

Prolonged hypocalcaemia after pamidronate infusion in Riedel's thyroiditis associated hypoparathyroidism

D. Boumans^{1,2*}, P.A.M. de Vries², N.E.T. Rikken², G.D. Laverman²

¹Department of Rheumatology, Medisch Spectrum Twente, Enschede, the Netherlands, ²Department of Internal Medicine, Ziekenhuisgroep Twente, Almelo, the Netherlands, *corresponding author: tel.: +31 (0)53 4872450, e-mail: boumansd@gmail.com

Dear Editor,

We want to draw attention to the important role of the parathyroid glands in maintaining normocalcaemia.

A 50-year-old woman with known hypoparathyroidism secondary to Riedel's thyroiditis initially presented with severe hypercalcaemia and acute renal failure luxated by a gastroenteritis (*table 1*). Her medications dihydrotachysterol (DHT; 0.4 mg/day), calcium carbonate (3000 mg/day) and hydrochlorothiazide were stopped and she was treated with normal saline and a single dose of 60 mg pamidronate. After recovery of the hypercalcaemia she was discharged on her previous medication (*figure 1*). Five days later she presented again, now with severe hypocalcaemia necessitating treatment with intravenous calcium glubionate (2160 mg/day) and oral calcium carbonate (4500 mg/day) for several weeks, and a doubled vitamin D dose (*table 1, figure 1*). Only after 21 days the intravenous calcium supplementation was completely tapered. Twenty-three days after admission, she was discharged on oral calcium carbonate (6000 mg/day) and alfacalcidol (0.50 µg/day) (*figure 1*).

A clustering of features contributed to the bidirectional extreme calcium plasma concentrations in this patient. In normal conditions plasma calcium is tightly regulated by a dynamic hormonal system that controls its transport in the gut, kidney, and bone. Key players are the parathyroid hormone (PTH) and active vitamin D (1,25(OH)₂D).^{1,2} Whereas normally any tendency towards hypocalcaemia or hypercalcaemia will result in a rapid increase or decrease in PTH secretion from the parathyroid glands, this response was obviously lacking in our patient.^{1,2} In addition, she was treated with calcium carbonate and DHT. The latter is a half synthetic vitamin D analogue that does not require renal hydroxylation.^{3,5} DHT is deposited in fat, liver, skin, muscle and bone. After withdrawal it

may take up to nine weeks for the physiological effects to completely resolve.^{3,6} Thus, while gastroenteritis was the initial trigger for volume depletion, hypercalcaemia and renal insufficiency, the cascade was fuelled by continued use of calcium carbonate, DHT and hydrochlorothiazide. In this situation, intoxication with DHT is likely to occur with concomitant inappropriate ongoing intestinal calcium absorption.^{1,3,6,7}

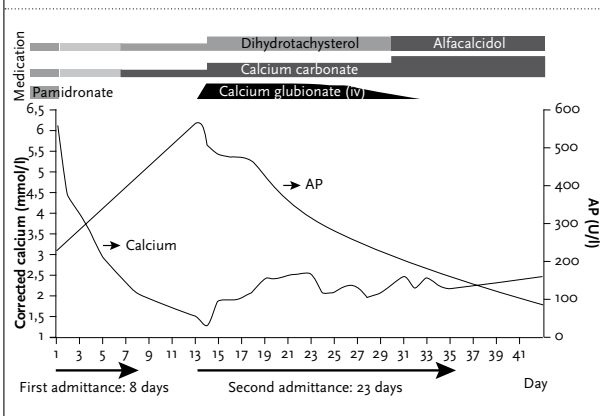
Administration of pamidronate was the main trigger in the development of the severe hypocalcaemia. This synthetic analogue of pyrophosphate – a natural regulator of bone metabolism found abundantly in bone matrix – has several physiological effects resulting in a net decreased osteoclast activity.^{8,9} As a result the drug is very effective in correcting hypercalcaemia, especially in case of vitamin D intoxication, which is characterised by increased bone resorption.^{1,10-13} The appropriate pamidronate dose depends on patient characteristics, including the risk of hypocalcaemia, which is increased in the presence of hypoparathyroidism.^{8,12,14} A few case reports indicate low-dose pamidronate (15-20 mg) to be safe in hypoparathyroidism with DHT intoxication.^{3,6,7} Our patient received a higher dose (60 mg) instead. Although the plasma half-life of pamidronate is short, the inhibiting effect on osteoclasts persists for many weeks.^{8,9,14,15} Administration of APD in the presence of renal failure can result in prolonged and stronger inhibitory effects on osteoclastic activity, with a concomitant increased risk of prolonged hypocalcaemia.^{9,15} The long half-life of DHT, the vitamin D analogue used in our patient, is an unfavourable characteristic in the clinical situation in which immediate vitamin D effects are warranted. When the patient presented with hypocalcaemia, we therefore decided to replace the DHT by the short-acting active vitamin D analogue alfacalcidol.

Table 1. Laboratory results before admission, during both admissions and in the outpatient department

Day	Before admission	Admission #1	Discharge #1	Admission #2	Discharge #2	Outpatient department
Laboratory results						
Calcium* (mmol/l)	2.29	6.16	2.07	1.53	1.33	2.31
Phosphate (mmol/l)	1.23	0.98	-	1.41	-	1.20
Creatinine (μmol/l)	85	234	119	101	-	90
AP (U/l)	83	231	-	566	-	88
GGT (U/l)	-	54	-	48	-	-
ASAT (U/l)	-	25	-	45	-	-
ALAT (U/l)	12	37	-	134	-	-
PTH (pmol/l)	<0.13	<0.13	-	<0.13	-	-

* Corrected for serum albumin; AP = alkaline phosphatase; ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase; GGT = Gamma-glutamyl transpeptidase; PTH = parathyroid hormone.

Figure 1. Most important administered drugs and course of calcium and alkaline phosphatase (AP) levels during both admissions



In conclusion, this case illustrates the importance of functioning parathyroid glands for calcium homeostasis. In hypoparathyroid patients, bisphosphonates should be used cautiously as they can result in severe life-threatening and prolonged hypocalcaemia.

REFERENCES

1. Body JJ, Bouillon R. Emergencies of calcium homeostasis. *Rev Endocr Metab Disord.* 2003;4:167-75.
2. Peacock M. Calcium metabolism in health and disease. *Clin J Am Soc Nephrol.* 2010;5(Suppl 1):S23-30.
3. Jensterle M, Pfeifer M, Sever M, Kocjan T. Dihydroxyvitamin D2 intoxication treated with pamidronate: a case report. *Cases J.* 2010;3:78.
4. Koytchev R, Alken RG, Vagaday M, Kunter U, Kirkov V. Differences in the bioavailability of dihydroxyvitamin D2 preparations. *Eur J Clin Pharmacol.* 1994;47:81-4.

5. Qaw F, Calverley MJ, Schroeder NJ, Trafford DJ, Makin HL, Jones G. In vivo metabolism of the vitamin D analog, dihydroxyvitamin D2. Evidence for formation of 1 alpha,25- and 1 beta,25-dihydroxy-dihydroxyvitamin D2 metabolites and studies of their biological activity. *J Biol Chem.* 1993;268:282-92.
6. Quack I, Zwernemann C, Weiner SM, et al. Dihydroxyvitamin D2 therapy for hypoparathyroidism: consequences of inadequate monitoring. Five cases and a review. *Exp Clin Endocrinol Diabetes.* 2005;113:376-80.
7. Boots JM, Burghouts JT, Jansen JL. Unaccountable severe hypercalcaemia in a patient treated for hypoparathyroidism with dihydroxyvitamin D2. *Neth J Med.* 1999;54:16-20.
8. Ross JR, Saunders Y, Edmonds PM, et al. A systematic review of the role of bisphosphonates in metastatic disease. *Health Technol Assess.* 2004;8:1-176.
9. Coukell AJ, Markham A. Pamidronate. A review of its use in the management of osteolytic bone metastases, tumour-induced hypercalcaemia and Paget's disease of bone. *Drugs Aging.* 1998;12:149-68.
10. Selby PL, Davies M, Marks JS, Mawer EB. Vitamin D intoxication causes hypercalcaemia by increased bone resorption which responds to pamidronate. *Clin Endocrinol (Oxf).* 1995;43:531-6.
11. Ralston SH, Coleman R, Fraser WD, et al. Medical management of hypercalcaemia. *Calcif Tissue Int.* 2004;74:1-11.
12. Chatterjee M, Speiser PW. Pamidronate treatment of hypercalcaemia caused by vitamin D toxicity. *J Pediatr Endocrinol Metab.* 2007;20:1241-8.
13. Lee DC, Lee GY. The use of pamidronate for hypercalcaemia secondary to acute vitamin D intoxication. *J Toxicol Clin Toxicol.* 1998;36:719-21.
14. Tanvetyanon T, Stiff PJ. Management of the adverse effects associated with intravenous bisphosphonates. *Ann Oncol.* 2006;17:897-907.
15. Sims EC, Rogers PB, Besser GM, Plowman PN. Severe prolonged hypocalcaemia following pamidronate for malignant hypercalcaemia. *Clin Oncol (R Coll Radiol).* 1998;10:407-9.