Cinacalcet

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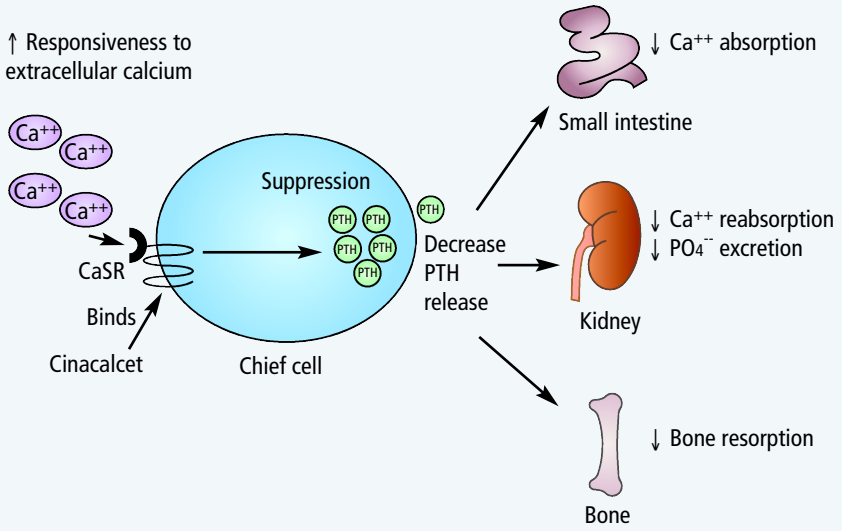

NOTES. Cinacalcet is an allosteric agonist at the calcium sensing receptor (CaSR) on the surface of chief cells in the parathyroid glands. Cinacalcet binds to the transmembrane portion of the CaSR, rendering the receptor more responsive to extracellular calcium resulting in intensified suppression of PTH release from intracellular granules.

Figure 1. The pharmacological action of cinacalcet

Introduction

Parathyroid hormone (PTH) is secreted from the chief cells of the parathyroid glands. Excessive release of PTH may be due to a primary pathology affecting the glands, or may be secondary to other metabolic disturbances. Primary hyperparathyroidism is the inappropriate secretion of PTH and is most commonly due to parathyroid adenoma. Less commonly, it can occur in patients with the multiple endocrine neoplasia-1 (MEN1) group of tumours (parathyroid, pancreatic, pituitary, duodenum and other sites) or in parathyroid carcinoma.

Secondary hyperparathyroidism is common in renal impairment due to hyperphosphataemia and vitamin D deficiency and is associated with alterations in bone turnover, bone mineralisation and vascular calcification. Observational data in the haemodialysis population have shown hyperparathyroidism, elevated serum calcium (Ca^{2+}), elevated serum phosphate (PO_4^-) and elevated $Ca^{2+}xPO_4^-$ product are associated with adverse clinical outcomes: cardiovascular disease, fractures and mortality.

Pharmacology

In the kidneys, PTH acts to increase production of 1,25 dihydroxyvitamin D3 which in turn enhances renal phosphate excretion, reduces renal calcium excretion, increases calcium and phosphate absorption from the gut and further increases calcium mobilisation from bone. 1,25 dihydroxyvitamin D3 reduces PTH production in chief cells by negative feedback at the gene transcription level.

The calcium sensing receptor (CaSR) is a cell membrane receptor that rapidly suppresses release of pre-formed PTH in response to tiny rises in extracellular calcium concentration. Following the cloning of the CaSR in 1993, a number of calcimimetics were developed. First generation calcimimetics had poor bioavailability with unpredictable pharmacokinetics and none were marketed.

Cinacalcet is a second-generation calcimimetic with predictable bioavailability and pharmacokinetics. Following oral administration, the bioavailability is around 25% and, with a half-life of 30–40 hours, steady state is reached in seven days. The pharmacokinetic profile is not significantly

affected by renal impairment or dialysis. Cinacalcet undergoes hepatic metabolism by enzymes from the cytochrome P450 system and significant hepatic impairment increases exposure. Cinacalcet inhibits CYP2D6 and may affect metabolism of drugs including flecainide and tricyclic antidepressants. Drugs that may affect the metabolism of cinacalcet include erythromycin and itraconazole.

Cinacalcet acts on the CaSR to suppress the release of PTH at any given concentration of extracellular calcium. Cinacalcet is an allosteric agonist at the CaSR (Figure 1). Cinacalcet binds to the transmembrane portion of the CaSR rendering the receptor more responsive to extracellular calcium resulting in intensified suppression of PTH release from intracellular granules of chief cells. Cinacalcet does not directly affect calcium binding sites.

Modest asymptomatic hypocalcaemia is common; however, significant hypocalcaemia can occur. Serum calcium should be monitored within one week of introduction or dose alteration and less frequently in continued use.

Cinacalcet has been approved by the US Food and Drug Administration and by the European Medicines Agency for treatment of persistent hyperparathyroidism in dialysis patients and for treatment of primary hyperparathyroidism, including parathyroid carcinoma, where parathyroidectomy is unsuccessful or inappropriate.

Trials of safety and efficacy

Primary hyperparathyroidism

In patients with primary hyperparathyroidism and preserved renal function, cinacalcet reduces serum PTH and subsequently serum $Ca2^{+}$. A fall in serum PTH reduces urinary PO_4^{-} excretion, often correcting the modest hypophosphataemia seen in many of these patients.

Peacock *et al.*[1] reported a randomised, double-blind, placebo controlled trial of cinacalcet in primary hyperparathyroidism. After 12 weeks' dose titration and 28 weeks' follow up, patients in the cinacalcet group were significantly more likely to achieve normocalcaemia ($p<0.001$) and there was a significant fall in PTH ($p<0.01$). Similar biochemical effects have been reported from other smaller trials; however, benefits on clinical endpoints have not been clearly demonstrated.

Secondary hyperparathyroidism

Early studies in the haemodialysis population demonstrated that cinacalcet significantly reduces PTH, Ca^{2+}, PO_4^{-} and $Ca^{2+}xPO_4^{-}$ product. These studies also highlighted the dose-dependent gastrointestinal side effects (nausea, diarrhoea, vomiting) which lead to a minority of patients discontinuing treatment.

Cunningham *et al.*[2] reported analysis of safety data from four early randomised control trials, with a total of 1184 patients randomised, that suggested improved clinical outcomes with reduced risk of fracture, cardiovascular hospitalisation and parathyroidectomy in patients randomised to cinacalcet.

The EVOLVE study[3] reported findings in 3883 patients undergoing haemodialysis studied over 64 months. Patients were randomised to receive standard therapy plus placebo or standard therapy plus cinacalcet. The primary composite endpoint was time to death or first non-fatal cardiovascular event. There was no significant difference in primary endpoint rates between the two groups in the unadjusted intention to treat analysis ($p=0.11$). There was a significantly higher rate of hypocalcaemia and gastrointestinal side effects in the cinacalcet group.

Specific evidence for use in diabetes

Diabetes is the leading cause of end-stage renal failure in Europe, North America, Australia and many other regions. As a result, patients with diabetes formed a significant proportion of patients in both the Cunningham *et al.*[2] analysis and EVOLVE at 31% and 34% respectively. Neither trial reported subgroup analysis in those with diabetes.

Discussion

Modest variation between international guidelines on the treatment of secondary hyperparathyroidism in renal disease reflects the lack of a clear evidence base. However, there is agreement that excessively elevated PTH should be controlled and serum Ca^{2+} and PO_4^{-} should be maintained near to normal. Conventional treatment with dietary phosphate restriction, phosphate binders and vitamin D analogues can be limited by hypercalcaemia.

The biochemical effects of cinacalcet are well documented and it has a role in managing resistant hyperparathyroidism. A proportion of such patients will have symptomatic hypercalcaemia and the potential symptomatic benefit in this subgroup is clear.

The role of cinacalcet in reducing long-term adverse outcomes of hyperparathyroidism is less clear. The last decade has seen attempts to tackle the excess cardiovascular risk in patients with chronic kidney disease and clinicians using cinacalcet will be disappointed that efforts to reduce PTH with cinacalcet have not been shown to reduce mortality. The EVOLVE trial also serves to highlight the magnitude of the challenge, with over 48% of patients reaching the primary composite endpoint of cardiovascular event or death. The objective for the next decade will be to expand our understanding of bone turnover and vascular risk in chronic kidney disease. This will undoubtedly bring into question the timing of intervention and whether there are other potential targets for therapy.

Key points

- Cinacalcet can be used in primary or secondary hyperparathyroidism to treat hypercalcaemia where parathyroidectomy has failed or is inappropriate
- Cinacalcet can cause hypocalcaemia and serum calcium should be monitored with introduction or dose adjustment
- Cinacalcet is used alongside dietary phosphate restriction, phosphate binders and correction of vitamin D deficiency, as part of an individualised treatment regimen for management of mineral metabolism in patients receiving dialysis

Declaration of interests

There are no conflicts of interest declared.

References

References are available online at www.practicaldiabetes.com.

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References

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