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CLINICAL OBSERVATIONS

Long-term control of hypercalcaemia in an infant with Williams-Beuren syndrome after a single infusion of biphosphonate (Pamidronate)

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Aim: To report the efficacy of Pamidronate to treat hypercalcaemia in a patient with Williams-Beuren syndrome (WBS). *Results:* We report a 14-mo-old male infant presenting hypercalcaemia, elfin face and other dysmorphological features of WBS, confirmed by the FISH fluorescent test. Due to the marked symptomatic hypercalcaemia, 13.0 mg/dl intravenous Pamidronate was administered in a single dose of 1 mg/kg. Two days later, serum calcium diminished to normal levels, and remained within normal range during 12 mo follow-up.

Conclusion: Pamidronate appears to be effective in paediatric patients with WBS and hypercalcaemia.

Key words: *Hypercalciuria, hypercalcaemia, Pamidronate, Williams-Beuren syndrome*

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Williams-Beuren syndrome (WBS) is an autosomal dominant disorder characterized by peculiar face, congenital cardiovascular anomalies, mental retardation and growth deficiency (1). The incidence varies between 1/20 000 to 1/50 000 newborns (2). Fifteen to 40% of patients with WBS also present hypercalcaemia and hypercalciuria, which becomes evident during the first year of life (1). Due to hypercalcaemia, patients may suffer feeding problems, irritability and lethargy (3). A variety of vitamin D abnormalities has been reported in the pathogenesis of the calcium disorder (4–9). However, findings are not consistent (10), and there is no definitive therapy for hypercalcaemia in WBS. We report the successful treatment of marked hypercalcaemia in a child with WBS, by administration of a single intravenous infusion of Pamidronate.

Case report

A 14-mo-old male infant was admitted to the University Hospital in August 2001 due to severe malnutrition, dehydration and maturative delay. He was a full-term newborn (birthweight 3070 g) after an uneventful pregnancy and delivery. He was breastfed during the first 2 mo, followed by administration of evaporated-milk formula containing 500 mg of calcium and 40 IU of vitamin D2/liter. At 6 mo of age, failure to thrive, feeding difficulties and neurological maturative delay became evident.

Progression of symptoms finally prompted consultation and admission to hospital, where physical examination revealed a malnourished infant with a weight of 6820 g and a height of 72 cm (both below the 3rd percentile), and showing typical "elfin" facies. Cardiovascular examination (including echocardiogram) was normal. Laboratory studies disclosed marked hypercalcaemia (3.25 mmol/l (NV: 2.23–2.63)) and high calcium/creatinine ratio (0.81 (NV: <0.26)), low PTH serum levels (<10 pg/ml (NV: 20–100)), but normal serum phosphate (1.29 mmol/l (NV: 1.29–2.00)), alkaline phosphatase (290 IU/ml (NV: <380)), 25OHD (50 nmol/l (NV: 37.5–125.0)) and 1–25 $(OH)_2D$ (48 pmol/l (NV: 34–91)). Routine laboratory examination was normal.

WBS was diagnosed and later confirmed by the FISH fluorescent test. Due to the marked symptomatic hypercalcaemia, intravenous Pamidronate was administered in a dose of 1 mg/kg diluted in 250 cc of isotonic saline, over a 4-h period.

Two days later, serum calcium had diminished to normal levels—2.4 mmol/l—and rapid improvement was observed (he recovered his appetite, and he seemed to be in a better mood and presented interest in his environment). The infusion of Pamidronate was well tolerated, and no side effects were observed. A diet

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Table 1. Biochemical parameters pre- and post-infusion.

	$_{s}$Ca (mmol/l)	$_{s}$P (mmol/l)	AP (IU/l)	PTH (pg/ml)	Cau/Cru
Pre-infusion	3.25	1.29	290	<10	0.81
1 wk post-infusion	2.20	0.87	268	45	0.03
6 wk post-infusion	2.45	1.71	253	30	0.25
Normal values	2.23–2.63	1.29–2.00	<380	20–100	<0.26

$_{s}$Ca: serum calcium; $_{s}$P: serum phosphate; AP: alkaline phosphatase; PTH: parathormone; Cau/Cru: urinary calcium/creatinine ratio.

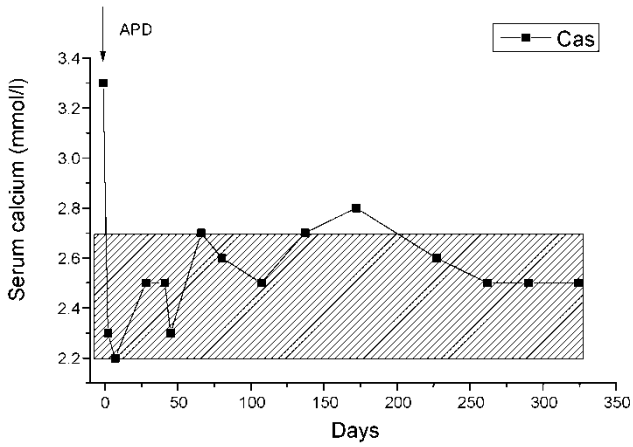

Fig. 1. Response of total serum calcium to a single intravenous infusion of Pamidronate (1 mg/kg) in an infant with Williams-Beuren syndrome. Dashed area indicates the normal range.

containing 300 mg of calcium per day and no vitamin D was given

Patient follow-up was performed at the outpatient clinic and included frequent biochemical examinations in the first 6 wk (Table 1) and during the following 12 mo (Fig. 1). Only one mild elevation in serum calcium was observed—2.7 mmol/l—and corresponded with a time when the patient was not following the prescribed diet. Urinary calcium excretion was markedly lower than that recorded prior to treatment, but some values above the upper normal range were observed, probably due to non-compliance with the diet.

Serum 25OHD, determined several times during follow-up, remained at the upper normal level. Marked weight gain was registered, but the patient's height remained at the 3rd percentile curve during 12 mo following discharge.

Discussion

To our knowledge, this is the first report on the successful control of hypercalcaemia in WBS by intravenous infusion of Pamidronate.

Abnormalities in vitamin D metabolism have been the most frequently considered mechanism of hypercalcaemia in WBS patients. Taylor et al. (7) reported that normo-calcaemic children with WBS displayed an abnormal increase in 25OHD serum levels in response to pharmacological doses of oral vitamin D. Garabedian et al. (8) observed elevated levels of serum 1,25 $(OH)_2$D in four children with WBS—two of whom were hypercalcaemic. Chesney (3) studied nine children with WBS, concluding that no consistent pattern of abnormal vitamin D, 25OHD or 1,25 $(OH)_2$D could be observed.

A deficit in calcitonin secretion postulated in one study (11) was not confirmed by other authors (10, 12). Other suggested mechanisms include increased vitamin A (3) or PTHrp serum levels leading to increased bone resorption rate (13).

We believe that increased bone resorption may play a role in hypercalcaemia associated with WBS as shown in the aforementioned case.

Future studies should explore this possibility. We recommend that biphosphonates should be considered in children with hypercalcaemia associated with WBS.

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