Is high dose vitamin D harmful? Authors reply

Kerrie M Sanders ¹
Geoffrey C Nicholson ^{2,1}
Peter R Ebeling ¹

¹Department of Medicine, Western Health
NorthWest Academic Centre,
University of Melbourne
PO Box 294
St Albans, Victoria 3021, Australia

²Rural Clinical School, School of Medicine
University of Queensland
Toowoomba, Queensland, Australia

CTI 2012 manuscript 'Is High Dose Vitamin D Harmful?' January 2013

AUTHORS RESPONSE TO TWO LETTERS TO THE EDITOR

Minisola S et al, CTI-13-0001 'Intermittent High doses of vitamin D: A need for further studies?'

Minisola and colleagues ¹ comment that the two RCTs (Sanders et al ² and Smith et al ³) lack important information concerning the distribution of risk factors for falls (cognitive impairment, drug use, alcohol use etc) in the two arms. Sanders et al reported that at baseline the prevalence of risk factors for falls and fractures, and previous fractures since the age of 50 years, were similar in the vitamin D and placebo groups. Smith et al reported that previous fractures were similar in the two groups. Since more than 90% of fractures occur after a fall ⁴ it is highly unlikely that a difference in baseline prevalence of risk factors for falls existed in either study. Furthermore, participants in both studies were randomised only if mentally competent to participate. Similar scores of mental well-being parameters and the use of antidepressants at baseline has been reported in the vitamin D and placebo groups in the Sanders et al study ⁵.

Most importantly, both trials had over 2,000 participants so random allocation would ensure that any common characteristic, such as falls in subjects in their late 70s, would be evenly distributed. This is a fundamental characteristic that ranks the RCT as the highest level of clinical evidence, only out-ranked by meta-analysis of multiple RCTs.

Minisola et al suggest that if it is fluctuation in serum 25(OH)D, rather than the peak value reached, that is associated with increased falls/fracture risk, then the problem might be overcome by using intramuscular injection, which causes a slower increase in plasma 25(OH)D than oral administration. We do not disagree that fluctuation may be the problem but the fact that similar

adverse effects on older women were seen in both RCTs, despite the different routes of administration, suggests that the cause is more complex than simply the route of administration or the rate of rise of 25D.

In both studies, 25(OH)D levels three to four month post-dose were only modestly (approximately 20%) elevated above pre-dose levels. In the Smith et al study the very small number assayed (n= 30 treated, 13 placebo) reduced the power to detect a significant difference in 25(OH)D at 4 months. However, there was a greater (35.7%) increase in 1,25-dihydroxyvitamin D, which was significant ($P<0.002$).

Minisola and colleagues confirm the urgent need for RCTs with physical outcomes as primary endpoints. Study design that adhere to the CONSORT guidelines and are appropriately randomised and adequately powered would be balanced in risk factors for falls and fractures between treatment and placebo groups.

Grant W, CTI-12-0347 “Is high dose vitamin D harmful?”

We agree that Grant ⁶ has identified common limitations of prospective cohort studies. Our paper states that we do not attempt to present a “balanced” view of potential risk/benefit ratio of vitamin D supplementation but have summarised results from studies using intermittent, high-doses of vitamin D, with particular attention to those finding evidence of adverse effects.

Grant states the limitation that in many prospective studies serum 25(OH)D was measured at the time of enrolment with long follow-up periods for cancer outcomes. We agree the vitamin D status taken years prior to the diagnosis, may be irrelevant but these population-based studies are hypothesis-generating and the associations need to be tested using gold standard randomised placebo-controlled study design. Grant also correctly points out the potential flaws of case-control studies where vitamin D status is compared between the groups with and without the disease. The cases may have taken measures to improve their vitamin D status as a consequence of the diagnosis.

We would welcome the conduct of “properly-designed” vitamin D RCTs. However, Grant’s guidelines for such are speculative and raise additional questions including: (1) determining the “concentration-health outcome relation” would rely on high-quality well-controlled data that are not available. Furthermore, any such data derived from observational studies will be problematic because the relation may be quite different in an interventional study when the concentrations are dynamic; (2) the rate and magnitude of the increase in serum 25(OH)D levels may be critical; (3) due to individual variation, a set dose may not achieve a concentration “near the upper end” – many will be well above, or below this. Therefore, the dose will need to be titrated in each participant causing issues with blinding and logistics; (4) at which time-points after dosing should the concentrations be

measured?; (5) finally, in the very large, long-term studies required to determine clinical endpoints the cost performing multiple biochemical assays is a major impediment.

1. Minisola S, Colangelo L, Cilli M, Cipriani C, Pepe J, Romagnoli E. Intermittent high doses of vitamin D: A need for further studies? (Letter). *Calcified Tissue International* 2013.
2. Sanders K, Stuart A, Williamson E, Simpson J, Kotowicz M, Young D, et al. Annual high-dose oral vitamin D for falls and fractures in elderly women: A randomised, double-blind, placebo-controlled study. *JAMA* 2010;303(18):1815-22.
3. Smith H, Anderson F, Raphael H, Maslin P, Crozier S, Cooper C. Effect of annual intramuscular vitamin D on fracture risk in elderly men and women - a population-based, randomized, double-blind, placebo-controlled trial. *Rheumatology* 2007;46(12):1852-7.
4. Tinetti ME, Speechley M, Ginter S. Risk factors for falls among the elderly persons living in the community. *New Eng J Med* 1988;319:1701-07.
5. Sanders K, Stuart A, Williamson E, Jacka F, Dodd S, Nicholson G, et al. Annual high dose vitamin D₃ and mental well-being: randomised controlled trial. . *Br J Psych* 2011;198:357-64 doi: 10.1192/bjp.bp.110.087544.
6. Grant W. Is high dose vitamin D harmful? (Letter). *Calcified Tissue International* 2013.

The authors have stated that they have no conflict of interest.