

# Use of bisphosphonates for resistant hypercalcemia in children with acute lymphoblastic leukemia: report of two cases and review of the literature

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**SUMMARY:** Andıran N, Alikasıfoğlu A, Küpeli S, Yetgin S. Use of bisphosphonates for resistant hypercalcemia in children with acute lymphoblastic leukemia: report of two cases and review of the literature. Turk J Pediatr 2006; 48: 248-252.

Hypercalcemia is a rare complication of malignancy in children. We present two children, one of whom is the youngest reported, with CALLA+ B-cell acute lymphoblastic leukemia (ALL) who developed hypercalcemia at the time of diagnosis and were treated with relatively low-dose (0.5 mg/kg) intravenous pamidronate successive to conventional therapy. No major side effects were encountered except transient hypocalcemia and hypophosphatemia, which were easily managed by replacement therapy.

Bisphosphonate therapy was found to be beneficial for the treatment of resistant hypercalcemia associated with ALL, even at relatively low doses.

**Key words:** bisphosphonate, hypercalcemia, ALL.

Hypercalcemia is a rare complication of malignancy in children<sup>1-2</sup>. The types of malignancy associated with hypercalcemia in children are leukemias, rhabdomyosarcoma, malignant rhabdoid tumor, Hodgkin's disease, non-Hodgkin's lymphoma, hepatoblastoma, neuroblastoma, and Ewing sarcoma<sup>1-8</sup>. It has been shown that patients with acute lymphoblastic leukemia (ALL) were more likely to present with hypercalcemia at the initial diagnosis, whereas children with solid tumors frequently present with hypercalcemia later in the course of their disease which is more resistant to therapy<sup>1</sup>.

Traditional treatment of hypercalcemia of malignancy consists of intravenous (IV) hydration of saline with loop diuretics, calcitonin and mithramycin, along with the specific treatment for primary disease. A few children with malignancy-associated hypercalcemia resistant to this therapy have been treated with bisphosphonates, among whom in eight cases, the underlying malignancy was ALL<sup>9-15</sup>.

We herein present two children with ALL who developed hypercalcemia at the time of diagnosis and were treated with intravenous

pamidronate in addition to conventional therapy. One of the patients is the youngest reported in the literature.

## Case Reports

### Case 1

A six-month-old male infant presented to Hacettepe University İhsan Doğramacı Children's Hospital with a history of irritability and abdominal distension for 10 days. On physical examination, body temperature was 36.2°C, pulse rate 158 per minute, respiratory rate 40 per minute and blood pressure 90/50 mmHg. The patient was pale, and bruising and petechiae were detected on left cheek and the skin of abdomen. The liver and spleen were both palpable 8 cm below the costal margin.

On admission, his hemoglobin was 6.9 g/dl, white blood cell count (WBC) 328,000/ $\mu$ l, and platelets 27,000/ $\mu$ l. The bone marrow aspiration and flow-cytometric studies showed the patient had CALLA+ B cell ALL. Blood urea nitrogen (BUN) was 17 mg/dl, creatinine 1.2 mg/dl, uric acid 23.1 mg/dl, calcium (Ca) 14.6 mg/dl, phosphorus (P) 0.2 mg/dl, alkaline

phosphatase (ALP) 870 U/L, sodium (Na) 131 mEq/L, and potassium (K) 3.7 mEq/L. Urine calcium to creatinine ratio was 0.62. The parathyroid hormone (PTH) level was <0.2 pg/ml (N: 12-72 pg/ml), and 25(OH)vitD level was 18.7 ng/ml (N: 7.6-75 ng/ml).

Intravenous saline infusion of 3 L/m<sup>2</sup> body surface area per day and furosemide (4 times/day) were started for the initial treatment of hypercalcemia. Serum calcium level decreased to 13.3 mg/dl at the 12<sup>th</sup> hour of the treatment. During the follow-up, heart rate increased and generalized edema developed suggesting congestive heart failure due to overhydration and partly due to anemia. We decreased the amount of fluid infused, and calcitonin (10 U/kg/day) infusion was started. After 24 hours of calcitonin infusion, the serum level of Ca was still 13.1 mg/dl, while the other biochemical parameters of renal function (serum level of P, BUN, creatinine and uric acid were 1.5, 15, 0.9 and 12.5 mg/dl, respectively) improved. The patient was consecutively started on pamidronate infusion (0.5 mg/kg over 6 hours). Serum Ca and P levels were 9.7 and 3 mg/dl, respectively, after six hours of pamidronate infusion. Serum Ca gradually decreased to 6.8 mg/dl on the second day after pamidronate infusion. He remained asymptomatic, but was given IV rather than oral Ca because a further decrease in the Ca level was expected. On the third day of hospitalization, chemotherapy was started for ALL. Unfortunately, the parents of the patient refused further treatment.

### Case 2

A six-year-old boy was admitted to the hospital with difficulty in walking and hip pain for a month. On physical examination, body temperature was 37°C, pulse rate 124 per minute, respiratory rate 26 per minute and blood pressure 110/70 mmHg. The patient was pale and a few petechiae were present on the neck region. The liver and spleen were palpable 5 and 2 cm, respectively, below the costal margin at the mid-clavicular line.

On admission, his hemoglobin was 9.9 g/dl, WBC count 40,400/μl, and platelets 36,000/μl, and on peripheral blood smear, blasts were present. After the bone marrow aspiration and flow cytometric studies, the patient was

diagnosed as CALLA + B cell ALL. BUN was 31 mg/dl, creatinine 0.8 mg/dl, uric acid 15 mg/dl, Ca 17.2 mg/dl, P 3.7 mg/dl, ALP 477 U/L, Na 133 and K 4.1 mEq/L. Urine Ca to creatinine ratio was 0.7. The PTH level was suppressed (<1 pg/ml, N: 12-72 pg/ml) and 25(OH)vitD level was 15.5 ng/ml (N: 7.6-75 ng/ml). On plain X-rays, there were lytic lesions on the proximal part of the left femur. There were no lesions on other bones.

Intravenous infusion of saline as 3 L/m<sup>2</sup> body surface area per day, furosemide treatment (1 mg/kg/6 hours i.v.), and calcitonin infusion (10 U/kg/day) were started for hypercalcemia. After 18 hours of this treatment regimen, Ca level was still 14.5 mg/dl while P was 2.7, BUN 22, creatinine 0.7, and uric acid 6.0 mg/dl. Thus, pamidronate infusion (0.5 mg/kg over 6 hours) was administered after which Ca and P levels were 13.1 and 3.7 mg/dl, respectively. On the fourth day after pamidronate infusion, symptomatic hypocalcemia as carpedal spasm developed with a serum Ca level of 7.2 mg/dl. At the same time, P level was 1.5 mg/dl. He was given IV and then oral Ca replacement for about two weeks. Oral P replacement was also given for two days after which P level was 3.4 mg/dl. There were no other adverse reactions. He was also put on chemotherapy for ALL on the second day of hospitalization. His ALL is presently in remission.

### Discussion

Hypercalcemia is a rare but serious complication necessitating urgent intervention in pediatric malignancies<sup>1-11</sup>. The incidence was reported as between 0.2 to 0.7% in large series<sup>1,2,7</sup>. ALL is one of the common malignancies of children associated with hypercalcemia, especially in the initial phase of the disease, with an incidence of 0.39% in the literature<sup>1</sup>.

Malignancy-associated hypercalcemia may be refractory to conventional approach as IV hydration with saline, furosemide, corticosteroids and calcitonin, or this therapy may be ineffective or not possible because of cardiac and/or renal limitations in some patients. An alternative therapy is the administration of bisphosphonates, which are very powerful inhibitors of bone resorption. This class of drugs was found to be very efficacious in controlling cancer-associated hypercalcemia in

adults<sup>16-18</sup>; however, pediatric experience about the use of bisphosphonates in the treatment of malignancy-associated hypercalcemia remains limited, with only a few case reports<sup>6-11</sup>. Among these reported children, in eight cases the cause of resistant hypercalcemia was ALL<sup>9-15</sup> (Table I). In seven patients, treatment of hypercalcemia was initially attempted with forced diuresis<sup>9-12,14,15</sup>. Calcitonin treatment in one patient<sup>15</sup>, corticosteroid and calcitonin treatment in one<sup>9</sup> and hemodialysis with a Ca-free dialysate in another patient<sup>11</sup> were also tried in the treatment of hypercalcemia in addition to forced diuresis. However, due to persistence of hypercalcemia, IV pamidronate infusion was administered, which seemed very effective and safe (Table I). The patients with the highest serum Ca levels were a 12-year-old boy with serum Ca level of 19.0 mg/dl who experienced hypercalcemia with acute renal failure before induction chemotherapy and who was treated immediately with furosemide, calcitonin, prednisolone and pamidronate<sup>12</sup>, and an eight-year-old girl whose serum Ca level was 20 mg/dl and who was treated with calcitonin and pamidronate together<sup>14</sup>.

Bisphosphonates are rapidly adsorbed onto hydroxyapatite crystals in bone mineral and decrease bone resorption directly or indirectly by inhibiting both osteoclast recruitment and activity, and by shortening the life span of osteoclasts<sup>19,20</sup>. Once the bisphosphonates are buried in the skeleton, they will be released only when the bone is destroyed in the course of the turnover. The skeletal half-life of various bisphosphonates is between three months and one year for mice and rats<sup>21-23</sup>, and is much longer, sometimes more than 10 years, for humans<sup>24</sup>.

After IV administration, transient hypocalcemia and hypophosphatemia can be seen as acute side effects of treatment with bisphosphonates, which are mostly asymptomatic and easily managed by replacement therapy as in the previously reported and present ALL cases (Table I). Transient hypomagnesemia was reported only in one patient<sup>14</sup>. The other possible side effects of these drugs include a transient pyrexia of usually 1-2°C, sometimes more, accompanied by flu-like symptoms with myalgia, lymphopenia and increased C-reactive protein, which was usually observed only once, even if treatment was continued and

**Table I.** Use of Bisphosphonates in Leukemia-Associated Hypercalcemia in Children

Diagnosis	Age (years)	Sex	Disease state	Bisphosphonate	Initial Ca levels (mg/dl)	Dose	Complication	Reference
Leukemia	10	M	No lytic lesions	Pamidronate	13.68 (3.42 mM)	60 mg for 5 days	Hypocalcemia	11
ALL	15	F	Remission, subsequently relapse	Pamidronate	16.4	1 mg/kg	Hypocalcemia* Hypophosphatemia	9
ALL (B cell)	9	F	Relapse	Pamidronate	15.2	2 mg/kg	Hypocalcemia	9
ALL	5	F	At diagnosis**	Pamidronate	17.9	2 mg/kg	Hypocalcemia	10
ALL (B cell)	12	M	At diagnosis bone infiltration present	Pamidronate	19	0.66 mg/kg	Hypocalcemia	12
ALL	11	M	Relapse	Pamidronate	15	30 mg/day	Hypocalcemia	13
ALL	8	F	At diagnosis	Pamidronate	20	1 mg/kg	Hypocalcemia Hypophosphatemia Hypomagnesemia	14
ALL	14	F	At diagnosis**	Pamidronate	15.6	1 mg/kg	No complication	15
ALL (B cell)	0.5	M	At diagnosis	Pamidronate	13.1	0.5 mg/kg	Hypocalcemia# Hypocalcemia	&
ALL (B cell)	6	M	At diagnosis	Pamidronate	14.5	0.5 mg/kg	Hypocalcemia Hypophosphatemia	&

\* She had abdominal pain with no other signs.

\*\* She presented with hypercalcemia of unknown etiology. Soon after, the diagnosis of ALL was made.

# Symptomatic hypocalcemia with carpopedal spasm.

& The present cases.

restarted later<sup>25</sup>, and renal failure, especially with rapid IV administrations of large amounts of bisphosphonates<sup>26</sup>. It was also reported that pamidronate could cause inflammatory reactions in the eye<sup>20,27</sup>. Although no major side effects were observed in any of the pediatric cases reported in the literature who were treated with bisphosphonates for hypercalcemia, their long-term effects in children, especially on growth, are unknown. Thus, it is important to give minimal effective dosage for treatment. Pamidronate was usually given in a dosage of 1-2 mg/kg for treatment of ALL-associated hypercalcemia in the children reported in the literature<sup>9-15</sup> (Table I). We used pamidronate infusion at a dosage of 0.5 mg/kg, which seemed to be effective in the present cases with moderate hypercalcemia.

The PTH-related protein (PTH-rP) produced by leukemic cells and increased bone resorption were thought to be the cause of hypercalcemia in patients with ALL<sup>12,28</sup>. Although the type of ALL was pointed out as "B cell" in only two patients among the seven previously reported cases, both of our patients were "B-cell leukemia", which raises the suspicion of tendency of hypercalcemia in this type of leukemia.

In our experience, ALL-associated hypercalcemia responds well to a single infusion of pamidronate therapy, even at 0.5 mg/kg dosage, which seems to be safe with no serious side effects and can be recommended as an adjunctive line of treatment for resistant hypercalcemia.

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