

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

Cinacalcet to prevent parathyrotoxic crises in hypercalcaemic patients awaiting parathyroidectomy

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Summary

Primary hyperparathyroidism is the third most common endocrine disorder. Hypercalcaemia exceeding 3 mmol/l is a major risk factor for parathyrotoxic crises, and management of patients at risk remains a medical challenge. The authors recently managed three such patients referred for severe nephrolithiasis. All had severe hypercalcaemia (at least 3 mmol/l). Instead of the usual management, which involves hospitalisation in an intensive care environment (for about 5–7 days) for rehydration and infusion of intravenous bisphosphonates, followed by emergency parathyroidectomy, the three patients received ambulatory cinacalcet (not an approved indication), 30 mg twice a day. The serum calcium normalised in two cases and declined to a safe level in the third case, allowing minimally invasive parathyroidectomy to be performed at a date chosen according to the patients' and surgeon's respective schedules. The authors consider that cinacalcet may benefit severely hypercalcaemic patients awaiting surgery for primary hyperparathyroidism.

BACKGROUND

Primary hyperparathyroidism is the third most common endocrine disorder. It is largely asymptomatic in 70–80% of patients, in whom it is diagnosed incidentally because of mild hypercalcaemia.¹ About 5% of cases are diagnosed in patients admitted urgently for severe hypercalcaemia (>3.5 mmol/l (14 mg/dl)) with dehydration, worsening renal function and neurologic deterioration, that is, a parathyrotoxic crisis. Hypercalcaemia exceeding 3 mmol/l (12 mg/dl) is a major risk factor for parathyrotoxic crises,¹ and management of patients at risk remains a medical challenge.

CASE PRESENTATION

We recently managed three such patients referred for severe nephrolithiasis (bilateral and recurrent phosphocalcic stones). All three patients had hypercalcaemia (at least 3 mmol/l (12 mg/dl)) and elevated serum intact 1-84 parathyroid levels but none had yet had a parathyrotoxic crisis (table 1).

INVESTIGATIONS

The parathyroid adenoma was identified and located on an ambulatory basis within 1 week after initial presentation by examinations including ultrasonography, iodine 123 scintigraphy and ⁹⁹technetium-MIBI and either CT (patient #1) or MRI (patients #2 and #3).

TREATMENT

Instead of the usual management of severe hypercalcaemia in this setting which involves hospitalisation in an intensive care environment for rehydration and infusion of intravenous bisphosphonates followed by emergency parathyroidectomy, the three patients received ambulatory cinacalcet (not an approved indication), 30 mg twice a day,

and were advised to avoid calcium intake and to drink at least 2 litres of calcium-poor mineral water a day.

OUTCOME AND FOLLOW-UP

The serum calcium normalised in two cases and declined to a safe level in the third case, the nadir of calcaemia being reached within a week (table 1), thus allowing minimally invasive parathyroidectomy to be performed at a date chosen according to the patients' and surgeon's respective schedules with a 2-day hospital stay.

DISCUSSION

Cinacalcet is the first member of the calcimimetic family to be marketed. It activates the calcium-sensing receptor and inhibits parathyroid hormone secretion.² Cinacalcet has been approved in the USA and Europe for the treatment of secondary hyperparathyroidism in patients with end-stage renal failure on dialysis maintenance therapy, and more recently, for the treatment of parathyroid carcinoma and also primary hyperparathyroidism not amenable to surgery.² In two pivotal controlled trials in primary hyperparathyroidism, cinacalcet normalised mild hypercalcaemia in respectively 22 and 78 patients^{3 4}: the total calcaemia fell from 2.64 mmol/l (10.56 mg/dl) to 2.59 mmol/l (10.36 mg/dl) in the first trial³ and from 2.66 mmol/l (10.64 mg/dl) to 2.44 mmol/l (9.76 mg/dl) in the second.⁴ More recently, in 17 patients with persistent primary hyperparathyroidism after parathyroidectomy or with severe hypercalcaemia (>3.1 mmol/l, 12.40 mg/dl) and contraindications to parathyroid surgery, cinacalcet (between 30 mg twice daily and 90 mg four times daily) reduced serum calcaemia by 0.25 mmol/l (1 mg/dl) or more in 15 cases.⁵ Together, these results suggest that cinacalcet may be safe and beneficial in severely hypercalcaemic patients awaiting surgery for primary hyperparathyroidism.

Table 1 Characteristics of the three hypercalcaemic patients awaiting parathyroidectomy

Patient number	1	2	3
Age (years)	61 Years	43 Years	41 Years
Sex	Male	Female	Female
Location of the parathyroid adenoma	Right inferior	Right inferior	Left inferior
Weight of the adenoma on histologic examination	5 g	2 g	2 g
Time between diagnosis and surgery	25 Days	15 Days	45 Days
Intact parathyroid hormone (1–84) level (Architect intact PTH chemoluminescent assay, Abbott) (normal range 15–68 pg/ml)	680 pg/ml	156 pg/ml	158 pg/ml
Total serum calcium before cinacalcet (colorimetric complexometry; Roche Diagnostics) (normal range 2.15–2.55 mmol/l) (normal range 8.60–10.20 mg/dl)	3.09 mmol/l (12.36 mg/dl)	3.03 mmol/l (12.12 mg/dl)	3.00 mmol/l (12 mg/dl)
Total serum calcium on cinacalcet (after 1 week)	2.78 mmol/l (11.12 mg/dl)	2.41 mmol/l (9.64 mg/dl)	2.37 mmol/l (9.48 mg/dl)
Ionised calcium before cinacalcet (ES-NOVA-Mercury) (normal range 1.15–1.37 mmol/l)	1.62 mmol/l	1.59 mmol/l	1.51 mmol/l
Ionised calcium on cinacalcet	1.53 mmol/l	1.34 mmol/l	1.32 mmol/l

Learning points

- ▶ Management of primary hyperparathyroidism with hypercalcaemia exceeding 3 mmol/l (12 mg/dl) remains a medical challenge as these patients are at a high risk of parathyrotoxic crises.
- ▶ Classical management in this setting involves rehydration and intravenous bisphosphonates followed by emergency classical parathyroidectomy. This strategy requires hospitalisation in an intensive care environment for about a week and carries a risk of significant hypocalcaemia after parathyroidectomy, related to bisphosphonate use, and a risk of injury to the recurrent laryngeal nerve with attendant cord vocal dysfunction.
- ▶ Cinacalcet may benefit these patients by allowing minimally invasive parathyroidectomy to be performed safely during a 2-day hospital stay after ambulatory normalisation of serum calcium or a reduction to a safe level within one week.
- ▶ Moreover, this new alternative medical strategy is cost-effective (3563 instead of 6159 with classical management).

Competing interests None.

Patient consent Obtained.

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