AIMN review
Australasian Institute for Medical Nutrition
www.aimnutrition.org
SEP 2016

High Dose Vitamin D3 (Colecalciferol)

Some clinical questions answered

Introduction

Vitamin D has received considerable attention in recent medical literature because of widespread deficiency being associated with numerous diseases. Massive doses of Colecalciferol are represented in the literature, up to 300,000 – 600,000 IU administered intramuscularly per dose. Originally these high doses were used in community settings to treat/prevent rickets in disadvantaged paediatric populations[1], but more recently such doses have appeared in the literature for prophylaxis of Vitamin D deficiency in elderly populations[2].

There is considerable debate about what constitutes a safe maximum dose. While single large doses are generally known to be safe, Vitamin D can become toxic if it is taken from more than one source - toxicity is cumulative. This has produced a wide range of opinions with maximum safe i.m. dose recommendations for D3 ranging from 100,000 IU – 600,000 IU. The higher the dose given, the less frequently it can be given. Very high doses are intended to be given once every 6 months or once per year. While the risk is small, doses of 600,000 IU carry a higher risk of hypercalcaemia than doses of 300,000 IU. The risk is increased if the patient regularly ingests significant Vitamin D from oral sources (especially supplementation).

Despite this, the risk is small and there is now a growing body of literature recommending very high doses in elderly patients[2].

In Vitamin D deficiency large doses of Vitamin D, 3,000 – 5,000 IU daily for 6 – 12 weeks may also be given orally[3], or even larger oral doses given less frequently. Vitamin D administered by any route has cumulative potential for toxicity and may become toxic after a person's vitamin D stores are replete.

In general intramuscular administration is preferable for severely deficient patients, those with poor digestion/assimilation or those who are unlikely to maintain oral medication.

> *"The pharmacokinetics of large doses of Colecalciferol are well described and the safety of high doses (both oral and intramuscular) is well established."*

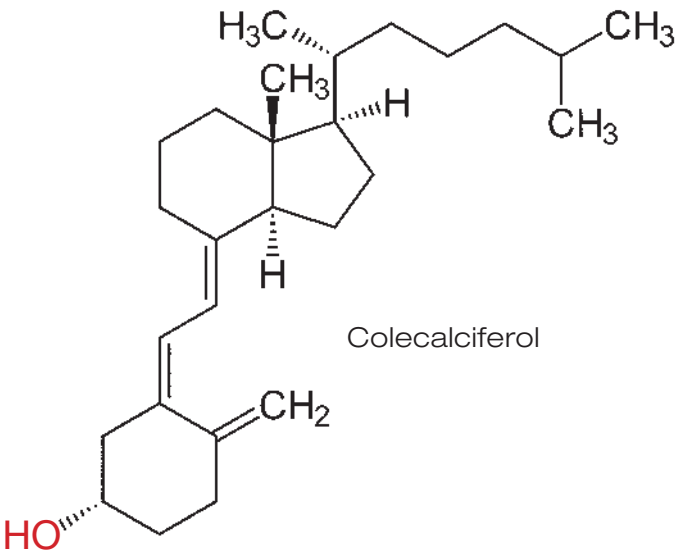
For oral supplementation the two main types of Vitamin D are D3 (Colecalciferol) and D2 (Ergocalciferol). Neither are "active" in the body until they are converted to the transport hormone form calcidiol and then to the active hormone form calcitriol. D3 is more effective than D2. There are several reports in the literature stating that ergocalciferol is 2–3 times less effective than Colecalciferol and remains active for a shorter time[4].

The pharmacokinetics of large doses of Colecalciferol are well described and the safety of high doses (both oral and intramuscular) is well established. *"100,000 IU Colecalciferol (oral) is a safe, efficient, and cost-effective means to increase calcidiol concentrations in the elderly. From this study we can safely recommend 100,000 IU Colecalciferol dosed every 2 mo in persons with moderate baseline calcidiol concentrations. However, in those persons with baseline calcidiol concentrations < 20 ng/mL, even this large dose will not adequately raise their calcidiol concentrations."*[5]

1. Colecalciferol: What is it?

Colecalciferol, or Vitamin D3 is "natural" vitamin D formed in skin by the action of sunlight (UV) on 7-dehydrocholesterol.

"Vitamin D3 and D2, made in the skin or ingested, are transported to the liver and metabolised to 25-hydroxyvitamin D *(calcidiol - 25(OH)D)*, the major circulating form. Further hydroxylation occurs in the kidney to form the highly biologically active 1,25-dihydroxyvitamin D *(calcitriol - 1,25-$(OH)_2D$)."*



Colecalciferol

2. Vitamin D deficiency is common

Normally most Vitamin D is manufactured in the skin by exposure to sunlight. In cold climates, or in any situation where people are predominantly indoors or have large amounts of their skin covered, Vitamin D deficiency is a serious risk. *"A significant number of Australians are deficient in vitamin D — it is a fallacy that Australians receive adequate vitamin D from casual exposure to sunlight."*[3]

> *"A significant number of Australians are deficient in vitamin D — it is a fallacy that Australians receive adequate vitamin D from casual exposure to sunlight."*

Even in warm sunny climates Vitamin D deficiency can be a significant problem. A study conducted in India[6] looked at the difference in 25(OH)D concentrations in urban vs. rural dwelling people. *"...with longer sunshine exposure subjects residing in rural area had better mean 25(OH)D values than that of urbans. However, 70% of them were still vitamin D deficient. These facts indicate the need for the countrywide vitamin D food fortification program irrespective of rural or urban setting."*

Groups most at risk of Vitamin D deficiency include institutionalized, the elderly, people with dark skin, people who are veiled and anybody who spends most time indoors or avoids sunlight.

3. How and when does Vitamin D become toxic?

Colecalciferol is not active. It must be metabolised into the active form calcitriol. It is the active form that becomes toxic if its concentration gets too high. Vitamin D as Colecalciferol is stored in fat and muscle and slowly released, particularly during winter. In vitamin D-deficient patients, it is necessary to replete the vitamin D stores.

Massive doses of Colecalciferol can be given in very deficient patients because Colecalciferol has extensive tissue distribution in fat and muscle (high storage) and long half life (approx. 2 months)[7] with slow conversion to circulating and active forms.

It becomes toxic if dosing is continued:
- when storage is full or near full
- when breakdown cannot keep up with dosing

Toxicity symptoms:

"Potential consequences of vitamin D toxicity include hypercalcemia, renal stones and soft tissue and vascular calcification. Clinical symptoms associated with hypercalcemia include nausea, vomiting, increased thirst and depression. Serum concentrations of 25(OH)D above 220 nmol/L have been associated with hypercalcemia."[8]

Is there a risk of hypercalcaemia?

If calcitriol (active dihydroxy hormone) levels become too high there is a significant risk for hypercalcaemia. Overall the risk of this occurring with Colecalciferol administration is small but the risk does increase with very large doses, especially if the patient is taking Vitamin D from other sources.

"... 100,000 to 300,000 IU by mouth or per injection have been used once every 6 months or once yearly because of the ease of administration, obviating the need of checking compliance (3 studies cited). In these studies, hypercalcemia was not observed. However, hypercalcemia has been observed in an older patient with a dose of 2,000 IU/d (study by Johnson et al[9]) and in one patient receiving a single oral dose of 600,000 IU (case cited by Sebert et al[10])."[11]

> *Groups most at risk of Vitamin D deficiency include institutionalized, the elderly, people with dark skin, people who are veiled and anybody who spends most time indoors or avoids sunlight.*

In the Johnson et al. study cited above the study participants received active Vitamin D (calcitriol - 1,25-$(OH)_2D$), 2,000 IU per day, not Colecalciferol. 2 out of 63 participants in this study developed hypercalcaemia.

With Colecalciferol administration the risk of hypercalcaemia is small. From Diamond et al:

"Higher doses of 100,000–300,000 IU have been administered orally or intramuscularly 6-monthly or once-yearly quite safely without causing hypercalcaemia or renal impairment. Also, in one study, graded oral dosing of vitamin D3 up to 50,000 IU daily for 8 weeks did not cause hypercalcaemia. In another, 50,000 IU of oral vitamin D2 was administered twice-weekly to 12 patients with vitamin D deficiency (serum 25OHD, < 35nmol/L) for 5 weeks (total dose, 500,000 IU). These patients also received 1,000mg of calcium orally. At 10 months, their serum 25OHD level had increased significantly by 145% (P<0.001), with the urine calcium/creatinine excretion index increasing by 20% above baseline (P<0.01) but still remaining within the normal range. Importantly, the serum calcium level did not change significantly... In our study, a single annual intramuscular injection of 600,000 IU Colecalciferol was administered to 50 vitamin D-deficient participants. The therapy was effective, with normalisation of serum 25OHD levels and maintenance of a level well above 50nmol/L at 12 months. This result was achieved with very little change in serum calcium levels and no deterioration in renal function, although there was a progressive increase in urine calcium excretion indices. The latter usually suggests an obligatory calcium loss, and may have been affected by oral calcium intakes. These findings raise the possibility of hypercalciuria."[2]

Is there a risk of Oxalate stone formation?

If there is a risk of hypercalciuria then there is potentially a risk of oxalate formation. Oxalate formation or the formation of frank stones has not been reported in high dose Colecalciferol studies.

"Hypercalciuria can be associated with vitamin D toxicity and may contribute to the development of nephrolithiasis, although other factors such as low urinary citrate and hyperoxaluria also predispose to renal stones."[8]

Oxalate formation is potentially a consequence of Vitamin D toxicity, not of normal levels associated with Colecalciferol supplementation. However there is potentially an increased risk if the patient is co-administered large i.v. doses of Vitamin C.

A study by Macintosh et al[12] in rats demonstrated that Vitamin D produced uroliths in rats that were deprived on Vitamin B6. Supplementing the rats with Vitamin C significantly *reduced* stone formation, addition of Vitamin B6 completely abolished stone formation.

Despite this, it would be prudent to avoid high doses of Vitamin C in the usual risk groups (stone formers, family history, serious renal disease and complications). If a patient has received high dose Vitamin D, it is wise to check serum/urinary calcium before giving high dose i.v. Vitamin C.

Also, it would be wise to ensure that patients receive adequate B6 and antioxidant support to minimize the risk of stone formation, even though the risk is small.

Measurement and Follow up

Deficiency may be defined by levels of serum 25-hydroxyvitamin D3 (*25(OH)D*), < 50nmol/L.[2]

Severely deficient people may show levels below 20nmol/L.

"... the wealth of animal studies and human anecdotal reports of vitamin D intoxication indicate that plasma 25(OH)D3 is a good biomarker for toxicity, and the threshold for toxic symptoms is ~750 nmol/L. This threshold value implies that 25(OH)D concentrations up to the currently considered upper limit of the normal range, namely 250 nmol/L, are safe and still leave a broad margin for error because values significantly higher than this value have never been associated with toxicity."[5]

Hypercalcaemia can be defined as a serum calcium concentration higher than 2.65mmol/L.

In any high dose regime it is wise to have serum 25-hydroxyvitamin D3 and calcium measured 2–4 weeks after therapy.

A study by Macintosh et al[12] in rats demonstrated that Vitamin D *produced uroliths in rats that were deprived on Vitamin B6. Supplementing the rats with Vitamin C significantly reduced stone formation, addition of Vitamin B6 completely abolished stone formation.*

4. Is parenteral Vitamin D more effective than oral doses?

Very large oral doses can safely and effectively be given in elderly people and oral doses of 100,000 IU every 2 months in this population are represented in the literature[5].

Very large doses are indicated in individuals who are demonstrated to be very deficient (serum 25OHD < 20nmol/L). It is variable to what extent an individual patient will absorb and distribute an oral dose, so the use of intramuscular injections is appropriate for people with poor digestion, GI disturbances or severe deficiency. With a parenteral dose given in clinic, the physician knows exactly what the patient got, what dose they got and when they got it.

5. What are the effects of Vitamin D deficiency and what conditions are associated with this?

"Vitamin D deficiency leads to hypocalcaemia, secondary hyperparathyroidism and increased bone turnover. This may be associated with osteoporosis and fractures. In prolonged and severe cases, osteomalacia and rickets (failure in mineralisation of new bone) may occur, resulting in progressive bone pains, myopathy and a waddling gait. The clinical spectrum ranges from subclinical to frank deficiency, with serum 25-hydroxyvitamin D (25OHD) levels less than 20nmol/L." [2]

There are a host of medical conditions which are associated with various levels of Vitamin D deficiency, including various cancers, eating disorders, dementias, cardiovascular disease, diabetes, bariatric surgical patients, osteoporosis and autoimmune diseases.

There are several excellent reviews about Vitamin D deficiency and its association with myriad disorders [13] [14] [15]. Without doubt Vitamin D deficiency is one of the most common nutritional deficiencies and one of the easiest to rectify cheaply and easily.

References:

[1] Cesur Y, Caksen H, Gündem A, Kirimi E, Odabaº D. Comparison of low and high dose of vitamin D treatment in nutritional vitamin D deficiency rickets. J Pediatr Endocrinol Metab. 2003 Oct-Nov;16(8):1105-9. PMID: 14594170

[2] Diamond TH, Ho KW, Rohl PG, Meerkin M. Annual intramuscular injection of a megadose of Colecalciferol for treatment of vitamin D deficiency: efficacy and safety data. Med J Aust. 2005 Jul 4;183(1):10-2. PMID: 15992330

[3] Working Group of the Australian and New Zealand Bone and Mineral Society; Endocrine Society of Australia; Osteoporosis Australia. Vitamin D and adult bone health in Australia and New Zealand: a position statement. Med J Aust. 2005 Mar 21;182(6):281-5. PMID: 15777143

[4] Grant WB. Colecalciferol, not ergocalciferol, should be used for vitamin D supplementation. Age Ageing. 2006 Nov;35(6):645; author reply 645. Epub 2006 Sep 18. PubMed PMID: 16982666

[5] Ilahi M, Armas LA, Heaney RP. Pharmacokinetics of a single, large dose of Colecalciferol. Am J Clin Nutr. 2008 Mar;87(3):688-91. PubMed PMID: 18326608

[6] Goswami R, Kochupillai N, Gupta N, Goswami D, Singh N, Dudha A. Presence of 25(OH) D deficiency in a rural North Indian village despite abundant sunshine. J Assoc Physicians India. 2008 Oct;56:755-7. PMID: 19263699

[7] Jones G. Pharmacokinetics of vitamin D toxicity. Am J Clin Nutr. 2008 Aug;88(2):582S-586S. Review. PubMed PMID: 18689406

[8] http://www.ahrq.gov/U.S. Department of Health & Human Services. Effectiveness and safety of Vitamin D in relation to bone health.

[9] Johnson KR, Jobber J, Stonawski BJ. Prophylactic vitamin D in the elderly. Age Ageing. 1980 May;9(2):121-7. PubMed PMID: 7395656

[10] Sebert JL, Fardellone P, Ruiz JC, Perdu V, Bellony R, Liu SY, Defrance D 1987 Vitamin D deficiency and supplementation in elderly institutionalized women. In: Christiansen C, Johansen JS, Riis BJ, eds. Osteoporosis 1987. Copenhagen: Osteopress ApS; 592–594

[11] Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocr Rev. 2001 Aug;22(4):477-501. Review. PMID: 11493580

[12] McIntosh GH, Belling GB, Bulman FH. Experimental oxalate urolith formation in rats. Aust J Exp Biol Med Sci. 1979 Jun;57(3):251-9. PMID: 231424

[13] Compher CW, Badellino KO, Boullata JI. Vitamin D and the bariatric surgical patient: a review. Obes Surg. 2008 Feb;18(2):220-4. Epub 2008 Jan 5. Review. PMID: 18176832

[14] Ali MM, Vaidya V. Vitamin D and cancer. J Cancer Res Ther. 2007 Oct-Dec;3(4):225-30. Review. PMID: 18270398

[15] Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Am J Clin Nutr. 2004 Mar;79(3):362-71. Review. Erratum in: Am J Clin Nutr. 2004 May;79(5):890. PMID: 14985208

Australasian Institute for Medical Nutrition

Version ID: AIMN_Review_High_Dose_Vit_D3_Answers_Sep_2016