Cinacalcet for the management of hypercalcemia secondary to calcium-sensing receptor mutation☆

Cinacalcet en el manejo de hipercalcemia secundaria a mutación en el receptor sensor del calcio

We report a 25-year-old female patient with a personal history of kidney stones, anxious-depressive syndrome, and a severe depression episode with psychotic symptoms, treated with risperidone 50 mg/day and one biperiden injection every 15 days. Her family history included hypercalcemia, moderate mental retardation attributed to perinatal anoxia, and borderline personality disorder in her 52-year-old father.

At 17 years of age, the patient was found to have a weight loss of 5 kg, paresthesia, anorexia, insomnia, asthenia, irritability, constipation, occasional morning nausea, cognitive and school achievement impairment, and attention and learning disorder. Physical examination revealed low blood pressure, facial acne, functional systolic murmur, and bone and tendon hyperreflexia. Laboratory tests showed high serum calcium levels ranging from 12.5 mg/dL (3.1 mmol/L) to 14 mg/dL (3.5 mmol/L) with inappropriately elevated parathyroid hormone (PTH) levels (217 pg/mL) and hypocalciuria, which initially ruled out primary hyperparathyroidism and multiple endocrine neoplasia. Because of the finding of hypocalciuric hypercalcemia, it was decided to study the calcium-sensing receptor (CaSR) gene, and a heterozygous R185Q mutation was identified in exon 4 of the CaSR gene. Bone mineral density was normal.

The patient was treated with hydration, furosemide, and pamidronate with no clinical or analytical improvement. Treatment with cinacalcet (15 mg/12 h) was not well tolerated at the first attempt, although the symptoms reported by the family were non-specific and not clearly attributable to the drug. Treatment with cinacalcet was restarted, the dosage gradually being increased from 15 mg to 90 mg/day over 12 months. This decreased asthenia, irritability, and attention deficit, increased appetite and weight, resolved gastrointestinal symptoms, decreased serum calcium levels to 10.3 mg/dL (2.5 mmol/L) and PTH levels to 67 pg/mL, and normalized urinary calcium levels.

Our patient had familial hypocalciuric hypercalcemia (FHH) of a severe phenotype. She carried a negative dominant mutation in the CaSR gene and had symptomatic hypercalcemia refractory to the standard hypocalcemic treatment. The use of cinacalcet was considered based on the symptoms and the type of mutation, and after one year of treatment, the drug normalized calcium levels and achieved physical and psychological improvement, and was well tolerated at increasing doses.

CaSR is a cell surface protein from the superfamily of G protein-coupled receptors. It is mainly expressed in the parathyroid glands and the kidney,[1] where activation by extracellular calcium (Ca) inhibits PTH secretion and decreases distal tubular reabsorption of Ca respectively. CaSR has also been found in other tissues including the central nervous system, pancreatic beta cells, thyroid, bone, bowel,[2] etc.

CaSR responds to a variety of bivalent and trivalent cations such as magnesium, aluminium, and gadolinium. It also interacts with Ca, and its activation generates a number of second messengers within a cascade of events that result in the inhibition of PTH synthesis and excretion.[3]

The mechanism through which extracellular Ca acts upon CaSR varies, depending on the type of cell in which it is located. In the kidney, hypercalcemia decreases the glomerular filtration rate and increases renal vasoconstriction. In the ascending limb of the loop of Henle, it decreases cAMP generation induced by several hormones. This inhibition of cAMP formation leads to decreased reabsorption of sodium (Na), potassium (K), and chlorine (Cl) through intracellular signals. The inhibition of cAMP mediated by CaSR also decreases the stimulating action of vasopressin and PTH in tubular epithelium. Na, K, and Cl co-transporters may transport ammonium instead of K and regulate urinary acid excretion, which suggests that CaSR may mediate processes that control acid–base balance. Other effects mediated by CaSR include decreased Cl reabsorption and K secretion through the apical channel in the ascending limb of the loop of Henle. This reduces positive voltage in the tubular lumen, inhibits Ca and Mg reabsorption, and increases the load in this part of the loop of Henle.[3]

The loss of function of this receptor due to inactivating mutations in the CaSR gene has been reported in the heterozygous state in FHH[1] and in homozygosis or compound heterozygosis in severe neonatal primary hyperparathyroidism. Approximately 200 different mutations of this type have been reported to date (http://www.casrdb.mcgill.ca). About one hundred activating mutations which, in heterozygosis, lead to dominant autosomal hypocalcemia have also been reported.

Most patients with FHH are asymptomatic, but some of them experience symptoms such as polydipsia, asthenia, pancreatitis, bile stones, chondrocalcinosis, and mental changes.[4] Medical or surgical treatment is usually not indicated, because serum calcium levels remain stable over time and no clinical signs appear.

Some studies have found that the effects of cinacalcet on Ca and PTH are dose-dependent. Peacock et al.[5] showed that, when administered twice daily, cinacalcet rapidly normalized serum Ca levels in most patients with primary hyperparathyroidism and slightly reduced PTH levels, with a maximum effect 2 h after administration, which decreased after 12 h. In this study, cinacalcet showed sustained effects for 52 weeks with no fluctuations in serum Ca levels. During the maintenance phase, 73% of patients treated with cinacalcet achieved normal serum calcium levels, with a decrease by at least 0.5 mg/mL as compared to baseline levels. By contrast, only 5% of patients in the placebo group achieved normal calcium levels, a significant difference.Experience with cinacalcet in patients with mutations in CaSR is limited. Timmers et al.[6] reported a 26-year-old male patient with hypercalcemia and an

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inactivating CaSR mutation who had episodes of psychosis and osteoporosis. After treatment with cinacalcet for 12 months, serum calcium levels gradually normalized. Festen-Spanjer et al.[7] reported a 37-year-old female patient with FHH and a 10-year history of recurrent pancreatitis who was treated with cinacalcet 30 mg/day for four weeks. Alon and Van DeVoorde[4] reported a 6-year-old boy with FHH in whom hypercalcemia appeared to interfere with tissue healing after a tympanoplasty. He was treated with cinacalcet for one year, and initially showed partial response to treatment with doses of 30 mg/day. When this dose was doubled, adequate healing and normalization of serum levels of Ca and PTH were achieved.

Cinacalcet is thought to interact with CaSR segments, enhancing transduction and activation signals from the receptor and inducing conformational changes in CaSR. However, the pharmacodynamic mechanisms by which cinacalcet increases sensitivity to Ca in the mutated CaSR are not known yet.

We report our positive clinical and analytical experience with cinacalcet in a 25-year-old patient with severe hypercalcemia due to FHH and an altered CaSR gene. Cinacalcet represents a new alternative for treating patients with hypercalcemia secondary to mutation in the calcium-sensing receptor.

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Well-differentiated gastric carcinoids treated with somatostatin analogues☆

Tratamiento de carcinoides gástricos bien diferenciados con análogos de somatostatina

Type 1 gastric carcinoids are tumors caused by the constant stimulation of hypergastrinemia on enterochromaffin-like cells occurring in chronic atrophic gastritis. They are the most common gastric carcinoids (70%) and have a good prognosis in most cases. Their indolent course is confirmed by the presence of a low number of mitoses, as measured by the Ki67 index, usually less than 30 per high magnification field, and by a 0–10% risk of angioinvasion or submucosal invasion.[1]

Metastases occur in 2–5% of cases, usually in regional lymph nodes or liver. Type 1 gastric carcinoids are located in the gastric body or fundus, are usually less than 2 cm in size, and are often multiple. Because of their association with chronic atrophic gastritis, the patients most commonly affected are women over 50 years of age, and tumors are incidentally found in gastroscopies performed for anemia or dyspepsia, which are among the symptoms of chronic atrophic gastritis.

Type 1 gastric carcinoids develop following a carcinogenesis model where hypergastrinemia initially causes hyperplasia of enterochromaffin-like cells, after which neoplasms are formed following a period of cell dysplasia.[2] The presence of cell dysplasia involves a 26-fold greater risk for the subsequent formation of carcinoid tumors as compared to chronic atrophic gastritis without dysplasia.[3] Molecular markers reported in the literature include elevation in most patients of V-MAT2, chromogranin A or synaptophysin, and occasionally histamine. Such elevations are quite non-specific as compared to other gastric neuroendocrine tumors.[4]

Because of the indolent course of type 1 gastric carcinoids, the therapeutic approach is less aggressive than for other gastric exocrine tumors. In addition, optimal treatment and monitoring of patients are controversial because

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