



From Rickets Prevention to Vitamin D Intoxication

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ABSTRACT

Hypervitaminosis D occurs in infants due to increased intake of vitamin D and results in hypercalcemia and hypercalciuria. We present the case of a 4.5-month old infant with signs of vitamin D intoxication, which occurred due to supplementation for the purpose of rickets prevention and diet with vitamin D-fortified milk. The clinical manifestations were constipation, vomiting and failure to thrive. After excluding hormonal, tumoral and malformative (Williams syndrome) causes, treatment included hyperhydration, loop diuretics and prednisone. This case highlights the need for proper informing of parents on the manners of vitamin D supplementation during the first year of life in order to avoid dangers of parental dosing errors.

Key words: Vitamin D intoxication, hypercalcemia, Williams syndrome, prednisone

Riketsin Önlenmesinden Vitamin D Zehirlenmesine

ÖZET

Infantlarda D vitamini fazlalığı artmış vitamin D alımı neticesinde olur ve hiperkalsemi ve hiperkalsiüri ile sonuçlanır. Biz, vitamin D intoksikasyonu bulguları olan 4.5 aylık bir infant vakası sunuyoruz. Bu vakada vitamin D fazlalığı, riketsden korumak amacıyla diyetle vitamin D ile takviye edilmiş süt kullanılması ile oluşmuştu. Klinik belirtiler kabızlık, kusma ve gelişme geriliği idi. Hormonal, tümöral ve malformatif (Williams syndrome) sebepler dışlandıktan sonra, hiperhidrasyon, loop diüretikleri ve prednison ile tedavi edildi. Sunulan vaka, parenteral doz hatalarının tehlikelerini önlemek için yaşamın ilk yılında vitamin D suplementasyon metodları hakkında ebeveynlerin bilgilendirilmesinin ne kadar önemli olduğunu göstermektedir.

Anahtar kelimeler: Vitamin D zehirlenmesi, hiperkalsemi, Williams sendromu, prednison

INTRODUCTION

Vitamin D (calciferol), a precursor of the steroid hormone calcitriol (1,25[OH]₂D) is now recognized as a prohormone and has an essential role in the homeostasis of calcium and phosphorus, i.e. bone and tooth mineralization, cell proliferation, immune and hormonal regulation, as well as other physiological processes (1). Its deficiency leads to rickets, which occurs in those periods of childhood when growth is most intense. As opposed to this, excessive intake of this vitamin may lead to hypervitaminosis and hypercalcemia (2). In this paper we report on a case of hypercalcemia due to vitamin D intoxication (VDI) in a 4.5-month old infant.

CASE

A 4.5-month old infant was admitted to the children's ward for loss of body weight, vomiting and constipation. The infant was breastfed for the first 2.5 months, and afterwards was only fed an adapted formula approximately 1000 ml daily. Starting from the third week of life, the infant was receiving 2 drops of oil solution of vitamin D daily, so that its daily intake was 1354-1772 IU (Table 1). For the first 3.5 months the infant thrived adequately, but later failure to thrive and body weight loss occurred (480 grams in the last month). The stools were harder and once weekly. In the last 7 days the infant vomited undigested milk once daily.

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Table 1. Daily intake of vitamin D

Source of Vitamin D	From 3 weeks to 2.5 months	From 2.5 to 4.5 months
Oil solution of vitamin D-2 drops (1 drop/666 IU)	1332 IU	1332 IU
Breast milk~1000 ml (22 IU/l)	~22 IU	/
Adapted formula~1000 ml (100 ml/44 IU)	/	~440 IU
Daily intake	~1354 IU	~1772 IU

At admission the female infant had BW 4520 grams (<P3), was normotensive, euhydrated, afebrile, with existing mild generalized hypotonia and minor malformations-round face, discrete strabismus, small mandible, prominent maxilla, and incomplete simian crease on the right hand. Laboratory testing showed a serum Ca concentration of 4.91 (normal: 2.15-2.74 mmol/l), 25[OH]D levels >150 (normal 25-45 ng/ml), intact PTH 2.1 (9-65 pg/ml), urinary Ca/Cr ratio was 2.81 (normal values <0.2) (Table 2.). The values for other electrolytes as well as other biochemistry findings were in the age-specific reference range limits. The sedimentation was 40, leukocyte count was $21.3 \times 10^9/l$ (with neutrophils predomination - 51.4%), while other complete blood count values were normal. The urine finding was proper, urine culture and hemoculture were sterile. Electrocardiogram showed normal sinus rhythm, with a regular rate and normal intervals. The cardiac ultrasound did not indicate presence of cardiac lesions. The radiograph of the heart and lungs is proper; calcifications are not observed in the renal ultrasound. Radiographs of the hand taken at admission, and 1 month after the admission did not show metaphyseal sclerosis. Within the additional testing for the elevated leukocyte values and excluding hypercalcemia in malignant diseases (leukemia) a peripheral blood smear was performed which, except for the increased leukocyte count, did not indicate existence of immature or malignant cells. Otolaryngology and ophthalmology specialists were consulted - the finding was age-appropriate. Due to the existing minor malformations, a genetics specialist was consulted who

performed cytogenetic analysis and by specific fluorescence in situ hybridization excluded Williams syndrome. After admission the vitamin D intake was discontinued, IV hydration (150 ml/kg/day) and furosemide (1.5 mg/kg) were administered. Prednisone 1 mg/kg was introduced into therapy for 2 weeks. Although on the third day the serum Ca peaked (4.98 mmol/l), normalization of the values occurred after a month (Ca 2.62 mmol/l), urinary Ca/Cr ratio (0.8) and leukocytes ($14.8 \times 10^9/l$). After 2 months 25[OH] D remains elevated (95 ng/ml) while the intact PTH normalizes (18.1 pg/ml) (Table 2).

DISCUSSION

Considering the fact that the quantity of vitamin D in human milk is small and that it depends on the diet of the breastfeeding mother (22 IU/l), American Academy of Pediatrics (AAP) recommended daily supplementation of vitamin D of 400 (10 µg) IU/day beginning in the first few days of life, unless the infant is weaned to at least 1 liter or 1 quart per day of vitamin D-fortified formula (3). When calculating the total intake of vitamin D for a infant, not only the doses taken with supplementation, but also the quantity of vitamin D taken through the adapted formula must be considered (4,5). Tolerable Upper Intake Levels (ULs) for Vitamin D in infants 0-6 month old is 1000 IU/day (6). The intake of as little as five times the recommended daily allowance of vitamin D (400 IU) has been associated with toxicity (7). The vitamin D doses taken through supplementation in our patient were over 1300 IU/day, while the total dose of

Table 2. Laboratory values during hospitalization and follow-up

Days	Serum Ca (mmol/l)	Urinary Ca/Cr	Le	iPTH (pg/ml)	25[OH]D levels (ng/ml)
Day 1	4.91	2.81	21.3	2.1	>150
Day 3	4.98	/	26.8	/	/
1 week	4.62	2.97	23.7	/	/
2 weeks	3.07	1.43	24.6	7.4	>150
1 month	2.62	0.8	14.8	8.2	>150
2 months	2.3	0.14	8.2	18.1	95

Normal laboratory values: Ca 2.15-2.74 mmol/l; Urinary Ca/Cr: <0.2; Le: $6-17.5 \times 10^9/l$; iPTH: (9-65 pg/ml); 25[OH]D levels: 25-45 ng/ml

vitamin D considering that the infant consumed adapted formula for 2 months was approximately 1800 IU/day, which led to VDI. Although the well taken history could indicate the cause of the VDI with great certainty, in the differential diagnosis we considered hyperparathyroidism, familial benign hypocalciuric hypercalcemia and hypercalcemia of malignancy which were differential diagnostically excluded by appropriate testing as well as with response to administered therapy. Williams syndrome should definitely be considered also, especially since our patient had some of the phenotype characteristics specific for deletion at chromosome band 7q11.23. However, by cytogenetic analysis and by specific fluorescence in situ hybridization we excluded the existence of this rare genetic condition.

Within the hematological disorders occurring in VDI anemia is sometimes present; the mechanism is unknown (2). It did not occur in our patient, but leukocytosis with neutrophilia did. It onset before the beginning of the corticosteroid therapy, and the leukocyte count reached normal values after 1 month. We did not find similar descriptions of occurrence of leukocytosis in VDI in available literature. Rehydration and loop diuretics are used for treatment of this disease. In more severe forms glucocorticosteroids (inhibit the conversion of 25[OH]D to 1,25[OH]₂D and promote the urinary excretion of calcium), calcitonin, hemodialysis, exchange transfusions, bisphosphonates (especially the pamidronate) and alendronate are used (2,7,8). Chambellan-Tison and colleagues administered hemodialysis, diuretic and sodium pamidronate infusion at calcium values of 4.55 mmol/l in a 4-month-old boy due to worsening of the neurological condition and ECG abnormality (9). Although the calcium values in our patient were 4.98 mmol/l, we did not have the stated hypercalcemia complications and therefore the need to administer some other type of therapy except for the forced diuresis, diuretics and corticosteroids. In our patient, the administered therapy resulted in normalization of the calcium values, urinary Ca/Cr ratio and intact PTH, but due to the fact that vitamin D is lipophilic and is stored in fat tissues, the 25[OH]D level remained elevated after 2 months as well.

Pediatricians in Serbia mainly advise on using the oil solution of vitamin D which contains (1ml/20,000 IU/30 drops) 666 IU of vitamin D in one drop. Since there are no vitamin D preparations containing 400 IU in one drop on the market in our country, it is necessary to give breastfed infants during the first year 1 drop of oil

solution of the supplement 5 days weekly, with 2 days of pause. Due to additional safety and fear of rickets, some parents give 2 drops daily of this solution instead of one, without a pause during the week. If the infant uses vitamin D-fortified milk, the use of vitamin D supplements increases the probability of VDI, which is what happened in our patient as a result of the parental dosing error. In conclusion, parents should be given detailed instructions and the use of vitamin D drops for the purpose of rickets prevention should be explicitly demonstrated to them. Also, parents should be warned and informed about the possible toxic effects resulting from overdosing. It is necessary to clearly emphasize that parents should discontinue the use of vitamin D supplements if the infant is fed an appropriate quantity of vitamin D-fortified milk. Prohibiting commercial availability and prescribing vitamin D supplements only on doctor's prescriptions would also help in the prevention of VDI.

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