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Case Report

Hypocalcemia Complicating Deferoxamine Therapy in an Infant with Parenteral Nutrition-Associated Aluminum Overload: Evidence for a Role of Aluminum in the Bone Disease of Infants

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Summary: Aluminum (Al) contaminates total parenteral nutrition (TPN) solutions given to infants, and high levels of Al have been demonstrated in their bone, serum, and urine. However, it is uncertain whether Al at current levels of contamination of TPN solutions is harmful to bone. We report an 8-month-old infant who developed osteopenic bone disease while receiving TPN, which did not respond to large amounts of calcium, phosphate, and vitamin D_2. Serum and urine Al levels were greatly elevated and fell after a short course of deferoxamine. However, shortly after treatment began, serum calcium levels fell in the absence of hypercalciuria. We postulate that chelation of Al from this patient's bone permitted increased bone calcium uptake. This would suggest that Al at current levels of contamination of TPN solutions may impair bone calcium uptake and thus contribute to the pathogenesis or exacerbation of TPN-related osteopenia. **Key Words:** Total parenteral nutrition—Aluminum contamination—Osteopenia.

Aluminum (Al) has been associated with low-turnover bone disease in adults receiving chronic total parenteral nutrition (TPN) (1,2). In 1985 Sedman and colleagues (3) demonstrated that infants receiving intravenous therapy had bone Al levels 10-fold greater than controls and that the sources of Al were primarily calcium and phosphate salts, but also heparin and albumin. These findings have subsequently been confirmed (4). However, it is not certain that the quantity of Al inadvertently infused during TPN therapy is sufficient to account for the bone demineralization seen in infants receiving TPN. We report the case of an infant who developed Al overload while receiving long-term nutritional support with TPN. Use of deferoxamine to treat the Al overload did not result in roentgenographic improvement but produced a hypocalcemic response, which suggests that Al at current levels of contamination of TPN solutions may contribute to the bone demineralization complicating TPN treatment.

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CASE REPORT

The patient was an 8-month-old girl born at 25 weeks of gestation, weighing 620 g. At 7 weeks she developed necrotizing enterocolitis and underwent partial bowel resection. She was managed by a combination of TPN and enteral feedings but by age

4 months necrotizing enterocolitis recurred, this time with intestinal perforation. She underwent colon resection and ileostomy and was treated exclusively with continuous TPN for 24 h/day. At age 7 months she was noted to have osteopenia, periosteal resorption, and cupping on x-ray film, suggestive of rickets (Fig. 1). Results of an initial biochemical evaluation were compatible with nutritional rickets (Table 1).

The TPN solution contained elemental calcium 33–36 mg/kg/day, phosphorus 31–40 mg/kg/day, copper 30 μg/kg/day, and vitamin D_2 5 μg/day. This was the maximum amount that could be added to the solution without calcium phosphate precipitation. The patient was given supplemental vitamin D_2 125 μg i.m. each week beginning 6 weeks prior to diagnosis and therapy for aluminum overload and was maintained on this dose throughout her course. This was done even though the patient had no biochemical evidence of vitamin D deficiency because of a previous report that rickets occurring in infants receiving chronic TPN therapy improved following high-dose vitamin D supplementation (5).

As part of the evaluation, serum Al concentration was found to be 182 μg/L (normal <10 μg/L) (2) and urinary Al/creatinine 0.7 μg/mg [normal 0.06 ± 0.08 (SD) μg/mg] (3). The TPN solution initially contained 229 μg Al/L, providing the patient with 22 μg/kg/day. Because of these high Al levels and because no additional calcium or phosphate could be added to the TPN solution, she was given deferoxamine, an agent used to chelate Al from bone in patients with dialysis osteomalacia (6). The purpose of this treatment was to attempt to improve the bone mineralization. During this therapeutic trial, all nutrients came exclusively from TPN.

TABLE 1. *Initial evaluation of patient with total parenteral nutrition–associated metabolic bone disease*

	Value	Normal range (ref.)
Serum parameter		
Total calcium (mg/dl)	8.5	9.0–11.5 (with normal albumin)
Ionized calcium (mg/dl)	4.82	4.50–5.50
Phosphorus (mg/dl)	3.7	4.0–7.0
Magnesium (mg/dl)	2.1	1.8–3.0
Creatinine (mg/dl)	0.6	<1.0
Albumin (g/dl)	2.8	3.0–5.0
Parathyroid hormone (ng/ml) (midregion assay)	3.5	<1
25-Hydroxyvitamin D (ng/ml)	20	9–52
1,25-Dihydroxyvitamin D (pg/ml)	150	14–80
Aluminum (μg/L)	182	<10
Copper (μg/dl)	121	110–175
Urine parameter		
Calcium/creatinine (mg/mg)	0.013	0.12 ± 0.02[a] (10)
Al/creatinine (μg/mg)	0.70	0.055 ± 0.046[a] (3)
TmP/GFR[b] (mg/dl)	3.4	4.2–8.0 (11)

[a] SD.
[b] Based on a constant infusion of phosphate per day and no oral intake.

METHODS

Calcium, phosphorus, and creatinine levels in serum and urine were analyzed by standard automated methods; ionized calcium levels in serum were ascertained by ion-selective electrode analysis

FIG. 1. Roentgenograph of femurs, illustrating osteopenia and periosteal resorption.

using a Radiometer A-1 electrode. Serum levels of magnesium were determined colorimetrically on an Ektachem 400 (Kodak, Rochester, NY, U.S.A.) and albumin levels were determined by serum protein electrophoresis on a cellulose-acetate gradient. Serum levels of 25-hydroxy- and 1,25-dihydroxyvitamin D were performed at Mayo Medical Laboratories (Rochester, MN, U.S.A.) using dual-cartridge extraction and a radioreceptor assay, with interassay variations of 10 and 15%, respectively (7). Analyses of sera for immunoreactive parathyroid hormone (PTH) levels were performed utilizing an antibody to the midmolecular region, with intraassay variation of 5% and interassay variation of 10% (8). Aluminum levels were determined utilizing flameless atomic absorption spectroscopy as previously described (9).

RESULTS

The patient was given deferoxamine 20 mg/kg i.v. over 2 h 3 evenings during week 1, but the dose was reduced to 10 mg/kg once weekly thereafter. Peak serum Al during the first week of therapy was 73 μg/L and this level fell over 6 weeks to 26 μg/L (Fig. 2). Urine Al/creatinine rose by ~350% 24 h following each administration of deferoxamine. Unexpectedly, total serum calcium levels fell by the fourth dose of deferoxamine and reached 6.5 mg/dl with serum ionized calcium 3.95 mg/dl by the beginning of the third week of therapy (Fig. 2). During this time she continued to receive calcium in her TPN, 33–36 mg/kg/day, as well as the phosphorus and vitamin D doses mentioned above. Thereafter, serum calcium levels fluctuated but remained low. Urinary calcium/creatinine was low initially (Table 1) (10) and did not change significantly when repeated during week 3, 0.04 mg/mg. Serum levels of PTH and 1,25-dihydroxyvitamin D did not change from baseline following reevaluation during the third week of deferoxamine therapy. Deferoxamine therapy was discontinued by week 6 owing to repeated episodes of gram-negative bacterial sepsis and difficulty in maintaining central venous catheters. No roentgenographic improvement was seen. The patient was ultimately discharged, receiving parenteral nutrition at home. She subsequently died at home and permission for an autopsy was refused.

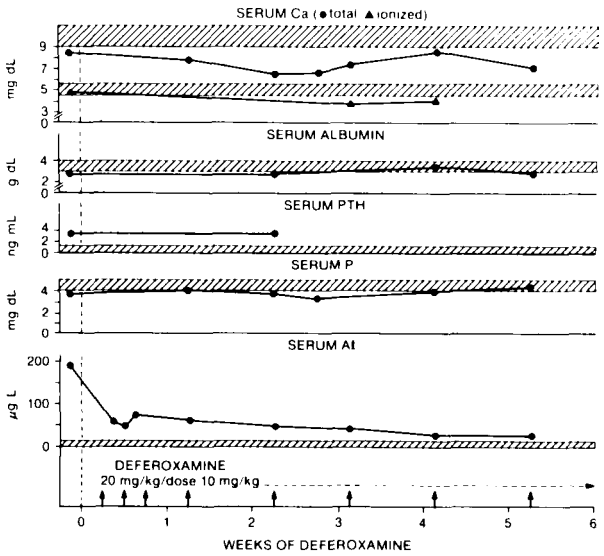

FIG. 2. Serial serum levels of calcium (total and ionized), albumin, parathyroid hormone (PTH), phosphorus, and aluminum during the course of deferoxamine therapy. Arrows indicate days on which deferoxamine was given. Each circle represents an individual determination. Normal serum levels are defined by the hatched areas.

DISCUSSION

Our patient developed sustained hypocalcemia in response to deferoxamine given to reduce the body burden of Al incurred as a result of chronic TPN therapy. The cause of the hypocalcemia is uncertain, but it occurred despite constant calcium infusion in the TPN solution and sustained elevation of serum levels of PTH and 1,25-dihydroxyvitamin D, hormones that should increase bone resorption to sustain serum calcium levels (11). Urine calcium excretion did not increase during deferoxamine therapy and ostomy calcium output was not measured. The affinity of deferoxamine for calcium is substantially lower than that for aluminum, $K_a = 10^2$ vs. 10^{21} (12). Inasmuch as deferoxamine did not increase urinary calcium excretion and at least 70% of deferoxamine is excreted in the urine (12), it is unlikely that deferoxamine therapy increased ostomy calcium excretion. Although urinary calcium/creatinine may vary over the course of a day, the patient received a continuous infusion of calcium in the TPN solution and received nothing by mouth. Thus, conditions were such as to minimize any variability that might occur. However, the lack of elevated urinary calcium excretion is consistent with this patient's hyperparathyroidism.

One can speculate that if calcium excretion was not increased, a likely explanation for the low se-

rum calcium would be deposition in the patient's demineralized bone, the chief repository of body calcium. It is known from previous studies that Al accumulates at the mineralization front of bone both in infants (4) and in adults (1) receiving TPN therapy. Administration of deferoxamine to our patient resulted in a significant increase in urinary Al and a fall in serum Al. This would suggest chelation of Al from bone, one of the major repositories of parenterally administered Al (1–5). Chelation of Al from bone followed by increased bone calcium deposition suggests that Al deposited in bone may impair bone calcium uptake.

Reduction of serum calcium has also been described during deferoxamine treatment for Al-associated dialysis osteomalacia (6,13–16), including a preliminary report of a series of 51 patients (16). Lack of roentgenographic improvement in our patient may be explained by a duration of deferoxamine therapy of <4 months, the minimum needed to show improvement in dialysis patients (6), the constant resupply of Al in the TPN solution, and lack of adequate provision of calcium and/or phosphate.

Inadequate provision of calcium and/or phosphate in TPN solutions has been most frequently implicated in the pathogenesis of what may well be multifactorial metabolic TPN-related bone disease in infants (17–19). Lack of calcium and/or phosphate may have been a primary pathogenic factor in the bone demineralization observed in our patient.

However, the amount of Al received by our patient in her TPN solution is similar to amounts previously reported to result in bone Al accumulation in infants 10-fold greater than in normal infants (3,4). Thus, Al in amounts currently contaminating TPN solutions may contribute to the pathogenesis or exacerbation of TPN-related bone disease in infants.

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REFERENCES

1. Ott SM, Maloney NA, Klein GL, et al. Aluminum is associated with low bone formation in patients receiving chronic parenteral nutrition. *Ann Intern Med* 1983;98:910–4.
2. Klein GL, Alfrey AC, Miller NL, et al. Aluminum loading during total parenteral nutrition. *Am J Clin Nutr* 1982;35:1425–9.
3. Sedman AB, Klein GL, Merritt RJ, et al. Evidence of aluminum loading in infants receiving intravenous therapy. *N Engl J Med* 1985;312:1337–43.
4. Koo WWK, Kaplan LA, Bendon R, et al. Response to aluminum in parenteral nutrition during infancy. *J Pediatr* 1986;109:877–83.
5. Klein GL, Cannon RA, Diament M, et al. Infantile vitamin D-resistant rickets associated with total parenteral nutrition. *Am J Dis Child* 1982;136:74–6.
6. Ott SM, Andress DL, Nebeker HG, et al. Changes in bone histology after treatment with desferrioxamine. *Kidney Int* 1986;29:S108–13.
7. Kao P, Heser D. Simultaneous determination of 25-hydroxy and 1,25-dihydroxy vitamin D from a single sample by dual cartridge extraction. *Clin Chem* 1984;30:56–61.
8. Mallette LE, Tuma SN, Berger RE, et al. Radioimmunoassay for the middle region of human parathyroid hormone using a homologous serum with a carboxyl fragment of bovine parathyroid hormone as radioligand. *J Clin Endocrinol Metab* 1982;54:1017–24.
9. LeGendre GR, Alfrey AC. Measuring picogram amounts of aluminum in biological tissue by flameless atomic absorption analysis of a chelate. *Clin Chem* 1976;22:53–6.
10. Tieder M, Modar D, Samuel E, et al. Hereditary hypophosphatemic rickets with hypercalciuria. *N Engl J Med* 1985;312:611–7.
11. Kruse K, Kracht U, Gopfert G. Renal threshold phosphate concentration. *Arch Dis Child* 1982;57:217–23.
12. Swartz RD. Deferoxamine and aluminum removal. *Am J Kidney Dis* 1985;6:358–64.
13. Ackrill P, Day JP, Garstang FM, et al. Treatment of fracturing renal osteodystrophy by desferrioxamine. *Proc Eur Dial Transplant Assoc* 1983;19:203–7.
14. Brown DJ, Ham K, Dawborn JK, Xippel JM. Treatment of dialysis osteomalacia with desferrioxamine. *Lancet* 1982;2:343–5.
15. Hood SA, Clark WF, Hodsman AB, et al. Successful treatment of dialysis osteomalacia and dementia using desferrioxamine infusions and oral 1-alpha hydroxycholecalciferol. *Am J Nephrol* 1984;4:369–74.
16. Nebeker HG, Andress DL, Ott SM, et al. Treatment of aluminum-related bone disease with deferoxamine: results in 51 cases. Presented at the Xth International Congress of Nephrology, London, July 1987.
17. Koo WWK, Tsang RC, Steichen JJ, et al. Parenteral nutrition for infants: effect of high versus low calcium and phosphorus content. *J Pediatr Gastroenterol Nutr* 1987;6:96–104.
18. Ricour C, Millot M, Balsan S. Phosphorus depletion in children on long-term parenteral nutrition. *Acta Paediatr Scand* 1975;64:385–92.
19. Vileisis RA. Effect of phosphorus intake in total parenteral nutrition infusates in premature neonates. *J Pediatr* 1987;110:586–90.