

HYPERVITAMINOSIS D: REPORT ON THREE PATIENTS

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Vitamin D, a fat-soluble vitamin, has been employed in the prevention and treatment of rickets.^{1,2} However, serious poisoning can result from overdosage.^{3,4} Sustained daily intake of as little as 4000 IU in adults and 1800 IU in children has been reported as toxic.^{5,6}

In the 1950s, a clinical study in England revealed a good number of cases of hypercalcemia, some of which may have been linked to excessive intake of vitamin D in fortified foods. However, the incidence of hypercalcemia dropped in 1957 after reducing the vitamin D content in fortified milks.^{7,8} Jacobus et al. reported eight cases of hypervitaminosis D, caused by excessive fortification of milk with vitamin D at one dairy.⁹ The clinical manifestations appear after weeks or even months, and hypercalcemia is a constant finding in the presence of toxic symptoms.¹⁰ To the best of our knowledge there has been no reported case of vitamin D intoxication in the Middle East in the past 10 years.

Case 1

An 8-month-old Egyptian girl was admitted with gastroenteritis. She was moderately dehydrated, had generalized hypotonia and a hepatomegaly 3 cm below the right costal margin. Laboratory investigations of serum revealed a urea of 8.1 mmol/L, creatinine of 71 μ mol/L, albumin of 32 g/L, calcium of 3.94 mmol/L, phosphorus of 1.16 mmol/L, and alkaline phosphatase of 109 IU/L. After administration of IV fluids, the blood urea and serum creatinine had normalized, but the serum calcium was still high at 4.0 mmol/L, and serum phosphorus was 1.48 mmol/L with a serum albumin of 30 g/L.

Approximately three months earlier, the patient had been given three injections of Vitamin D 600,000 IU over a period of six weeks for developmental delay. Frusemide and extra fluids were added, and 24 hours later, as the serum calcium was still elevated at 3.93 mmol/L, hydrocortisone 20 mg/kg/day was added, resulting in a fall

of the high plasma calcium levels in 72 hours. Prednisolone 1 mg/kg/day and a high fluid intake was continued for three weeks. The vitamin D preparation was discontinued. The patient made an uneventful recovery and the serum calcium eight months later was 2.54 mmol/L. This case demonstrates that the cause of hypercalcemia was the overdose of vitamin D given earlier. The clinical effectiveness of glucocorticoids in the treatment of vitamin D intoxication has been attributed primarily to a reduction of intestinal absorption of calcium.¹¹ Hypercalcemia has been reported to persist up to 14 months after vitamin D has been stopped.¹²

Case 2

A 3½-month-old Indian boy was admitted for evaluation of weight loss, poor feeding and hepatomegaly. Examination revealed an enlarged smooth liver 5 cm below the right costal margin. His weight was in the 5th percentile, and length and head circumference were in the 25th percentile. The biochemistry of a serum sample was as follows: urea 2.8 mmol/L, creatinine 35 μ mol/L, calcium 3.64 mmol/L, phosphorus 1.9 mmol/L, alkaline phosphatase 125 IU/L, and albumin 37 g/L. There was also a mild increase in the serum transaminases. An ultrasound of the abdomen showed diffuse uniform enlargement of the liver. Urine for vanillylmandelic acid was negative. On close questioning, the mother, who is a nurse, revealed that during her 8th month of pregnancy she was given vitamin 50,000 IU/day (ergocalciferol) with calcium sandoz tablets. She took the capsules until she delivered and then approximately two weeks after her delivery, she again took vitamin D 50,000 IU once daily for recurring backache, this time without medical advice. The baby was only on breast milk and took no vitamin D preparation. The mother's plasma 25(OH)D levels were 829 nmol/L (reference range 25-104 nmol/L), with the serum calcium of 3.61 mmol/L, serum phosphorus of 1.21 mmol/L, and alkaline phosphatase of 82 IU/L.¹³ Vitamin D intake was stopped and the baby was given artificial formula. The infant's serum calcium normalized in 14 weeks. Goldberg et al.¹⁴ reported a case where large doses of vitamin D were given to the mother, resulting in the appearance of 25-hydroxycholecalciferol in her milk and causing hypercalcemia in her baby.

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Case 3

A four-year-old Arab boy with chronic renal failure was on medical management which included one alpha hydroxy vitamin D and calcium carbonate. He was admitted with vomiting, drowsiness, low grade fever and dehydration. A septic work-up including a lumbar puncture was negative. Laboratory investigations revealed blood urea 16.1 mmol/L, serum creatinine 292 μ mol/L, serum calcium 3.48 mmol/L, serum phosphorus 1.52 mmol/L, alkaline phosphatase 248 IU/L, serum albumin 29 g/L, and serum parathormone 10.47 pmol/L (normal values 1.26-7.58 pmol/L). Further enquiries revealed that while his mother was in the hospital, his 11-year-old sister had been responsible for administering his medicines. Over a period of 10 days, the patient was given 40 μ g of one alpha hydroxy vitamin D. It is obvious that vitamin D overdosage was responsible for the clinical picture. The symptoms subsided after administration of IV fluids and frusemide. Vitamin D and calcium carbonate were stopped for 10 days. The calcium fell slowly and on the 12th day it was low normal, but the serum phosphorous was a little higher at 2.6 mmol/L.

In vitamin D overdosage, production of parathormone ceases, so the phosphaturic effect of vitamin D is overridden by the reduction in parathormone secretion. In our case, the parathormone secretion was elevated. In chronic renal failure the parathormone levels may be elevated due to secondary hyperparathyroidism. However, if the chronic renal failure is of long duration, the chronic parathyroid stimulation may result in autonomous parathormone secretion and hypercalcemia, but the serum calcium in our patient fell after the withdrawal of vitamin D and calcium.¹⁵

Discussion

Excess vitamin D leads to increased absorption of calcium from the gastrointestinal tract and enhanced bone resorption, as well as a consequent loss of renal concentrating ability. If a child presents initially with loss of appetite, vomiting, polyuria or irritability associated with increased concentration of calcium, a number of metabolic and systemic diseases should be considered. Hypervitaminosis should be suspected when some of the above symptoms develop in a patient receiving vitamin D. Primary hyperparathyroidism should also be given prime consideration. Although many of the features also occur with primary hyperparathyroidism, the serum phosphorous and alkaline phosphatase levels in hypervitaminosis D are normal, whereas in the former disorder the serum phosphate is usually low, associated with marked elevation of alkaline phosphatase. If the patient has dysmorphic features (epicanthic folds, wide mouth, thick lips), developmental delay, aortic stenosis and has associated hypercalcemia, it fits well with Williams syndrome. It is

now rare,¹⁶ although the incidence was reported to be higher when fortified milks were used.⁷ Familial hypocalciuric hypercalcemia, a disorder with autosomal dominant transmission, should also be considered in the differential diagnosis. These patients have a symptomatic hypercalcemia without hypercalciuria. The diagnosis is made by the pattern of hypercalcemia in the family and the low urine calcium excretion.¹⁷ The occurrence of hypercalcemia in malignant diseases may be due to secondary deposits in bone with local destruction, leukemia being the most common in children. It also may occur by a humorally mediated mechanism which leads to the production of PTHrp or some other humoral substance, as in multiple myeloma, breast cancer, etc., which stimulates bone resorption. The other causes of vitamin D-induced hypercalcemia are miliary tuberculosis,¹⁸ and sarcoidosis. These granulomatous disorders have accompanying hypercalcemia because of inappropriate 1,25(OH)₂D synthesis by macrophages.^{1,19}

When unusual symptoms develop in a patient receiving vitamin D, toxic hypervitaminosis D should be suspected. In the event of discontinuing treatment with vitamin D, a low-calcium diet and administration of extra fluids with loop diuretics is advised. However, severe acute hypercalcemia needs urgent administration of steroids. Pharmacological doses of hydrocortisone result in a fall of high plasma calcium levels in almost all cases, except in primary hyperparathyroidism.¹¹ It should be the responsibility of the physician initiating the treatment to ensure that adequate monitoring is undertaken. In diseases which require very high doses of vitamin D, 1,25(OH)₂D₃ should be used. It has the advantage of having a much more rapid onset of action and a rapid fall (within days) after its withdrawal, due to its short half-life. An increased awareness of the potential seriousness of the problem among doctors will result in a decline in the morbidity from vitamin D poisoning, and prohibition of over-the-counter sales (case 2) should be strongly encouraged and advocated. An additional measure should be the education of mothers and mothers-to-be in the hazards of using over-the-counter medicaments. If the mother is forewarned, she may be less likely to use these dangerous substances. After one year of follow-up there has been no recurrence of hypercalcemia after the discontinuance of vitamin D.

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