

Medical treatment of Primary Hyperparathyroidism

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Primary hyperparathyroidism (PHPT) is known as an endocrinopathy diagnosed by elevated serum calcium and inappropriately high normal or increased serum PTH. Disease complications vary from cases of asymptomatic disease to cases with classical symptoms as renal stones, loss of bone mass, neurocognitive symptoms and fractures.

The cure of PHPT is parathyroidectomy, but in case of contraindications of surgery, in patients who refuse surgery, or do not meet current operative guidelines and in the rare cases where parathyroidectomy fail to cure, medical treatment is an option (1).

The Calcium-sensing receptor (CaSR) is expressed on the parathyroid cell and seems to be the principal regulator of the PTH secretion (2). However CaSR is also expressed in the intestine and kidneys. The enhanced sensitivity towards extracellular calcium leads to decreased calcium reabsorption by the renal tubules. Calcimimetics has been developed by the pharmaceutical industry enables the clinicians to quickly and directly reduction of the patients elevated serum PTH levels by the compounds binding to CaSR and thereby leading to an increasing sensitivity to extracellular Calcium (3). Cinacalcet is approved for reduction of hypercalcemia in patients with PHPT for whom parathyroidectomy is indicated on the basis of calcium levels but in whom surgery is clinically inappropriate or is contraindicated.

Shoback et al have demonstrated that short-term (15 d) cinacalcet treatment reduced serum Calcium and serum PTH in patients with PHPT (4). The same research group showed in a later 1-year RCT in patients with mild to moderate PHPT that cinacalcet almost normalized serum Calcium and decreased, but did not normalise, serum the PTH levels. This could be due to the decreased renal reabsorption. (5).

In a newly published study by Peacock et al (6) they have assessed long-term tolerability, safety, and efficacy of cinacalcet evaluating serum Calcium, serum PTH and BMD in patients with mild to moderate PHPT. Patients with PHPT who participated in the 1-year RCT (5) were followed in an open-label extension lasting an additional 4.5 years. The study confirms the observations from the 1-year study. Cinacalcet can almost normalize serum Calcium and decrease, but not normalise, serum the PTH levels for up to 5 years. However, BMD is not affected by the treatment (6).

One of the challenges in Cinacalcet treatment is the side effects. In the study of Peacock 99% had mild side effects, most commonly nausea (36%) (6).

An American multicentre retrospective study has in seventy PHPT patients treated with Cinacalcet, found that the medical treatment were stopped in 26% (19 patients) due to side effects i.e. nausea and vomiting. Only 6% (3 patients) had relieve of symptoms and none had gained BMD. All patients had a curative parathyroidectomy after medical treatment which in all cases lasted more than 1,5 years. These patients where followed prospectively after surgery and all had partial or complete resolution of symptoms within 3 months (7). However, the patients in this study were all referred to parathyroidectomy due to failed medical treatment.

Silverberg et al have shown that patients with intractable parathyroid carcinoma, Cinacalcet treatment reduces hypercalcemia in approximately two third of patients (8). Mayes et al have shown that cinacalcet treatment is effective in complex primary hyperparathyroidism patients like MEN-1. Both studies were open labelled (9).

In conclusion,

At the present time Cinacalcet is a secondary choice in managing PHPT where surgery remains the superior treatment option.

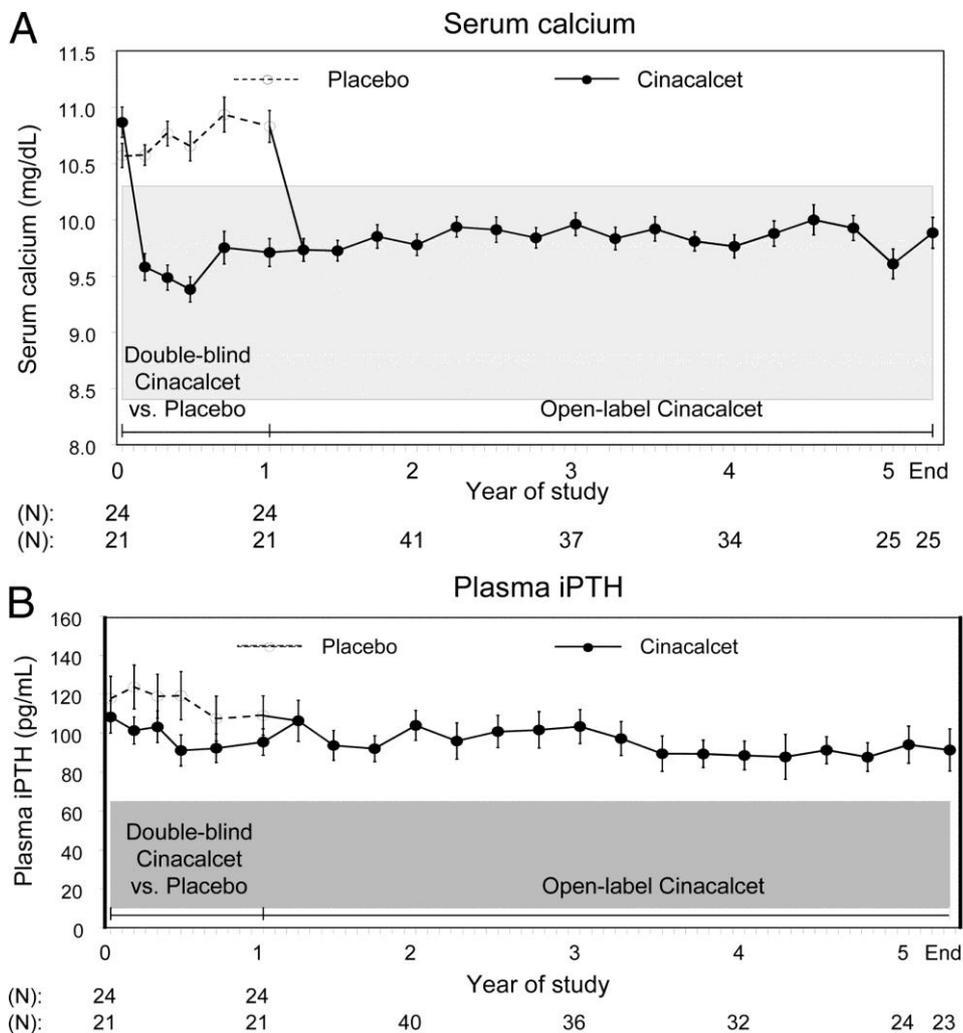
In patients where surgery is not possible calcium levels and PTH levels can be reduced by cinacalcet and for some patients symptoms can be reduced. However, osteoporosis should be treated, as in osteoporosis patients in general as Cinacalcet have no positive effect on BMD.

In patients with parathyroid cancer Cinacalcet is effective in lowering serum calcium and is easier tolerated than in PHTP patients.

We need more randomized controlled studies before we know when or if Cinacalcet has a beneficial effect on the long time risk factors for PHPT patients as well as how many patients can get symptom relief.

Figure 1.

Pre-dose serum Ca and plasma intact PTH levels over time in 5 years RCT (6)



References.

1. Bilezikian JP, Khan AA, Potts Jr JT 2009 Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop. *J Clin Endocrinol Metab* 94:335–339
2. Brown EM, Gamba G, Riccardi D, Lombardi M, Butters R, Kifor O, Sun A, Hediger MA, Lytton J, Hebert SC 1993 Cloning and characterization of an extracellular Ca²⁺-sensing receptor from bovine parathyroid. *Nature* 366:575–580.
3. Nemeth EF, Fox J 1999 Calcimimetic compounds: a direct approach to controlling plasma levels of parathyroid hormone in hyperparathyroidism. *Trends Endocrinol Metab* 10:66–71.

4. Shoback DM, Bilezikian JP, Turner SA, McCary LC, Guo MD, Peacock M 2003 The calcimimetic cinacalcet normalizes serum calcium in subjects with primary hyperparathyroidism. *J Clin Endocrinol Metab* 88:5644–5649.
5. Peacock M, Bilezikian JP, Klassen PS, Guo MD, Turner SA, Shoback D 2005 Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism. *J Clin Endocrinol Metab* 90:135–141.
6. Peacock M, Bolognese MA, Borofsky M et al. Cinacalcet treatment of primary hyperparathyroidism: biochemical and bone densitometric outcomes in a five-year study. *J Clin Endocrinol Metab*. 2009; 94(12): 4860-7.
7. Norman J, Lopez J and Politz D Cinacalcet (Sensipar) Provides no Measurable Clinical Benefits for patients with Primary Hyperparathyroidism and may Accelerate Bone Loss with Prolonged Use. *Ann Surg Oncol*. 2012; 19: 1466-1471
8. Silverberg SJ, Rubin MR, Faiman C, Peacock M et al. Cinacalcet Hydrochloride REduces the Serum Calcium Concentration in Inoperable Parathyroid Carcinoma. *JCEM* 2007; 92(10): 3803-3808
9. Moyes VJ et al. Clinical use of Cinacalcet in MEN 1 Hyperparathyroidism. *Int J Endocrinol*. 2010; 906163