CASE REPORT

Vitamin supplementation: unmonitored prescription can be dangerous

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SUMMARY

A 75-year-old illiterate woman presented with severe dehydration and altered sensorium. Investigations revealed severe hypercalcaemia with deranged renal function. ECG showed changes of hypercalcaemia and hypokalaemia. Since the patient was aged and had an acute presentation, malignancy was considered as the probable aetiology. Following prompt supportive treatment, she regained consciousness on the second day of admission. Later on, she provided a history of daily intake of vitamin D₃ (cholecalciferol) sachet (60 000 IU/sachet) for the last 2 weeks, which had actually been prescribed to be taken once per week. Further investigation revealed very high levels of serum vitamin D. This case has been presented to reiterate the importance of known, but often overlooked facts: ECG can provide an important clue regarding the underlying metabolic encephalopathy; mega-dose supplementation of these seemingly innocuous vitamins should be monitored; and treatment regimes should be properly explained and monitored in elderly people.

BACKGROUND

It is a common misconception that 'vitamins' are beneficial for health and cannot be potentially toxic.¹ Fat-soluble vitamins are essential at physiological levels, but can lead to severe toxicity at high doses.² The risk multiplies many folds, if their prescriptions are not monitored, particularly among the elderly population. Here we describe a case where vitamin D was prescribed in high doses to an old illiterate woman, who instead of taking it once per week kept taking one sachet per day. She presented with life-threatening hypercalcaemia, but recovered promptly on supportive treatment.

CASE PRESENTATION

A 75-year-old woman presented with weakness, lethargy, headache, increased frequency of micturition, constipation, nausea for 2 weeks and confusion, gradually decreasing sensorium and urinary incontinence for 5 days. There was a history of fall with injury to head 4 weeks previously, but with no loss of consciousness and she was doing well after the episode. She was a diagnosed case of osteoporosis on regular treatment. There was no history of vomiting, seizure, fever, diabetes, hypertension or any other chronic illness. On examination, the patient was stuporous, irritable, Glasgow Coma Scale of 8/15 and severely dehydrated. Blood pressure was 190/100 mm Hg, pulse 92/min, temperature 97.8°F, oxygen saturation (SpO₂) 98% on room air. There was no pallor, icterus, lymphadenopathy

or clubbing. On examination of the nervous system, pupils were found to be constricted with sluggish reaction, power was 4/5 in all four limbs, tone was reduced, deep tendon reflexes were normal, plantar reflex was bilaterally withdrawal and neck rigidity was present. Fundus examination was normal, with no papilloedema. On abdominal examination, there was diffuse tenderness; however, there was no guarding, and bowel sounds were present. Rest of the systemic examination was normal.

INVESTIGATIONS

On investigation, she had leucocytosis (total leucocyte count 21 000/mL, 90% polymorphs) with haemoconcentration (haemoglobin 14 g/dL, packed cell volume 48%). There was severe hypercalcaemia (17.3 mg/dL; 9–11 mg/dL), hypernatraemia (150 mEq/L; 135–145 mEq/L), hypokalaemia (2.6 mEq/L; 3.5–5 mEq/L) with normal phosphate (4.1 mg/dL; 2.5–4.5 mg/dL). Other investigations were: urea 204 mg/dL (17–30 mg/dL), creatine 3.2 mg/dL (0.7–1.2 mg/dL), uric acid 21.2 mg/dL (4–8 mg/dL); ECG had changes of hypercalcaemia and hypokalaemia (figure 1); urine routine had 20–25 pus cells per high power field with uric acid crystals. Chest radiographs, liver function test, arterial blood gas, ultrasonography of abdomen were normal. Non-contrast CT head showed age-related atrophy. Cerebrospinal fluid (CSF) examination showed raised protein levels (147 mg/dL; 15–60 mg/dL), but no cells. Upper gastrointestinal endoscopy had diffuse oesophagitis. Ionised calcium was raised (1.86 mmol/L; 1.16–1.32 mmol/L), 24 h urinary calcium was very high (9220 mg/day; 100–300 mg/day), but serum parathyroid hormone (PTH) was normal (34.7 pg/mL; 15–68 pg/mL). Level of 25-hydroxy vitamin D was very high (>160 ng/mL; toxicity with >100 nm/mL). Thyroid function tests and serum ACE levels were normal and HIV was non-reactive. Her bone marrow aspiration and myeloma workup were normal. Breast and thyroid examination were normal. Contrast-enhanced CT neck, chest and abdomen were performed which had no significant pathology.

TREATMENT

The patient was given rapid saline infusion, intravenous calcitonin, intravenous pamidronate (extended infusion as renal functions were deranged) and empirical antibiotics for urinary tract infection.

OUTCOME AND FOLLOW-UP

By the second day of admission, her sensorium started improving, and by fourth day, she was

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Figure 1 ECG showing prolonged PR interval (210 ms) and short QTc interval (280 ms) due to hypokalaemia and hypercalcaemia respectively. It also has ST depression and U waves, features of both of them.

conscious and oriented. On the fourth day, serum calcium was 12.5 mg/dL; serum sodium and potassium were normal; urea, creatine and uric acid were 140, 1.1 and 6.3 mg/dL, respectively. On regaining consciousness, she gave a history of daily intake of vitamin D₃ (cholecalciferol) (each containing 60 000 IU) for last 2 weeks. Apart from that, she was also given an injection of vitamin D (6 lakh IU/injection) 1 month previously and was prescribed combination pill of calcium and vitamin D for daily intake. The patient was discharged on a bisphosphonate and a diet low in calcium and phosphate was advised. When the patient came for follow-up 2 weeks after discharge, her vitamin D level was still very high (114 ng/mL), but serum calcium (9 mg/dL; 9–11 mg/dL) and kidney function tests had reverted to normal. She was educated about the danger signs of hypervitaminosis and asked to review again with a fresh vitamin D report after 1 month.

DISCUSSION

Vitamin D is a prohormone, and has an important role in bone mineral metabolism. It is now also recognised to have a role in cell differentiation, cell growth and modulation of immune system. The daily requirement of vitamin D is about 200–600 IU.³ The current upper intake level in both Europe and North America is 50 µg/day (2000 IU/day).⁴ However, evidence indicates that prolonged intake of even 10 000 IU/day of vitamin D₃ likely poses no risk; it could be because the synthesis of the active form, 1,25 (OH)₂D₃ is tightly regulated. Because of this wide therapeutic index, vitamin D toxicity is extremely rare. However, the dose of vitamin D which will produce toxicity in an individual is variable, which could be due to vitamin D receptor polymorphisms.^{4,5}

Symptoms of vitamin D toxicity depend on age of the patient, level and duration of hypercalcaemia. Severity of hypercalcaemia is defined as, <12 mg/dL is mild, between 12 and 14 mg/dL is moderate and >14 mg/dL is severe. Patients with mild-to-moderate hypercalcaemia are usually asymptomatic, particularly if it does not develop rapidly. Hypercalcaemia leads to peptic ulcer, oesophagitis, gastritis which further leads to nausea, vomiting, pain abdomen; decrease bowel motility and tone leading to constipation; pancreatitis. It can also produce nephrogenic diabetes insipidus leading to polyuria, polydipsia, weakness and dehydration.⁶ Other renal manifestations are chronic interstitial nephritis; hypernatraemia, hypomagnesaemia, hypokalaemia. Latter is due to distal renal tubular acidosis leading to potassium wasting, which sometime can be severe.⁶ It acts as a direct central nervous system (CNS)

depressant leading to confusion, drowsiness, stupor or coma; other CNS manifestations are headache, psychiatric symptoms, hypotonia, depressed deep tendon reflexes, raised CSF protein with albumin-cytological dissociation.⁷ Hypercalcaemia can lead to ECG changes (short QT interval, QRS widening, PR elongation, ST changes and U wave), arrhythmias (bradyarrhythmia, blocks) and cardiomyopathy. The patient can be in hypertensive crisis due to direct calcium mediated vasoconstriction or renal hypertension. When calcium phosphate is >60, calcium phosphate crystals start getting deposited in soft tissue leading to metastatic calcifications: painful periarticular calcinosis, vascular calcification, nephrocalcinosis, renal stone, band keratopathy and conjunctival calcification.

The characteristic laboratory findings of vitamin D intoxication are hypercalcaemia, hyperphosphataemia, elevated alkaline phosphatase, low PTH and high vitamin D level, and is typically associated with hypercalciuria. Calcitriol (1,25(OH)₂D₃) has a short half-life; hence hypercalcaemia due to its toxicity usually lasts only 1–2 days.⁸ In contrast, hypercalcaemia induced by preparations which get deposited in fat have a half-life of up to 2 months (vitamin D₃ and vitamin D₂) and takes longer to settle; a more aggressive therapy is needed for their management.⁸ The hypercalcaemia can persist for up to 6 months in such cases.

It is a common practice to prescribe vitamin D for non-specific body ache, back and leg pains; they are partly believed to be because of vitamin D deficiency. Self-medication with over the counter vitamin D preparations is also very common. Moreover, if treatment is not monitored in elderly, it can lead to toxicity.

Learning points

- ▶ Hypercalcaemia should always be kept in differential diagnosis of patients presenting in emergency with polyuria, polydipsia, vomiting, dehydration, azotaemia and encephalopathy.
- ▶ ECG can be a clue to important metabolic disturbances.
- ▶ Treatment with high-dose vitamin preparations should be monitored. Physicians must keep watch for their potential toxic effects.
- ▶ Treatment in elderly should be monitored by fellow attendants.
- ▶ The patient with vitamin D intoxication should be kept under close follow-up, till its level returns to normal.

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