Reviewer’s report

Title: Pharmacokinetics of a single oral dose of vitamin D3 (70,000 IU) in pregnant and non-pregnant women.

Version: 2 Date: 18 June 2012

Reviewer: Robert P Heaney

Reviewer’s report:

The authors describe a pharmacokinetic study of a single 70,000 IU dose of vitamin D3 in pregnant and non-pregnant women. The studies have been carefully done and well analyzed using state-of-the-art pharmacokinetic methods. The resulting information is useful and should be shared with the scientific community.

The reviewer has two major concerns with which the authors should be able to deal without undue difficulty.

Major Concerns

The reviewer understands that there were actually two studies going on, one of a single dose followed for approximately 10 weeks, and the other of repeated weekly doses. Only data accumulated during the first seven days of the weekly dose study were used for this paper. However, since both Cmax and Tmax do not occur within the first seven days after dosing, it is not clear how the data accumulated in the first seven days in individuals from the weekly dose study can be validly or usefully combined with the single dose data. Nor is it clear that the paper would suffer if their data were omitted entirely. If the first 7-day data are to be retained, the fact of the second study with a different regimen is irrelevant, and it would be sufficient to say simply that 10 week data were obtained on 31 individuals, and one week data on an additional 30 (or whatever the precise numbers may be).

The second concern relates to the length of the paper. Some way needs to be found to shorten both the Methods (8 pages!) and the Results and Discussion. Removing the description of the second study would be one small part of the shortening.

Minor Comments

• Abstract – The Abstract needs explicit quantification of the baseline 25(OH)D value in both groups.
• Page 8, line 4 up from bottom – “14” is a Reference citation, and needs parentheses.
• Page 5, second paragraph, line 3 – Change the word order to: “. . . only those participants . . .”
• Table 2 is probably unnecessary, as there were no significant differences between the groups. (Yes, the entrance 25(OH)D values were different, but there
is no point in computing the probability for them, inasmuch as study design was responsible for the difference, not random chance.)

- Table 3, the entry for half-time – How can the number be 46 days overall, while the two components of the total are 44 and 44, respectively?
- Figure 2 could be omitted.
- Page 13, line 10 – Do the authors mean milligrams or micrograms? The same question arises on page 17, lines 10 and 12.
- What is the justification for computing the geometric mean for serum 25(OH)D? The geometric mean is particularly appropriate for a group of ratios or fractions, such as Ca:Cr, but there is no such ratio for 25(OH)D concentrations.
- Page 17, top paragraph – The explanation given here for toxicity is incomplete and probably incorrect. The best explanation for acute toxicity is the fact that a large dose of cholecalciferol, while still in the circulation, saturates the DBP and displaces calcitriol, thereby increasing its free concentration (which, because of bypassing of physiological controls, produces classic toxicity). For toxicity produced by steady state dosing, it is correct to say that the toxicity coincides with the peak 25(OH)D values. But that may not be true (and probably is not) for acute toxicity, in response to very large single doses. As the authors’ own data show, 25-hydroxylation in many individuals can be quite slow, and in the early days after a very large cholecalciferol dose, most of the binding sites on DBP will be occupied by cholecalciferol, not 25(OH)D. That kind of toxicity can be suspected only from direct measurement of the high serum level of the cholecalciferol and/or by measurement of free calcitriol.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.

Robert P. Heaney, M.D.