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

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## CASE REPORT

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

Priyesh Chauhan,<sup>1</sup> Neil J Gittoes,<sup>2</sup> Tarekegn Geberhiwot<sup>3</sup>

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,

he required multiple surgical interventions. Given the

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

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

A recent prospective study identified that 55% of

all patients with primary hyperparathyroidism

(HPT) showed evidence of stone formation on

urological intervention has been required.

BACKGROUND

and urinary calcium had normalised and parathyroid

lack of medical therapies to definitively treat his

episodes of renal colic became increasingly frequent and

symptoms, he was started on a trial of the calcimimetic,

### SUMMARY

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renal ultrasound assessment.<sup>1</sup> Renal and urinary tract stones are therefore a relatively common complication of long-standing hypercalcaemia. Parathyroidectomy remains the definitive goldstandard 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.<sup>2</sup> <sup>3</sup> 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 87 were consistent with a diagnosis of primary HPT. 88 There was no significant medical history. The 89 patient subsequently underwent an elective parathy-90 roid exploration, which was unsuccessful in locat-91 ing the suspected parathyroid adenoma. As a direct 92 complication of the procedure, the patient sus-93 tained a recurrent larvngeal nerve palsy resulting in 94 unilateral vocal cord paralysis. Prior to this surgery, 95 no formal localisation studies were conducted. 96 Following the attempted parathyroidectomy, a 97 99m-technetium sestamibi scan failed to demon-98 strate any abnormal uptake in the neck or mediasti-99 num, despite persistently elevated PTH levels. 100 Given the grossly normal operative appearance of 101 the parathyroid glands, it was suggested that the 102 true source of PTH secretion could be ectopic in 103 origin; however, this was never definitively proven. 104 The patient declined any further surgery. 105

Over the next 25 years, he suffered from mul-<br/>tiple episodes of renal colic, which appeared to be<br/>increasing in frequency. During this time, he passed<br/>six renal stones spontaneously while larger stones,<br/>up to 20 mm in size, required surgical intervention.<br/>In total, the patient underwent four percutaneous<br/>nephrolithotomy procedures.106<br/>106<br/>107<br/>108<br/>109

### INVESTIGATIONS

Renal stone analysis undertaken in 2011 revealed 115 that calcium oxalate crystals were a predominant 116 constituent. Throughout his long follow-up, the 117 patient's serum calcium was consistently elevated, 118 between 2.8 and 2.99 mmol/L, whereas his PTH 119 concentration fluctuated (mean PTH: 7.8 pmol/L) 120 and peaked at 10.9 pmol/L. Prior to the initiation 121 of Cinacalcet, a 24-hour urine calcium excretion 122 test was performed, and this was recorded as 123 17.2 mmol/24 hours. No other urinary calcium 124 tests were performed during this pretreatment 125 period. Other biochemical parameters, including 126 estimated glomerular filtration rate and 25-hydroxy 127 vitamin D, were within normal ranges. 128

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#### 129 **TREATMENT**

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Given the increasing risk of further stone formation and associated complications, such as renal failure, ureteric strictures and pyelonephritis,<sup>4</sup> 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.

#### 138 139 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.

144 There was a marked reduction in 24-hour urinary calcium 145 excretion from the 17.2 mmol/24 hours in June 2004 (pretreat-146 ment) to 7.4 mmol/24 hours in January 2013 (during treat-147 ment). In April 2015, this had changed marginally to 8.7 mmol/ 148 24 hours. This has been mirrored by the complete cessation of 149 nephrocalcinosis, since starting Cinacalcet, for a period of 150 50 months. The patient has not passed any further stones, 151 remains asymptomatic and has not required any additional uro-152 logical intervention. 153

#### DISCUSSION

Primary HPT is the most common cause of hypercalcemia.<sup>5</sup> 156 Most patients are asymptomatic at diagnosis, and their manage-157 158 ment is generally conservative. However, a small subgroup may 159 present with target organ involvement, such as renal stones or osteoporosis, and may require a parathyroidectomy. If surgery is 160 161 contraindicated or the patient refuses the procedure, then 162 patients with osteoporosis may receive antiresorptive agents; 163 currently, there is no alternative equivalent for patients with symptomatic renal stones. Cinacalcet is a second-generation cal-164 cimimetic that acts as an allosteric modulator of calcium-sensing 165 receptors (CaSRs) in the parathyroid glands. It is also thought 166 to act on CaSRs expressed at bone and renal levels.<sup>3</sup> <sup>6</sup> By 167 increasing CaSR sensitivity to extracellular calcium, it suppresses 168 PTH secretion and thereby reduces serum calcium 169 concentrations.<sup>3</sup> 170

It is difficult to establish the exact effect of Cinacalcet on 171 urinary calcium for a variety of reasons.<sup>7</sup> At a renal tubular 172 level, PTH acts to increase calcium reabsorption from the glom-173 erular filtrate. Therefore, as Cinacalcet suppresses PTH levels it 174 175 should act to increase urinary calcium. This is counteracted by a 176 reduction in serum calcium and the filtered load of calcium, which should lead to a decrease in urinary calcium. The overall 177 effect of Cinacalcet on urinary calcium excretion should there-178 fore be almost negligible. 179

In patients with primary HPT, serum hypercalcaemia activates 180 CaSRs in the kidneys resulting in a decreased renal tubular 181 calcium reabsorption and an overall urinary dilution, which 182 183 ultimately helps to protect against stone formation.<sup>8</sup> It is likely that patients with HPT and a predisposition to renal stone devel-184 opment have a deactivating CaSR allelic variant.<sup>8</sup> This provides 185 a likely explanation as to why our patient responded so favour-186 ably to Cinacalcet, given this drug's understood mechanism of  $Q_{187}$ action.<sup>3</sup> 188

At present, there appears to be very little evidence in the literature to suggest that the use of Cinacalcet can be associated

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with a reduction in the rate of renal stone formation. However, 193 a pilot study conducted by Brardi et al<sup>9</sup> demonstrated a statistic-194 ally significant reduction in the overall number and diameter of 195 renal stones in a small sample of patients with a background of 196 primary HPT and active nephrolithiasis. They were treated with 197 Cinacalcet for a period of 10 months. Similarly, an audit under-198 taken by Moyes *et al*<sup>10</sup> showed that patients with multiple endo-199 crine neoplasia type 1, primary HPT and a history of renal 200 calculi demonstrated no recurrence of renal stone formation 201 after taking Cinacalcet for an average duration of 23 months. 2.02

In contrast, Seager *et al*<sup>3</sup> reported the first well-documented 203 case of Cinacalcet use directly contributing to the development 204 of renal stones in a post-transplant patient with HPT. It should 2.05 be noted that Seager *et al*<sup>3</sup> make reference to the fact that the 206 use of calcineurin inhibitors and prednisone as immunosuppres-207 sive agents could have contributed to the increased renal 2.08 calcium load and urinary excretion. Thus, a definitive causal 209 link between Cinacalcet use and renal stone formation cannot 210 easily be established; it appears that the case presented by 211 Seager *et al*<sup>3</sup> is indeed exceptional. 212

Our case demonstrates a potential use of Cinacalcet as a 213 longer term medical therapy for patients with primary HPT and 214 recurrent renal stones who are unsuitable for parathyroidectomy. More data are required to determine whether this observation is generalisable. 217

### **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.

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**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.

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## Novel treatment (new drug/intervention; established drug/procedure in new situation)

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