Calcimimetic agents and secondary hyperparathyroidism: treatment and prevention

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Introduction

Calcimimetic agents are small organic molecules that act as allosteric activators of the calcium sensing receptor (CaSR) in the parathyroid glands and other tissues. They lower the threshold for CaSR activation by extracellular calcium ions and diminish parathyroid hormone (PTH) release from parathyroid cells. By targeting the molecular mechanism that modulates PTH secretion on a minute-to-minute basis, calcimimetic compounds offer a novel approach to managing excess PTH secretion in several clinical disorders [1].

Despite abundant in vitro and in vivo experimental work, experience with calcimimetic agents in humans is rather limited. Preliminary reports describe their use in small numbers of patients with primary hyperparathyroidism and in somewhat larger numbers of patients with secondary hyperparathyroidism due to end-stage renal disease [2–4]. Although the duration of treatment in published studies has been confined to 1 or 2 weeks, calcimimetic compounds consistently and reproducibly lower plasma PTH levels when given to normal volunteers or to patients with either primary or secondary hyperparathyroidism. Results from early clinical trials in humans are consistent, therefore, with data obtained in experimental animals [5].

Apart from their effect to diminish PTH secretion, calcimimetic compounds may fundamentally influence the process of parathyroid gland hyperplasia, and their administration to experimental animals can favorably affect skeletal calcium balance. If confirmed by studies in humans, these ancillary features of calcimimetics broaden their appeal as a therapeutic approach to secondary hyperparathyroidism due to chronic renal failure.

Mechanism of action

In parathyroid cells, increases in extracellular calcium concentration activate the CaSR and diminish the release of PTH that is stored within secretory granules [6]. In contrast, decreases in extracellular calcium concentration inactivate the CaSR and promote PTH release. These interactions are summarized by the inverse sigmoidal curve that describes the relationship between ionized calcium and PTH concentrations in vivo and in vitro [6,7]. By lowering the threshold for activation of the CaSR by extracellular calcium ions, calcimimetic agents modify this relationship across a range of extracellular calcium concentrations. In effect, calcimimetic compounds lower the set point for calcium-regulated PTH release rendering parathyroid cells more sensitive to the inhibitory action of calcium.

Changes in PTH release that are mediated through the CaSR occur within seconds or minutes, whereas other more widely recognized modifiers of PTH secretion in vivo lower plasma PTH levels over many hours or several days [8]. Both vitamin D and calcium inhibit pre-pro-PTH gene transcription directly by interacting with distinct upstream negative regulatory elements within DNA. The exogenous administration of vitamin D or calcium can also diminish PTH secretion indirectly by raising serum calcium concentrations, but the effects of these interventions on serum calcium and plasma PTH levels typically unfold over several days. In contrast, calcimimetic agents abruptly lower plasma PTH levels without an antecedent rise in serum calcium concentration.

Calcimimetic agents probably alter signal transduction by inducing conformational changes in the CaSR. They do not appear to compete with calcium for binding to the extracellular domain of the CaSR nor do they activate the receptor in the absence of extracellular calcium ions [9].

Lessons from early clinical trials with calcimimetic agents in secondary hyperparathyroidism

Effect on plasma PTH levels

The calcimimetic agent R-568 was the first drug of this class to be evaluated in humans with secondary hyperparathyroidism due to end-stage renal disease. In two separate studies, plasma PTH levels decreased by as
much as 70–75% from baseline values only 2 h after single oral doses [3,4]. For patients with mild secondary hyperparathyroidism, given doses ranging from 40 mg to 200 mg for two consecutive days, the magnitude of the reduction in plasma PTH levels was largely dose-dependent. Decreases in plasma PTH levels were transient, lasting a few hours, in patients who received low doses of R-568, whereas values remained below pre-treatment levels for 24 h in those given larger doses [3]. The magnitude of the reduction in plasma PTH levels, expressed as a percentage of pre-dose values, has been remarkably consistent regardless of the biochemical severity of secondary hyperparathyroidism in patients given either R-568 or various doses of the second generation calcimimetic compound AMG 073 [4,17]. Subsets of individuals who are resistant or refractory to the biological actions of calcimimetics have yet to be identified [3–5]. Although the number of patients studied to date is relatively small, such findings suggest that reductions in CaSR expression in the parathyroid glands, such as those reported in tissues removed surgically from patients with either primary or secondary hyperparathyroidism, do not substantively influence the in vivo response to calcimimetics [10].

Calcimimetic agents produce rapid reductions in plasma PTH levels within a few hours but values increase towards pre-dose levels after 18–24 h [3,4]. Measurements in blood samples obtained 24 h after the preceding dose underestimate, therefore, the extent to which plasma PTH levels have been lowered during the daily dosing cycle. Although practical and convenient for the ongoing clinical management of patients with secondary hyperparathyroidism, pre-dose PTH determinations may not fully reflect the impact of calcimimetic-induced changes in PTH secretion on bone histology or on the rates of bone formation and turnover in patients given regular doses of calcimimetic compounds. Considerable additional work will be required to establish the relationship between plasma PTH levels and the corresponding histological features of renal osteodystrophy in patients treated with calcimimetics.

When given as single daily doses to patients with end-stage renal disease, calcimimetic agents induce an oscillatory day-to-day hormone concentration profile with PTH levels falling rapidly by as much as 50–70% shortly after drug administration then rising subsequently later in the day [3,4]. In contrast, plasma PTH levels vary much less in untreated patients and in patients receiving vitamin D sterols with smaller minute-to-minute fluctuations of 10–15% reflecting pulsatile PTH secretion [11]. The impact on bone formation and turnover and on various biochemical markers of mineral metabolism due to large intra-day variations in plasma PTH levels during calcimimetic therapy has yet to be determined in patients with secondary hyperparathyroidism. Variable rather than constant hormone concentrations may exert substantially different effects on osteoclastic and osteoblastic activity. Moreover, oscillating plasma PTH levels favorably influence bone mass in certain types of osteoporosis in humans and they are associated with increases in bone mass in experimental animals [12–14]. Whether similar trophic skeletal effects occur in patients with chronic renal failure is not yet known.

**Effect on blood ionized and serum calcium concentrations**

When given repeatedly and/or in sufficiently large doses to humans or experimental animals, calcimimetic compounds not only lower plasma PTH levels but also reduce blood calcium concentrations [3–5]. Decreases in serum calcium follow temporally the decline in plasma PTH levels. In patients with secondary hyperparathyroidism, blood calcium concentrations reach a nadir 4–8 h after individual doses.

The effect of calcimimetics to lower serum calcium levels represents a potentially dose-limiting side effect of treatment and it largely accounts for deliberate progress in the clinical development of these compounds to manage excess PTH secretion due to secondary hyperparathyroidism. Studies thus far have used modest doses to reduce the risk of hypocalcaemia and to assure the safety of study participants until greater clinical experience can be obtained.

The mechanism responsible for the fall in blood calcium concentration after doses of calcimimetics remains uncertain. This response may simply reflect decreases in PTH-mediated calcium efflux from bone similar to those that occur when plasma PTH levels are lowered abruptly after surgical parathyroidectomy. The finding that blood ionized calcium concentrations decline after plasma PTH levels fall following drug administration is consistent with such a mechanism. Alternatively, the activation of calcium-sensing receptors in bone, in the gastrointestinal tract or in other tissues could also contribute [15].

Recent preliminary observations suggest that the calcium-lowering effect of calcimimetic agents can be attenuated by using small initial doses and by making subsequent gradual upward dosage adjustments [16]. A similar approach is used commonly to minimize the risks of hypercalcaemia and/or hyperphosphataemia during the treatment of secondary hyperparathyroidism with vitamin D sterols. In an 18-week placebo controlled trial with the calcimimetic agent AMG 073, plasma PTH levels were lowered by 25–30% from pre-treatment values, whereas serum total calcium concentrations decreased by an average of only 0.3–0.4 mg/dl, or 0.075–0.1 mmol/l [16]. None of the patients developed signs or symptoms of hypocalcaemia. If confirmed in additional studies, such findings suggest that calcimimetics represent a viable and acceptably safe alternative to vitamin D as primary therapy for secondary hyperparathyroidism.
Effect on serum phosphorus levels

In two recent preliminary studies, serum phosphorus concentrations decreased unexpectedly by 20–30% in patients treated for either 8 days or 18 weeks with the calcimimetic agent AMG 073, whereas values were unchanged or rose modestly in those given placebo [16,17]. In both studies, measurements of the calcium–phosphorus ion product in serum also declined during treatment with AMG 073. Such findings suggest that calcimimetic therapy can substantially improve several biochemical disturbances that have been associated with adverse clinical outcomes in patients with secondary hyperparathyroidism due to end-stage renal disease [18–20]. In future clinical trials it may be possible to assess the impact of calcimimetic therapy on the development and/or progression of cardiac valve, vascular and other soft-tissue calcifications, using new radiographic imaging techniques.

Parathyroid gland hyperplasia

The development of parathyroid gland hyperplasia is an important contributor to excess PTH secretion in patients with secondary hyperparathyroidism, and it often accounts for disease progression. There is evidence, however, that calcimimetic agents can impede this process in sub-totally nephrectomized rats [21,22]. Although vitamin D sterols such as calcitriol have traditionally been considered to be key modifiers of parathyroid gland hyperplasia, recent observations challenge this view. Mice that are homozygous for inactivating mutations of the vitamin D receptor (VDR) develop hypocalcaemia, severe secondary hyperparathyroidism and marked parathyroid gland hyperplasia, findings consistent with the inability of target tissues to respond to vitamin D in the absence of a functional VDR. Maintaining animals on a high-calcium diet supplemented with lactose to promote passive intestinal calcium absorption prevents these manifestations in VDR knockout mice [23]. Such findings strongly suggest that calcium, probably acting through the CaSR, is a more important determinant of parathyroid gland hyperplasia than vitamin D. Calcimimetic agents by signaling through the CaSR may provide a means for controlling parathyroid hyperplasia, particularly during the course of progressive renal disease.

Summary

Calcimimetic agents represent a novel therapeutic approach to secondary hyperparathyroidism. They directly target the molecular mechanism that regulates PTH secretion from the parathyroid glands. In addition to controlling PTH secretion, treatment with calcimimetic agents may attenuate or prevent the development of parathyroid gland hyperplasia and maintain or enhance bone mass. Although much has yet to be learned about the clinical use of these compounds, calcimimetic agents represent a potentially attractive alternative to vitamin D sterols for managing secondary hyperparathyroidism due to chronic renal failure.

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References

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