Title - Extreme Hypercalcemia Due to Accidental Vitamin D Intoxication

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Consent from the child's parents was gained for publication of this report.

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Learning points

1. Treatment of hypervitaminosis D involves cessation of vitamin D, hyperhydration, ~~furosemide~~, glucocorticoid and low calcium-containing diet, aiming to normalize hypercalcemia quickly by reducing intestinal calcium absorption, increasing renal calcium excretion and reducing endogenous production of vitamin D.
2. Vitamin D3 intoxication is likely to occur when 25(OH)D >375nmol/L (150ng/ml). Complications of vitamin D3 intoxication include prolonged hypercalcaemia, dehydration, failure to thrive, abdominal and bone pain, renal calculi and nephrocalcinosis.
3. Vitamin D is stored in the liver. Weeks to months may be required for serum levels to normalize. Rebound hypercalcemia can occur after cessation of acute treatment.
4. This case highlights the potential for inadvertent gross over-dosage of widely accessible and unrestricted preparations of 25(OH)D to the general public.

Case Report

An 8-month-old boy was brought to a metropolitan emergency department (ED) with a two-month history of progressive lethargy, feeding difficulties, weight loss 760grams, inability to sit unsupported, and irritability. He was breast fed with addition of solids at 5 months. For this presentation he had been reviewed at same metropolitan ED and twice by a General Practitioner, with reassurance by doctors that the symptoms were attributable to a viral illness with associated gingivostomatitis. His past medical history and family history, were unremarkable, and was not reported to be taking any medications.

On examination he was pale, lethargic and irritable; weight 7.05 kg (3rd centile), length 69.5 cm (37th centile), head circumference 43.5 cm (20th centile). General vital signs

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were unremarkable. He had sunken eyes, dry lips and tongue, cool peripheries, generalised hypotonia, and was unable to hold his head upright or sit unassisted. Spontaneous movements were symmetrical but weak. Deep tendon reflexes were intact. His oral cavity demonstrated multiple small white gingival lesions. With this exception, ear, nose and throat, cardiorespiratory and abdominal examinations were normal.

Investigations revealed extreme hypercalcaemia 5.3 mmol/L (NR 1.9-2.7), phosphate 1.42mmol/l (NR 1.3-2.3), parathyroid hormone 0.7 pmol/L (NR 1.3-6.8), and mild renal impairment, urea 7.9 mmol/L (NR 1.6-6.6) and creatinine 46 umol/L. His electrocardiogram showed sinus rhythm with a short QT interval. Urine calcium creatinine ratio was significantly elevated 5.06mmol/mmol (range <0.7), and renal ultrasound demonstrated bilateral nephrocalcinosis.

Hypercalcemia with suppressed PTH suggested the likelihood of vitamin D intoxication. Upon specific questioning, it was revealed that an Australian preparation of vitamin D, 1000 units per day (25(OH)D) had been initiated 4 months prior following a mild illness with bronchiolitis, with escalating doses due to perceived parental concerns about the baby's poor growth and feeding. The formulation was thought to be inadequate as the baby's health was not improving, so another preparation was purchased online from the United States. As the baby became progressively weaker, the number of drops administered increased; reportedly 4 to 5 drops per day of 5000 units/drop of 25(OH)D, thus a total of 25000 units/day, given over the 4 weeks prior to ED presentation. Serum 25(OH)D was 1634 nmol/L (NR 50-160), confirming a diagnosis of hypervitaminosis D. The white gingival lesions were thought to be calcium deposits.

The infant was treated with intravenous hyper-hydration (Plasmalyte-148 + 5% glucose at 150ml/kg/day) and hydrocortisone, and serum calcium slowly improved, as did his alertness, mood and breastfeeding. The parents chose to continue breastfeeding rather than use an advised low-calcium formula. Complications from hyper-hydration included peripheral oedema and hypokalaemia, requiring treatment with frusemide and potassium replacement. The baby was discharged home on weaning oral hydrocortisone on day 10.

Poor feeding and recurrence of moderate hypercalcaemia (serum calcium 2.8 mmol/L) necessitated re-admission 5 days later and a brief period of nasogastric feeds until breastfeeding had improved. Serum 25(OH)D levels continued to fall (Table 1), and growth improved (Figure 1). The baby was developmentally appropriate for chronological age at outpatient review 3 months after discharge.

Discussion

The role of vitamin D in maintenance of bone health has been published in recent years both in news media and medical literature. A wide range of vitamin D supplements are available for purchase in pharmacies and on-line, to the general population. Potential toxicity of high dose vitamin D is not well recognized or understood in the general community. An Australian Health Survey found that 5% of Australian adults take supplemental vitamin D¹, and an American study of reports to poison centers demonstrated a 1600% increase in accidental vitamin D exposures between 2000 and

2014², suggesting an increased presence of these supplements in American households. Government restriction on vitamin D testing has been imposed in Australia, due to unnecessary testing of essentially normal populations. Recent published guidelines for vitamin D aim to address these issues³.

Vitamin D sufficiency is defined as a blood level $>50\text{nmol/l}$, insufficiency $30\text{--}50\text{nmol/l}$ and deficiency $<30\text{nmol/L}$ ⁴. Supplementation for high risk groups and treatment for those who are deficient has become standard care³, but injudicious use of vitamin D with unrestricted availability of high doses and misinformation as to its postulated benefits have created serious potential for a rise in vitamin D intoxication in all age groups.

Vitamin D supplementation is now advised for all pregnant women and for all infants, at a dose of 400 units per day⁵. This is in stark contrast to our patient who received approximately 25,000 units per day for several weeks, resulting in hypercalcaemia and hypervitaminosis D.

Vitamin D levels $>250\text{ nmol/L}$ are of concern but symptoms are uncommon below a level of 375 nmol/L (150ng/ml), a level suggested to define intoxication^{4,6}. Vitamin D intoxication is reported very rarely on standard treatment doses of $25(\text{OH})\text{D}$. Most cases of intoxication are due to accidental overdose as part of a prescribed regime, formulation mishaps, or self-initiated supplementation⁶. Potential complications of vitamin D intoxication are serious, including renal failure requiring hemodialysis⁷. Death attributed to acute pancreatitis induced by hypercalcemia has been described in one child⁸.

Management challenges are exemplified in our patient, including fluid overload, hypokalemia, and rebound hypercalcemia. His response to corticosteroid was typical, involving reduction in calcium absorption from the gut and enhanced renal excretion of calcium. This process is slow with a lag period of weeks until hepatic vitamin D stores are reduced. Intravenous bisphosphonate can be utilised for rapid reduction in calcium but was not deemed necessary in this infant. Calcitonin use is limited by tachyphylaxis and was not considered. For mothers wanting to continue breastfeeding, this can be facilitated by expressing and topping up with a low calcium and vitamin D free formula such as Locasol, although this was declined in this case.

In our case, the child's parents were very surprised that the vitamin D was responsible for his symptoms and had no idea that it could be harmful. As with all cases of accidental harm, it was especially important to support the family through the stressful experience of their child's illness, the realisation of the cause for illness and the associated feelings of guilt, as well as the importance of open discussion surrounding use of supplemental medicines.

In an era where parents and patients are turning to the internet and online-sources for health-information, this case report highlights the potential for gross over-dosage of widely accessible and unrestricted preparations of vitamin D to the general public. This case is novel in that intoxication was not iatrogenic, rather due to misplaced parental concern and general lack of public awareness of the harm of vitamin D over-dose.

Multiple Choice Questions

1. Vitamin D3 intoxication is rarely seen below what level of 25(OH)D?
  - A. 200 nmol/L
  - B. 400 nmol/L
  - C. 800 nmol/L
  - D. 1000 nmol/L
  - E. 1200 nmol/L

Answer: A. Levels of >200nmol/L have been reported in cases of children with rickets but the ensuing hypercalcaemia was asymptomatic. Suggested definition of Vitamin D3 intoxication is 25(OH)D >375nmol/L. The highest reported levels have been >2000 nmol/L in children who received an erroneously manufactured fish-oil supplements.

2. Treatment of vitamin D intoxication with glucocorticoids results in the following:
  - A. Reduced intestinal absorption of calcium
  - B. Reduced renal reabsorption of calcium
  - C. Reduced endogenous production of calcitriol
  - D. A and B
  - E. A, B and C

Answer: E. Glucocorticoids suppress intestinal absorption and renal reabsorption of calcium, as well as conversion of calcifidiol to calcitriol in the kidneys.

3. Which of the following diuretics are indicated in the treatment of hypercalcaemia induced by vitamin D intoxication?
  - A. Frusemide and hydrochlorothiazide
  - B. Frusemide alone
  - C. Frusemide or hydrochlorothiazide
  - D. Frusemide and amiloride
  - E. Amiloride alone

Answer: B. Frusemide's effects on the Na-K-2CL transporter in loop of Henle result in reduced calcium reabsorption and desired urinary calcium loss. Thiazide diuretics have an opposite effect, increasing reabsorption of calcium in the distal convoluted tubule. Amiloride's effects on the sodium channels of the distal nephron also result in increased calcium reabsorption.

Alternative MCQ 3

3. Which is true in regards to diuretic use in the management of hypercalcaemia from vitamin D intoxication?
  - A. Hydrochlorothiazide can be used to increase renal calcium excretion
  - B. Frusemide should be routinely used to increase renal calcium excretion
  - C. Frusemide is ineffective as it results in increased calcium reabsorption

- D. Frusemide results in reduced calcium reabsorption and desired calcium loss, however should be used with caution due to the dehydration present in severe hypercalcaemia
- E. Frusemide should be routinely used in conjunction with intravenous potassium replacement

Answer: D. Frusemide's effects on the Na-K-2CL transporter in the loop of Henle result in reduced calcium reabsorption and desired urinary calcium loss. However, it can be hazardous due to the dehydration that occurs with severe hypercalcaemia. It may be introduced to treat complications of hyper-hydration, but not as routine therapy to lower serum calcium. Thiazide diuretics increase calcium reabsorption in the distal convoluted tubule and are not recommended for hypercalcaemia.

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Table 1 - Progression of hypervitaminosis D and hypercalcaemia.

Weeks after discharge	0	1	3	12	20	53
Serum 25(OH)D (range 50-160 nmol/L)	1634	1490	1178	389	384	201
Serum calcium (range 2.1-2.6 mmol/L)	5.3	4.36	2.87	2.6	2.69	2.66

Figure 1 - Growth Chart

Growth Chart Figure1_300.tiff

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