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Case Report

Efficacy of Oral Cinacalcet in Non-PTH Nonmalignant Hypercalcemia from Excess 1,25-Dihydroxyvitamin D

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Abstract

Elevated 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) is a rare cause of non–parathyroid hormone (PTH)–mediated hypercalcemia seen in granulomatous disease, malignancy (most often lymphoma), or genetic mutations. Therapeutic options are limited. We report the case of a 67-year-old White man with nonmalignant, nongranulomatous, $1,25(OH)_2D$-mediated hypercalcemia treated successfully with cinacalcet. At presentation, he had hypercalcemia, hypercalciuria with recurrent nephrolithiasis, low PTH, elevated $1,25(OH)_2D$, and normal 25-hydroxyvitamin D. The $1,25(OH)_2D$ levels were inappropriate in the setting of hypercalcemia with low PTH. Evaluations for sarcoidosis, tuberculosis, and malignancy were negative. Genetic testing showed biallelic variants in the *CYP24A1* gene. Cinacalcet was trialed and showed normalization of calcium levels. On cinacalcet, biochemical indices showed a slight increase in $1,25(OH)_2D$ and 24-hour urine calcium and mild decrease in PTH. He briefly experienced symptomatic hypocalcemia that resolved after reducing cinacalcet dose. Due to limited symptomatic benefit, he opted to stop cinacalcet. Additional follow-up showed intermittently elevated serum calcium levels after stopping cinacalcet, most recently 10.3 mg/dL. Cinacalcet may be a therapeutic option in nonmalignant, $1,25(OH)_2D$-mediated hypercalcemia. Further study is necessary to confirm efficacy, understand risks and benefits, and elucidate mechanism(s) of action.

Key Words: hypercalcemia, 1,25-dihydroxyvitamin D, cinacalcet, hypercalciuria

Abbreviations: $1,25(OH)_2D$, 1,25 dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; CaSR, calcium-sensing receptor; PTH, parathyroid hormone.

Introduction

Non–parathyroid hormone (PTH)–mediated hypercalcemia has a variety of causes, among which excess 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) is a rare but distinct entity (1). $1,25(OH)_2D$ is the activated form of vitamin D produced by hydroxylation of 25-hydroxyvitamin D (25(OH)D) by the enzyme 1-α hydroxylase under PTH regulation in the kidneys. In calcium-sufficient states, the enzyme 24-hydroxylase acts on 25(OH)D and $1,25(OH)_2D$ to form the inactive compounds 24,25-dihydroxyvitamin D ($24,25(OH)_2D$) and 1,24,25 trihydroxyvitamin D, respectively (1).

Elevated $1,25(OH)_2D$ can be caused by unregulated extrarenal production of 1-α hydroxylase in granulomatous diseases such as sarcoidosis, infections such as tuberculosis and fungal disease, and lymphomas (1). Genetic mutations in *CYP24A1* decrease 24-hydroxylase activity, reducing inactivation of $1,25(OH)_2D$, leading to hypercalcemia, which can be challenging to manage (2). Treatment options may include glucocorticoids, ketoconazole, fluconazole, and rifampin, though all have inherent limitations (1). We describe the case of a patient with non-PTH–mediated, nonmalignant chronic hypercalcemia secondary to elevated $1,25(OH)_2D$ who was effectively managed with normalization of serum calcium after initiation of cinacalcet.

Cinacalcet is a calcimimetic effective in controlling PTH-mediated hypercalcemia but has only recently been noted to have efficacy in non-PTH–mediated hypercalcemia of malignancy. Several case reports have demonstrated successful management of humoral hypercalcemia of malignancy in solid tumors, including one from our institution (3, 4). Extrapolating this observation, we used cinacalcet in our patient with resolution of hypercalcemia. The mechanism of this effect is unclear, but our findings may offer a novel therapeutic option to manage individuals with nonmalignant causes of hypercalcemia related to excess $1,25(OH)_2D$.

Case Presentation

A 67-year-old Caucasian man presented for evaluation of hypercalcemia with low PTH and hypercalciuria with longstanding, recurrent nephrolithiasis (calcium phosphate and calcium oxalate stones) since age 20 years. His family history was notable for nephrolithiasis in several first- and second-degree relatives. There was no history of tuberculosis exposure.

Diagnostic Assessment

Evaluation at presentation is noted in Tables 1 and 2. He had elevated $1,25(OH)_2D$ with high-normal 25(OH)D, lower

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Table 1. Laboratory values at baseline and postcinacalcet therapy

Laboratory	Reference range	Baseline	Pre-cinacalcet	Post-cinacalcet
Total calcium	8.4-10.4 mg/dL (2.1-2.6 mmol/L)	11.1 mg/dL (2.8 mmol/L)	10.8 mg/dL (2.7 mmol/L)	9.5 mg/dL (2.38 mmol/L)
Phosphorus	2.5-4.5 mg/dL (0.8-1.5 mmol/L)	3.1 mg/dL (1.0 mmol/L)	3.0 mg/dL (1.0 mmol/L)	3.8 mg/dL (1.2 mmol/L)
Parathyroid hormone	18-84 pg/mL (18-84 ng/L)	15 pg/mL (15 ng/L)	35 pg/mL (35 ng/L)	19 pg/mL (19 ng/L)
Creatinine	0.59-1.04 mg/dL (52.2-91.4 µmol/L)	1.4 mg/dL (123.8 µmol/L)	1.67 mg/dL (147.6 µmol/L)	1.62 mg/dL (143.1 µmol/L)
Estimated glomerular filtration rate	>60/mL/min/BSA	48 mL/min/BSA	42 mL/min/BSA	43 mL/min/BSA
25-Hydroxyvitamin D	20-70 ng/mL (49.9-174.7 nmol/L)	70 ng/mL (174.7 nmol/L)	51 ng/mL (127.3 nmol/L)	77 ng/mL (192.2 nmol/L)
24,25-Dihydroxyvitamin D	Not applicable—ng/mL	0.15 ng/mL	Not available	<0.10 ng/mL
25-Hydroxyvitamin D:24,25-Dihydroxyvitamin D ratio	Normal ratio <25; 25-80: low vitamin D or heterozygous *CYP24A1* mutations; > 80: probable biallelic *CYP24A1* mutation or deletion	467	Not available	770 (taking 0.1 for 24,25(OH)$_2$D)
1,25-Dihydroxyvitamin D	15-75 pg/mL (36.0-180.0 pmol/L)	85 pg/mL (204.0 pmol/L)	51 pg/mL (122.4 pmol/L)	62 pg/mL (146.4 pmol/L)
24-h Urinary calcium	<200 mg/24 h (<5 mmol/24 h)	416 mg/24 h (10.4 mmol/24 h)	400 mg/24 h (10.0 mmol/24 h)	483 mg/24 h (12.1 mmol/24 h)

Values in parenthesis are International System of Units (SI).
Abbreviation: BSA, body surface area.

Table 2. Additional diagnostic assessment

Test (reference range—conventional; SI units)	Result
Bone mineral density (*T* scores)	+1.4 in lumbar spine and −1.6 in right femoral neck
Alkaline phosphatase (45-115 U/L; 0.75-1.92 µkat/L)	81 U/L (1.35 µkat/L)
Vitamin A (32.5-78 µg/dL; 1.1-2.7 µmol/L)	83.5 µg/dL (2.9 µmol/L)
Thyrotropin (0.3-4.2 mIU/L; 0.3 mIU/L)	2.3 mIU/L (2.3 mIU/L)
Angiotensin-converting enzyme level (16-85 U/L; 266.7-1416.7 µkat/L)	32 U/L (533.3 µkat/L)
Complete blood count	Normal
Serum protein electrophoresis	Normal
Chest x-ray	No infiltrates or hilar lymphadenopathy

Abbreviation: SI, International System of Units.

than expected 24,25(OH)$_2$D, and elevated 25(OH) D-to-24,25(OH)$_2$D ratio, suggestive of *CYP24A1* mutation. DNA sequencing revealed 2 mutations in the *CYP24A1* gene—p.R396W and E143del-Het, confirming the diagnosis. Familial testing showed similar mutations in several first- and second-degree relatives (2). Additional laboratory values were notable for mild elevation in vitamin A (see Table 2), which was not thought to be contributory given the minimal elevation and clinical and family history with confirmed *CYP24A1* mutations associated with excess 1,25(OH)$_2$D.

Treatment

The patient was initially managed conservatively for several years with hydration and avoidance of calcium and vitamin D supplements. Although he had stable, bilateral nonobstructive nephrolithiasis, he was concerned about his persistent hypercalcemia and potential related symptoms. After discussion of the risk and benefits, he opted to begin cinacalcet at 30 mg once daily. Laboratory values just before starting cinacalcet are shown in Table 1.

Outcome and Follow-up

His calcium initially decreased to 10.2 mg/dL (2.55 mmol/L). Fig. 1 shows the trend of his total calcium levels alongside changes in cinacalcet dosage. Cinacalcet was increased to 30 mg twice daily, resulting in symptomatic hypocalcemia with a calcium of 8.1 mg/dL (2.02 mmol/L). Cinacalcet was then reduced to 30 mg daily with stabilization of calcium around 9.5 mg/dL (2.38 mmol/L). Additional laboratory values following cinacalcet therapy are demonstrated in Table 1. Failing to notice any substantial symptomatic improvement despite the achievement of eucalcemia, he opted to discontinue cinacalcet after 8 months. After cessation of cinacalcet, his calcium levels fluctuated between 9.5 to 10.7 mg/dL (2.37-2.67 mmol/L), most recently at 10.3 mg/dL (2.57 mmol/L).

Discussion

We present the case of a patient with non-PTH–mediated, nonmalignant hypercalcemia secondary to 1,25(OH)$_2$D

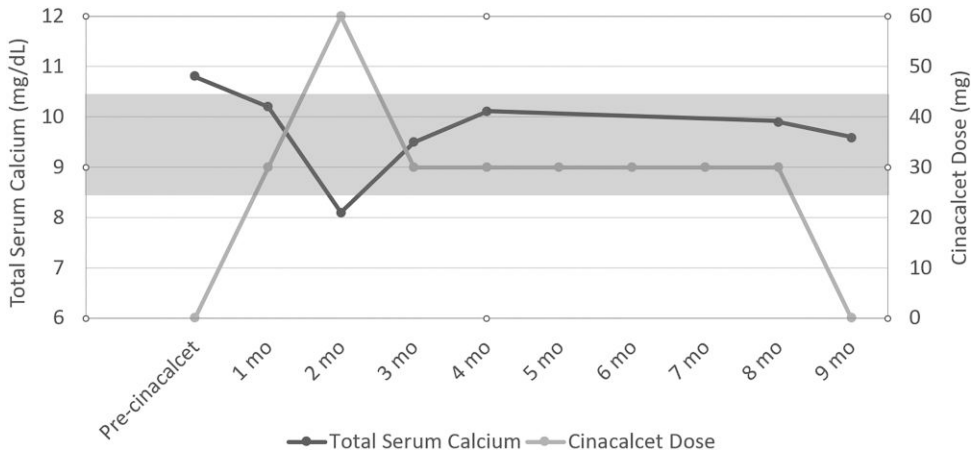

Figure 1. Trend of total serum calcium with varying doses of cinacalcet in a patient with non–parathyroid hormone–mediated hypercalcemia due to excess $1,25(OH)_2D$ from a *CYP24A1* mutation. The shaded area represents normal range for total serum calcium (8.4-10.4 mg/dL).

Table 3. Possible therapeutic options for hypercalcemia related to elevated 1,25 dihydroxyvitamin D

Medication [references]	Mechanism of action	Effect on $1,25(OH)_2D$ levels	Potential adverse effects
Azoles (ketoconazole, fluconazole) (5-7)	Inhibition of renal and extrarenal 1-α hydroxylase activity	Reduced due to decreased production	Orthostatic hypotension, headache, nephrotoxicity, hepatotoxicity, drug interactions due to inhibition of CYP3A4 (both ketoconazole and fluconazole), inhibition of CYP2C19 (fluconazole)
Glucocorticoids (1, 6)	Inhibition of renal and extrarenal 1-α hydroxylase activity	Reduced due to decreased production	Hypertension, hyperglycemia, weight gain, osteoporosis, muscle and dermal atrophy, exogenous Cushing syndrome
Rifampin (6, 8)	CYP3A4 inducer—providing alternate pathway for inactivation of 25(OH)D and $1,25(OH)_2D$	Reduced due to increased inactivation	Drug interactions due to CYP3A4 and CYP269 activation, orange discoloration of body fluids, hepatotoxicity, adrenal insufficiency
Cinacalcet (4, 9-11)	Calcimimetic—activates CaSR on parathyroid cells. In states of low parathyroid hormone—Possible effect on CaSR in distal nephron, intestine, and bone with altered renal calcium handling and reduction in intestinal calcium absorption	Variable changes, possibly consistent with interference of action	Hypocalcemia, increased urinary calcium excretion, nephrolithiasis, nausea, and vomiting

Abbreviations: $1,25(OH)_2D$, 1,25 dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; CaSR, calcium-sensing receptor.

from biallelic *CYP24A1* mutation demonstrating reduction in serum calcium with cinacalcet. The patient experienced a rapid and sustained drop in serum calcium despite continued inappropriately high-normal levels of $1,25(OH)_2D$ in the context of low PTH and renal insufficiency. Furthermore, the medication was tolerated, except for symptomatic hypocalcemia that necessitated dose reduction. To our knowledge, this is one of the first case descriptions using cinacalcet in nonmalignant hypercalcemia outside primary hyperparathyroidism, with one prior report describing a patient with hypercalcemia secondary to exogenous hypervitaminosis D who responded rapidly to cinacalcet despite high 25(OH)D levels and completely suppressed PTH (12).

Current lifestyle recommendations for long-term management of non-PTH, nonmalignant hypercalcemia related to $1,25(OH)_2D$ excess from *CYP24A1* mutation include reducing calcium intake, avoiding excessive vitamin D and sunlight, and maintaining good hydration. While some patients respond, many have persistent hypercalcemia. Pharmacotherapeutic options include ketoconazole and fluconazole (5-7), corticosteroids(1), and rifampin (6, 8), which may all be associated with considerable side effects. Table 3 summarizes these therapeutic options, including mechanism of action, clinical effect, and potential side effects.

Cinacalcet is a calcimimetic effective in PTH-mediated hypercalcemia through its activation of the calcium-sensing receptor (CaSR) on parathyroid cells, inhibiting PTH secretion. The CaSR is also present in other tissues, including sites along the distal nephron, intestine, and bone (4, 9, 10). The exact mechanism by which cinacalcet lowers calcium in non-PTH–mediated hypercalcemia is uncertain. Reduction in PTH may be a significant component given the low-normal PTH levels observed in our patient prior to starting cinacalcet. It is notable that PTH levels are commonly not completely suppressed despite hypercalcemia and elevated $1,25(OH)_2D$ in patients with *CYP24A1* mutations (2). Taking into account findings from prior case reports showing reduction in calcium levels with cinacalcet despite a completely suppressed PTH

(4, 12), the effect of cinacalcet at other tissue sites may also contribute to the decline in serum calcium. At the distal nephron, alteration in renal calcium handling may play a role (9) whereby increased urine calcium excretion would be of clinical concern. However, PTH, urine calcium excretion, and bone mineral density demonstrate minimal changes in patients with primary hyperparathyroidism treated with cinacalcet, arguing against a renal and/or skeletal mechanism predominating (11). Given these observations, the role of the CaSR in intestinal calcium absorption may be of fundamental importance, especially given that the mechanism of hypercalcemia in *CYP24A1* mutation is intestinal calcium hyperabsorption (1). Specifically, activation of the CaSR may antagonize the effect of $1,25(OH)_2D$ on transcellular intestinal calcium absorption through the transient receptor potential vanilloid 6 (TRPV6) channel (4). This effect of cinacalcet in the small intestine may provide a mechanism whereby a calcimimetic could reduce serum calcium; however, we did not identify a drop in 24-hour urine calcium excretion as would be expected.

Limitations of cinacalcet use include hypocalcemia, potential for increased urinary calcium excretion with progression of nephrolithiasis, nausea, and vomiting, and expense (11). Unlike patients with hypercalcemia of malignancy, in the subset of patients with non-PTH–mediated, nonmalignant hypercalcemia, long-term medication reliance is crucial given their presumed normal life expectancy in the absence of other comorbidities. Long-term safety of cinacalcet has been demonstrated in patients with primary and secondary hyperparathyroidism, supporting its consideration for prolonged use (11).

We conclude that cinacalcet may be a therapeutic option for managing non-PTH–mediated, nonmalignant hypercalcemia related to $1,25(OH)_2D$ excess when refractory to conservative measures. Further studies are needed to establish long-term efficacy and safety in this patient population while elucidating mechanism(s) of action.

Learning Points

- Elevation in 1,25(OH)2D is a rare cause of non-PTH–mediated hypercalcemia and can be elevated due to granulomatous diseases, malignancy, and genetic mutations.
- Non-PTH–mediated, nonmalignant hypercalcemia related to elevation in 1,25(OH)2D has limited treatment options, including azoles, glucocorticoids, and rifampin, which have several adverse effects.
- Cinacalcet effectively reduced calcium levels to normal range in a patient with non-PTH–mediated, nonmalignant hypercalcemia related to elevated 1,25(OH)2D due to *CYP24A1* mutation.
- Cinacalcet is a potential therapeutic option in managing hypercalcemia related to 1,25(OH)2D.

Contributors

All authors made individual contributions to authorship: R.W. was involved in the diagnosis and management of the patient; S.M. and R.W. were involved in the preparation and submission of the manuscript; M.S. and P.T. provided expert input on the structure and content of the manuscript. All authors were responsible for review and approval of the final draft.

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None declared.

Informed Patient Consent for Publication

Signed informed consent could not be obtained from the patient or a proxy but has been approved by the treating institution.

Data Availability Statement

Original data generated and analyzed for this case report are included in this published article.

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