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

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ABSTRACT

Aim: To evaluate the efficacy and safety of an annual intramuscular injection of cholecalciferol for vitamin D deficiency.

Design: Prospective open-label study.

Participants: Five men and 45 women (mean age 66.3 years) with vitamin D deficiency who were given a single therapeutic intramuscular injection of 600 000 IU (15 mg) cholecalciferol (vitamin D_3).

Outcome measures: Serum levels of calcium, creatinine, 25-hydroxyvitamin D_3 ($25OHD_3$) 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 ±1 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 $25OHD_3$ levels normalised in all participants and remained above 50 nmol/L throughout the study. Serum $25OHD_3$ 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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Vitamin D deficiency leads to hypocalcaemia, secondary hyperparathyroidism and increased bone turnover.[1,2] This may be associated with osteoporosis and fractures.[1] 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.[3] Vitamin D deficiency is not uncommon in "sunny" Australia.[4] 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%.[5] Severe deficiency was also reported in 80% of "veiled" pregnant women.[6] Other high-risk groups include ethnic populations from the Horn of Africa, India and Pakistan, and patients with gastrointestinal malabsorption syndromes.[4,7] Vitamin D repletion can improve bone mineral density and reduce fracture risk.[8] The usual method of supplementation with oral ergocalciferol tablets (1000 IU) is often inadequate, especially in severe deficiency states.[4,9] In Australia, there are currently no effective high-dose vitamin D preparations.

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 D_3; "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,[10] and its safety has previously been evaluated.[9]

Men and women with biochemical evidence of vitamin D deficiency (serum 25-hydroxyvitamin D_3 [$25OHD_3$], < 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, > 2.65 mmol/L), primary hyperparathyroidism (hypercalcaemia with inappropriately elevated serum parathyroid hormone levels), thyrotoxicosis, Paget's disease, malignancy, significant renal impairment (serum creatinine, > 0.15 mmol/L), significantly elevated early-morning 2-hour urine calcium/creatinine excretion index (> 0.8), liver disease (alanine aminotransferase or aspartate aminotransferase level > 2 times the upper limit of the normal range), or current treatment with calcitriol or high-dose oral calcium supplements (1200 mg/day of elemental calcium).

Participants were evaluated by biochemical assessments at baseline and after 4 and 12 months of therapy. The study was performed according to National Health and Medical Research Council guidelines and with approval of the South Eastern Area Health Service Research Ethics Committee.

Serum (fasting) and urinary (2 hour) calcium, urea and creatinine levels were determined by autoanalyser methods. Hypercalcaemia was defined as a serum calcium concentration higher than 2.65 mmol/L. Two-hour urine calcium/creatinine excretion

FOR EDITORIAL COMMENT, SEE PAGE 4

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Serum and urine biochemical findings in 50 patients with vitamin D deficiency at baseline and after 4 and 12 months of therapy, and the serum 25-hydroxyvitamin D_3 reponse over that period

Variable	Reference range	Baseline	4 months	12 months	Change (baseline to 12 months)
Serum					
Calcium*	2.2–2.65 mmol/L	2.40 ± 0.11	2.40 ± 0.12	2.45 ± 0.10	+ 2%
25-hydroxyvitamin D_3*	> 50 nmol/L	32 ± 8.4	114 ± 35§	73 ± 13§	+ 128%
Creatinine†	< 0.11 mmol/L	0.08 ± 0.02	0.07 ± 0.02	0.08 ± 0.03	0
Parathyroid hormone†	< 7.5 pmol/L	7.4 ± 4	6 ± 3	5.2 ± 3*	–30%
Urine					
2-hour urine calcium/ creatinine excretion index†	< 0.6	0.25 ± 0.2	0.29 ± 0.3	0.40 ± 0.3‡	+ 60%

Values expressed as mean ±1 SD. * Comparison by analysis of variance and post hoc Scheffe test. † Comparison with Kruskal–Wallis test. ‡ $P < 0.01$ and § $P < 0.001$ (compared with baseline).

indices were used to determine hypercalciuria. This was based on a previous study,[11] and validated in our laboratory. A urine calcium/creatinine excretion index over 0.60 was considered abnormal.

Serum $25OHD_3$ levels were measured by radioimmunoassay (Immuno Diagnostic Systems, Boldon, UK). Specificity for $25OHD_3$ 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 4.3 pmol/L and 3.4% 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 $25OHD_3$ 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 been referred for management of osteoporosis (37) and musculoskeletal pains (13). Thirteen participants were receiving low dose glucocorticoids for rheumatological conditions, two 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%).[9] Treatment with intramuscular cholecalciferol normalised serum $25OHD_3$ 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 $25OHD_3$ 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 adenomectomy. 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 in four participants was 0.60–0.80, and in six it was > 0.80 at 12 months; in three of these, 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.[12] 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.[13] In a landmark trial in elderly institutionalised women, 800 IU of oral vitamin D_3 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.[8] In another randomised controlled trial involving 2686 men and women aged over 65, 100 000 IU of oral vitamin D_3 given every 4 months reduced major osteoporotic fractures by 33% compared with placebo over 5 years.[14] There are also data to suggest that an annual intramuscular injection of 150 000–300 000 IU of ergocalciferol (vitamin D_2)

has been associated with a reduction in fractures of the upper limbs.[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.[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.[17] However, for those with severe vitamin D deficiency, higher doses are recommended.[4]

The main vitamin D supplements available in Australia are oral vitamin D_2 and D_3 preparations. The largest single dose is Ostelin (Boots Healthcare Australia), a 1000 IU D_2 preparation. Other vitamin D_2 preparations have lower doses (about 400 IU), and are usually combined with elemental calcium. A popular vitamin D_3 preparation is Caltrate 600 MG + Vitamin D Tablets (Wyeth Consumer Healthcare), which contain 200 IU of vitamin D_3 combined with 600 mg of elemental calcium. Other D_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_2 or D_3 preparations available in Australia.

Doses of 400–800 IU are safe and reportedly have no side effects.[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.[9,19-21] Also, in one study, graded oral dosing of vitamin D_3 up to 50 000 IU daily for 8 weeks did not cause hypercalcaemia.[22] In another, 50000 IU of oral vitamin D_2 was administered twice-weekly to 12 patients with vitamin D deficiency (serum 25OHD, <35 nmol/L) for 5 weeks (total dose, 500 000 IU).[23] These patients also received 1000 mg 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. Similarly, a report from New Zealand described supplementation with 500 000 IU in a 10-day course of 50 000 IU of oral cholecalciferol.[24] Participants' mean serum calcium level increased by 0.06 ± 0.08 mmol/L ($P<0.001$) after treatment, but in none did the calcium level exceed the reference range after treatment.

In our study, a single annual intramuscular injection of 600 000 IU cholecalciferol 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_2 or D_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 Ostelin capsules daily (suggested dosages to treat vitamin D deficiency),[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.

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