Reviewer's report

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

Version: 3 Date: 28 August 2012

Reviewer: Robert P Heaney

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Major Comments

The paper has been substantially improved in revision. I believe, however, that further shortening and clarification would be both possible and helpful. As just one example, the Discussion somewhat duplicates the Results.

There appears to be some internal inconsistency in the presentation, which probably contributes to the length, and which, if cleared up, could both make the authors' points better, and more economically. The authors stress in their Introduction and the Abstract that they focused on a “model-free” PK analysis, i.e., Cmax, Tmax, and AUC, principally. However on pages pp. 10–11 the focus seems to be on a specific model, and in the authors’ reply to my prior comment about discrepancies in the half-time values, the authors state that they used “three models” to compute the half-times. My recommendation is to concentrate on the foregoing PK parameters and on safety, and drop much or all of the rest.

I was initially puzzled by the half-time issue, but focused too exclusively on the discrepancy in the numbers, when perhaps I should have paid more attention to how the half-time was actually calculated (which is not clear in the paper). Presumably it would have been derived from the slope of a log-linear plot of the deltaD25 values after the peak. However, Ilahi and others did not find an exponential curve after a bolus dose, and inspection of Fig. 4 in this paper does not suggest an exponential drop-off. Instead, there is a nearly linear decline in deltaD25 with time. That is not terribly surprising because, despite the authors’ conclusion that a single compartment model works, that is probably not the case, inasmuch as continued, slow release from the fat depots of the native D that was not immediately converted to D25 constitutes a continuing fresh infusion of the precursor for the 25-hydroxylase, thereby “propping up” the serum D25 concentration. In the final analysis I am not sure what a half-time estimate contributes in this context. Nor am I sure what it means. Half-time of what? D or D25? in what body compartment?

The authors make reference to some of the other papers describing D25 status in pregnancy, but completely omit the Hollis/Wagner paper [JBMR 2011;26(10)234-257], which is substantially larger than the current study (though it involved continuous moderately high dosing rather than a bolus dose). Hollis and Wagner were also concerned with safety, and provided a great deal of data to that end. At very least their findings need to be integrated with those of the present study.
Minor Comments

• Page 8, bottom – Please give the units for the adjusted calcium algorithm.

• Pages 12–13 – The authors state that the day 2 value was significantly lower in the pregnant group (which the graphs seem to support), but significantly higher at day 21, which is not apparent from inspection of the graphs, particularly Fig. 3. I do agree, however, that the overall shape of the graphs suggests slower 25-hydroxylation in the pregnant women.

• The term “deltaCavg28” is unclear, and might be best simply spelled out.

• Page 18, line 3, et seq. – The authors state that references to the mechanism of toxicity were removed from the paper, but this one remains, and I still think that it is incorrect. According to Vieth, the toxicity is due primarily to displacement of 1,25D from the D-binding protein. For bolus doses, such as used in this study, there would not be time for a substantial rise in 25D. Interestingly, and consistent with some displacement of 1,25D from the D-binding protein, is the trend for a rise in serum calcium (though within normal limits) in the days following the single dose.

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 interest.