Annual intramuscular injection of a megadose of cholecalciferol for treatment of vitamin D deficiency: efficacy and safety data

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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. Vitamin D deficiency is not uncommon in “sunny” Australia. The clinical spectrum ranges from subclinical to frank deficiency, with serum 25-hydroxyvitamin D (25OHD) levels less than 20 nmol/L. The prevalence of vitamin D deficiency among elderly people living in residential homes has been estimated to be at least 50%. Severe deficiency was also reported in 80% of “veiled” pregnant women. Other high-risk groups include ethnic populations from the Horn of Africa, India and Pakistan, and patients with gastrointestinal malabsorption syndromes.

METHODS

We conducted a prospective open-label study in a single institution to assess the safety and efficacy of a single therapeutic annual intramuscular injection of 600,000 IU (15 mg) cholecalciferol (vitamin D₃; “Arachitol”, Solvay Pharma, India Ltd) in treating vitamin D deficiency. This preparation is currently being used to treat vitamin D deficiency in India and Canada, and its safety has previously been evaluated.

Men and women with biochemical evidence of vitamin D deficiency (serum 25-hydroxyvitamin D₃ [25OHD₃], < 50 nmol/L) were recruited from the metabolic bone clinic at St George Hospital. All gave informed consent, and treatment was administered on an Individual Patient Use (IPU) special access scheme according to Therapeutic Goods Administration of Australia guidelines. Patients were excluded if they had hypercalcaemia (serum calcium, > 2.70 mmol/L), primary hyperparathyroidism (serum calcium, > 2.65 mmol/L), or current treatment with calcitriol or high-dose oral calcium supplements.

Outcome measures: Serum levels of calcium, creatinine, 25-hydroxyvitamin D₃ (25OHD₃) and parathyroid hormone, as well as early morning 2-hour urine calcium/creatinine excretion index. Specimens were collected at baseline and after 4 and 12 months of therapy. Data are reported as mean ± SD.

RESULTS: Vitamin D deficiency was severe (< 12.5 nmol/L) in one participant, moderate (12.5–24 nmol/L) in 14, and mild (25–49 nmol/L) in 35. Twenty-four participants (48%) had secondary hyperparathyroidism. Following intramuscular cholecalciferol injection, serum 25OHD₃ levels normalised in all participants and remained above 50 nmol/L throughout the study. Serum 25OHD₃ levels were significantly higher at 4 months (114 ± 35 nmol/L) and 12 months (73 ± 13 nmol/L) compared with baseline (32 ± 8 nmol/L) (P < 0.001), increasing by an average of 128% over the 12 months. There was a corresponding decrease in serum parathyroid hormone levels at 4 months (6 ± 3 pmol/L) and at 12 months (5.2 ± 3 pmol/L), with a 30% decrease at 12 months from baseline (7.4 ± 4 pmol/L) (P < 0.01). Primary hyperparathyroidism was unmasked in one participant at 4 months and mild hypercalcaemia (serum calcium, < 2.70 mmol/L) was noted in two participants (4%) at 12 months. Serum creatinine levels remained normal in all participants throughout the study, while increases in 2-hour urine calcium/creatinine excretion index were seen in 10 participants (20%) at 12 months, three of whom had had elevated values at baseline.

Conclusions: Once-yearly intramuscular cholecalciferol injection (600,000 IU) is effective therapy for vitamin D deficiency. While this therapy appears to be safe, the potential for developing hypercalciuria needs to be examined in a large randomised controlled trial.

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indices were used to determine hypercalcemia. This was based on a previous study, and validated in our laboratory. A urine calcium/creatinine excretion index over 0.60 was considered abnormal.

Serum 25OHD₃ levels were measured by radioimmunoassay (Immuno Diagnostic Systems, Boldon, UK). Specificity for 25OHD₃ was 100%, and intra-assay precision was 5.3% at 26.5 nmol/L and 6.1% at 151 nmol/L.

Serum levels of intact parathyroid hormone (PTH) were measured by chemiluminometric technology (Advia Centaur Assay, Bayer Corp, USA). The intra-assay precision was 5.2% at 7.4 pmol/L and 6.3% at 23.7 pmol/L. Hyperparathyroidism was defined as a serum PTH level over 7.5 pmol/L.

Statistical analysis
Data are presented as mean ± 1 SD. Group mean values were compared by analysis of variance with a post hoc Scheffe test for parametric data and Kruskal–Wallis test for non-parametric data. Logarithmic regression analysis was used to determine the relationship between serum PTH and 25OHD₃ levels.

RESULTS
There were 5 men and 45 women with evidence of vitamin D deficiency and who fulfilled the inclusion criteria. They were aged 32–87 years (mean age, 66.3 years). They had previously undergone gastrectomy and one had biopsy-proven coeliac disease. No patient declined intramuscular cholecalciferol therapy and none reported any serious adverse events. One patient developed a localised erythematous reaction at the injection site, which resolved after 2 weeks of applying a topical glucocorticoid preparation. There were no reports of bruising or bleeding at the injection site.

Vitamin D deficiency among the 50 participants was classified as mild (25–49 nmol/L) in 35 (70%), moderate (12.5–24 nmol/L) in 14 (28%), and severe (< 12.5 nmol/L) in 1 (2%).

Treatment with intramuscular cholecalciferol normalised serum 25OHD₃ levels in all patients, with levels remaining above 50 nmol/L after 12 months of therapy (Box). Twenty-four participants (48%) had secondary hyperparathyroidism. Intramuscular cholecalciferol injection normalised serum PTH levels in 16 participants (67%). The mean serum PTH level decreased by 30%, from a baseline value of 7.4 ± 4.4 pmol/L to a 12-month value of 5.2 ± 3.2 pmol/L (Box). There was an inverse relationship between baseline serum 25OHD₃ and PTH levels (y = 18.5–3.25[log x]; r = 0.21; P = 0.02).

Primary hyperparathyroidism was unmasked after intramuscular cholecalciferol injection in one participant who subsequently underwent parathyroid adenectomy. This patient’s serum calcium level increased from 2.64 mmol/L to 2.78 mmol/L at 4 months, and was associated with an elevated serum PTH level of 7.7 pmol/L. Two participants (4%) were noted to have mild hypercalcaemia at 12 months. Their serum calcium levels measured 2.66 mmol/L and 2.68 mmol/L, respectively, and PTH levels were 0.7 pmol/L and 2.2 pmol/L, respectively. Serum calcium levels in the rest of the cohort were normal at 4 and 12 months after therapy.

Serum creatinine levels remained within the normal range and unchanged throughout the study in all participants, but a small progressive increase in urine calcium/creatinine excretion index of 0.15 was noted with time (Box). The urine calcium/creatinine excretion index was elevated at baseline.

DISCUSSION
Vitamin D repletion in individuals presenting with vitamin D deficiency has been shown to have a positive effect on bone biology, resulting in mineralisation of osteoid, increases in bone mineral density measurements and reduced fracture rates. A report of bone histomorphometric changes in 28 patients with osteomalacia treated with various vitamin D preparations and calcium showed an 80% reduction in osteoid volume and an increase in mineralised bone volume in cortical (+ 7.5%) and trabecular bone (+ 40%) after therapy. Moreover, in a recent meta-analysis, there were significant increases in lumbar spine bone mineral density after only 12 months of therapy, while increases in femoral neck bone mineral density were much slower. In a landmark trial in elderly institutionalised women, 800 IU of oral vitamin D₃ with calcium supplements resulted in significant reduction in both non-vertebral (3.8%) and hip (2%) fractures, and a significant improvement in femoral neck bone density after 36 months of therapy. In another randomised controlled trial involving 2686 men and women aged over 65, 100 000 IU of oral vitamin D₃ given every 4 months reduced major osteoporotic fractures by 33% compared with placebo over 5 years. There are also data to suggest that an annual intramuscular injection of 150 000–300 000 IU of ergocalciferol (vitamin D₂)
has been associated with a reduction in fractures of the upper limbs.\textsuperscript{15}

The major source of vitamin D in humans is sunlight. In the absence of adequate sunlight exposure, supplementation becomes important. The target for vitamin D supplementation is suggested to be a serum level of 50 nmol/L, which is protective against secondary hyperparathyroidism and decreased bone density.\textsuperscript{16} In Australia, the National Health and Medical Research Council recommends a daily oral intake of at least 400 IU vitamin D for those who are at risk of vitamin D deficiency.\textsuperscript{17} However, for those with severe vitamin D deficiency, higher doses are recommended.\textsuperscript{4}

The main vitamin D supplements available in Australia are oral vitamin D\textsubscript{2} and D\textsubscript{3} preparations. The largest single dose is Ostein (Boots Healthcare Australia), a 1000 IU D\textsubscript{2} preparation. Other vitamin D\textsubscript{2} preparations have lower doses (about 400 IU), and are usually combined with elemental calcium. A popular vitamin D\textsubscript{3} preparation is Caltrate 600 MG + Vitamin D Tablets (Wyeth Consumer Healthcare), which contain 200 IU of vitamin D\textsubscript{3} combined with 600 mg of elemental calcium. Other D\textsubscript{3} preparations include Pluravit (400 IU, Bayer Australia) and Elevit (500 IU, Roche Products). Currently there are no parenteral or oral megadoses of vitamin D\textsubscript{2} or D\textsubscript{3} preparations available in Australia.

Doses of 400–800 IU are safe and reportedly have no side effects.\textsuperscript{9,18} Such formulations can be purchased by anyone over the counter without the need for signed prescription. However, vitamin D preparations with doses above 1000 IU are considered as pharmaceutical agents, and are regulated by a much stricter code by the Australian Therapeutic Goods and Drug Administration Committee. 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.\textsuperscript{9,16-21} Also, in one study, graded oral dosing of vitamin D\textsubscript{3} up to 50 000 IU daily for 8 weeks did not cause hypercalcaemia.\textsuperscript{22} In another, 5000 IU of oral vitamin D\textsubscript{2} was administered twice-weekly to 12 patients with vitamin D deficiency (serum 25OHD, 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 50 nmol/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. Future randomised controlled trials which include 24-hour urine calcium excretion measurements will be essential for validating the safety of megadose intramuscular cholecalciferol therapy.

We suggest that a once-yearly intramuscular cholecalciferol injection (600 000 IU) should be further investigated as a therapeutic option for treating vitamin D deficiency. This treatment is currently unavailable in Australia, and there is no ideal preparation of megadose vitamin D\textsubscript{2} or D\textsubscript{3} to fill this therapeutic gap. However, at a cost of $5–$10 per injection annually compared with $35 for a monthly course of 5 Ostein capsules daily (suggested dosages to treat vitamin D deficiency),\textsuperscript{4} it is remarkably cost-effective. The simple dosing regimen also allows convenient outpatient management and may improve patient compliance.

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COMPETING INTERESTS

None identified.

REFERENCES


14 Trivedi DR, Doll R, Khaw KT. Effect of four monthly oral vitamin D\textsubscript{3} (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised controlled trial. BMJ 2003; 326: 469-474.


Megadose therapy for vitamin D deficiency
Treating the paradox of an important emerging public health problem

The international perception of bronzed Australians inhabiting a “sunburnt country” is under threat. Most Australians, including children, now sensibly avoid excessive sunlight exposure to reduce the risk of skin cancer. However, other Australians, particularly those who are older, disabled or institutionalised often do not receive even modest levels of sunlight exposure. This has led to the paradox of vitamin D deficiency emerging as a public health issue in sunny Australia.

Besides older and institutionalised Australians, others particularly at risk of vitamin D deficiency are people with pigmented skin from Africa, India and Pakistan; women who practise veiling; those on certain medications (eg, anti-epileptic drugs); and those with malabsorption or a low vitamin D intake. Even young Australians, pregnant women and their infants are at risk of this emerging health problem.1 The prevalence of vitamin D deficiency among Indigenous Australians has not been determined, but is likely to be high.

The problem was highlighted recently in the Journal in a position statement on vitamin D and bone health in adults.2 Vitamin D deficiency is usually classified as mild (25-hydroxyvitamin D [25OHD] level, 25–49 nmol/L), moderate (12.5–24 nmol/L) or severe (< 12.5 nmol/L). The Geelong Osteoporosis Study detected mild or moderate deficiency in more than one in three women surveyed in summer, which rose to one in two in winter.3 Even in south-east Queensland, Western Australia, New South Wales and Victoria, nearly a third of men and women have mild to moderate vitamin D deficiency.4 Almost half of nursing home patients, and almost all patients in aged care facilities surveyed have at least mild vitamin D deficiency.

Thus, despite Australia being a “sunburnt country”, vitamin D deficiency is common. But why is it important?

Severe vitamin D deficiency results in osteomalacia in adults andrickets in children. Milder vitamin D deficiency results in secondary hyperparathyroidism and increased bone turnover, predisposing to osteoporosis. Proximal myopathy and muscle pains may result from vitamin D deficiency and, as commercially available radioimmunoassays do not always measure vitamin D2 as well as vitamin D3, measuring treatment response is difficult. Daily dosing is also difficult or unrealistic for many community-dwelling older people in whom compliance would be expected to be poor. A single intramuscular “megadose” of cholecalciferol would overcome this compliance issue in a simple and cost-effective manner. The mild hypercalcaemia and fasting hypercalciuria are of concern, but further controlled trials are planned, which will include 24-hour urine calcium excretion measurements, to evaluate the safety of “megadose” cholecalciferol therapy. The effect of this treatment on fracture risk is not established. A recent British study of 9440 community-dwelling participants aged 75–100 years, randomly allocated to receive either an annual injection of 300 000 IU cholecalciferol or placebo, showed no reduction in fracture rate.10 Nevertheless, the greatest clinical utility of an annual megadose injection is likely to be in older institutionalised people, most of whom are vitamin D deficient.

The most important outcome in osteoporosis prevention or treatment is a reduction in fracture risk. Some data suggest treating vitamin D deficiency may prevent low-trauma fractures. A large French study in institutionalised, ambulatory older women found that daily doses of 800IU of cholecalciferol and 1.2 g of calcium significantly decreased the incidence of hip and non-vertebral fractures compared with placebo after 18 months.11 Daily vitamin D and calcium treatment also reduced non-vertebral fractures in community-dwelling older American men and women.12 A recent large trial in community-dwelling British men and women aged over 65 years showed that a large oral dose of cholecalciferol (100 000 IU) every 4 months reduced osteoporotic fractures by 33%.13 The RECORD trial attempted to determine the relative contribution of calcium versus vitamin D on fractures. Ambulatory patients (5292) who had sustained a low-trauma fracture were randomly allocated to receive calcium (1000 mg/day), vitamin D3 (800 IU/day), a combination of the two, or placebo. After at least 24 months, fracture rates did not differ between the four groups. However, compliance at 2 years was poor.14 Further large studies of vitamin D and its effects on fractures and falls are still needed, particularly in populations at risk of vitamin D deficiency; these

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studies need to use varying oral doses of vitamin D and to include men.

The treatment described by Diamond et al is a good start to introducing new alternatives for treatment of vitamin D deficiency in targeted people. However, much more work is needed to identify successful public health approaches that can be more broadly applied to this emerging public health problem.

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