Successful treatment of recurrent renal stones with Cinacalcet in a patient with primary hyperparathyroidism

Chauhan, Priyesh; Gittoes, Neil; Geberhiwot, Tarekegn

DOI:
10.1136/bcr-2016-216311

Document Version
Peer reviewed version

Queries for Author

Journal: BMJ Case Reports
Paper: bcr-2016-216311
Title: Successful treatment of recurrent renal stones with Cinacalcet in a patient with primary hyperparathyroidism

The proof of your manuscript appears on the following page(s).

It is the responsibility of the corresponding author to check against the original manuscript and approve or amend these proofs.

Please read the proofs carefully, checking for accuracy, verifying the reference order and checking figures and tables. When reviewing your page proof please keep in mind that a professional copyeditor edited your manuscript to comply with the style requirements of the journal.

This is not an opportunity to alter, amend or revise your paper; it is intended to be for correction purposes only. The journal reserves the right to charge for excessive author alterations or for changes requested after the proofing stage has concluded.

During the preparation of your manuscript for publication, the questions listed below have arisen (the query number can also be found in the gutter close to the text it refers to). Please attend to these matters and return the answers to these questions when you return your corrections.

Please note, we will not be able to proceed with your article if these queries have not been addressed.

A second proof is not normally provided.

Note Reference	Note
N1	IMPORTANT: Corrections at this stage should be limited to those that are essential. Extensive corrections will delay the time to publication and may also have to be approved by the Editor. **Alterations cannot be made after the article has published online**.
N2	Author SURNAMES (family names) have been highlighted - please check that these are correct. Please check all names are spelt correctly, and that affiliations and correspondence details are accurate.
N3	Your article should display in PubMed within 2 working days of publication.

Query Reference	Query
Q1	Please check whether the phrase ‘drug’s understood mechanism of action’ provides intended meaning.

If you are happy with the proof as it stands, please email to confirm this. Minor changes that do not require a copy of the proof can be sent by email (please be as specific as possible).
Email: **production.bmjcases@bmj.com**

If you have any changes that cannot be described easily in an email, please mark them clearly on the proof using the annotation tools and email this by reply to the eProof email.

Author query sheet

We will keep a copy of any correspondence from you related to the author proof for six months. After six months, correspondence will be deleted.

Please respond within 48 hours

CASE REPORT

Successful treatment of recurrent renal stones with Cinacalcet in a patient with primary hyperparathyroidism

Priyesh Chauhan,[1] Neil J Gittoes,[2] Tarekegn Geberhiwot[3]

[1]Department of Endocrinology, University of Birmingham, Birmingham, UK
[2]University of Birmingham, Birmingham, UK
[3]Department of Endocrinology, University Hospital of Birmingham, Birmingham, UK

Correspondence to
Dr Tarekegn Geberhiwot, Tarekegn.hiwot@uhb.nhs.uk

Accepted 26 July 2016

SUMMARY

A man aged 72 years with long-standing primary hyperparathyroidism (HPT), a background of recurrent bilateral renal stones and failed parathyroid surgery is described. During the 27 months preceding treatment, episodes of renal colic became increasingly frequent and he required multiple surgical interventions. Given the lack of medical therapies to definitively treat his symptoms, he was started on a trial of the calcimimetic, Cinacalcet. Cinacalcet has previously been shown to reduce hypercalcaemia in patients with primary HPT. Despite this, there is a paucity of evidence to suggest that its use is associated with a long-term reduction in urinary calcium excretion and renal stone recurrence. In our case, within 4 months of starting treatment, serum and urinary calcium had normalised and parathyroid hormone concentrations were within reference ranges. To date, over a 50-month treatment period, there has been a complete cessation in stone formation, and no further urological intervention has been required.

BACKGROUND

A recent prospective study identified that 55% of all patients with primary hyperparathyroidism (HPT) showed evidence of stone formation on renal ultrasound assessment.[1] Renal and urinary tract stones are therefore a relatively common complication of long-standing hypercalcaemia. Parathyroidectomy remains the definitive gold-standard treatment for patients with primary HPT and target organ involvement. In patients who are deemed unsuitable for parathyroid surgery, conservative management should be considered; the mainstay of which is ensuring adequate hydration to minimise the risk of renal stone formation. Additionally, as part of regular outpatient monitoring, renal ultrasound scans, renal function tests, bone mineral density scans and urinary calcium excretion tests should be performed to actively screen for target organ damage.

In our case, a combination of failed parathyroid surgery and a disappointing response to conservative management resulted in consideration of a trial of Cinacalcet. We believe that for this subgroup of patients, where treatment options remain limited, there is currently an unmet need for a definitive medical therapy. Cinacalcet, a second-generation calcimimetic drug, was approved by the European Medicines Agency in June 2008 as a medical treatment of hypercalcaemia in patients with primary HPT.[2 3] In our patient, initiation of Cinacalcet dramatically reduced urinary calcium excretion and renal stone recurrence.

CASE PRESENTATION

The patient we present is a Caucasian man aged 72 years. At the age of 43, after suffering from an episode of severe renal colic, which warranted surgical intervention with an open pyelolithotomy, routine blood tests revealed a serum hypercalcaemia and an inappropriately elevated serum parathyroid hormone (PTH) concentration; these results were consistent with a diagnosis of primary HPT. There was no significant medical history. The patient subsequently underwent an elective parathyroid exploration, which was unsuccessful in locating the suspected parathyroid adenoma. As a direct complication of the procedure, the patient sustained a recurrent laryngeal nerve palsy resulting in unilateral vocal cord paralysis. Prior to this surgery, no formal localisation studies were conducted. Following the attempted parathyroidectomy, a 99m-technetium sestamibi scan failed to demonstrate any abnormal uptake in the neck or mediastinum, despite persistently elevated PTH levels. Given the grossly normal operative appearance of the parathyroid glands, it was suggested that the true source of PTH secretion could be ectopic in origin; however, this was never definitively proven. The patient declined any further surgery.

Over the next 25 years, he suffered from multiple episodes of renal colic, which appeared to be increasing in frequency. During this time, he passed six renal stones spontaneously while larger stones, up to 20 mm in size, required surgical intervention. In total, the patient underwent four percutaneous nephrolithotomy procedures.

INVESTIGATIONS

Renal stone analysis undertaken in 2011 revealed that calcium oxalate crystals were a predominant constituent. Throughout his long follow-up, the patient's serum calcium was consistently elevated, between 2.8 and 2.99 mmol/L, whereas his PTH concentration fluctuated (mean PTH: 7.8 pmol/L) and peaked at 10.9 pmol/L. Prior to the initiation of Cinacalcet, a 24-hour urine calcium excretion test was performed, and this was recorded as 17.2 mmol/24 hours. No other urinary calcium tests were performed during this pretreatment period. Other biochemical parameters, including estimated glomerular filtration rate and 25-hydroxy vitamin D, were within normal ranges.

To cite: Chauhan P, Gittoes NJ, Geberhiwot T. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2016-216311

TREATMENT

Given the increasing risk of further stone formation and associated complications, such as renal failure, ureteric strictures and pyelonephritis,[4] we sought to find an intervention to moderate his ongoing symptoms. However, the apparent lack of definitive medical therapies for patients with long-standing HPT resulted in consideration of a trial of Cinacalcet at a dose of 30 mg twice daily, which was started in April 2011.

OUTCOME AND FOLLOW-UP

By July 2011, serum calcium and PTH levels had normalised to 2.5 mmol/L and 5.9 pmol/L, respectively. Further surveillance of his bone profile in recent years also revealed serum calcium and PTH concentrations within reference ranges; in December 2015, these were 2.4 mmol/L and 6.5 pmol/L, respectively.

There was a marked reduction in 24-hour urinary calcium excretion from the 17.2 mmol/24 hours in June 2004 (pretreatment) to 7.4 mmol/24 hours in January 2013 (during treatment). In April 2015, this had changed marginally to 8.7 mmol/24 hours. This has been mirrored by the complete cessation of nephrocalcinosis, since starting Cinacalcet, for a period of 50 months. The patient has not passed any further stones, remains asymptomatic and has not required any additional urological intervention.

DISCUSSION

Primary HPT is the most common cause of hypercalcemia.[5] Most patients are asymptomatic at diagnosis, and their management is generally conservative. However, a small subgroup may present with target organ involvement, such as renal stones or osteoporosis, and may require a parathyroidectomy. If surgery is contraindicated or the patient refuses the procedure, then patients with osteoporosis may receive antiresorptive agents; currently, there is no alternative equivalent for patients with symptomatic renal stones. Cinacalcet is a second-generation calcimimetic that acts as an allosteric modulator of calcium-sensing receptors (CaSRs) in the parathyroid glands. It is also thought to act on CaSRs expressed at bone and renal levels.[3 6] By increasing CaSR sensitivity to extracellular calcium, it suppresses PTH secretion and thereby reduces serum calcium concentrations.[3]

It is difficult to establish the exact effect of Cinacalcet on urinary calcium for a variety of reasons.[7] At a renal tubular level, PTH acts to increase calcium reabsorption from the glomerular filtrate. Therefore, as Cinacalcet suppresses PTH levels it should act to increase urinary calcium. This is counteracted by a reduction in serum calcium and the filtered load of calcium, which should lead to a decrease in urinary calcium. The overall effect of Cinacalcet on urinary calcium excretion should therefore be almost negligible.[7]

In patients with primary HPT, serum hypercalcaemia activates CaSRs in the kidneys resulting in a decreased renal tubular calcium reabsorption and an overall urinary dilution, which ultimately helps to protect against stone formation.[8] It is likely that patients with HPT and a predisposition to renal stone development have a deactivating CaSR allelic variant.[8] This provides a likely explanation as to why our patient responded so favourably to Cinacalcet, given this drug's understood mechanism of action.[3 6]

At present, there appears to be very little evidence in the literature to suggest that the use of Cinacalcet can be associated with a reduction in the rate of renal stone formation. However, a pilot study conducted by Brardi *et al*[9] demonstrated a statistically significant reduction in the overall number and diameter of renal stones in a small sample of patients with a background of primary HPT and active nephrolithiasis. They were treated with Cinacalcet for a period of 10 months. Similarly, an audit undertaken by Moyes *et al*[10] showed that patients with multiple endocrine neoplasia type 1, primary HPT and a history of renal calculi demonstrated no recurrence of renal stone formation after taking Cinacalcet for an average duration of 23 months.

In contrast, Seager *et al*[3] reported the first well-documented case of Cinacalcet use directly contributing to the development of renal stones in a post-transplant patient with HPT. It should be noted that Seager *et al*[3] make reference to the fact that the use of calcineurin inhibitors and prednisone as immunosuppressive agents could have contributed to the increased renal calcium load and urinary excretion. Thus, a definitive causal link between Cinacalcet use and renal stone formation cannot easily be established; it appears that the case presented by Seager *et al*[3] is indeed exceptional.

Our case demonstrates a potential use of Cinacalcet as a longer term medical therapy for patients with primary HPT and recurrent renal stones who are unsuitable for parathyroidectomy. More data are required to determine whether this observation is generalisable.

Patient's perspective

After many years suffering from kidney stones and undergoing several operations to have them removed, it was a great relief to finally come into contact with people who suggested a way of reducing the calcium levels in my blood. I am grateful to the friendly team at Queen Elizabeth Hospital, Birmingham, for the treatment and the positive outcome achieved.

Learning points

- Long-term treatment with Cinacalcet resulted in a normalisation of biochemical parameters in a patient with primary HPT.
- Use of Cinacalcet was associated with a reduction in renal stone formation in a patient with primary HPT over a 50-month period.
- Cinacalcet may have a role in the treatment of patients with primary HPT and recurrent renal stones who are unsuitable for parathyroidectomy.

Acknowledgements The authors thank the patient for his permission to use his data for publication and agreeing to write his perspective.

Contributors PC and TG wrote the manuscript. All authors reviewed the draft and approved the final version. TG and NJG cared for the patient.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Cipriani C, Biamonte F, Costa AG, *et al*. Prevalence of kidney stones and vertebral fractures in primary hyperparathyroidism using imaging technology. *J Clin Endocrinol Metab* 2015;100:1309–15.
2 Luque-Fernández I, García-Martin A, Luque-Pazos A. Experience with cinacalcet in primary hyperparathyroidism: results after 1 year of treatment. *Ther Adv Endocrinol Metab* 2013;4:77–81.
3 Seager CM, Srinivas TR, Flechner SM. Development of nephrolithiasis in a renal transplant patient during treatment with Cinacalcet. *Ann Transplant* 2013;18:31–5.
4 Guidelines on Urolithiasis. European Association of Urology (2015). http://uroweb.org/wp-content/uploads/22-Urolithiasis_LR_full.pdf (Date accessed: 01/02/16)
5 Fraser W. Hyperparathyroidism. *Lancet* 2009;374:145–58.
6 Jensen AA, Bräuner-Osborne H. Allosteric modulation of the calcium-sensing receptor. *Curr Neuropharmacol* 2007;5:180–6.
7 Bushinsky DA, Laplante K, Asplin JR. Effect of cinacalcet on urine calcium excretion and supersaturation in genetic hypercalciuric stone-forming rats. *Kidney Int* 2006;69:1586–92.
8 Vezzoli G, Terranegra A, Arcidiacono T, *et al*. Calcium kidney stones are associated with a haplotype of the calcium-sensing receptor gene regulatory region. *Nephrol Dial Transplant* 2010;25:2245–52.
9 Brardi S, Cevenini G, Verdacchi T, *et al*. Use of cinacalcet in nephrolithiasis associated with normocalcemic or hypercalcemic primary hyperparathyroidism: results of a prospective randomized pilot study. *Arch Ital Urol Androl* 2015;87:66.
10 Moyes V, Monson J, Chew S, *et al*. Clinical use of Cinacalcet in MEN1 hyperparathyroidism. *Int J Endocrinol* 2010;2010:1–4.