INTRODUCTION

We present a rare case of severe symptomatic hypocalcemia complicated by cardiac arrhythmias following cinacalcet administration. Severe symptomatic hypocalcemia and arrhythmia are rare side effects seen with cinacalcet therapy. Clinicians should closely monitor patients on calcimimetics for hypocalcemic symptoms.

Cinacalcet (Sensipar™), a member of calcimimetics family, suppresses parathyroid hormone (PTH) secretion by binding allosterically to the calcium-sensing receptor on the membrane surface of parathyroid cells. This drug has been used to treat secondary hyperparathyroidism, frequently associated with chronic renal disease and also selected cases of primary hyperparathyroidism (PHPT).

Hypocalcemia is a known side effect of cinacalcet administration and FDA guidelines discourage its use if serum calcium is less than the lower limit of the normal range. The occurrence of mild and self-limited hypocalcemia with cinacalcet therapy is common. We report a case of severe symptomatic hypocalcemia complicated by cardiac arrhythmia caused by cinacalcet in a patient with primary hyperparathyroidism.

CASE REPORT

A 61-year-old man with severe hypocalcemia following cinacalcet administration was admitted to our hospital. The patient had a reported history of “PHPT” diagnosed 9 years ago, at age 52 when laboratory findings showed a serum calcium of 11.2 mg/dL with a serum albumin of 4.9 g/dL, ionized serum calcium 5.6 mg/dL, PTH 44 pg/mL, and 25-OH vitamin D 15 ng/mL. After supplementing vitamin D >30, 24-hour urine calcium level was at the upper limit of normal 298 mg/24 hour (Table 1). Family history was negative for primary hyperparathyroidism and MEN.

Physical examination was completely normal, including a BMI of 24. A thorough hypercalcemia work-up done at the time of diagnosis was negative (Table 1). The patient had two asymptomatic renal stones noted on renal
ultrasound. While the patient did not meet NIH surgical criteria at that time, he was offered parathyroidectomy; however, subsequent thyroid ultrasound and parathyroid scan did not localize a parathyroid adenoma. Several years later, the patient was started on cinacalcet (Sensipar™) 30mg twice daily by an out-of-network provider, while the serum calcium level was 10.3 mg/dL, presumably for the treatment of his hypercalcemia. Four months prior to his current presentation, the patient had cinacalcet dose increased to 60 mg twice daily while the serum calcium was 8.9 mg/dL.

At the time of his current presentation, the patient reported several months of progressive fatigue, muscle weakness, palpitations, and paresthesias of his hands and feet. Laboratory evaluation showed a corrected serum total calcium of 6.6 mg/dL (Figure 1) down from 7.4 mg/dL two months earlier. Additional laboratory testing showed ionized serum calcium 3.4 mg/dL, PTH 68.2 pg/mL (Figure 1B), 25-OH Vitamin D 37.0 ng/mL, and magnesium 2.1 mg/dL. Cinacalcet was discontinued, and the patient was admitted to the ICU. EKG showed AVNRT (atrioventricular nodal reentry tachycardia) (Figure 2A), which required ablation. Patient was treated with continuous intravenous calcium infusion with normalization of his serum calcium after 36 hours of treatment (Figure 1) and resolution of the patient’s arrhythmia (Figure 2B), paresthesias and fatigue. He was discharged on oral calcitriol and calcium supplementation.

One week after discharge, the patient continued to report resolution of symptoms. Calcitriol and calcium supplementation were discontinued 2 weeks later, and patient was advised for routine laboratory surveillance.

3 | DISCUSSION

The CaSR negatively controls parathyroid function by suppressing acute PTH secretion and also inhibits cell proliferation and thus cell number and parathyroid gland size and reducing PTH gene transcription. It also activates the local synthesis, particularly in parathyroid oxyphil cells of 1,25(OH)2D3, an inhibitor of PTH synthesis.2-5 In patients with chronic renal disease and secondary hyperparathyroidism, sustained treatment with cinacalcet suppresses parathyroid gland size and serum PTH levels. Similarly, exposure of parathyroid cells to cinacalcet in vitro suppresses proliferation and promotes apoptosis, and hence, it is not surprising that cinacalcet treatment can cause hypocalemia in certain susceptible patients. However, in our patient, cinacalcet was started by an outside network provider for presumed treatment of primary hyperparathyroidism and severe hypocalemia developed due to a combination of inappropriate use of cinacalcet and wrongful dose escalation.

While life-threatening events and fatal outcomes were rarely reported in cinacalcet trials,1 the majority of cases are asymptomatic and resolved without further intervention. However, despite precautions put in place for

| TABLE 1 showing basal laboratory data |
|--------------------------------------|
| **Serum values** | **Observed values** | **Normal range** |
| Total calcium | 11.2 | 8.6–10.0 mg/dL |
| Ionized calcium | 5.6 | 4.5–5.6 mg/dL |
| Albumin | 4.9 | 3.9–5.0 g/dL |
| Magnesium | 2.1 | 1.6–2.6 mg/dL |
| PTH | 44 | 15–65 pg/L |
| PTH-related protein | 4 | 14–27 pmol/L |
| 25-hydroxyvitamin D | 15 | 29–100 ng/mL |
| 24-hour urine calcium | 298 | 42–353 mg |

Note: The laboratory values were obtained initially when patient was diagnosed with primary hyperparathyroidism. The 24-hour urine calcium was obtained after the administration of cholecalciferol (serum 25-hydroxyvitamin D 37 ng/dL). Additional work-up for other causes of hypercalcemia included thyroid functions; serum and urine protein electrophoresis and chest X-ray were normal.

Abbreviation: PTH—parathyroid hormone.
prescribing cinacalcet, patients can still develop severe hypocalcemia as shown in our case. The mildly elevated PTH seen in our patient may be related to the parathyroid compensatory mechanism for the severe hypocalcemia, although the PTH would have been much higher for the degree of hypocalcemia if the patient was not receiving cinacalcet.

The majority of studies related to cinacalcet-induced hypocalcemia involved patients with secondary hyperparathyroidism and chronic kidney disease, especially on dialysis. Post hoc analysis of the EVOLVE trial noted hypocalcemia in 58% of 1938 patients randomized to cinacalcet. In this study, hypocalcemia resolved spontaneously within 14 days without modification of treatment, and the authors concluded that mild hypocalcemia was frequent following initiation of cinacalcet but generally asymptomatic and self-limited. Severe hypocalcemia was rare and associated with higher baseline serum PTH, lower corrected total serum calcium, higher serum alkaline phosphatase, and higher body mass index. Interestingly, our patient did not have any of these risk factors. There was no detectable relationship between cinacalcet dose immediately prior to first hypocalcemic episode and its severity. Similarly, in a more recent study of 905 normocalcemic hyperparathyroid patients taking cinacalcet, 67% developed hypocalcemia within 12 months. Nine percent of patients in this study developed severe hypocalcemia defined as serum calcium under 7.5 mg/dL. Patients with severe hypocalcemia were more likely to have diabetes mellitus, body mass index ≥25 kg/m², higher iPTH levels, and lower uncorrected calcium levels.

The use of calcimimetic drugs to lower serum calcium in both mild and intractable PHPT had been demonstrated in small cohorts of patients. In another study of 78 patients with PHPT, five patients out of 40 receiving cinacalcet developed hypocalcemia. Two patients experienced treatment-related paresthesias and had serum calcium levels of 7.8 and 8.1. An open-label extension of this study was performed and noted that five of 41 subjects developed mild hypocalcemia after being established on maintenance dosing of the medication. There were no cases of severe hypocalcemia, but the study protocol specified withholding treatment for serum calcium less than 8 mg/dL for at least one week and only restarting the medication at a lower dose once serum calcium increased above 8.4 mg/dL. The prevalence of hypocalcemia including severe hypocalcemia in general appears much lower in patients treated for PHPT (Table 2). It should be noted that our patient did not have overt PHPT although he may have normocalcemic hyperparathyroidism. It is interesting to note that the largest studies of this population had protocols in place to hold cinacalcet when serum calcium became low, while it was often continued in patients with secondary hyperparathyroidism who were being monitored more frequently and most commonly had resolution of hypocalcemia without any intervention.
One patient with intractable PHPT with a baseline serum calcium of 12.4 mg/dL had a decline to 7.2 mg/dL 4 weeks after the end of the titration phase of the trial and required a dose reduction from 60mg four times daily to 60mg three times daily. His serum calcium level returned to normal by the end of the study. Similarly, a patient in the same study had his serum calcium decrease from 11.8 to 7.8 mg/dL 3 weeks after initiation therapy with cinacalcet. In this instance, serum calcium normalized without any interruption in therapy. Similar significant declines have been noted in other studies. Our patient had no common risk factors for cinacalcet-associated hypocalcemia, such as secondary hyperparathyroidism, PTH greater than 100 pg/dL, or elevated alkaline phosphatase. Intuitively, it makes sense that his calcium level decreased after an increase in cinacalcet dose. Inexplicably, the cinacalcet dose was increased in up to 14% of patients with severe hypocalcemia, less than 7.5 mg/dL, and even in this population, severe symptomatic hypocalcemia was rare. Our patient developed AVNRT arrhythmia when his serum calcium was 6.4 mg/dL in the ICU and needed cardioversion. Since this episode, he has no recurrences of arrhythmias. Dalmazi et al. reported a patient with primary hyperparathyroidism developing severe hypocalcemia, related to parathyroid adenoma infarction apparently due to cinacalcet administration. In our patient, the gradual onset of hypocalcemia, the follow-up ultrasound findings, and complete recovery when cinacalcet was discontinued strongly suggest the hypocalcemia was not related to parathyroid infarction. The incidence of sudden cardiac death related to cinacalcet administration was investigated in one study involving secondary hyperparathyroidism due to chronic renal disease and noted no differences between cinacalcet and non-cinacalcet-treated group. However, etelcalcetide, another calcimimetic drug, was compared with placebo in two clinical trials involving secondary hyperparathyroidism and chronic renal disease. In this study, hypocalcaemia was more common in the etelcalcetide group and prolongation of QT intervals was also seen in some patients in the etelcalcetide group. No cardiovascular outcomes were reported. Additionally, Temiz et al. showed a correlation between the cinacalcet treatment dose and prolongation of QT interval. Novick et al. described a 44-year-old man with a history of end-stage renal disease and secondary hyperparathyroidism treated with cinacalcet presented with hypocalcemia resulting in torsades de pointes and cardiac arrest. It is not clear whether the cardiac adverse effects of cinacalcet are due to hypocalcemia or direct effects of cinacalcet on the myocardium. Interestingly, cinacalcet has antioxidant properties, and this may be beneficial in reducing cardiac mortality in patients with secondary hyperparathyroidism and chronic renal disease.

4 | CONCLUSION

Clinicians should closely monitor patients on calcimimetics for hypocalcemic symptoms and arrhythmia, even though asymptomatic hypocalcemia typically resolves without intervention.

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CONFLICT OF INTERESTS

The authors have no multiplicity of interest to disclose.

AUTHOR CONTRIBUTIONS

Dr. Schmidt and Dr. Weaver drafted the manuscript. Dr. Hoang and Dr. Shakir critically reviewed and edited the paper.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editor in chief of this journal.

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REFERENCES

1. US Food and Drug Administration. Sensipar (cinacalcet) tablets. Highlights of prescribing information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/021688s023lbl.pdf. 2019. Accessed September 9, 2020.
2. Conigrave AD. The calcium-sensing receptor and the parathyroid: past, present, future. Front Physiol. 2016;15(7):563.
3. Fan Yi, Liu W, Bi R, et al. Interrelated role of Klotho and calcium-sensing receptor in parathyroid hormone synthesis and parathyroid hyperplasia. Proc Natl Acad Sci U S A. 2018;115(16):E3749-E3758.
4. Chen RA, Goodman WG. Role of the calcium-sensing receptor in parathyroid gland physiology. Am J Physiol Renal Physiol. 2004;286(6):F1005-F1011.
5. Ritter CS, Haughey BH, Armbricht HJ, Brown AJ. Distribution and regulation of the 25-hydroxyvitamin D3 1α-hydroxylase
in human parathyroid glands. J Steroid Biochem Mol Biol. 2012;130(1-2):73-80.

6. Floege J, Tsirtonis K, Iles J, Drueke TB, Chertow GM, Parfrey P. Incidence, predictors and therapeutic consequences of hypocalcemia in patients treated with cinacalcet in the EVOLVE trial. Kidney Int. 2018;93(6):1475-1482.

7. Louie KS, Erhard C, Wheeler DC, Stenvinkel P, Fouqueray B, Floege J. Cinacalcet-induced hypocalcemia in a cohort of European haemodialysis patients: predictors, therapeutic approaches and outcomes. J Nephrol. 2020;33:803-816.

8. Silverberg SJ, Bone HG 3rd, Marriott TB, et al. Short-term inhibition of parathyroid hormone secretion by a calcium-receptor agonist in patients with primary hyperparathyroidism. N Engl J Med. 1997;337(21):1506-1510.

9. Marcocci C, Chanson P, Shoback D, et al. Cinacalcet reduces serum calcium concentrations in patients with intractable primary hyperparathyroidism. J Clin Endocrinol Metab. 2009;94(8):2766-2772.

10. Marcocci C, Bollerslev J, Khan AA, Shoback DM. Medical management of primary hyperparathyroidism: proceedings of the fourth international workshop on the management of asymptomatic primary hyperparathyroidism. J Clin Endocrinol Metab. 2014;99(10):3607-3618.

11. Khan AA, Hanley DA, Rizzoli R, et al. Primary hyperparathyroidism: review and recommendations on evaluation, diagnosis, and management. A Canadian and international consensus. Osteoporos Int. 2017;28(1):1-19.

12. Peacock M, Bilezikian JP, Klassen PS, Guo MD, Turner SA, Shoback D. Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism. J Clin Endocrinol Metab. 2005;90(1):135-141.

13. Peacock M, Bolognese MA, Borofsky M, et al. Cinacalcet treatment of primary hyperparathyroidism: biochemical and bone densitometric outcomes in a five-year study. J Clin Endocrinol Metab. 2009;94(12):4860-4867.

14. Cetani F, Saponaro F, Banti C, et al. Cinacalcet efficacy in patients with moderately severe primary hyperparathyroidism according to the European Medicine Agency prescription labeling. J Endocrinol Invest. 2012;35(7):655-660.

15. Nguyen S, Gosmanova EO, Gosmanov AR. Cinacalcet-associated resolution of primary hyperparathyroidism in a patient with normal kidney function. J Investig Med High Impact Case Rep. 2020;8:1-5.

16. Di Dalmazi G, Giuliani C, Napolitano G. Parathyroid apoplexy following cinacalcet treatment in primary hyperparathyroidism. Front Endocrinol. 2018;9(777):1-6.

17. Messa P, Alfieri C, Brezzi B. Cinacalcet: pharmacological and clinical aspects. Expert Opin Drug Metab Toxicol. 2008;4(12):1551-1560.

18. Eidman KE, Wetmore JB. Treatment of secondary hyperparathyroidism: how do cinacalcet and etelcalcetide differ? Semin Dial. 2018;31(5):440-444.

19. Temiz G, Yalcin AU, Mutluay R, Bozaci I, Bal C. Effects of cinacalcet treatment on QT interval in hemodialysis patients. Anatol J Cardiol. 2016;16(7):520-530.

20. Novick T, McMahon BA, Berliner A, Jaar BG. Cinacalcet-associated severe hypocalcemia resulting in torsades de pointes and cardiac arrest: a case for caution. Eur J Clin Pharmacol. 2016;72(3):373-375.

21. Imafuku T, Tanaka M, Tokunaga K, et al. Effect of cinacalcet on the redox status of albumin in secondary hyperparathyroidism patients receiving hemodialysis. Biol Pharm Bull. 2020;43(10):1583-1590.

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