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ПРИКАЗ БОЛЕСНИКА / CASE REPORT
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Case Report of Acute Vitamin D Intoxication in an Infant

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SUMMARY

Introduction Vitamin D intoxication represents a rare and potentially serious pathological condition caused by the excess of calcium and phosphorus. We are presenting an infant with vitamin D intoxication due to excessive daily administration, as well as therapeutic procedures that prevented its adverse effects.

Case Outline A 1.5-month-old female infant, born at term, exclusively breastfed and without any complaints and abnormalities of physical findings, was observed due to the data that during the preceding month, by her mother's mistake, she had received about 200,000 IU of vitamin D3. Laboratory analyses showed a high serum level of 25(OH)D (>400 nmol/L) and calcium (2.72 mmol/L), lowered PTH (6.6 pg/ml) and high urinary calcium/creatinine ratio (1.6), while other findings, including urotract ultrasonography image, were within normal limits. Treatment based on the discontinuation of vitamin D administration, infant's forced water intake, as well as the application of 2-month prednisolone and 4-month phenobarbitone and furosemide, resulted in complete normalization of the laboratory indicators of vitamin D overdose, as well as the prevention of its adverse effects.

Conclusion By timely recognition and adequate treatment, including triple therapy with prednisolone, phenobarbitone and furosemide, adverse effects of acute vitamin D intoxication can be prevented.

Keywords: vitamin D intoxication; infant; therapy

INTRODUCTION

Vitamin D (calciferol) is the precursor of $1,25(OH)_2D$ (calcitriol), a liposolubile hormone of essential importance for the homeostasis of calcium and phosphorus**,** bone and tooth mineralization, as well as regulation of cell proliferation, differentiation and apoptosis, immunoregulation, hormonogenesis and other physiological processes in organism [1-4]. Therefore, its lack, beside negative effects caused by calcium and phosphorus deficiency, has essential participation in the pathogenesis of various malignant, autoimmune, allergic and other diseases [1-6]. Viewed from the biological aspect, physiological needs in vitamin D in humans are primarily accomplished by cutaneous synthesis, i.e. photolysis of 7-dehydrocholesterol into cholecalciferol (D3), while, generally viewed, food is its very scarce resource [4, 5]. However, the modern life-style followed by insufficient exposure to sun, as well as the fear of skin malignancies, above all melanoma, has mostly deprived the man of the natural and basic source of vitamin D [5, 7]. Accordingly, as well as based on numerous epidemiological studies indicating an increase in diseases with underlying essential participation of vitamin D deficiency, has enforced the necessity for its additional intake [5, 8, 9]. The recommended daily vitamin D intake, either in the form of supplements and/or as addition to food, which can satisfy optimal body needs is 400 IU for age 0-18 years, 600 IU for 19-70 years and 800 IU for age over 70 years [4, 8, 9]. Since the physiological effect of vitamin D as well as of other bioactive substances is accomplished within strictly defined limits, it is clear that its excess can also seriously endanger health [4, 9]. Although the negative balance of vitamin D is very much present worldwide, both in children and adults, in rare cases the opposite condition can be also seen [4, 5, 9, 10-14]. With this aim, we are presenting an infant with vitamin D intoxication due to excessive daily administration, as well as therapeutic procedures that have prevented its adverse effect.

CASE REPORT

A female infant aged 1.5 months hospitalized on November 2012 due to excessive administration of vitamin D_3 (Vigantol oil Merck KGaA, 10 drops daily, total about 200,000 IU per month). She was born after an uneventful term pregnancy, with body weight (BW) 3600 g and body length (BL) 54 cm. Since birth the infant has been exclusively breastfed. The aforesaid dose of vitamin D3, which was the consequence of misunderstanding between the mother and the pediatrician, the infant had received between the mid-first and mid-second month after birth. The problems which would have pointed at the excess of vitamin D had not been registered. On admission: a normally

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Table 1. Laboratory findings in patients with vitamin D intoxication at admission and after 2 and 4 months of treatment

Parameter	At admission	After 2 months	After 4 months	Referent range [4, 15, 16]
25(OH)D (nmol/L)	>400	146.9	56.7	50–125
Ca, total (mmol/L)	2.72	2.64	2.53	2.2–2.7
P, inorganic (mmol/L)	2.06	1.74	1.63	1.25–2.10
PTH (pg/ml)	6.6	8.1	22.3	10–69
Ca/Cr (mg/mg) in 24-hour urine	1.6	2.3	0.22	≤0.8*

* for infants <7 months
Ca – calcium; P – phosphorus; PTH – parathyroid hormone; Cr – creatinine

developed and well nourished infant (BL 56 cm, P50; BW 4600 g, P50), with normal physical findings. Laboratory analyses showed a high serum level of 25(OH)D, milder hypercalcemia, decreased serum PTH level and significant hypercalciuria (Table 1). ECG, urotract ultrasonography image, serum level of inorganic phosphorus, creatinine, acid-base status of blood, liver and urine tests, and other standard analyses were normal. As D hypervitaminosis was confirmed, beside withdrawal of its administration and forced water intake, the infant was initiated on therapy with prednisolone (2 mg/kg per day), phenobarbitone (3 mg/kg per day) and furosemide (2 mg/kg per day). In order to compensate renal potassium loss caused by furosemide and prednisolone, KCl (2 mmol/kg oral daily) was also administered. In addition, ranitidine was administered as well, not only to prevent steroid ulcer but also for its negative effect on intestinal absorption of calcium. Having in mind the significance of mother's milk at this age, as well as a low concentration of vitamin D and a relatively low content of calcium and phosphorus, exclusive breastfeeding of the infant was further continued (Table 1).

After 17 days of treatment, the level of 25(OH)D in serum was still >400 nmol/L, while other laboratory indicators of vitamin D overdose normalized, except high calcium to creatinine ratio (mg/mg) in 24-hour urine (UCa/UCr) (1.8). On the next checkup that followed after 1.5 months of unchanged treatment, serum levels of 25(OH)D an PTH were considerably improved, hypercalciuria remained high, while other relevant laboratory findings were within normal limits (Table 1). Control urotract ultrasonography images were also normal so that prednisolone was slowly tapered and discontinued, while other therapeutic measures were continued. As control findings after the next months were within the referent values [4, 15, 16], except for slightly higher values of UCa/UCr (0.8), the treatment of the infant was continued with lower dosages of phenobarbitone and furosemide; 1.5 mg/kg daily for 30 days and then 1 mg/kg daily over the next 30 days. After 4 months of treatment all relevant laboratory findings were normal (Table 1), as well as urotract unltrasonography image, so that complete therapy was interrupted. During the whole period of observation the child's development was optimal and without clinical indicators either of vitamin D intoxication or adverse effects of the treatment. Serum level of 25(OH)D, calcium, phosphorus and PTH, UCa/UCr, urotract ultrasonography image and X-ray findings of the wrist 2 months later were within normal limits. Beside breastfeeding and complementary food introduced at 5 months, vitamin D3 (400 IU daily) was also included at age 7.5 months. On the last checkup at age 10 months, a complete infant's clinical status, serum levels of calcium and phosphorus, UCa/UCr and urotract ultrasonography image were also normal.

DISCUSSION

Due to the presence of melanin, a limited transport capacity of transcalciferin and photoisomerisation of cholecalciferol into inactive metabolites (lumisterol, tachysterol, suprasterol I and II and 5.6-trans-cholecalciferol), and permanent skin desquamation, vitamin D intoxication by exposure to sun is not possible [4, 9, 17, 18]. Contrarily, excessively high oral intake of vitamin D is followed neither by limited intestinal absorption and transport nor, in the victim's condition of excess by its over-high activation [4, 17]. These facts, as well as a highly deficient capacity of 25(OH)D and $1.25(OH)_2D$ inactivation and elimination, are the basis of the pathogenesis of vitamin D intoxication in its excessive oral and/or parenteral application [4, 17, 19]. The upper tolerance level of vitamin D daily oral intake is 1000 IU for age 6 months, 1500 IU from 6-12 months, 2500 IU from 1-3 years, 3000 IU from 4-8 years and 4000 IU for ages over 9 years [4, 9]. However, in some pathological conditions these values can be much lower or higher. Thus, for example, in chronic granulomatous and some malignant diseases, because of uncontrolled local hyperproduction of 1.25(OH)D, they are considerably lower, i.e. higher as is the case of vitamin D-dependent and resistant forms of rickets [4, 9, 18, 20]. Increased sensitivity to vitamin D is also present in the conditions of massive osteolysis, primary hyperparathyroidism and some familial forms of hypercalcemia and hypercalciuria [4, 9, 21]. Also, some medications modulate the biological effect of vitamin D. In this sense, negative influence have glucocorticoids and phenobarbitone that induce 24-hydroxylase, and thus inactivation and elimination of 25(OH)D and $1.25(OH)_2D$ [4, 18, 22].

Vitamin D intoxication occurs due to renal hyperproduction and excessively high calcitropic effect of $1.25(OH)_2D$ [4]. This metabolite of vitamin D, a derivate of $25(OH)_2D$ and by all characteristics a liposoluble hormone, stimulates in enterocytes and tubulocytes the synthesis of calcium channels, calbindin, Ca^{2+}ATP-ase, $3Na^+/Ca^{2+}$ ion-exchanger and $2Na^+/HPO_4^{2}$ cotransporter, thus enabling intestinal absorption and renal reabsorption of these ions as well as their transfer into circulation [1-5]. The optimal level of calcium and phosphorus in body

fluids is of essential significance for numerous metabolic processes, neuromuscular bioelectric transmission and mineralization of skeleton and teeth [1, 4]. However, in vitamin D intoxication exactly on this characteristic of 1.25 $(OH)_2D$ followed by increased balance and elevated levels of serum calcium and phosphorus its toxic effects are based [4, 23]. Due to hypercalcemia, the initial phase of intoxication is dominated by the signs of neuromuscular dysfunction (hypotonia, constipation, cardiovascular disturbances), while its prolonged combination with hyperphosphatemia is complicated with nephrocalcinosis and/or urinary lithiasis, as well as calcifications in blood vessels, myocardium and other soft tissues [4, 9, 13, 24]. Having in mind a wide differential diagnosis of hypercalcemia, hyperphosphatemia and hypercalciuria, a reliable confirmation of vitamin D overdose or intoxication requires the verification of 25(OH)D serum levels above 125 nmol/L [4]. This parameter has a key diagnostic significance as 25(OH)D, with half-life in circulation of about 15 days, and it is the best indicator of balance and effect of vitamin D in organism [4, 5, 19]. With the aim to prevent immediate and postponed complications of vitamin D intoxication, the basis of treatment involves the interruption of its intake, maximal restriction of calcium and phosphorus in food, forced diuresis and administration of glucocorticoids [4, 13, 23, 24]. In more severe intoxication, calcitonin and bisphosphonates are administered, and in the cases of life-threatening medically unmanageable hypercalcemia hemodialysis or exchange transfusions [13, 23].

Vitamin D intoxication of the presented infant was due to its excessive daily administration. Although the total dose of vitamin D taken during one month was about 200,000 IU, i.e. serum level of 24(OH)D >400 nmol/L, symptoms and clinical signs of intoxication were not registered. The explanation lies in the fact that the signs of vitamin D excess usually manifest just after 1-3 months, which is also supported by the value of calcemia in our patient which never exceeded 3 mmol/L [4, 18]. Beside standard measures intended for the treatment of this condition, with the goal of additional inactivation and better elimination of vitamin D active metabolites in our patient, we also administered phenobarbitone [4, 22]. In addition, we also introduced ranitidine which, by its suppressive effect on gastric secretion, besides preventing peptic ulcer within a longer-lasting glucocorticoid therapy, contributes to a lower intestinal absorption of calcium as well [25]. The administered therapy passed without adverse effects and with full effect.

In conclusion**,** vitamin D intoxication represents a potentially most serious pathologic condition followed by numerous immediate and later complications. If timely registered and adequately treated, including triple therapy with prednisolone, phenobarbitone and furosemide, possible complications can be prevented.

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Приказ одојчета с акутним тровањем витамином Д

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КРАТАК САДРЖАЈ

Увод Тровање витамином Д је ретко и потенцијално тешко патолошко стање узроковано превисоким билансом калцијума и фосфора. Приказујемо одојче које је доживело акутно тровање витамином Д, као и терапијске поступке којима су предупређене нежељене последице.

Приказ болесника Девојчица узраста од месец и по дана, рођена у термину, храњена само мајчиним млеком и без икаквих тегоба и поремећаја у физикалном налазу, примљена је на преглед због податка да је током претходног месеца грешком мајке унела око 200000 ИЈ витамина $Д_3$. Лабораторијске анализе су показале висок серумски ниво *25(OH)D* (>400 *nmol/l*) и калцијума (2,72 *mmol/l*), снижене вредности *PTH* (6,6 *pg/ml*) и висок однос калцијума и креатинина у мокраћи (1,6), док су остали налази, укључујући и ултразвучни изглед мокраћног тракта, били нормални. Лечење, које се заснивало на обустави даљег уноса витамина Д, појачаном појењу детета водом, као и двомесечној примени преднизолона и четворомесечној примени фенобарбитона и фуросемида, довело је до потпуне нормализације лабораторијских показатеља тровања витамином Д, те спречило нежељене ефекте интоксикације.

Закључак Уз благовремено препознавање и одговарајуће лечење, укључујући примену преднизолона, фенобарбитона и фуросемида, нежељене последице акутног тровања витамином Д могу се предупредити.

Кључне речи: интоксикација витамином Д; одојче; лечење

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