Clinical effects of calcimimetics in hyperparathyroidism

M. Peacock

Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA

Keywords: Calcimimetics, Primary Hyperparathyroidism, Secondary Hyperparathyroidism, Parathyroid Cancer

Hyperparathyroidism is a term that encompasses several conditions, the essential features of which are an increase both in secretion rate of PTH and in mass of the parathyroid tissue. Bone is a major target organ for PTH and skeletal disease in hyperparathyroidism is common. In secondary hyperparathyroidism the stimulus to increased PTH secretion and gland hyperplasia is chronic hypocalcemia and the gland mass may increase over 20-fold in weight. Chronic renal failure causes the severest form of secondary hyperparathyroidism, particularly if the patient is managed by long-term dialysis. In primary hyperparathyroidism there is a primary increase in parathyroid gland mass causing an increase in PTH secretion which in turn leads to hypercalcemia. Depending on the level of increase in PTH secretion the disease complications can range from mild to severe. Very rarely the cells may undergo cancerous change and maintain their ability to secrete PTH whilst spreading locally in the neck or metastasising, parathyroid cancer. In these cases the disease is always severe. In some patients, the increased parathyroid tissue in secondary hyperparathyroidism may become autonomous. Hypocalcemia converts to hypercalcemia and the condition is referred to as tertiary hyperparathyroidism. In primary and tertiary hyperparathyroidism, the increase in PTH secretion remains responsive to changes in serum ionized calcium concentrations but the dose-response curve is shifted to the right.

Secondary and tertiary hyperparathyroidism lead to renal osteodystrophy, osteoporosis and increased risk of fracture. Despite dialysis treatment these remain major clinical problems. Until very recently surgical removal of parathyroid glands, suppression of the parathyroid tissue by 1,25 vitamin D or its analogues, and maintenance of normophosphatemia by reduction of dietary phosphate absorption have been the mainstay of management. However, these treatment modalities are only partially successful. Further, if serum PTH is reduced to normal or low levels, there is an increased risk of developing adynamic bone disease. Thus, there remains a pressing need to regulate serum PTH levels more precisely. In primary hyperparathyroidism surgical removal of the abnormal parathyroid is usually curative. However a number of patients fail surgery or are unsuitable candidates for surgery and in these, reduction of serum PTH and calcium are important if osteoporosis and fracture, hyperparathyroid bone disease, and other features of the disease are to be avoided. Metastatic parathyroid cancer is resistant to anti-cancer treatment and these patients usually die of hypercalcemia. Normalization of hypercalcemia greatly improves the patient’s quality of life although it does not affect the progression of the cancer. Thus, there is great clinical interest in the use of calcimimetics in all these hyperparathyroid diseases.

The development of a clinically useful calcimimetic from the time of cloning the CaR to FDA approval has been rapid. A cell surface receptor for calcium on the parathyroid cell was predicted from early studies on rapid intracellular calcium mobilization by extracellular calcium. The CaR was cloned in 1993, and oral calcimimetics with potent and selective on the parathyroid gland were rapidly developed soon afterwards. Human studies using the second generation calcimimetic AMG 073 then followed in secondary hyperparathyroidism, primary hyperparathyroidism, and parathyroid cancer. These led to the FDA approval of cinacalcet hydrochloride (SensiparTM) in 2004 for treatment of secondary hyperparathyroidism and parathyroid cancer.

This presentation will cover the studies using cinacalcet in humans with hyperparathyroid disorders with a focus on the effect of cinacalcet on the associated bone disorders.

References


