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**EDİTÖRE MEKTUP / LETTER TO THE EDITOR**

# Clinical Pharmacokinetic and Pharmacodynamic Profile of Cinacalcet

## Cinacalcet'in Klinik Farmakokinetik ve Farmakodinamik Profili

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The purpose of this letter is to explain clinical pharmacokinetic, pharmacodynamic profile and indication of cinacalcet therapy particularly in chronic kidney disease. Chronic kidney disease and progressive renal failure are associated with phosphate retention and impaired formation of active vitamin D, or calcitriol (1α-25-dihydroxyvitamin D), leading to hypocalcemia, increased secretion of parathyroid hormone, and, eventually, hyperplasia of the parathyroid gland. Secondary hyperparathyroidism is frequent and progresses over time in patients with chronic kidney disease. It develops as a result of disturbance in parathyroid hormone, calcium, phosphate, and vitamin D homeostasis. Risk factors are mainly hyperphosphatemia and increased calcium-phosphate products[1].

The related mineral and bone disorders are early onset, common and serious complications because of their significant impact on morbidity and mortality due to skeletal (renal osteodystrophy, loss of bone mineral density, bone pain, and fractures) and extra skeletal manifestations particularly cardiovascular manifestations[2,3]. Conventional treatment with a calcium supplement, phosphate binders and active vitamin D derivatives lead in part to amelioration of secondary hyperparathyroidism, but are simultaneously associated with unacceptable side-effects, including hypercalcemia, hyperphosphatemia, and increased calcium-phosphate products[1].

Recent approaches to its management include calcimimetics which are drugs increasing the activity of the calcium-sensing receptor by enhancing allosterically the action of calcium ions at this receptor[4,5,6,7]. The calcium-sensing receptor residing on parathyroid cells belongs to the super family C of G-protein-coupled receptors, all members of which have a large extracellular domain called Venus flytrap, akin to bacterial nutrient sensor[5,6]. The activation of the calcium-sensing receptor by small changes in extracellular calcium regulates parathyroid hormone, calcitonin secretion, urinary calcium excretion, and ultimately, bone turnover[8].

Out of several small molecules that act as calcimimetics, Cinacalcet (Sensipar/ Mimpara) is the first and most extensively studied[6]. Cinacalcet is orally administered at the dose of 30-180 mg daily. Peak plasma concentrations occur within 2-6 hours[9]. The absolute bioavailability is 20-25%. The terminal elimination half-life is 30-40 hours, and steady-state concentrations are achieved within 7 days[9]. The pharmacokinetic of cinacalcet is not notably affected by varying degrees of renal impairment, method of dialysis (haemodialysis and peritoneal dialysis), age, sex, body weight, race and mild hepatic impairment. Moderate or severe hepatic impairment increases the exposure by approximately 2- and 4-fold[9].

Cinacalcet is extensively metabolised by multiple hepatic cytochrome P450 enzymes with than 1% of the parent drug is excreted in the urine[9]. Therefore, cinacalcet has interactions with cytochrome P450 inhibitor medications (e.g.ketoconazole, Itraconazole, erythromycin) or medications metabolized by cytochrome P450 enzymes (e.g. lecainide, vinblastine, thioridazine and most tricyclic antidepressants) and dose adjustments of cinacalcet and these medications may be necessary[9]. Cinacalcet has no significant interaction with calcium carbonate or non calcium- non aluminium phosphate binder (sevelamer hydrochloride) [9].

Cinacalcet is approved for the treatment of secondary hyperparathyroidism in patients with end stage chronic kidney disease receiving dialysis and to lower hypercalcaemia in patients with parathyroid carcinoma[5]. In end stage chronic kidney disease receiving dialysis, cinacalcet is a very effective therapeutic tool in mineral and bone disorder by suppressing bone turnover and demineralisation and effectively reduces with stable suppression of serum parathyroid hormone[5]. In fact, parathyroid hormone concentrations are greatest before dose administration of cinacalcet. Nadir parathyroid hormone levels occur approximately 2-3 hours after dosing[9]. However for lowering parathyroid hormone, available evidence from recent studies suggests that combination therapy calcimimetics and active vitamin D derivatives

should be preferred to single drug treatment because of less side-effects and greater efficiency in controlling parathyroid over function[4]. In contrast to the effect of active vitamin D derivatives, cinacalcet simultaneously decreases calcium, phosphate and calcium- phosphate product levels[4,11,12]. Additionally, some studies have shown that cinacalcet reduce the risk of vascular calcification, parathyroidectomy, bone fracture, cardiovascular hospitalisation and decrease parathyroid hyperplasia among long-term dialysis patients with secondary hyperparathyroidism[2,4,11,13].

In chronic kidney disease patients not yet on dialysis, treatment of secondary hyperparathyroidism should rather be focused on dietary phosphate restriction than on cinacalcet[10]. In kidney transplantation, cinacalcet prevent nephrocalcinosis of the graft[10].

Therapeutic monitoring if treatment with cinacalcet includes measurement of serum calcium concentrations and parathyroid hormone especially if the patient initiates or discontinues therapy with a strong Cytochrome P450 inhibitor[5,9].

Recent case reports providing Cinacalcet in calciphylaxis which is a severe disease with a mortality rate of 80% in the first year presenting with ischemia and necrosis of the skin, subcutaneous adipose tissue, muscles and rarely viscera[14]. Cinacalcet don't affect the death rate[13].

Because of its high cost, cinacalcet cannot be widely used in developing countries. Therefore its prescription should be limited to patients undergoing dialysis due to secondary hyperparathyroidism associated with refractory hyperphosphatemia and hypercalcemia[15]. Dietary phosphate restriction, conventional treatment and adequate hemodialysis remain the main strategy for the control of hyperphosphatemia and secondary hyperparathyroidism[13].

In conclusion, cinacalcet is indicated particularly in treatment of secondary hyperparathyroidism in end stage chronic kidney disease receiving dialysis and in kidney transplantation. In developing countries, cinacalcet cannot be widely used and then adequate hemodialysis, dietary phosphate restriction and treatment of hypocalcaemia are essential for prevention and treatment of secondary hyperparathyroidism.

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