Use of recombinant parathyroid hormone with significant improvement of debilitating hypocalcaemia and hypomagnesaemia.

E Panteliou, E Casey, A Hawkins, A James, S Jones, P Kwong, D Gupta, Y Razzak, K Nikookam

King George's Hospital, Barking Havering and Redbridge University Hospitals NHS Trust

Introduction

Primary hypoparathyroidism has an incidence of 4 in 100.000 people, with postoperative and autoimmune aetiology being the commonest. Idiopathic hypoparathyroidism is unusual affecting 7.2 per million people. Although acute hypomagnesaemia increases parathyroid hormone (PTH) secretion, profound magnesium depletion paradoxically depresses PTH and increases resistance inducing severe hypocalcemia.

Teriparatide a type of recombinant PTH containing the biologically active N terminal of the hormone (1-34) when given intermittently leads to increased number and activity of osteoblasts.

Case

A 45 year old woman presented with gradually worsening paraesthesia and limb weakness. Clinical examination only revealed a positive Chovstek's sign.

Initial investigations showed low serum calcium of 1.58 (2.2 - 2.6 mmol/L), magnesium of 0.4 (0.7 - 1.05 mmol/L), potassium of 3 (3.5 - 5 mmol/L) and normal phosphate 1.21 (0.8 - 1.5 mmol/L), bicarbonate 27 (22 - 28 mmol/L), liver and renal function. ECG showed prolonged QTc segment.

She was initially treated with intravenous calcium and magnesium and subsequently switched to oral supplements. She had recurrent admissions over a 10 month period with persistently low calcium and magnesium. Hypertension was diagnosed eight months after her initial presentation.

Investigations

She was found to be hypocalcaemic and severely hypomagnesaemic (Figure 1) in all occasions.

Further investigations showed low PTH at 0.6 (1.3 - 6.8 pmol/L), vitamin D at 14 (25 - 200 nmol/L) with elevated 24 hour urine calcium excretion of 13.1 (2.5 - 7.5 mmol/24hr), urine magnesium excretion of 3.9 (2.4 - 6.5 mmol/24hr), normal thyroid function, haematinics and a basal cortisol of 375 nmol/L. She had osteopenia on dual energy X ray absorptiometry and normal whole body computed tomography, gastroscopy and coeliac screen.

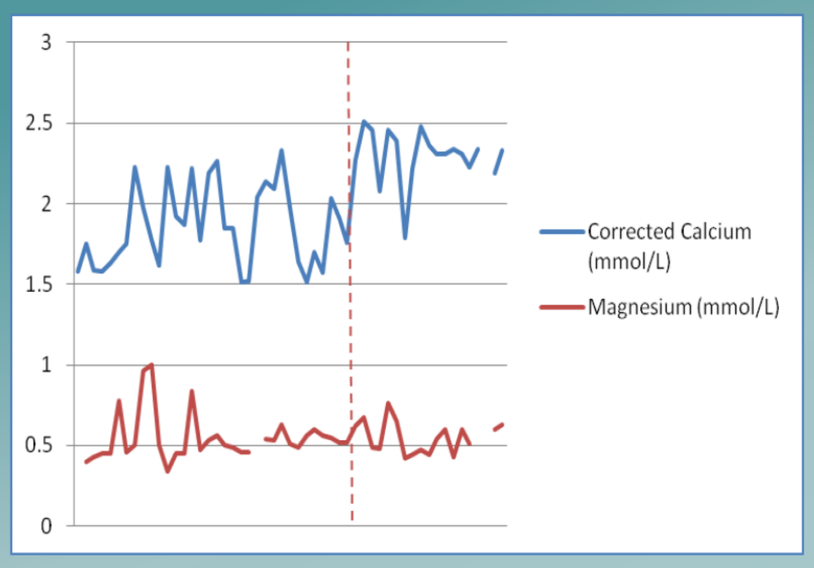

Figure 1: Levels of calcium and magnesium before and after teriparatide, initiation of which is marked with the red dotted line.

Treatment

Her oral treatment was escalated gradually without significant biochemical and clinical response. She was subsequently electively admitted for the initiation of teriparatide despite which she continued to require significant amounts of magnesium sulphate and calcium gluconate intravenously, additional to her oral supplements. Double the recommended teriparatide dose was eventually required in order to overcome the increased end organ resistance. Despite experimental studies showing a direct effect of PTH on renal magnesium reabsorption, hypomagnesaemia showed little response.

Outcome and Follow Up

Recombinant PTH (1-34) (teriparatide) led to normalisation of calcium and no further hospital admissions.

A 24 hour collection of urine electrolytes, while on teriparatide and oral supplements, showed a magnesium excretion of 8.1 (2.4 - 6.5 mmol/24hr), calcium of 11.2 (2.5 - 7.5 mmol/24hr), potassium of 72 (25 - 125 mmol/24hr) and phosphate of 20 (14 - 50 mmol/24hr). In hypomagnesaemia of extrarenal origin, 24 hour urine magnesium excretion remains below 1 mEq/day whereas in tubular defects is greater than 4 mEq/day.

As a result her hypoparathyroidism is thought to be functional secondary to severe hypomagnesaemia suppressing the endogenous PTH production and increasing PTH resistance.

Conclusion

In our case, in view of her normal gastrointestinal investigations and excessive urine electrolyte losses, the hypoparathyroidism was attributed to a renal tubular defect related to an acquired mutation or a hereditary disorder clinically emerging in adulthood leading to excessive magnesium renal wasting.

In the United Kingdom, the N terminal active fragment (1–34) of recombinant human PTH (teriparatide) is currently only licensed for the treatment of osteoporosis.

In the United States, the full length PTH (1–84) was approved for the treatment of hypoparathyroidism in 2015. The "Efficacy and safety of recombinant human PTH (1-84) in hypoparathyroidism" (REPLACE) study [1] showed good tolerance and therapeutic effect of PTH (1-84) in hypoparathyroidism. Further studies are required to evaluate the role and efficacy of PTH in the management of patients with resistant and/or persistent hypocalcaemia and hypomagnesaemia.

1. Mannstadt M, Clarke BL, Vokes T, Brandi ML, Ranganath L, Fraser WD, Lakatos P, Bajnok L, Garceau R, Mosekilde L, Lagast H, Shoback D, Bilezikian JP. Efficacy and safety of recombinant human parathyroid hormone (1-84) in hypoparathyroidism (REPLACE): a double-blind, placebo-controlled, randomised, phase 3 study. *Lancet Diabetes Endocrinol* 2013 **1(4)** 275-83.