Endocrinology, Diabetes & Metabolism CASE REPORTS

A S Jones and others | Challenging post-operative hypocalcaemia

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The challenges of post-bariatric surgery hypocalcaemia in pre-existing hypoparathyroidism

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Summary

Conventional treatment of hypoparathyroidism relies on oral calcium and calcitriol. Challenges in managing post-parathyroid- and post-thyroidectomy hypocalcaemia in patients with a history of bariatric surgery and malabsorption have been described, but postoperative management of bariatric surgery in patients with established hypoparathyroidism has not. We report the case of a 46-year-old woman who underwent elective sleeve gastrectomy on a background of post-surgical hypoparathyroidism and hypothyroidism. Multiple gastric perforations necessitated an emergency Roux-en-Y gastric bypass. She was transferred to a tertiary ICU and remained nil orally for 4 days, whereupon her ionised calcium level was 0.78 mmol/L (1.11–1.28 mmol/L). Continuous intravenous calcium infusion was required. She remained nil orally for 6 months due to abdominal sepsis and the need for multiple debridements. Intravenous calcium gluconate 4.4 mmol 8 hourly was continued and intravenous calcitriol twice weekly was added. Euthyroidism was achieved with intravenous levothyroxine. Maintaining normocalcaemia was fraught with difficulties in a patient with pre-existing surgical hypoparathyroidism, where oral replacement was impossible. The challenges in managing hypoparathyroidism in the setting of impaired enteral absorption are discussed with analysis of the cost and availability of parenteral treatments.

Learning points:

- Management of hypoparathyroidism is complicated when gastrointestinal absorption is impaired.
- Careful consideration should be given before bariatric surgery in patients with pre-existing hypoparathyroidism, due to potential difficulty in managing hypocalcaemia, which is exacerbated when complications occur.
- While oral treatment of hypoparathyroidism is cheap and relatively simple, available parenteral options can carry significant cost and necessitate a more complicated dosing schedule.
- International guidelines for the management of hypoparathyroidism recommend the use of PTH analogues where large doses of calcium and calcitriol are required, including in gastrointestinal disorders with malabsorption.
- Approval of subcutaneous recombinant PTH for hypoparathyroidism in Australia will alter future management.

Background

Conventional treatment of hypoparathyroidism relies on gastrointestinal absorption of oral calcium and calcitriol. The management of hypocalcaemia in patients with a history of bariatric surgery or malabsorption is difficult. While the challenges in managing post-thyroidectomy hypocalcaemia in patients with a history of bariatric surgery has been described (1, 2), postoperative management of bariatric surgery in patients with established hypoparathyroidism has not. We present the case of marked and prolonged hypocalcaemia in a 46-year-

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old woman who underwent elective sleeve gastrectomy with multiple complications on a background of surgical hypoparathyroidism and hypothyroidism.

Case presentation

A 46-year-old woman decided to undergo elective sleeve gastrectomy. The patient weighed 95 kg with a BMI of 38.5 kg/m^2 at the time of surgery. Her past medical history included obesity, psoriatic arthritis treated with multiple immunosuppressants as well as surgical hypoparathyroidism and hypothyroidism following total thyroidectomy for a multinodular goitre 20 years previously. She had no history of diabetes, dyslipidaemia, hypertension or obstructive sleep apnoea. Her hypoparathyroidism was well managed on long term oral calcium carbonate and calcitriol . In November 2018 at a private metropolitan hospital, she had a planned sleeve gastrectomy, which was converted to emergency Roux-en-Y gastric bypass surgery due to multiple gastric perforations because of friable mucosa. Consequent abdominal sepsis required transfer to intensive care at a tertiary hospital 4 days post-operatively. Upon arrival, having remained nil orally, her calcium level was critically low at 0.78 mmol/L (1.11–1.28), though she was asymptomatic without seizure or arrhythmia (Table 1). A continuous intravenous calcium gluconate infusion was required to achieve normocalcaemia, followed by maintenance intermittent IV calcium boluses. The patient had a prolonged ICU admission of 6 months and required more than 20 abdominal operations. During this period, she received all medication and nutrition intravenously and lost 14 kg. Endocrinology advice was required throughout her admission to manage her pre-existing hypoparathyroidism and hypothyroidism parenterally.

Treatment

Two weeks into her admission, Endocrinology advice was sought regarding the management of hypothyroidism; her TSH was 5.83 mU/L (ref range 0.30–5.00 mU/L) at this time. Intravenous triiodothyronine (T3) 10 µg BD was commenced and euthyroidism was achieved after gradual up titration to 40/20/40 µg daily based on TSH levels. On review, it was noted that high dose intravenous calcium, 4.4 mmol five times daily, was required through a central line to maintain normocalcaemia with ionised calcium being measured daily via routine blood gases. Serum phosphate level was 1.07 (ref range: 0.75–1.5mmol/K) and remained in the normal range throughout the hospital admission.

Intravenous calcitriol 1 µg alternate daily was, therefore, commenced 6 weeks into her admission, but was subsequently ceased 5 days later due to limited stock and high cost. Eight weeks into her admission, 150 000 units of intramuscular cholecalciferol was trialled as it was readily available, but the low 1,25(OH)vitamin D3 level failed to increment, being 31 pmol/L (ref range 50–190) prior to administration and 29 pmol/L 3 weeks after administration. Renal function was normal with eGFR > 90 mL/min/1.73 m^2.

Three months into her admission, the patient still required intravenous calcium gluconate 4.4 mmol five times daily to maintain normocalcaemia. Additional intravenous calcitriol was obtained and recommenced at a dose of 1 µg alternate daily. This gradually reduced calcium gluconate requirements to 4.4 mmol three times per day (Fig. 1). Of note, at this time, intramuscular thyroxine 600 µg was trialled as a substitute for intravenous triiodothyronine, however, the patient found the injection painful. Therefore, intravenous thyroxine was commenced 4 days later at a dose of 200 µg alternate daily. Eventually, a maintenance schedule that controlled both the hypocalcaemia and hypothyroidism was established (Table 2).

Table 1 Ionised calcium results.

	Ionised calcium, mmol/L
Reference Range	1.11–1.28
On admission to tertiary hospital (07/11/18)	0.78
At the time of referral to endocrinology (25/11/18)	1.04
At the time of discharge from tertiary hospital (30/5/19)	1.23

Outcome and follow-up

After a prolonged hospital stay of over 8 months, the patient recovered sufficiently to recommence oral intake. She was discharged on her preoperative calcitriol dose (0.75 µg daily) and an increased dose of calcium (1200 mg orally twice daily compared to 1200 mg daily pre-operatively). She remained well replaced with normocalcaemia on review 6 weeks, 12 weeks and 4 months after discharge. At the time of her 4-month follow up, she weighed 71.8 kg and had a BMI of 29 kg/m^2.

Discussion

Calcium replacement may be difficult when enteral absorption is impaired. While oral treatment of

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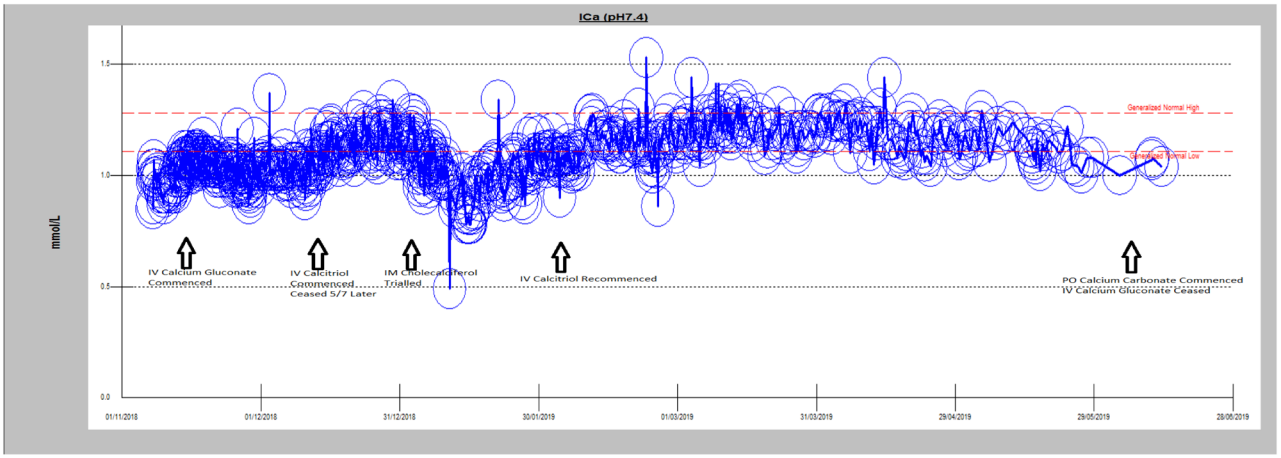

Supplementation administered		7-21/11/18	21/11 – 2/12/18	2-31/12/18	1-14/1/19	16-25/1/19	25/1-13/2/19	13-20/2/19	20-24/2/19	24/2-15/3/19	15/3-27/5/19	27-29/5/19	29/5-28/8/19	28/8-30/11/19
Calcium dose mmol/l or mg	IV	Continuous	4.4 x 5/d	4.4 x 4/d	4.4 x 4/d	4.4 x 6/d	4.4 x 5/d	4.4 x 4/d	4.4 x 3/d	4.4 x 4/d	4.4 x 3/d			
	O											1200/d	1200 x 2/d	1200 x 2/d
Calcitriol dose mcg	IV			1 x 3 doses alt/daily				1 alt daily	1 alt daily	1 alt daily	1 alt daily			
	O											0.75/d	0.75/d	0.75/d
Cholecalciferol IU					150 000 x 1 dose									

Figure 1
Ionised calcium levels with associated parenteral treatment for hypoparathyroidism during admission.

hypoparathyroidism with calcium carbonate and calcitriol is cheap and relatively simple, available parenteral options can carry significant costs, require central line access and necessitate a more complicated dosing schedule (Table 3).

Our patient was managed with intravenous calcium gluconate, and subsequently, intravenous calcitriol was added. As may have been expected, parenteral cholecalciferol did not alter the 1,25(OH)vitamin D level due to absent endogenous PTH, which is required to activate cholecalciferol.

We explored the costs of possible alternative treatment options for non-oral management of hypoparathyroidism (Table 2). The PTH analogue PTH 1–34 (teriparatide) is used for osteoporosis. Some studies have demonstrated the benefit of subcutaneous PTH 1–34 in maintaining normocalcaemia in patients with hypoparathyroidism (3). Continuous PTH 1–34 treatment almost eliminated diurnal variations in calcium levels and improved hypercalcaemia in two studies comparing pump and injection therapy in adults and children (4, 5). Similarly, continuous PTH (1–34) treatment via a pump improved calcium homeostasis in three patients with uncontrolled hypocalcaemia post-operatively despite receiving subcutaneous PTH 1–34 treatment (6). Unlike with PTH 1–84, which is discussed below, there are no clinical trials for registration on teriparatide treatment in hypoparathyroid patients, however, a prospective open-label study in post-surgical patients with fixed twice daily dosing demonstrated a significant reduction in calcium requirements and improved quality of life (7).

The full recombinant human PTH molecule, PTH 1–84 (NatPara) has been shown to be effective and well tolerated with improved quality of life vs standard therapy (8, 9) A US randomised controlled trial addressing the safety and efficacy of daily PTH (1–84) demonstrated that 53% of patients receiving PTH (1–84) achieved the primary end point of a ≥50% reduction in their baseline dose of oral calcium and vitamin D while maintaining normal serum calcium levels, compared to 2% in the placebo group (8). International guidelines

Table 2 Comparison between oral and intravenous doses required for maintenance treatment of hypoparathyroidism and hypothyroidism.

	Pre-existing oral treatment	Maintenance i.v. treatment
Calcium carbonate	1200 mg daily	Calcium gluconate 4.4 mmol three times per day
Calcitriol	0.75 µg daily	1 µg every 2 days
Levothyroxine	200 µg daily	200 µg every 3 days

Table 3 Parenteral options for the treatment of hypoparathyroidism.

Treatment option and dose	**Dosing schedule**	**Cost per month** (approx.) **AUD**	**Availability in Australia**
IV Calcitriol	1 µg IV every 4 days 0.25 µg IV daily	$120 $480	Available
IV Calcium gluconate	4.4 mmol IV 5x daily 4.4 mmol IV 3x daily	$1674 $1004	Available
Teriparatide (PTH 1–34)	20 µg subcut twice daily	$824	Off-label Indication
NatPara (PTH-1–84)	50–100 µg subcut daily	$11 995 (via Special Access Scheme)	Special access scheme only (FDA approved 2015)

for the management of hypoparathyroidism (2016), therefore, recommend the use of PTH 1–84, where large doses of calcium and calcitriol are required, including in gastrointestinal disorders with malabsorption (10). However, this practice has not become standard in our institution as its use is not government subsidised because it has not yet been included in the Australian Register of Therapeutic Goods.

Other groups have reported how they improved enteral absorption of calcium and calcitriol in patients with surgical hypoparathyroidism where parathyroidectomy occurred after bariatric surgery. Their approaches included escalating oral doses, gastrostomy tube insertion and pancreatic enzyme supplementation (11, 12). None would have been appropriate in our case because of abdominal sepsis and friable mucosa. Ours represents the first case in the literature, to our knowledge, whereby gastric bypass surgery was undertaken in an individual with pre-existing hypoparathyroidism.

We propose careful consideration be given before elective bariatric surgery in patients with pre-existing hypoparathyroidism due to potential difficulties in managing hypocalcaemia in the setting of impaired gastrointestinal absorption, which is exacerbated when complications occur. Approval of subcutaneous recombinant PTH for hypoparathyroidism in Australia will alter future management.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement
All authors were involved in the clinical care of the patient and contributed to the writing of this manuscript.

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