though high serum phosphorus levels contribute to SHPT, controlling serum phosphorus in the context of advanced SHPT may not be sufficient to effectively prevent disease progression.

Vitamin D and vitamin D sterols

Vitamin D (1,25-dihydroxyvitamin D_3) has multiple beneficial effects on the body, including its role as a growth factor in certain tissues and its regulation of serum calcium at physiologic levels, in addition to potential roles in the prevention of cancer, diabetes, heart disease and osteoporosis [30]. High doses of vitamin D may not be appropriate, however, for treating SHPT in CKD patients. During the course of therapy, vitamin D doses must be increased frequently. This is likely due to decreased expression of the vitamin D receptor (VDR), which is observed in advanced SHPT [31]. Because vitamin D also promotes absorption of calcium and phosphorus by the intestine [32], escalating doses of vitamin D may contribute to imbalances in biomarkers associated with increased mortality risk in dialysis patients.

Few clinically relevant differences between the efficacy profiles of available vitamin D products have been demonstrated in humans. Animal studies have suggested that paricalcitol (19-nor-1,25-dihydroxyvitamin D_2) may have a wider therapeutic window than vitamin D [33,34]. Administration of calcitriol in rats is associated with hypercalcaemia, resulting from an increase in intestinal VDR expression, which contributes to increased calcium absorption from the intestine [33,34]. In contrast, paricalcitol appears to have selective action on the VDR in parathyroid glands compared with the intestine, allowing it to exert beneficial effects on PTH secretion without elevating intestinal VDR content and increasing the risk

of hypercalcaemia [34]. However, in clinical trials, the differential effects of paricalcitol compared with calcitriol on mineral metabolism have been limited [35].

Some evidence suggests that high doses of vitamin D may contribute to vascular calcification [36,37]. Molecular studies have shown that vitamin D increased calcification, alkaline phosphatase activity and osteopontin expression in bovine vascular smooth muscle cells (VSMCs) in a dose-dependent manner [38]. The increased calcification was also attributed in part to a vitamin D-mediated suppression of PTH-related peptide (PTHrP) secretion by VSMCs. Because PTHrP is an endogenous inhibitor of calcification, a decrease in circulating levels of PTHrP may be a key factor in the genesis of vascular calcification. Furthermore, studies have shown that vitamin D treatment induces significant morphologic changes in aortic smooth muscle cells and induces their proliferation [39]. Calcitriol has been shown to dose-dependently provoke gene changes consistent with a transition of VSMCs to mineralizing osteoblast-like cells [38]. These changes in the gene expression profile of affected cells appear to be pivotal in the events leading to bonelike mineralization within the vascular endothelium. Because cardiovascular disease is the leading cause of death among stage 5 CKD patients [40], an increased potential for vascular calcification events is a real concern. Vitamin D at physiologic levels appears to play a role in the maintenance of cardiovascular health. It has been suggested that the reduced mortality associated with vitamin D treatment in retrospective studies might be due to vitamin D-mediated improvements in cardiac structure and function and inhibition of atherosclerosis [41]. However, supraphysiologic levels of vitamin D may pose an additional health risk for the vulnerable CKD patient population by promoting vascular calcification.

Calcimimetics

Cinacalcet is a type II calcimimetic with demonstrated efficacy in treating SHPT in CKD patients on dialysis. The results of several phase 3 clinical trials conducted in this population have demonstrated a significant therapeutic benefit of cinacalcet in combination with standard therapy (vitamin D analogues or phosphate binders) compared with standard therapy alone. Both short-term [42–46] and long-term [47] clinical studies have shown that cinacalcet effectively lowers PTH levels and maintains PTH levels within KDOQI^{TM}-recommended target ranges [1] for the majority of patients [43]. Additionally, cinacalcet has been shown to significantly reduce both serum phosphorus and Ca × P (Figure 1) [42,43,45,46], both of which are independent factors contributing to the elevated risk of mortality in CKD patients [16]. In a rat model, cinacalcet halted the progression of parathyroid hyperplasia [48], presumably through its influence on CaR signalling.

These experimental findings provide the mechanistic basis for potential therapeutic benefits of cinacalcet, the first calcimimetic agent approved for the treatment of CKD patients with SHPT undergoing dialysis. Although generally well tolerated, cinacalcet has been associated with an increased frequency of some gastrointestinal adverse events, including mild to moderate nausea and vomiting

[42,46]. In addition, treatment with cinacalcet can occasionally result in the development of hypocalcaemia, although this is generally modest and manageable [42,46].

Proposed SHPT treatment principles

The management of CKD patients, who frequently present with several comorbid conditions, requires consideration of numerous factors when choosing an optimal treatment regimen for SHPT. Severe forms of SHPT may require surgical parathyroidectomy, and conversely, aggressive treatment of SHPT may result in undesired low levels of PTH. A compre-

Fig. 1. Influence of cinacalcet and placebo on important biomarkers in phase 3 trials. All comparisons between cinacalcet and placebo were significant ($P < 0.001$). Data are mean ± standard error. Data from Block *et al.* [46].

hensive approach to treatment that takes into account the importance of early biomarker monitoring, dietary structure, mode of renal replacement therapy and drug therapy options may help improve clinical outcomes and prevent SHPT disease progression.

Because each of the different treatments for SHPT has different effects on serum PTH, calcium, phosphorus and Ca × P (Table 1), as well as the variability observed in these parameters, combinations of available drugs should be used to maintain KDOQI™ targets [14,49]. The initial choice of treatment in a CKD patient with SHPT is based on plasma calcium, phosphorus and PTH levels, and therapy should be tailored to each patient depending on his or her laboratory values and other intercurrent diagnoses. If the laboratory values are outside of recommended ranges, low-dose vitamin D sterols with calcium supplements are potentially the best initial regimen. Addition of calcimimetics should be considered for stage 5 CKD patients with PTH levels >300 pg/mL and for those with PTH levels of 150–300 pg/mL with poorly controlled calcium or phosphorus (Table 2). Calcium-containing phosphate binders can be used to control phosphorus levels if calcium levels are low or controlled (8.4–9.5 mg/dL); otherwise, calcium-free binders such as sevelamer or lanthanum carbonate should be used. Because cinacalcet lowers serum calcium and phosphorus, its use might allow for a decrease in the dose of phosphate binders.

Although cinacalcet has been shown to lower serum calcium and phosphorus, calcimimetics will not likely replace phosphate-binder therapy, but rather be used in conjunction with phosphate binders with the primary goal of controlling circulating PTH. Similarly, vitamin D therapy will not be rendered obsolete by the introduction of calcimimetics for the treatment of SHPT. Vitamin D supplementation at low doses will continue to be an important component of
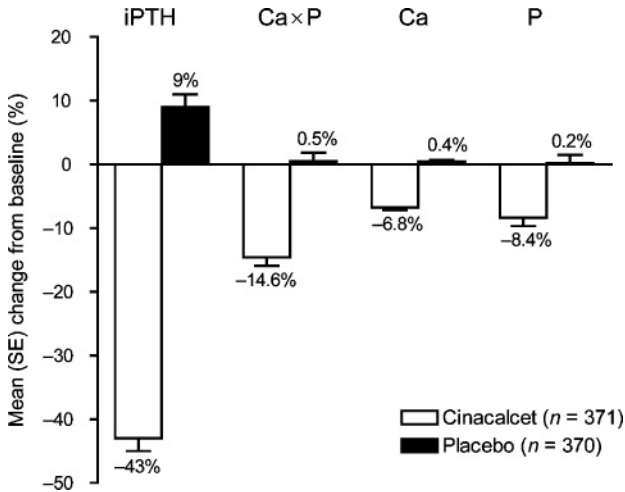
Table 1. Effects of SHPT treatments on serum calcium, phosphorus, Ca × P and PTH

Parameter	Treatment option			
	Calcium-based phosphate binder	Calcium-free phosphate binder	Vitamin D sterols	Calcimimetic
Calcium	↑↑	↔ or ↑	↑	↓
Phosphorus	↓↓	↓↓	↑	↓
Ca × P	↓↓	↓↓	↑	↓
PTH	↓↓	↓	↓↓↓	↓↓↓

↑, increased; ↓, decreased; ↔, no change. Number of arrows indicates the magnitude of the effect.
Adapted with permission from Steddon *et al.* [49].

Table 2. Proposed guidelines for SHPT treatment for patients on conventional therapy not yet treated with cinacalcet

	Calcium and phosphorus controlled	Calcium or phosphorus uncontrolled
PTH <150 pg/mL	• Consider reduction of vitamin D dose	• Reduce vitamin D dose • Adapt dose and/or type of phosphate binder
PTH 150–300 pg/mL	• Maintain reduced dose of vitamin D • Maintain phosphate binder	• Reduce vitamin D dose • Titrate cinacalcet to control PTH, calcium, and phosphorus • Adapt dose and/or type of phosphate binder
PTH >300 pg/mL	• Titrate cinacalcet to control PTH • Maintain current dose of vitamin D	• Titrate cinacalcet to control PTH, calcium, and phosphorus • Reduce vitamin D dose • Adapt dose and/or type of phosphate binder

treatment regimens for CKD patients because vitamin D is essential for a variety of processes, and its use may also be indicated to counter the calcium-lowering effect of CaR modulators. Some patients experience transient reductions in serum calcium to levels below recommended KDOQI^{TM} targets; this can be corrected without ceasing cinacalcet by increasing vitamin D or calcium-based phosphate binders. Cinacalcet has a potent, fast-acting effect on serum PTH levels. One preliminary study provides evidence that cinacalcet is efficacious for the treatment of SHPT in patients with CKD not receiving dialysis [50]. Consequently, early use of calcimimetics in this patient population may help prevent SHPT disease progression, although further studies are needed to confirm this.

Conclusions

SHPT is a common manifestation of CKD, with potentially harmful effects on bone tissue [51], immune [52] and endocrine function [53] and the central nervous system [54], to name a few. SHPT arises in patients with CKD as a result of renal failure and consequent disturbed mineral metabolism. Both calcium and phosphorus exert significant influences on PTH synthesis and release, and normalized levels of both are important for maintaining proper PTH and associated metabolic functions.

The introduction of calcimimetics offers a new treatment paradigm currently based on cinacalcet and low-dose vitamin D therapy. Some marked advantages are associated with incorporating cinacalcet into existing therapy for SHPT, particularly the speed of action for lowering PTH and the lack of undesired effects on mineral balance. The use of cinacalcet earlier in SHPT disease rather than later may also help prevent parathyroid hyperplasia and development of severe SHPT; this is important because parathyroid tissue may become refractory to use of conventional therapies alone. Because high-dose vitamin D has potentially deleterious effects on mineral balance and vascular calcification, low-dose vitamin D used in conjunction with calcimimetics for treating SHPT currently represents the most promising option for these patients.

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