Letter to the Editors

It's time for new rules on vitamin D food supplements

**Silvia Benemei,¹ Eugenia Gallo,¹ Elisa Giocaliere,² Gianluca Bartolucci,²
Francesca Menniti-Ippolito,³ Fabio Firenzuoli,¹ Alessandro Mugelli¹ & Alfredo Vannacci¹**

¹Department of Preclinical and Clinical Pharmacology, Centre of Molecular Medicine CIMMBA, Centre for Integrative Medicine, Florence University, Florence, ²Mass Spectrometry Centre, Florence University, Florence and ³National Institute of Health, Rome, Italy

There is considerable discussion on the serum concentrations of 25-OH vitamin D associated with deficiency, overall health and toxicity. Currently, the upper limit of safety for daily doses is 10 000 IU and adequate concentrations are suggested to be >50 nmol l⁻¹. Although definitive cut points have not been developed, it is accepted that serum concentrations >500 nmol l⁻¹ (>200 ng ml⁻¹) can be associated with adverse effects [1, 2]. There are several reports of patients who developed asymptomatic or severely symptomatic hypercalcaemia due to vitamin D supplements [3–5]. Vitamin D preparations are available worldwide as food supplements.

Recently, three cases of hypervitaminosis D, hypercalcaemia and renal insufficiency in patients taking the same type of oral preparation for vitamin D supplementation were reported to the Italian National Institute of Health reporting system for natural health products.

The first case was a 34-year-old woman affected by osteoporosis, atopic dermatitis and coeliac disease who had taken six capsules each day of a vitamin D supplement for 4 months before the adverse reaction. The patient was hospitalized because of hypercalcaemia and renal insufficiency. Bilateral nephrocalcinosis was seen on renal ultrasound. The patient suffered from polyuria, polydipsia, episodic emesis and dyspepsia. Fourteen days after stopping vitamin D supplementation, total calcium was 3.25 mmol l⁻¹ (13.0 mg dl⁻¹, normal range 2.25–2.63 mmol l⁻¹, 9–10.5 mg dl⁻¹), serum creatinine was 274.04 mmol l⁻¹ (3.1 mg dl⁻¹, normal range 44.2–132.6 mmol l⁻¹, 0.5–1.5 mg dl⁻¹) and serum 25-OH vitamin D (7575.36 nmol l⁻¹, 3035.0 ng ml⁻¹) was elevated greatly over the toxic level.

The second case was a 57-year-old man with hypertension who took three capsules each day of a vitamin D supplement for 11 months, eventually developing symptoms and signs of acute renal insufficiency. Serum vitamin D values over 748.80 nmol l⁻¹ (300 ng ml⁻¹, laboratory

upper detection limit), hypercalcaemia (3.23 mmol l⁻¹, 12.9 mg dl⁻¹), renal insufficiency (serum creatinine 235.14 mmol l⁻¹, 2.66 mg dl⁻¹) and tubular damage found on renal biopsy, were all attributed to the oral vitamin D preparation prescribed to the patient as a dietary supplement.

The third case was a 47-year-old man who took seven to nine capsules daily of a vitamin D supplement for 5 months as a self-prescribed supplementation. The patient was admitted to the hospital for renal insufficiency (creatinine 221 mmol l⁻¹, 2.5 mg dl⁻¹). Serum vitamin D values were over 748.80 nmol l⁻¹ (300 ng ml⁻¹, laboratory upper detection limit) and total calcium was elevated (3.08 mmol l⁻¹, 12.3 mg dl⁻¹).

For all three cases, no pre-existing diseases or other drugs taken by the patients could be considered as causal or contributing factors. All patients completely recovered, regaining their normal renal function 3–4 months after discontinuation of vitamin D supplementation and supportive medical treatment. In all three cases, the causal relationship between the vitamin D preparation and the adverse reaction, as assessed by the Naranjo scale [6], was defined as 'certain'. All patients had taken the same supplement, MerluzzoVis (SerVis SRL®) capsules, that had come from two different lots with a declared vitamin D₃ content of 1.5 µg (600 IU) per capsule. A liquid chromatography mass spectrometry analysis of the actual content of each capsule (performed as previously described [7]) showed values of 1320 ± 66 µg (about 52 800 IU), more than 880 times higher than what was reported on the product's label. Patient 1 therefore received approximately 316 800 IU day⁻¹ for 4 months, patient 2 received approximately 158 400 IU day⁻¹ for 11 months and patient 3 received approximately 422 400 IU day⁻¹ for 5 months.

When taken in correctly prescribed doses, vitamin D can be considered a safe treatment. Nevertheless the three cases here described, similar to others previously reported

[3–5], suggest that vitamin D intoxication due to the use of vitamin D supplements is not rare. Vitamin D preparations do not undergo quality control for good manufacturing practice because they are ‘food supplements’. The vitamin D intoxication that occurred in these three cases was a result of inadequate quality control, resulting in the selling of a product dangerous to consumers’ health. In terms of safety, most people consider a ‘food supplement’ to be much safer than a ‘drug’. Given that a preparation labelled as ‘food’ can be commonly used without a medical prescription, its content of active principles should be carefully monitored.

In conclusion, the present cases of vitamin D intoxication emphasize the need to prepare supplements such as vitamin D under precise rules so that the amount of potentially toxic ingredients is the correct and safe dose. The urgent need for a more strict regulation may be extended to other food supplements containing active principles and used for health purposes.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare (i) no support from any organization for the submitted work, (ii) no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and (iii) no other relationships or activities that could appear to have influenced the submitted work.

REFERENCES

- 1 Institute of Medicine Food and Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academy Press, 2010.
- 2 Sanders KM, Nicholson GC, Ebeling PR. Is high dose vitamin D harmful? *Calcif Tissue Int* 2013; 92: 191–206.
- 3 Koutkia P, Chen TC, Holick MF. Vitamin D intoxication associated with an over-the-counter supplement. *N Engl J Med* 2001; 345: 66–7.
- 4 Klontz KC, Acheson DW. Dietary supplement-induced vitamin D intoxication. *N Engl J Med* 2007; 357: 308–9.
- 5 Lowe H, Cusano NE, Binkley N, Blaner WS, Bilezikian JP. Vitamin D toxicity due to a commonly available ‘over the counter’ remedy from the Dominican Republic. *J Clin Endocrinol Metab* 2011; 96: 291–5.
- 6 Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30: 239–45.
- 7 Bartolucci G, Giocaliere E, Boscaro F, Vannacci A, Gallo E, Pieraccini G, Moneti G. Vitamin D3 quantification in a cod liver oil-based supplement. *J Pharm Biomed Anal* 2011; 55: 64–70.

RECEIVED

16 November 2012

ACCEPTED

15 March 2013

ACCEPTED ARTICLE PUBLISHED ONLINE

18 April 2013

CORRESPONDENCE

Dr Alfredo Vannacci MD, Department of Preclinical and Clinical Pharmacology viale Pieraccini 6, 50139, Florence, Italy.
Tel.: +3905 5427 1417
Fax: +3905 5427 1280
E-mail: alfredo.vannacci@unifi.it