

Beneficial effect of cinacalcet in a child with familial hypocalciuric hypercalcemia

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Abstract We describe a child with familial hypocalciuric hypercalcemia (FHH) in whom the hypercalcemia seemed to interfere with tissue healing after tympanoplasty. Consequently, he was placed on cinacalcet (30 mg/day), changed after 2 weeks to 60 mg/day. The treatment resulted in a decrease in serum parathyroid hormone (PTH) from 148 to 32 pg/mL (normal 7–75) and ionized calcium from 1.48 to 1.23 mmol/L (1.13–1.34), as well as successful healing of the revised surgical scar. Over the 12-month treatment period no complications were noted. We conclude that cinacalcet may be considered a new, and currently the only, tool in treating children with symptomatic FHH.

Keywords Hypercalcemia · Familial hypocalciuric hypercalcemia · Calcimimetics · Calcium sensing receptor · Parathyroid hormone

Introduction

Familial hypocalciuric hypercalcemia (FHH) is an autosomal dominant genetic disorder that results in loss of function of the calcium sensing receptor (CaSR) [1–3]. The abnormality leads to mild to moderate hypercalcemia associated with inappropriately elevated serum parathyroid hormone (PTH) level and low urine calcium [1–3]. Many patients are asymptomatic, but some develop symptoms, such as

polydipsia, fatigue, weakness, recurrent pancreatitis, gallstones, chondrocalcinosis and mental changes [2–5].

The introduction in recent years of cinacalcet for the treatment of patients with primary hyperparathyroidism, as well as with secondary hyperparathyroidism due to end-stage renal disease (ESRD), resulted in improved control of serum PTH and calcium in both adults and children [6–11]. At the time of writing, only one adult with symptomatic FHH has been reported to respond favorably to short-term treatment with cinacalcet [12]. We describe here a child with FHH in whom hypercalcemia was thought to interfere with surgical scar healing and therefore he was treated with cinacalcet for 12 months.

Case report

A 6-year-old child was seen in the ENT clinic for bilateral chronic otitis media with perforated ear drums and chronic otorrhea from the right ear. He had significantly decreased hearing on the right side and moderately decreased hearing on the left, as assessed by audiology, and resulting delayed speech. He underwent an uneventful right tympanoplasty. At the 3-month follow-up it was noted that he developed dense tympanosclerosis with multiple calcium deposits and no improvement in his audiogram. It was felt that the inappropriate healing of the tissue was due to the calcium deposits. Blood work showed serum calcium of 12.1 mg/dL and he was referred to our clinic for evaluation.

His history revealed a long-standing poor appetite, chronic bilateral otitis media since the age of 2.5 years with a moderate conductive hearing defect associated with delayed speech. The family history was positive for the 35-year-old mother having long-standing high serum calcium of unknown etiology. Besides multiple decayed

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teeth she had no other medical problems. On physical examination we found the child to be small; his height and weight on the 5th centile, blood pressure 95/61 mmHg and heart rate 93/min. His development was appropriate for age, but hearing and speech were impaired. Besides the known findings in the ear drums no other appreciable abnormalities were noted.

Blood tests showed normal complete blood count, serum creatinine 0.5 (normal 0.4–0.8), calcium 12.8 (8.6–10.5), magnesium 2.1 (1.6–2.3), phosphorus 3.3 mg/dL (3.0–6.0), ionized Ca^{2+} 1.47 mmol/L (1.13–1.34), PTH 139 pg/mL (7–75), 25(OH) vitamin D 35 ng/mL (20–100), and normal Na, K, Cl, and CO_2 concentrations. Urinalysis was normal and urine Ca/creatinine 0.01 mg/mg. Renal ultrasound was normal; in particular showing no evidence of nephrocalcinosis. Skeletal X-rays were normal.

The mother's blood work showed creatinine 0.9 (0.7–1.2), calcium 12.4, phosphate 3.0 mg/dL, PTH 102 pg/mL, and a urine calcium/creatinine ratio of 0.01 mg/mg. The father and a younger brother had normal serum calcium concentrations.

Following a discussion with the parents in which they expressed their approval, the child was admitted to the hospital. At that time serum creatinine was 0.5 mg/dL, PTH 148 pg/mL, ionized Ca 1.48 mmol/L, P 3.3 mg/dL, and urine Ca/creatinine 0.01 mg/mg. He underwent surgery for revision of the right tympanoplasty. Once fully recovered from anesthesia the treatment with cinacalcet (30 mg once daily) was started with careful attention paid to vital signs and possible latent tetany. With treatment, both serum ionized Ca and PTH decreased, but did not reach the normal range (Figs. 1, 2). He was dismissed home after 3 days with serum Ca^{2+} 1.33 mmol/L and PTH 119 pg/mL, but a week later the values were 1.36 and 131 respectively. As the child remained clinically stable, the

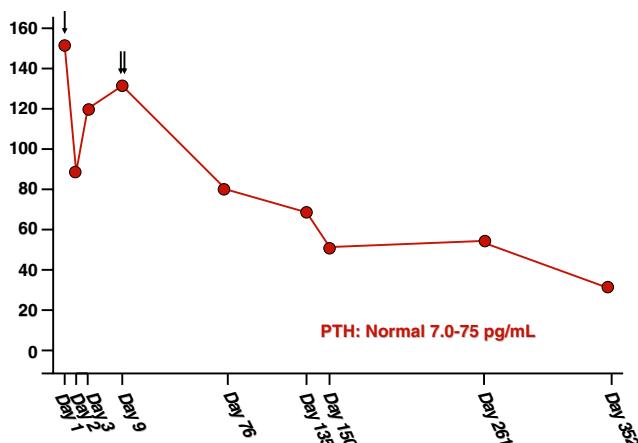


Fig. 1 Effect of cinacalcet in a 6-year-old child with familial hypocalciuric hypercalcemia on serum intact parathyroid hormone (PTH). Treatment was begun on day 1 with 30 mg once daily (↓) and after 8 days was doubled to 30 mg twice daily (↓↓)

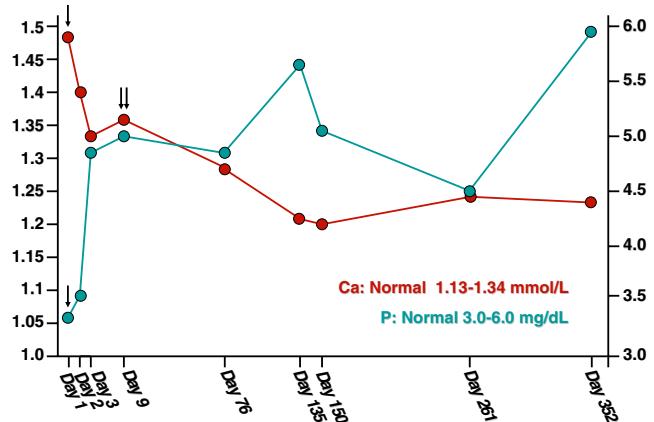


Fig. 2 Effect of cinacalcet in a 6-year-old child with familial hypocalciuric hypercalcemia on serum ionized calcium (Ca^{2+}) and phosphorus (P) concentrations. Treatment was begun on day 1 with 30 mg once daily (↓) and after 8 days was doubled to 30 mg twice daily (↓↓)

dosage of cinacalcet was increased to 30 mg twice a day. With that, both serum Ca^{2+} and PTH normalized and remained as such for the rest of the year (Figs. 1, 2). Concomitantly with the aforementioned changes, serum Mg slightly decreased to 1.8 mg/dL and serum P increased to 5.9 mg/dL at the last clinic visit while still receiving the calcimimetic (Fig. 2). Urine Ca/creatinine remained low while in the hospital, but due to a laboratory error was not appropriately followed afterward. There was no evidence of adverse effect to treatment. His appetite improved and 1 year after treatment had been started his height was at the 17th percentile and weight at the 7th percentile, and he has remained normotensive. At the last follow-up visit while still receiving the calcimimetic medication his blood pressure was 89/57 mmHg, heart rate 89/min and there were no signs of precocious puberty.

Genetic testing yielded a nucleotide change (c.659G>A) with an amino acid change (p.Arg220Gln), in chromosomal location at 3q13.3-q21, and with transmission in a dominant fashion.

A follow-up visit at the ENT clinic 10 weeks after surgery (and the start of treatment with cinacalcet) showed a good outcome with all tissues well healed and with no calcifications. Hearing test showed normalization in the right ear and stable moderate deficiency in the left ear. Further follow-ups continued to reveal the same otological findings.

Because the ENT department was pleased with the patient's condition, the treatment with cinacalcet was discontinued. A week later blood work showed creatinine 0.6, calcium 12.2, phosphate 3.9, magnesium 2.1 mg/dL, albumin 4.9 g/dL, ionized Ca^{2+} 1.52 mmol/L, PTH 139 pg/mL, and normal liver functions and pancreatic enzymes levels. Renal ultrasound and skeletal X-rays were normal.

Discussion

In 1993, the CaSR was cloned and characterized in bovine parathyroid glands by Brown et al. [13]. The receptor senses extracellular calcium and establishes the reciprocity between it and PTH secretion. The CaSR is also found in other tissues, and is abundant in the cortical thick ascending limb of the loop of Henle [14, 15]. Activation of the tubular receptor results in decreased sodium reabsorption and consequently an increase in calciuria [14, 15]. In 1998, Nemeth et al. [16] were the first to report on the use of calcimimetics. These agents bind to the transmembrane domain of the CaSR and allosterically increase its sensitivity to calcium. In a way, calcimimetics “bluff” the receptors in the parathyroid glands and the kidney into believing that serum calcium is higher than it actually is [3, 8].

Calcimimetics have been shown to be very effective in lowering serum parathyroid hormone and calcium concentrations in adult patients with primary and secondary hyperparathyroidism [6–8]. Three recent articles demonstrated their efficacy in small groups of children with ESRD [9–11]. However, experience with cases of mutations in the receptor is very limited. In a letter to the editor, Festen-Spanjer et al. [12] reported a 37-year old woman with FHH with mutation of the CaSR gene, who for 10 years suffered from recurrent pancreatitis thought to be due to the hypercalcemia. After taking cinacalcet (30 mg per day for 4 weeks), the subject's serum PTH and calcium decreased, while serum phosphate and urine calcium increased, though all staying within their normal ranges. The results of the treatment with the calcimimetic were similar to those observed by Timmers et al. [5] in a 26-year-old male patient with two episodes of psychosis, hypercalcemia, and osteoporosis, who was found to have elevated serum PTH level and an inactivating mutation of the CaSR. The authors, however, did not think that the patient had FHH because of the findings of normocalciuria and normal serum calcium and PTH levels in his parents and son. Furthermore, urine calcium excretion was unaffected by the treatment with cinacalcet. In reality, the patient probably developed primary hyperparathyroidism due to a de novo mutation. The authors speculated that in their case the renal tubular CaSR was unaffected by the mutation [5].

In our patient, treatment with cinacalcet at a daily dose of 30 mg resulted in partial response, and, after a further increase in the dose to 30 mg twice a day, led to gradual normalization of serum PTH and calcium concentrations (Figs. 1, 2). The treatment was well tolerated and no clinical or biochemical adverse effects were noted. Furthermore, concomitantly with the normalization of serum calcium, the surgical scar that had previously failed to heal because of the formation of excessive calcifications, healed uneventfully, resulting in improvement in the patient's

hearing. The treatment with the calcimimetic did not interfere with the child's growth and skeletal X-rays continued to be normal. As expected in a patient with normal kidney function, serum phosphate concentration showed reciprocity with that of PTH (Figs. 1, 2). Unfortunately, we do not have data on the effect of the calcimimetic on urine calcium, but it is reassuring to know that follow-up ultrasound did not show any abnormalities. Future studies will have to address this important issue, and carefully assess the patients for all other clinical and biochemical observations.

Over 250 inactivating mutations of the CaSR gene have so far been described (<http://www.casrdb.mcgill.ca>). Our patient's missense mutation in the extracellular domain of the CaSR has been previously described by Pearce et al. [2], and is included in the aforementioned database.

The mechanism by which calcimimetics are capable of restoring sensitivity to serum calcium in spite of the mutation in the CaSR is still under investigation. There was speculation that calcimimetics will restore sensitivity of only the extracellular mutations, but Rus et al. [17] showed in an in vitro study on human CaSR that both intra- and extracellular mutating receptors respond. More recently, Lu et al. [18] demonstrated that deactivation mutations cause a shift to the right (decrease) in the sensitivity of the CaSR to calcium, which is restored back to the left with the addition of a calcimimetic agent to the medium.

In conclusion, our findings in a young child with FHH support the few anecdotal reports in adults of the beneficial effect of calcimimetics in treating patients with inactivating mutations of the CaSR. Considering the fact that at the moment, no other chronic pharmacological treatment is available for this disorder, further studies are needed to assess the long-term effects of calcimimetics.

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