Pamidronate treatment in acute vitamin D intoxication

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ABSTRACT. Management with glucocorticoid, high iv fluid saline intake, furosemide and calcitonin may not result in a favorable reduction of hypercalcemia and may cause several side effects in infants with acute vitamin D intoxication. The bisphosphonate pamidronate, a specific inhibitor of bone resorption through osteoclast mediation was successfully used in a 6-month old infant with acute vitamin D intoxication managed in the Pediatric Emergency and Intensive Care Unit, after an ineffective trial of hydration, furosemide, calcitonin and prednisolone. After a double infusion of pamidronate on two consecutive days (1 mg/kg/day), an early and safe correction of hypercalcemia/hypercalciuria was supplied. Pamidronate therapy may be considered in patients with hypercalcemia secondary to acute vitamin D poisoning.


INTRODUCTION

Acute vitamin D intoxication is a relatively rare, but treatable cause of hypercalcemia, associated with severe and prolonged morbidity because of its fat solubility. Conventional management with glucocorticoid, high iv fluid, furosemide and calcitonin may not result in an early favorable outcome, and may cause several side effects. Previous observations have suggested that chronic hypercalcemia of vitamin D intoxication in patients with malignancy, immobilization or chronic renal failure is mediated by increased bone resorption and bisphosphonates as specific inhibitors of bone resorption through osteoclast mediation might provide more effective treatment (1-4). We report here the use of pamidronate, a bisphosphonate, in a case with acute severe hypercalciemia secondary to iatrogenic vitamin D poisoning managed in the Pediatric Emergency and Intensive Care Unit.

CASE REPORT

A 6-month old female infant was inadvertently administered 300,000 units of oral vitamin D daily for 10 days. Only a total dose of 300,000 units had been given by a local physician because of suspected rickets. After the end of the 10 days the patient was admitted to our Pediatric Emergency Unit with symptoms of anorexia, nausea, vomiting, polydipsia, polyuria and constipation. At physical examination, she had a sick appearance, with lethargy and anxiety, and positive craniotabes as an early sign of rickets. Growth percentiles of the patient were in normal ranges. Body weight was 8200 g (75th-90th percentile) and height 66 cm (50th-75th percentile). Her heart rate was 130/min, respiratory rate 32/min and blood pressure 130/70 mmHg (> 95th percentile). Complete blood count and routine blood chemistry were normal except serum calcium (Ca) concentration of 16.8 mg/dl (normal range: 9-11). Serum phosphorus level was of 6.0 mg/dl (normal: 4.5-6.5 mg/dl) and alkaline phosphatase of 368 IU/l (normal range: 145-420 for the appropriate age). The patient had grossly elevated serum 25-hydroxyvitamin D level of 340 ng/ml (normal range: 10-50) and normal 1,25-dihydroxyvitamin D level of 44 pg/ml (normal range: 25-45 pg/ml) (measured by vitamin D$_3$, HPLC kit, Immun Diagnostic). Parathyroid hormone level was less than 1 pg/ml (normal range: 8-70, measured by Immulite 2000-Intact PTH chemiluminescence enzyme-labeled immunometric assay, Diagnostic Products Corporation). There was an increased rate of bone resorption as shown by elevated calcium/creatinine ratio of 2.0 mg/mg (normal less than 0.86 for the appropriate age) (5). Plain radiography of the
hand and wrist was compatible with the appropriate age and exhibited slight rachitic metaphyseal abnormalities. Renal and abdominal ultrasonography did not show any abnormality and, shortening of the QT interval was seen on the electrocardiogram.

The patient was initially treated in Pediatric Emergency Unit with hydration (3000 cc/m²/day, 1/3 saline, additional 20 mEq/l potassium chloride) and furosemide (1 mg/kg/dose, every 6 h), and then transferred into the Pediatric Intensive Care Unit. Two doses of calcitonin were given (2 U/kg/dose) on the first day of hospitalization, and one on the second. Prednisolone (2 mg/kg per day) was added for 2 days. Meanwhile the patient was given oral nifedipine (1 mg/kg/day) for the hypertension. On the second day of hospitalization, despite the above treatment, serum calcium level was still measured inside the life-threatening values (15.8 mg/dl), and the patient remained symptomatic. After this measurement, calcitonin was discontinued, and pamidronate (Aredia, Ciba) was infused on two consecutive days (1 mg/kg/day), and the serum calcium declined to 13.4 mg/dl by the third day and 10.3 mg/dl by the fourth day of hospitalization, and did not exceed these values afterwards. No side effects were noted with this treatment. The patient was discharged without any symptoms on the fifth day. Urinary calcium/creatinine ratio was found to be 1.0 at discharge, 0.89 after 15 days and 0.11 after 2 months. Further renal ultrasonographic evaluations at the same follow-up periods did not show nephrocalcinosis or any other abnormalities.

DISCUSSION

Management with glucocorticoid, high iv fluid saline intake, furosemide and calcitonin are the known conventional methods for the treatment of hypercalcemia. Glucocorticoids (hydrocortisone 1 mg/kg/dose/6h or prednisolone 2 mg/kg/day) are mainly used to decrease the elevated vitamin D production in malignant tumors or sarcoidosis, but are generally believed to be ineffective for the treatment of hypercalcemia in acute D vitamin poisoning. Administration of normal saline iv increases the extracellular fluid and furosemide enhances the excretion of the urine calcium. Since hypercalcemia of acute vitamin D intoxication is mainly mediated by increased bone resorption, inhibitors of bone resorption might provide more effective treatment (6-8). Calcitonin (2-4 U/kg/dose/12h) was given for this purpose, but a remarkable decrease in serum Ca concentration was not obtained and our patient remained symptomatic. Calcitonin is known to have a rapid effect, but has some limitations for its use: it does not have a long lasting effect, can only lower 10-20% of the initial serum calcium concentration, can cause tachyphylaxis and needs prior test for hypersensitivity (9). Plicamycin (mithramycin) is another group of bone resorption inhibitors, but we did not use it because of its serious side effects including hepatotoxicity, nephrotoxicity and platelet dysfunction.

Biphosphonates are specific inhibitors of bone resorption through osteoclast mediation, mainly known as pamidronate, etidronate, clodronate and alendronate (3). We thought pamidronate could be a good alternative treatment in our patient because of its increasing experience in children (3, 10). Oral alendronate was another choice of treatment but had some gastrointestinal side effects which could not be tolerated in an infant. The main indications for the treatment of biphosphonates in children have been reported as: chronic causes of hypercalcemia (e.g. malignancy, immobilization, hyperparathyroidism) and osteoporotic conditions like soft tissue calcification, generalized bone disease (e.g. osteogenesis imperfecta, idiopathic juvenile osteoporosis, steroid-induced osteoporosis), and localized bone disease (e.g. Gaucher’s disease and McCune-Albright syndrome) (3).

The use of pamidronate in acute causes of hypercalcemia has rarely been reported. A successful management was reported in a 77-yr-old woman (7). In another recent study, a 3-month-old infant was refractory to initial treatment with hydration, furosemide and prednisolone but had normalized serum calcium concentrations and relief of symptoms by 24 h after pamidronate treatment (10). In another experience with oral alendronate treatment, effective correction of hypercalcemia/hypercalciuria and decreased duration of hospitalization was reported in a 3-month-old infant with vitamin D intoxication (11). We have also observed that in our child pamidronate has provided a safe, rapid and effective means of lowering the dangerously high calcium levels refractory to the conventional treatment, without any probable side effects like fever, hypophosphatemia or hypomagnesemia. Since current treatments of patients with vitamin D intoxication (glucocorticoids, calcitonin, etc) are unsatisfactory and associated with prolonged hypercalcemia, the biphosphonates may be a safe and effective alternative for the treatment of acute hypervitaminosis D in children.

REFERENCES