CASE REPORT

Steroid-induced hypocalcaemia with tetany in a patient with hypoparathyroidism

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SUMMARY

Although glucocorticoids have a known negative effect on calcium balance, they do not normally cause clinically significant hypocalcaemia. A young woman with post-surgical hypoparathyroidism developed symptomatic hypocalcaemia on two occasions following treatment with intravenous hydrocortisone for allergic reactions. Oral calcium and vitamin D supplementation could not prevent the development of hypocalcaemia. She was treated successfully with intravenous calcium gluconate infusions and discontinuation of glucocorticoids.

In patients with hypoparathyroidism, impaired parathyroid hormone response to steroid-induced negative calcium balance may result in severe symptomatic hypocalcaemia requiring hospitalisation.

BACKGROUND

Although glucocorticoids (GC) are known to exert a hypocalcaemic effect through decreased intestinal absorption and increased renal excretion of calcium, clinically significant hypocalcaemia is not a recognised complication of GC administration to normocalcaemic individuals.[1 2] However, there are isolated case reports suggesting that normocalcaemic patients with deficiency of parathyroid hormone (PTH) or vitamin D may develop symptomatic hypocalcaemia following GC therapy.[3–6] We present herein the case of a patient with hypoparathyroidism who maintained normal serum calcium levels on long-term oral calcium and vitamin D supplementation but developed severe hypocalcaemia and tetany following high-dose GC treatment. This case offers insights into the management of PTH-deficient patients requiring GC therapy.

CASE PRESENTATION

A 29-year-old woman presented to the emergency department with tetany 2 days after receiving treatment with intravenous GC and antihistamines for an allergic skin rash at another hospital. The rash had erupted 4 days after starting oral amoxicillin-clavulanic acid for an upper respiratory tract infection. On examination she presented with perioral numbness and paraesthesiae of fingers and toes. She had spontaneous carpopedal spasm bilaterally and positive Chvostek sign. There was a widespread, erythematous, pruritic maculopapular rash covering torso and limbs. Body temperature was normal. Her pharynx was erythematous with white exudate on the tonsils. Mild, painless cervical lymphadenopathy was also present. The rest of physical examination was unremarkable.

The patient had a history of hypoparathyroidism complicating subtotal parathyroidectomy performed at the age of 25 because of primary hyperparathyroidism associated with familial multiple endocrine neoplasia type 1 (MEN-1). She was taking long-term oral calcium and vitamin D supplementation, maintaining normal serum calcium levels on regular follow-up measurements. Apart from multiple, small (<1 cm), non-functioning adenomas of the pancreas there were no other manifestations of MEN-1. Her medication at the time of admission consisted of oral calcium 1000 mg daily, alphacalcidol 0.5 µg daily, azithromycin and levocetirizine.

INVESTIGATIONS

Serum biochemistry revealed hypocalcaemia (corrected serum calcium 1.82 mmol/L, reference range 2.2–2.7) with inorganic phosphorus at the upper limit of normal (1.45 mmol/L, reference range 0.8–1.45) and normal magnesium. There was also marginal elevation of alanine aminotransferase (47 iu/L) and γ-glutamyl transpeptidase (44 iu/L). Plasma PTH levels were low at 7.27 pg/mL (reference range 15–65). A full blood count showed mild lymphocytosis (4.88×10^9/L) with many atypical lymphocytes present on the blood film. High titres of IgM antibodies against the Epstein-Barr viral capsid antigen confirmed the diagnosis of infectious mononucleosis.

TREATMENT

The hypocalcaemia was treated with intravenous infusions of calcium gluconate, while the daily doses of oral calcium and alphacalcidol were increased to 2000 mg and 1 µg, respectively. Intravenous hydrocortisone 125 mg four times a day and ranitidine 150 mg twice daily, together with oral levocetirizine 5 mg once daily were administered for the allergic skin reaction. On the third hospital day symptomatic hypocalcaemia recurred, associated with a serum calcium level of 1.67 mmol/L. The patient was given further intravenous calcium by continuous infusion while hydrocortisone was tapered quickly and discontinued on day 6, resulting in gradual normalisation of serum calcium which was 2.07 mmol/L on day 7. She was discharged asymptomatic on maintenance therapy with oral calcium and alphacalcidol.

OUTCOME AND FOLLOW-UP

On outpatient review after 2 weeks she was normocalcaemic (2.3 mmol/L). Three years later she presented again with a severe, generalised allergic skin eruption following treatment with amoxicillin for a tooth infection. She was admitted for administration

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of intravenous hydrocortisone (100 mg four times a day). Despite doubling her maintenance doses of oral calcium and alphacalcidol, she developed symptomatic hypocalcaemia on the second hospital day with her serum calcium levels falling from 2.32 mmol/L to 1.92 mmol/L. She responded well to intravenous Ca gluconate and rapid tapering of hydrocortisone.

DISCUSSION

The first case of GC-induced tetany was reported in 1964 by Kahn *et al*:[3] A 38-year-old woman with latent hypoparathyroidism complicating an old thyroidectomy presented with tetany and generalised seizures 1 month after starting prednisone for arthritic pains. Vardi *et al*[4] described a 7-year-old girl with hypoparathyroidism whose serum calcium was maintained within normal range on oral vitamin D and calcium supplementation therapy. She developed marked hypocalcaemia following prednisolone administration for aplastic anaemia, despite her serum $1,25(OH)_2D_3$ being in the high-normal range. Handa *et al*[5] reported a 35-year-old woman with hypoparathyroidism who presented to the emergency department with altered sensorium and generalised convulsions associated with hypocalcaemia 10 h after receiving intramuscular methylprednisolone for an exacerbation of rheumatoid arthritis. More recently, Kinoshita *et al*[6] described a 47-year-old woman with normal parathyroid function who developed symptomatic hypocalcaemia on the second day of high-dose intravenous methylprednisolone therapy for haemophagocytic lymphohistiocytosis associated with cord-blood transplantation. The patient was found to have vitamin D insufficiency and responded well to calcium and alphacalcidol administration.

Our patient with post-surgical hypoparathyroidism developed symptomatic hypocalcaemia on two separate occasions following intravenous hydrocortisone for allergic skin reactions associated with amoxicillin. On the first occasion, the antibiotic was given for an upper respiratory tract infection which eventually proved to be infectious mononucleosis—not a known cause of hypocalcaemia. On the second, the patient took amoxicillin for a tooth infection. On neither occasion did she have severe systemic sepsis or gastrointestinal manifestations to account for the fall in serum calcium. Applying the Naranjo probability scale for adverse drug reactions,[7] we calculated a score of 9, which indicates a definite causal association between administration of GC and hypocalcaemia.

The above cases suggest that, in the presence of deranged calcium homoeostasis, GC administration may result in clinically significant hypocalcaemia. Glucocorticoids decrease intestinal absorption of calcium.[2 8] Although the exact mechanism is not fully understood, there is evidence that it involves diminished expression of Ca^{2+} transporting channels in the duodenum, the main site of calcium absorption. Additionally, GC increase calcium excretion by the kidney through decreased tubular reabsorption.[9 10] However, healthy participants who are given GC maintain normal serum calcium levels because the hypocalcaemic effect of GC is counteracted by the immediate secretion of PTH through a negative feedback mechanism involving the calcium sensing receptor on the chief cells of the parathyroid glands. Indeed, increased plasma PTH was found as early as 15 min after the onset of a 4 h intravenous infusion of 200 mg cortisol in healthy volunteers.[11] In the same study, patients receiving oral prednisone treatment for up to 50 months maintained normal serum calcium but had significantly elevated PTH levels. PTH plays a central role in the homoeostatic response to hypocalcaemic challenges. It raises serum calcium levels directly by increasing Ca^{2+} reabsorption in the distal nephron and by stimulating Ca^{2+} release from its bone pool, and indirectly by promoting renal production of $1,25(OH)_2D_3$ which increases intestinal absorption of calcium.[12] Therefore, whereas CG-induced hypocalcaemia would normally be prevented by increased PTH secretion, the latter would not be possible in patients with hypoparathyroidism.

There is experimental evidence that Ca malabsorption caused by glucocorticoids is independent of vitamin D.[2] This is consistent with the apparent failure of alphacalcidol administration to prevent the development of GC-induced hypocalcaemia observed in our patient.

It is concluded that clinically significant hypocalcaemia resistant to oral Ca and vitamin D supplementation should be anticipated when GC therapy is given to patients with PTH deficiency. Such patients may need hospitalisation for intravenous calcium administration.

Learning points

- In the setting of parathyroid hormone deficiency, administration of glucocorticoids may cause clinically significant hypocalcaemia.
- Serum calcium levels should be closely monitored in patients with hypoparathyroidism receiving glucocorticoid therapy.
- Patients with hypoparathyroidism receiving high-dose glucocorticoid therapy may require hospitalisation for intravenous calcium administration, as oral calcium and vitamin D supplementation may not be adequate.

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Competing interests None.

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