Achieving therapeutic targets in the treatment of secondary hyperparathyroidism

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Abstract
Disturbances in the control of extracellular ionized calcium and phosphorus concentrations, and vitamin D metabolism, in patients with chronic kidney disease (CKD) are associated with prolonged stimulation of the parathyroid glands. This results in increased synthesis and release of parathyroid hormone (PTH) and parathyroid hyperplasia—secondary hyperparathyroidism (SHPT). SHPT is in turn a major driver of the skeletal disturbance that characterizes renal osteodystrophy and is associated with vascular and other soft tissue calcification. Current therapeutic strategies based on vitamin D compounds and calcium-containing phosphate binders are difficult to implement effectively because both agents are associated with substantial, and often dose-limiting, calcaemic actions that prevent the attainment of treatment targets. Calcimimetics are novel agents that increase the sensitivity of calcium-sensing receptors in the parathyroid glands. Consequently, they allow simultaneous reduction of both PTH and extracellular calcium concentrations, thus differing from currently available vitamin D therapies. Reduction of the calcium–phosphorus product (Ca\(^2\)/C\(^2\)P) is a consistent feature of calcimimetic therapy and may facilitate the achievement of SHPT treatment targets.

Keywords: calcimimetic therapy; calcium \times\ phosphorus; chronic kidney disease; parathyroid hormone; secondary hyperparathyroidism

Introduction
In patients with chronic kidney disease (CKD), persistent reductions in serum concentrations of calcium and calcitriol, together with increases in the concentration of phosphorus, stimulate parathyroid hormone (PTH) synthesis and release from the parathyroid glands. Continued stimulus to the glands accelerates parathyroid hyperplasia (Figure 1). Parathyroid hyperplasia is difficult to reverse, and large parathyroid glands are likely to contain areas of nodular hyperplasia in which there is significant under-expression of the calcium-sensing receptor (CaR) and the vitamin D receptor (VDR). These cells therefore lack crucial elements of the machinery that is required to mount an appropriate response to elevated ambient calcium concentration and/or suppressive input of calcitriol. The resulting hyperparathyroidism is an important driver for renal osteodystrophy. Furthermore, it almost certainly contributes to soft tissue, vascular and cardiac calcification, and probably to mortality, in patients with CKD [1].

The need for better control of hyperphosphataemia, PTH and calcium in SHPT
Poor control of PTH and calcium–phosphorus product (Ca×P) has been associated with cardiovascular morbidity and mortality. In a study of 12,833 haemodialysis patients, raised levels of PTH (\(P<0.05\)), phosphorus (\(P<0.01\)) and Ca×P (\(P<0.005\)) were associated with a significantly increased risk of sudden death [2]. Moreover, in a study that included almost 6,500 haemodialysis patients, Block et al. demonstrated that the severity of hyperphosphataemia was associated with increased risk of death [1]. Compared with the lowest risk quintiles, in the group with hyperphosphataemia at 1.80–2.11 mmol/l, the relative risk of death was 1.02, rising to 1.18 (\(P=0.03\)) when phosphorus was 2.12–2.53 mmol/l, and to 1.39 (\(P<0.0001\)) when phosphorus reached 2.54–5.46 mmol/l (Figure 2). These are powerful associations, but causal links between hyperphosphataemia and mortality have yet to be confirmed, and to date there is no prospectively collected evidence showing that...
correction of hyperphosphataemia leads to improved survival.

Therapeutic targets

Phosphorus, calcium and PTH concentrations are attractive as indicators of the overall effectiveness of SHPT treatment because they are easy to measure. They are not, however, robust indicators of the progression of complications of SHPT, having only an indirect bearing on events in the skeleton and soft tissues.

Target concentrations for PTH and phosphorus in different stages of CKD have been outlined by an international working group of experts and by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) in the USA [3–5]. Suggested therapeutic target phosphorus levels for patients with CKD stages 3 or 4 are similar to the normal physiological range (0.87–1.49 mmol/l) (Table 1). Even at CKD stage 5 (end-stage renal disease (ESRD)), the upper limit of the target range for phosphorus remains quite close to the normal range and is often very difficult to achieve in practice.

In the case of PTH, the K/DOQI target concentration is again close to normal in patients with CKD up to stage 3. In CKD stages 4 or 5, however, target PTH is somewhat higher, reflecting observational data that suggest that normal bone turnover is most likely to be achieved when measured PTH is moderately elevated. Thus, in patients with CKD stage 5, the target PTH is generally set at 3–6 times the upper limit of normal.

Even though the therapeutic value of these PTH targets has yet to be confirmed in clinical practice, the associations are generally reproducible. For example, Torres et al., among others, have shown that high and low levels of PTH can be correlated with the level of bone turnover and, therefore, the risk of some of the components of renal osteodystrophy [6]. They found that a PTH concentration >450 pg/ml was predictive of normal to high bone turnover in both pre-dialysis patients and patients with ESRD (positive predictive value = 1). Similarly, relatively low levels of PTH (<120 pg/ml) were associated with low bone turnover (the positive predictive values were 0.83 and 0.90 in pre-dialysis patients and patients with ESRD, respectively). PTH concentrations between these extremes, however, did not reliably predict bone turnover. It is of note that there are few if any data confirming that achieving a given PTH target necessarily achieves the desired effect on bone turnover.

In addition to bone disease, cardiac and vascular calcification is a frequent complication of dialysis and SHPT [7,8]. Several studies have shown an association between Ca x P and cardiac calcification [8,9]. For example, Goodman et al. showed that Ca x P was a good indicator of cardiac calcification between young

| Table 1. Target PTH, calcium, phosphorus and calcium–phosphorus product levels in patients with CKD |
|--------|--------|--------|--------|--------|--------|
| CKD stage | GFR (ml/min) | PTH (pg/ml) | Calcium (mmol/l) | Phosphorus (mmol/l) | Ca x P (mmol²/l²) |
| 3 | 30–59 | 35–70 | Normal | 0.87–1.49 | Normal |
| 4 | 15–29 | 70–110 | Normal | 0.87–1.49 | Normal |
| 5 | <15 or dialysis | 150–300 | 2.1–2.4 | 1.13–1.78 | <4.51 |

GFR = glomerular filtration rate.
Adapted from the National Kidney Foundation K/DOQI clinical practice guidelines [4].
dialysis patients with or without confirmed calcified deposits (Table 2) [9].

Despite the presumed benefits of maintaining PTH, calcium and phosphorus concentrations within these target ranges, there is mounting evidence to suggest that the vast majority of dialysis patients are uncontrolled in this regard. For example, in a new analysis of data from 7512 Spanish patients, only 22% had PTH concentrations within the new K/DOQI target range, while only 13% met targets for both PTH and Ca × P (Figure 3) [10]. These data emphasize the difficulty physicians are having to face in achieving these tougher targets, and the need for more effective therapeutic options.

### Table 2. Factors that might predict cardiac (coronary artery) calcification

<table>
<thead>
<tr>
<th>Factor</th>
<th>Coronary calcification (n=14)</th>
<th>No coronary calcification (n=25)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors that differed significantly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium intake from phosphate binders (mg/day)</td>
<td>6456±4278</td>
<td>3325±1490</td>
<td>0.02</td>
</tr>
<tr>
<td>Ca × P (mmol²/dl²)</td>
<td>65.0±10.6</td>
<td>56.4±12.7</td>
<td>0.04</td>
</tr>
<tr>
<td>Age (years)</td>
<td>26±3</td>
<td>15±5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of dialysis (years)</td>
<td>14±5</td>
<td>4±4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Factors that did not differ significantly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum calcium (mmol/l)</td>
<td>2.4±0.2</td>
<td>2.3±0.2</td>
<td>0.25</td>
</tr>
<tr>
<td>Serum phosphorus (mmol/l)</td>
<td>2.2±0.3</td>
<td>2.0±0.4</td>
<td>0.06</td>
</tr>
<tr>
<td>Serum PTH (pg/ml)</td>
<td>361±182</td>
<td>445±490</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Mean ±SD data from 39 patients aged 7–30 years (mean = 19 years) with end-stage renal disease. Reproduced, with permission, from Goodman et al. [9].

Fig. 3. Proportions of patients achieving new K/DOQI targets for PTH and Ca × P in a Spanish observational study [10].

### SHPT treatment

Ideally, treatment of SHPT would prevent parathyroid gland hyperplasia, ensure optimal PTH concentrations and maintain normal physiological circulating concentrations of phosphorus and calcium. It would also prevent soft tissue calcification and maintain normal bone metabolism. Currently, in addition to adjustment of dialysate calcium concentration, the management levers available to the nephrologist are diet, vitamin D compounds and phosphate binders. In the near future, calcimimetic agents should provide a further therapeutic tool. The differing pharmacological actions of these agents are summarized in Table 3.

#### Vitamin D compounds

On the basis of experimental data, it had been anticipated that certain new vitamin D compounds, such as doxercalciferol, 22-oxacalcitriol and paricalcitol, would offer improved control of PTH and Ca × P compared with calcitriol, but clinical evidence supporting this view is still weak [11]. In the pre-dialysis setting, these drugs reduce PTH levels effectively, but often at the cost of hypercalcaemia and hypercalciuria. Nordan and Dahl found that in patients treated with low doses of calcitriol, serum calcium levels rose and urinary calcium levels more than doubled [11]. Moreover, in a study haemodialysis patients comparing paricalcitol with calcitriol, both agents were associated with multiple hypercalcaemic episodes and raised levels of Ca × P, albeit less sustained in the paricalcitol group [12]. Finally, the evidence supporting the use of intermittent rather than continuous, and of parenteral rather than oral, vitamin D dosing regimens to suppress parathyroid gland function is limited [13–15]. All are effective, but all seem similarly prone to increase calcium and Ca × P.

#### Phosphate binders

For the past 20 years, calcium-containing phosphate binders have been a standard therapy for controlling hyperphosphataemia. These agents lack potency and usually reduce serum phosphorus levels only at the expense of large increases in calcium load, which may increase the likelihood of cardiac calcification [9,12]. Calcium-free phosphate-binding agents available now or in the near future include aluminium hydroxide, magnesium hydroxide, magnesium carbonate, sevelamer hydrochloride and lanthanum carbonate. It is unfortunate that aluminium-based compounds, which remain the most effective binders available, carry inherent risks because of their association with osteomalacic bone...
disease and dementia. Consequently, their use has virtually ceased in many countries.

The non-absorbed polymer sevelamer is the most recent calcium-free agent to reach the market. Chertow et al. compared the effects of sevelamer with those of calcium-based phosphate binders in haemodialysis patients [16]. The most striking biochemical differences were a reduction in the number of hypercalcaemic episodes in the sevelamer group, and greater PTH suppression in the group treated with calcium-based phosphate binders. There were no significant differences between the Ca×P in the two treatment groups, although serum calcium concentrations were consistently slightly higher in patients who received calcium-based drugs throughout the 1 year study. After 1 year, calcification of the coronary arteries and aorta had advanced less in the patients who received sevelamer than in those who received calcium-based phosphate binders (P = 0.03 and 0.01, respectively) [16]. Such data are consistent with a link between high oral calcium load, in many cases augmented by concomitant vitamin D therapy, and the progression of cardiac and vascular calcification (Table 2) [9].

When should treatment be started?

In the pre-dialysis setting, an overt increase of serum phosphorus is a relatively late development. PTH usually increases earlier in the natural history of CKD and is a better early marker for metabolic abnormalities that require intervention. Conventionally, PTH increased above the target range has triggered the prescription of a calcium-based phosphate binder to supplement calcium levels and prevent phosphorus elevation, with the addition of alfacalcidol or calcitriol if the PTH response is inadequate. There are no data concerning the use of the newer calcium-free binders in this setting.

Efficacy and potential role for calcimimetic therapies

Calcimimetic drugs increase the sensitivity of CaRs on the parathyroid glands to their principal ligand, calcium. In so doing, they directly counter one of the key pathophysiological developments in ureaemia, namely the underexpression of the parathyroid CaR and partial loss of calcium-regulated PTH suppression. Predictably, calcimimetics lower PTH, calcium and Ca×P, effects that have now been convincingly demonstrated in a number of clinical studies. In this respect, the calcimimetic agents differ qualitatively and quantitatively from both calcium-containing phosphate binders and vitamin D metabolites—which, respectively, raise calcium, lower phosphorus and lower PTH, or raise both calcium and phosphorus while suppressing PTH (Table 3).

Cinacalcet is a new calcimimetic that currently is undergoing clinical trials. In a 6 month randomized, placebo-controlled, double-blind study, 331 haemodialysis patients with uncontrolled SHPT (despite treatment with phosphate binders and/or vitamin D compounds) received once-daily oral doses of cinacalcet (30–180 mg; n = 166) or placebo (n = 165) [17]. Cinacalcet was titrated to achieve a target concentration of intact PTH (iPTH) of ≤250 pg/ml, and efficacy was assessed over weeks 13–26. The study design allowed evaluation of the effect of the addition of cinacalcet to existing standard therapy with vitamin D analogues and phosphate binders. iPTH levels were significantly reduced in patients receiving cinacalcet compared with those receiving placebo (P < 0.001). In all, 46% of patients receiving cinacalcet achieved the target iPTH, compared with 7% of patients receiving placebo (P < 0.001). Significant decreases in plasma calcium and Ca×P were also seen in the cinacalcet-treated patients. Cinacalcet was well tolerated in this study, and most adverse events were mild or moderate in severity. Only nausea and vomiting occurred more frequently in the cinacalcet group than in the placebo group. A similar efficacy and safety profile is emerging from a number of preliminary reports of more recent studies [18–20].

Clinical approaches to SHPT treatment

The simultaneous reductions in PTH, calcium, phosphorus and Ca×P seen in most of the cinacalcet clinical trials to date are actions that effectively complement those of vitamin D compounds in the treatment of SHPT. Proposed detailed algorithms for the use of cinacalcet in vitamin D-treated (Figure 4a) and vitamin D-naïve patients (Figure 4b) are designed to take advantage of different actions of cinacalcet and vitamin D on plasma calcium, phosphorus and Ca×P. These algorithms reflect cinacalcet use in the context of an ongoing clinical trials programme that will ultimately provide guidance on the most effective way to utilize the drug in CKD patients. In time, therefore, simpler algorithms are likely to emerge that will guide the use of cinacalcet in everyday clinical practice.

Cinacalcet use will be determined not only by PTH but also by the prevailing calcium and phosphorus concentrations and by whether or not the patient is already receiving vitamin D. If calcium and phosphorus levels are normal or high, cinacalcet is the logical treatment choice. In these cases, the dose of vitamin D can usually be reduced, or possibly even discontinued. In patients who are vitamin D-naïve, cinacalcet might be an appropriate first-line treatment for SHPT, provided that calcium is not already low (Figure 4b).

If patients present with raised PTH and calcium levels below the K/DOQI target range (<2.1 mmol/l), initial treatment with vitamin D compounds is appropriate. However, if vitamin D therapy fails to suppress PTH levels adequately and/or hypercalcaemia develops, then cinacalcet may also be administered.
Fig. 4. Proposed use of cinacalcet in clinical practice. (a) Algorithm 1, patients already receiving vitamin D. (b) Algorithm 2, patients not receiving vitamin D. PTH concentrations in pg/ml; calcium and phosphorus concentrations in mmol/l.
PTH and bone: is there an ideal concentration?

The aim of SHPT treatment is to achieve a balance of normal bone turnover and serum PTH levels within a defined target range, but with existing therapeutic options this is a difficult challenge. In practice, PTH levels are easily oversuppressed by current therapy with vitamin D and/or calcium-containing phosphate binders, leading to excessively reduced bone turnover. It is not known whether ‘oversuppression’ caused by over-enthusiastic cinacalcet therapy will lead to the same difficulty—the adynamic bone disorder may depend on direct vitamin D (calcitriol) actions on bone cells, as well as on a lack of PTH effect.

Achieving an appropriate balance between bone turnover and treatment of SHPT is difficult. In patients with CKD, normal PTH concentrations in the region of 20–65 pg/ml are associated with little risk of hyperplasia, but may precipitate the adynamic bone disorder. Thus, the target PTH is set higher at 150–300 pg/ml, a level that risks parathyroid hyperplasia. Physicians face a dilemma in that the relationship between PTH and bone turnover may be too variable to allow a specific PTH concentration to predict the underlying level of bone turnover reliably. Substantial inter-patient variability is likely and indicates a clear need for other means to assess bone turnover. It also indicates that slavish adherence to targets should not take precedence over individual patient considerations.

Conclusion

Calcimimetic agents are likely to make it easier to achieve even the more refined treatment targets that have been formulated recently. Properly used, calcimimetics should increase the chances of preventing bone disease and cardiovascular morbidity/mortality in patients with CKD. These are, however, potent agents and will require careful titration to ensure that patients meet and remain within target ranges for PTH, calcium and phosphorus.

Many of the therapeutic targets discussed above reflect greater understanding of how the achievement of the desired therapeutic response leads to improved biological end-points. Few, if any, are convincingly associated with clinical end-points that are likely to be noticed by the patient—genuine clinical benefit is frequently a presumption that still lacks proof. The arrival of safe and effective new treatments is, nevertheless, most welcome and, amongst these, the calcimimetics clearly provide a new and important therapeutic tool.

Conflict of interest statement. None declared.

References