JOURNAL OF BONE AND MINERAL RESEARCH
Volume 15, Number 10, 2000

Case Report

Intravenous Pamidronate for Treatment of Reflex Sympathetic Dystrophy During Breast Feeding

K. SIMINOSKI,[1] A.A. FITZGERALD,[2] G. FLESCH,[3] and M.S. GROSS[4]

ABSTRACT

A 39-year-old woman presented in the first month of pregnancy with reflex sympathetic dystrophy involving both lower legs. Symptoms became so severe that she could not walk unassisted, and the pain worsened after delivery. Radiographs showed patchy reduction in apparent density in the tarsal bones and around the ankles and knees. Uptake was increased in these areas on technetium methylene diphosphonate bone scan. Bone density (dual-energy X-ray absorptiometry) was reduced in the spine, hip, and radius. Biochemical tests were normal except for an increase in urinary excretion of the N-telopeptide cross-linking region of type I collagen (NTx). Because the patient wanted to continue breast-feeding, intravenous pamidronate was administered at monthly intervals. Breast milk was collected for 48 h after the infusion. The pain began to decrease soon after drug administration was initiated, and it was virtually gone by 6 months. NTx excretion fell by 78% and bone density increased by as much as 18.9% over the 6-month treatment interval. The baby was healthy and grew normally. Milk expressed after the first treatment was assayed for pamidronate content by high-performance liquid chromatography with fluorescence detection. None was detected (limit of quantitation, 0.4 μmol/liter). This case shows that pamidronate may be considered for treatment of lactating women. (J Bone Miner Res 2000;15:2052–2055)

Key words: reflex sympathetic dystrophy, pamidronate, bisphosphonate, lactation, breast-feeding

INTRODUCTION

REFLEX SYMPATHETIC dystrophy is a syndrome of unknown etiology that can encompass a wide range of manifestations in affected limbs. These may include pain, tenderness, increased sweating, coolness, color change (variations of pallor, cyanosis, and redness), soft tissue swelling, and patchy osteoporosis.[1,2] Reflex sympathetic dystrophy can occur in association with pregnancy.[3]

We describe a woman who developed reflex sympathetic dystrophy during pregnancy. It worsened after delivery and became debilitating, necessitating pharmacologic treatment during the period of lactation. Intravenous pamidronate was chosen because it appears to reduce pain and enhance resolution of the condition for a significant proportion of patients,[2,4,5] and we hypothesized that excretion of the drug into milk would be minimal. Chemical assay of the patient's breast milk confirmed the absence of pamidronate.

[1]Endocrine Center of Edmonton and Medical Imaging Consultants, Edmonton, Canada.
[2]Royal Alexandra Hospital, Edmonton, Canada.
[3]Novartis Pharma AG, Basle, Switzerland.
[4]Edmonton Breastfeeding Clinic and University of Alberta, Edmonton, Canada.

CASE REPORT

A 39-year-old woman ($G_2P_0SA_1$) presented at 4 weeks gestation complaining of spontaneous pain in her feet and ankles. It was absent with rest and precipitated with weight bearing. Over the next several months she developed swelling of the ankles and dusky coloration of the skin below the knees. The pain worsened over the following months so that she could not walk unassisted. Physical examination at 37 weeks gestation showed blue discoloration of the legs distal to the knees. There was no edema. The skin felt cool and moist. There was marked tenderness below the knees to both light and deep palpation and to percussion. There was no evidence of synovitis or tendinitis. The remainder of the musculoskeletal examination was normal. Pulses were normal and there were no neurological deficits. Radiographic studies were not performed during the pregnancy.

There was no past history of bone or joint problems, fractures, or trauma. A prior pregnancy at age 38 had resulted in miscarriage. No similar symptoms had occurred at that time. There was no smoking history. Three servings of caffeinated beverages were consumed each day; alcohol intake was minimal. Calcium (500 mg elemental calcium per day) and vitamin D (1000 IU per day) had been taken since soon after the start of symptoms. There was no known family diagnosis of osteoporosis or bone disorders.

A healthy male child was delivered at 40 weeks. Technetium methylene diphosphonate bone scan 1 month later showed increased blood flow to the ankles and tarsal joints with relative sparing of the remainder of the feet. Skeletal uptake was increased around the ankles and in the tarsal bones, with minor focal uptake in the left third distal phalanx at the site of a suspected healing fracture (Fig. 1). Increased focal uptake also was noted around the knees, particularly in the right medial femoral condyle. Radiographs of the patient's legs and feet showed patchy reduction in apparent density bilaterally around the ankles, in the tarsal bones, and around the knees.

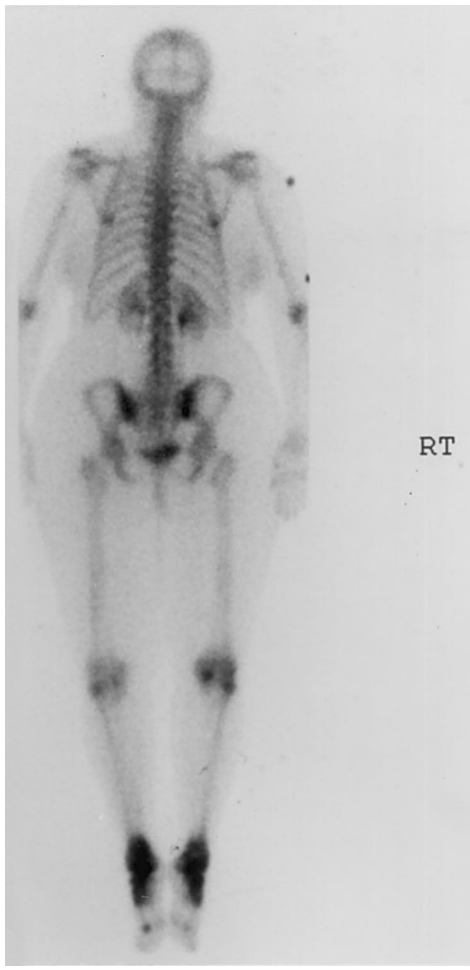

FIG. 1. Technetium methylene diphosphonate bone scan showing increased activity around ankles, tarsal joints, and knees of both legs.

In the first few weeks postpartum there was mild, transient improvement in leg pain. Over the subsequent months pain worsened substantially in the feet, ankles, and shins, and pain began in the knees. Repeat radiographs and bone scan showed results similar to the initial studies. Bone densitometry (DXA; Hologic 4500, Waltham MA, U.S.A.) done 6 months after delivery revealed decreased bone mass, particularly in the hip (Table 1; Hologic white reference population database for spine; National Health Education and Nutritional Survey[6] white reference population database for hip). Serum calcium, phosphate, albumin, creatinine, alkaline phosphatase, parathyroid hormone, 25-hydroxyvitamin D, hemoglobin, blood cell counts, protein electrophoresis, electrolytes, and liver function tests were all normal. Urine calcium excretion was 3.28 mmol/day with a creatinine of 7.5 mmol/day. Urinary excretion of the N-telopeptide cross-linking region of type I collagen (NTx) was elevated at 98 nmol/mmol creatinine (24 h collection; normal, 0–80 nmol/mmol creatinine).

The patient did not want to discontinue breast-feeding. The decision was made to administer intravenous pamidronate (30 mg per infusion) at 1-month intervals and to have her pump and discard breast milk for 48 h afterward. She would then resume breast-feeding the baby between pamidronate administrations. During the 6 months of pamidronate infusions, she breast-fed more than 80% of the time. Within several days after the first pamidronate infusion, leg pain began to decrease. Several weeks later, she was able to walk at a slow pace. After the third administration, she rated the pain as being reduced in intensity by 50%. After the sixth infusion, the pain was virtually gone, with only slight sensitivity to pressure on the soles of the feet. There were no objective findings at this time. Radiographs of the legs had returned to normal. Repeat bone densitometry (9 months after baseline) showed an increase of +2.7% in the spine and from +5.5% to +18.9% in the hip regions. Urinary NTx excretion declined by 78% to18 nmol/mmol creatinine. Serum alkaline phosphatase activity declined by 48%. Pamidronate was discontinued. The baby remained healthy and grew normally.

TABLE 1. BONE DENSITOMETRY (DXA) RESULTS AT BASELINE AND FOLLOWING TREATMENT WITH 6 MONTHLY INFUSIONS OF PAMIDRONATE

	Baseline density			*Change after treatment*
	(gm/cm²)	*(T score)*	*(Z score)*	*(% change)*
Spine				
A-P Spine (L1–4)	0.739	−2.80	−2.59	+2.7
Lateral spine (L2–4)	0.678	−1.69	−1.03	N/A*
Hip				
Total hip	0.642	−2.77	−2.57	+14.3
Neck	0.602	−2.93	−2.43	+5.5
Trochanteric area	0.440	−3.14	−2.96	+18.9
Intertrochanteric area	0.770	−2.70	−2.53	+15.5
Ward's area	0.463	−3.03	−2.02	+16.0
Radius				
⅓ radius	0.654	−0.66	−0.28	N/A
Midradius	0.601	−0.12	+0.25	N/A
Ultradistal radius	0.379	−1.11	−0.84	N/A
Total radius	0.548	−0.58	−0.23	N/A

N/A, not available.

Assay of pamidronate in breast milk

After the first infusion of pamidronate, breast milk was pumped and collected in two portions: 0–24 h and 25–48 h. All milk produced during each of the 24-h periods was pooled and each pool was assayed in triplicate for pamidronate content using a modification of the fluorescamine high-performance liquid chromatography (HPLC) technique previously described.[7,8] To 2.0 ml of milk, 0.1 ml of internal standard was added. After protein precipitation, 7.0 ml of ethylacetate was added to extract lipids. Pamidronate was quantified by HPLC with a limit of quantitation of 0.4 μmol/liter. The interassay CV was 7.8% to 12.1%. Pamidronate readings were below the limits of quantitation for all aliquots of milk tested.

DISCUSSION

The finding of a generalized reduction in our patient's bone density was somewhat unexpected and would fall in the realm of "pregnancy-related osteoporosis."[9] There are three possible explanations. The first is that she had preexisting idiopathic osteoporosis.[8] The second is that she lost a large amount of bone mass during her pregnancy. In normal pregnancies, moderate amounts of bone can be lost, and a certain percentage of women can experience substantial reductions in density, losing more than 15% at some sites.[10] A third possibility has been raised by some reports, which is that generalized or multifocal loss of bone may occur in association with reflex sympathetic dystrophy.[11–13]

Our patient was committed to breast-feeding and did not want to discontinue, despite the disabling pain from reflex sympathetic dystrophy. Evidence suggests that intravenous pamidronate may be effective in this condition.[2,4,5] No information has been available on transference of pamidronate into human milk,[14] although rat studies show that such transference is possible. The choice was made to administer intravenous pamidronate to our patient and to discard milk produced in the subsequent 48 h. The points in support of this approach included the following:

(1) Pamidronate has a short biological half-life. The clearance of intravenously administered pamidronate is multiphasic, but a linear approximation produces a half-life for plasma clearance of less than 3 h.[15–17] There are no metabolites.[15] Therefore, by 48 h after administration there would be minimal drug in the bloodstream for transference to milk.
(2) Pamidronate is acidic (an alternate name is pamidronic acid),[15] and acids are relatively poorly concentrated in breast milk.[18]
(3) Bisphosphonates readily complex with calcium and become unavailable for absorption from the gastrointestinal tract.[19] Mature milk has a high calcium concentration (200–340 mg/liter).[20] A large fraction of any pamidronate that made it into the milk would be converted to a nonabsorbable form.
(4) Oral bioavailability of pamidronate is poor even in the absence of calcium. In adults, less than 2% of orally administered pamidronate is absorbed in the fasting state.[14,15,19] Although no direct information is available about bisphosphonate absorption in neonates, it is likely that it would be similarly poor.

Breast-feeding is the recommended form of infant nutrition.[21] This case indicates that intravenous pamidronate is a viable option for treatment of reflex sympathetic dystrophy after pregnancy, if breast-feeding is to be continued. Assay of pamidronate in expressed milk showed that excretion of the drug into milk was minimal. Although breast milk was discarded for 48 h after infusion, this precaution may not be necessary.

REFERENCES

1. Geertzen JH 1998 Reflex sympathetic dystrophy. Outcome and measurement studies. Acta Orthop Scand Suppl **279:**1–3.
2. Schott GD 1997 Bisphosphonates for pain relief in reflex sympathetic dystrophy. Lancet **350:**1117.
3. Poncelet C, Perdu M, Levy-Weil F, Philippe HJ, Nisand I 1999 Reflex sympathetic dystrophy in pregnancy: Nine cases and a review of the literature. Eur J Obstet Gynecol Reprod Biol **86:**55–63.
4. Cortet B, Filipo RM, Coquerelle P, Duquesnoy B, Delcambre B 1997 Treatment of severe, recalcitrant reflex sympathetic dystrophy: Assessment of efficacy and safety of the second generation bisphosphonate pamidronate. Clin Rheumatol **16:** 51–56.
5. Rehman MT, Clayson AD, Marsh D, Adams J, Cantrill J, Anderson DC 1992 Treatment of reflex sympathetic dystrophy with intravenous pamidronate. Bone **13:**116.
6. Looker AC, Johnston CC Jr, Wahner HW, Dunn WL, Calvo MS, Harris TB, Heyse SP, Lindsay RL 1995 Prevalence of low femoral bone density in older US women from NHANES III. J Bone Miner Res **10:**796–802.
7. Flesch G, Hauffe SA 1989 Determination of the bisphosphonate pamidronate disodium in urine by pre-column derivitiza-

tion with fluorescamine, high performance liquid chromatography and fluorescence detection. J Chromatogr **489:**446–451.
8. Flesch G, Tominaga N, Degen P 1991 Improved determination of the bisphosphonate pamidronate disodium in plasma and urine by pre-column derivitization with fluorescamine, high performance liquid chromatography and fluorescence detection. J Chromatogr **568:**261–266.
9. Smith R, Phillips AJ 1998 Osteoporosis during pregnancy and its management. Scand J Rheumatol Suppl **107:**66–67.
10. Naylor KE, Iqbal P, Fledelius C, Fraser RB, Eastell R 2000 The effect of pregnancy on bone density and bone turnover. J Bone Miner Res **15:**129–137.
11. Cepollaro C, Gonnelli S, Pondrelli C, Martini S, Montagnani A, Rossi B, Gennari C 1998 Usefulness of ultrasound in Sudeck's atrophy of the foot. Calcif Tissue Int **62:**538–541.
12. Dequeker J, Geusens P, Verstaeten A, De Roo M 1986 Vertebral crush fracture syndrome and reflex sympathetic dystrophy. Bone **7:**89–94.
13. Kozin F, Soin JS, Ryan LM, Carrera GF, Wortmann RL 1981 Bone scintigraphy in the reflex sympathetic dystrophy syndrome. Radiology **138:**437–443.
14. Welbanks L (ed) 2000 Compendium of Pharmaceuticals and Specialties, 35th ed. Canadian Pharmacists Association, Ottawa, Canada, pp. 128–130.
15. Fitton A, McTavish D 1991 Pamidronate. A review of its pharmacological properties and therapeutic efficacy in resorptive bone disease. Drugs **41:**289–318.
16. Hyldstrup L, Flesch G, Hauffe S 1993 Pharmacokinetic evaluation of pamidronate after oral administration: A study on dose proportionality, absolute bioavailability, and effect of repeated administration. Calcif Tissue Int **53:**297–300.
17. Leyvraz S, Hess U, Flesch G, Bauer J, Hauffe S, Ford JM, Burckhardt P 1992 Pharmacokinetics of pamidronate in patients with bone metastases. J Natl Cancer Inst **84:**788–792.
18. Anderson PO 1991 Drug use during breast-feeding. Clin Pharmacokinet **10:**594–624.
19. Fogelman I, Smith L, Mazess R, Wilson MA, Bevan JA 1986 Absorption of oral diphosphonate in normal subjects. Clin Endocrinol **24:**57–62.
20. Lawrence R 1994 Breastfeeding. A Guide For The Medical Profession, 4th ed. Mosby, St. Louis, MO, U.S.A., p. 109.
21. American Academy of Pediatrics Working Group on Breastfeeding 1997 Pediatrics **100:**1035–1039.

Address reprint requests to:
Dr. K. Siminoski
608 College Plaza, 8215–112 Street
Edmonton, Alberta T6G 2C8, Canada

Received in original form June 7, 1999; in revised form March 14, 2000; accepted May 10, 2000.