

## COMMENTARIES

### Medical Therapy of Primary Hyperparathyroidism: Are We There Yet?

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**Commentary on:** Peacock M, Bilezikian JP, Klassen PS, Guo MD, Turner SA, Shoback D. Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2005; 90:135-41.

Developing an effective “medical parathyroidectomy” for treating primary hyperparathyroidism (HPT) has been an elusive goal. Estrogens and bisphosphonates lower serum calcium modestly, if at all, and have not been accepted as alternatives to parathyroidectomy in HPT. Indeed, a skilled parathyroid surgeon can successfully excise the offending parathyroid tissue in 95% of cases. Furthermore, recent advances in parathyroid localization techniques (e.g., technitium 99m sestamibi) and the use of minimally invasive parathyroidectomy in cases with successful localization have made it possible for an experienced parathyroid surgeon to perform outpatient parathyroidectomy with minimal morbidity. Is there a need for a medical treatment for primary hyperparathyroidism?

As pointed out by Peacock *et al.* (1), a substantial reservoir of patients with proven HPT are candidates for medical therapy because they have previously failed surgery, refuse parathyroid exploration, or have contraindications to surgery. Moreover, most patients with newly diagnosed HPT have mild asymptomatic disease (2) and do not fulfill current guidelines for surgery (e.g., they are older than age 50 years, serum calcium is elevated < 1 mg/dL, urine calcium is < 400 mg/day, creatinine clearance is decreased < 30%, and bone mineral density [BMD] shows a T score > -2.5) (3). Effective medical treatment of the latter patients might

potentially reverse any parathyroid hormone-induced bone loss, because there is about a 10% increase in BMD within one to two years after parathyroidectomy (4). Successful medical treatment might also forestall the progression of HPT to the point where surgery is warranted, which occurs in about one-fourth of patients with asymptomatic HPT followed expectantly for 10 years (2). Medical parathyroidectomy might also be useful in patients with lithium-induced hypercalcemia and potentially in those with mild HPT and vague nonspecific (but nevertheless troubling) symptoms of uncertain relationship to the HPT, in whom a diagnostic test could be useful. Finally, the increasing recognition that normocalcemic HPT can cause clinically significant bone loss, particularly in postmenopausal women, represents another clinical setting wherein medical treatment of HPT might provide a valuable therapeutic option (5). These considerations have driven the search for an effective medical treatment for HPT.

The cardinal biochemical abnormalities of HPT (e.g., hypercalcemia with an inappropriately high or normal PTH level) result from varying combinations of increased parathyroid cell mass and defective parathyroid  $Ca^{2+}$ -sensing manifested by an increased set-point (i.e., the level of  $Ca^{2+}$  half-maximally suppressing PTH release) (6). The latter can be viewed as a form of extracellular  $Ca^{2+}$  “resistance.” The parathyroid cell “senses” the ambient

level of  $Ca^{2+}$  through the calcium-sensing receptor (either CaSR or CaR), a cell surface G protein-coupled receptor that is the body's "thermostat for  $Ca^{2+}$ "(7). In response to hypocalcemia, the CaR signals to the parathyroid cell that more PTH is needed, thereby increasing PTH secretion, PTH gene expression, and parathyroid cellular proliferation. Although there is reduced expression of the parathyroid CaR in HPT (8), the receptor's role in the defective  $Ca^{2+}$ -regulated PTH secretion and increased parathyroid cell mass in HPT remains to be firmly established. Nevertheless, preventing or correcting these abnormalities in parathyroid cell function would be the "gold standard" for an effective medical treatment of HPT.

Prior to the advent of the so-called calcimimetics, which are allosteric activators of the CaR (9), there was no way to effectively reduce parathyroid hyperfunction in HPT. Bisphosphonates effectively reduced bone turnover and increased BMD but had no effect on serum  $Ca^{2+}$  in a recent study of patients with mild HPT (10). Estrogens can lower serum  $Ca^{2+}$  modestly without increasing PTH, raising the possibility that they shift the parathyroid set-point to the left (11). Calcimimetics, such as cinacalcet, however, much more effectively correct the functional abnormalities in HPT. By binding to the transmembrane domains of the CaR, cinacalcet sensitizes the receptor to  $Ca^{2+}$ , thereby lowering PTH release at any given level of  $Ca^{2+}$  and preventing (but not reversing) parathyroid cellular hyperplasia in animal models of uremic hyperparathyroidism (9).

An earlier 26-week study (12) showed that administering cinacalcet effectively reduced the severity of secondary hyperparathyroidism in patients undergoing dialysis, but no long-term study of their use in HPT had been carried out. The present study extends to 52 weeks the earlier work of Peacock *et al.* (13) showing that cinacalcet administered for 15 days normalized serum calcium concentration, while reducing PTH levels by about 50% at four hours after a dose of the drug. In the present study, mean serum calcium concentration in the treated group was in the

middle of the normal range, and 88% of these subjects achieved normocalcemia during the maintenance phase of the study vs. only 5% of the subjects in the placebo group. The principal side effect of the drug was self-limited nausea, which occurred in 28% of cinacalcet-treated subjects and 16% of those in the placebo group. It may seem surprising that there was only a 7% reduction in serum PTH when measured 24 hours after the prior day's dose. This finding, however, reflects the fact that the effect of the drug on the parathyroid cell had worn off by that time. At earlier times (*e.g.*, two hours), when the blood level of the drug was higher, the PTH level decreased by about 50%. In effect, the leftward shift in the parathyroid set-point induced by the drug is a moving target, exhibiting a maximal shift to the left shortly after administration and then gradually shifting back to the right as the drug wears off. If one measured PTH at frequent intervals, the integrated level in the treated patients would presumably be reduced more substantially. Not surprisingly, serum phosphorus increased in the treated patients, owing to an increase in renal tubular maximum for phosphate that resulted from a lower mean integrated PTH. No change was seen in 24-hour renal calcium excretion in the treated subjects. Nevertheless, it is hard to tease out whether cinacalcet had any effect on renal distal calcium handling -- an important site of renal expression of the receptor, where it promotes calciuria -- because several parameters changed that could have affected renal calcium handling. The decrease in serum calcium concentration would decrease the filtered load, reducing calcium excretion; conversely, the decrease in mean serum PTH would enhance calcium excretion. From a clinical perspective, the lack of change in urinary calcium excretion is reassuring with regard to the potential long-term risk of renal stones. Serum 1,25-dihydroxyvitamin D did not change with treatment, thereby not affecting intestinal absorption of calcium, even though a decrease in serum PTH and an increase in serum phosphorus might reasonably have been expected to reduce its level.

There were ~30% increases in both serum bone-specific alkaline phosphatase and

NTx, findings consistent with the lack of change in Z scores observed in the lumbar spine, total femur, and distal radius of the cinacalcet-treated group (as well as the control group). It is curious, however, that markers of bone turnover increased in the cinacalcet group, in the face of reduced PTH and unchanged 1,25-dihydroxyvitamin D levels. There is considerable controversy as to whether osteoblasts and osteoclasts express the CaR (14;15); however, the increased bone turnover seen in the treated group raises the possibility that the drug may act directly on bone cells and/or their precursors (e.g., monocytes express CaR) or perhaps indirectly through other cells (e.g., stromal cells) in the bone microenvironment (14). Alternatively, perhaps the inverse pulses of PTH resulting from the pharmacokinetics of the drug activated bone turnover (16). One thing, however, is clear: medical parathyroidectomy does not produce the same increase in BMD seen in patients undergoing successful parathyroidectomy -- at least within the first year (4).

What can we take away from the study of Peacock *et al.* (1)? As in secondary

hyperparathyroidism, cinacalcet effectively controls biochemical hyperparathyroidism in HPT, producing normocalcemia in the great majority of patients who are treated with the starting dose of 30 mg/day. Cinacalcet exerts its calcium-lowering effect without producing hypercalciuria and maintains stable bone density in a setting wherein an increase might have otherwise been expected based on the follow-up of patients cured of their HPT by surgery. Therefore, although not yet approved by the US Food and Drug Administration for use in HPT (other than in the setting of parathyroid cancer), cinacalcet does have documented efficacy and safety during a one-year trial. Further experience with the drug should elucidate its place in the therapy of patients with failed parathyroid surgery, those not wishing to undergo surgery, those in whom surgery is contraindicated, and other possible indications noted at the outset of this commentary. Considerable further experience will be needed to assess its long-term safety and efficacy and any impact that it might have on putative long-term complications of HPT, such as the decrease in longevity noted in some studies in Europe (17).

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