Use of alendronate in the treatment of vitamin D intoxication in infants

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Vitamin D intoxication remains a challenging problem due to lack of an efficient treatment. Bisphosphonates, inhibitors of osteoclast-mediated bone resorption, however, have been proposed as a safe and effective alternative in the treatment of vitamin D intoxication. We present here two infants with vitamin D intoxication who were successfully treated with alendronate. We propose that oral alendronate is an alternative to intravenous bisphosphonates in the treatment of vitamin D intoxication in infancy.

Key words: bisphosphonates, vitamin D intoxication, infancy.

Vitamin D intoxication as well as vitamin D deficiency remain problems in developing countries and/or communities. Vitamin D intoxication for the most part is iatrogenic in our country and attributed to extensive use of high-dose vitamin D by physicians without having a confirmed diagnosis of rickets or to administration of high doses of vitamin D by parents to infants as a remedy for delays in teething or walking. Vitamin D intoxication has serious consequences, including fatal arrhythmias due to hypercalcemia, nephrocalcinosis and renal failure. Its treatment is usually symptomatic and supportive. The classical treatment regimens include intravenous hydration, loop diuretics, glucocorticoids and sometimes calcitonin. Bisphosphonates, inhibitors of osteoclast-mediated bone resorption, are effective in reducing serum calcium levels and have been widely used in adults in the treatment of hypercalcemia[1-3], but experience in childhood, particularly with enteral forms, is limited[4]. We here report two infants with vitamin D intoxication who were successfully treated with an oral bisphosphonate, alendronate.

Case Reports

Case 1

An 11-month-old female infant presented with a five-month history of decreased appetite, vomiting and excessive water intake. She was administered three doses of cholecalciferol (300,000 IU) at 5, 5.5 and 9 months of age while she continued to receive daily doses of vitamin D (400 IU). Laboratory evaluation revealed serum calcium of 18 mg/dl (4.5 mmol/L). Serum 25 (OH) vitamin D level was 200 ng/ml and parathyroid hormone (PTH) 1.84 pg/ml. Her urinary calcium excretion was 10 mg/kg/d. X-ray of the left hand and wrist showed bilateral metastatic calcification, and renal ultrasound examination demonstrated bilateral peripheral nephrocalcinosis. Based on these findings, the patient was diagnosed with vitamin D intoxication. With her treatment plan that included calcitonin, glucocorticoid and oral phosphates, serum calcium levels were reduced to 14.4 mg/dl at the end of the first month. Alendronate sodium (5 mg/d) was then added to the treatment, and on the 15th day of alendronate treatment, serum calcium levels had dropped to 11.3 mg/dl. The patient was discharged for follow-up on a regular basis. The treatment was ceased on the 21st day of alendronate treatment when the patient was normocalcemic with normal urinary calcium excretion. Serum calcium levels remained within normal limits on subsequent follow-up examinations for four months. No adverse reaction was observed during alendronate treatment.

Case 2

A four-month-old female infant who had been misdiagnosed with rickets at two months of age and had been treated with cholecalciferol

(300,000 IU intramuscularly) twice in three weeks presented to a local hospital with poor feeding, lethargy, vomiting and fever. Her laboratory evaluation revealed serum calcium: 14.9 mg/dl; alkaline phosphatase 166 U/L; calcium/creatinine ratio in spot urine: 2.06; serum 25 (OH) vitamin D level >160 ng/ml; and PTH 4.1 pg/ml. The patient was diagnosed with vitamin D intoxication, and treatment was initiated with intravenous hydration, diuretics and glucocorticoids. Calcitonin and phosphate solution were then added to the treatment when serum calcium remained elevated. Nevertheless, the patient did not respond to this treatment and pamidronate (1 mg/kg/d) was given for a total of 19 days without a satisfactory response. The patient was then referred to our hospital because of persistent hypercalcemia and high calcium excretion (calcium: 19.6 g/dl, calcium/creatinine ratio: 5.3). Abdominal ultrasound revealed bilateral medullary nephrocalcinosis. We started the patient on alendronate (10 mg/d) while intravenous hydration and calcitonin treatment were continued. Alendronate was given for six weeks and discontinued gradually when serum calcium levels decreased to normal levels. Serum calcium levels remained normal thereafter and no side effects associated with use of alendronate were observed (Table I).

Table I. Laboratory Values and Treatment During Admission and Follow-up of Case 2

Time	Calcium (mg/dl)	Parathyroid hormone (pg/ml)	Urinary Calcium/ Creatinine	P (mg/dl)	Vitamin D (ng/ml)	Center	Treatment
Day 1	11.9	4	2.06	3	>160	First	Hydration, diuretic, steroid
Day 17	17.1		1.09			First	Calcitonin added
Day 41	10.3		2.7			First	Calcitonin stopped, diuretic, steroid
Day 50	14.9		2.08			First	Pamidronate (1 mg/kg), diuretic, steroid
Day 53	10.8		0.12			First	Pamidronate stopped, diuretic, steroid
Day 55	15.8		1.4			First	Pamidronate again, diuretic, steroid
Day 78	15.4					First	19th dose pamidronate, discharge (parent request)
Day 78	15.5					Our	Alendronate 10 mg, diuteric, hydration
Day 81	18.7		3.58	2.7		Our	Alendronate 10 mg, calcitonin, diuretic
Day 87	14.5					Our	Alendronate 10 mg only
Day 98	12.1		1.65			Our	Alendronate 5 mg, discharge
4 mo	10.4		0.42			Our	Alendronate stopped
5 mo	10.6		0.29	6		Our	No treatment
8 mo	10.9	100	0.27	5.5		Our	No treatment
Normal range	8.9-10.1	18-74	<0.2	3.6-5.5	10-40		

Discussion

While vitamin D provides mineralization in physiological conditions via a positive effect on intestinal calcium resorption and proliferation of osteoblast precursors, high levels of 1,25 $(OH)_2$ D increase osteoclastic activity and leads to increased calcium resorption from bones[5,6]. This dual effect becomes manifest during vitamin D intoxication and results in hypercalcemia and increased calcification in the provisional zone. Because of deposition of vitamin D in fat tissue and the prolonged period before osteoclastic activity normalizes, hypercalcemia may be persistent and risk of nephrocalcinosis increases. Supportive measures such as hydration, loop diuretics and glucocorticoids are useful, but usually ineffective alone. More specific treatment alternatives for vitamin D intoxication should include agents that inhibit osteoclastic activity. Calcitonin conventionally has been used for this purpose. However, because of lack of significant changes in bone morphology and calcium balance in calcitonin-releasing tumors such as medullary thyroid carcinoma, the effect of calcitonin on osteoclasts in pharmacological doses is questionable[7]. On the other hand, it is known that bisphosphonates effectively inhibit osteoclastic activity and markedly reduce serum calcium levels[8-10].

Pamidronate has been used in children successfully for the treatment of hypercalcemia caused by a variety of problems[11-13]. However, treatment indications of bisphosphonates in children typically do not include hypercalcemia due to vitamin D intoxication[14]. We observed in our first patient that hypercalcemia, unresponsive to the conventional treatment, was normalized with alendronate in two weeks. More interestingly, in our second patient who re-developed hypercalcemia after treatment with pamidronate for 19 days, hypercalcemia was corrected easily by alendronate at a daily dose of 10 mg. A previously published case report has shown

that alendronate was also effective in the treatment of vitamin D intoxication with more rigorous symptoms in early infancy[4]. Alendronate and risedronate are nitrogen-containing bisphosphonates inactivating osteoclasts through cholesterol biosynthesis[15]. Although there is insufficient evidence that use of alendronate is effective in the treatment of osteogenesis imperfecta, its efficacy has been demonstrated in mouse models[16]. For this reason, it is not surprising that alendronate is an effective treatment in hypercalcemia related to vitamin D intoxication. Although oral bisphosphonates (especially alendronate) have the potential of causing esophageal and occasionally gastric ulceration, no side effects were observed in our infants who were administered this drug.

Intravenous pamidronate at a dose of 1 mg infused over four to six hours on two to three consecutive days is highly effective in treating symptomatic hypercalcemia due to high 1,25 $(OH)_2$ D levels, for example, in T-cell leukemia and neonatal subcutaneous fat necrosis. We were thus very surprised that in Case 2 intravenous pamidronate at the dose of 1 mg/kg/day administered for 19 days failed to normalize serum calcium concentrations in the infant. It is not clear yet why intravenous pamidronate treatment failed and oral alendronate was successful. Possible explanations are that alendronate is a more potent osteoclast inhibitor than pamidronate, or alendronate may have been more efficacious because of the high dosage used.

In conclusion, it is necessary to initiate bisphosphonates in early stages in patients with vitamin D intoxication in order to prevent or minimize nephrocalcinosis. Treatment should be continued until normocalcemia has been established. The existing evidence suggests that use of alendronate as an alternative to parenteral bisphosphonates in patients with vitamin D hypervitaminosis is a more practical and effective treatment choice.

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