Discussion Supplement


Ocampo-Pelland, Alanna S.* (1,3), Gastonguay, Marc R. (1,2,3), French, Jonathan F. (2), Riggs, Matthew M. (2)

(1) University of Connecticut, Department of Biomedical Engineering, Storrs, CT USA (2) Metrum Research Group LLC, Tariffville, CT USA (3) Metrum Institute, Tariffville, CT USA

Journal of Pharmacokinetics and Pharmacodynamics

*alannao@metrumrg.com

Data Limitations

There were several limitations to the model development, including shortcomings of the data itself. Very few studies collect serum parent concentration data because it is difficult to measure [1]. There is a similar shortage of data measuring 25OHD3 after dosing metabolite. Only 12 arms of parent data (D3-D3) from 7 different studies were found during the literature search. Eleven individuals and 7 arms of metabolite data (25D3-25D3) were found from across 5 different studies. This paucity of parent data made it especially difficult to develop the parent model on its own in a piece-wise fashion, particularly the estimation of its non-linear parameters. Even though the 25D3-25D3 dataset was very limited as well, the metabolite model was better informed by its data than the parent model because of a combination of individual and arm-level data as well as IV data. Another issue with the parent (D3-D3) and metabolite (25D3-25D3) data was sparse sampling. The first samples began >= 20 hours post-baseline in almost every study, making the estimation of KA very difficult. It was for this reason that KA was fixed to an estimate from a D2 parent model, which has not yet been published.

The single dose data in both the D3-D3 and D3-25D3 datasets were not well described by the model. There was a tremendous amount of variability in the single dose data. Vieth et al [2] excluded all single dose data from their review of several Vitamin D3 studies because of similar large variability present in their metabolite data. The single dose data in the dataset was retained, but there was no concern about being unable to fit it as well as the multiple dose data because large bolus doses (e.g. >= 10,000 IU/d) are not typical clinical regimens in the United States [2]. The large variability may have been due to the data’s sparse sampling (especially during the absorption phase) or a failure to control D3 intake external to the study dose. In Ilahi et al [3] the maximum D3 concentration for an arm (n = 30) given a single 100,000 IU/d dose of D3 (baseline D3 concentration = 5 nmol/L) was 532 nmol/L at 24 hours post dose. In Armas et al [4] the maximum D3 concentration for a single D3 dose of 50,000 IU/d (n =10) was only 38 nmol/L at 24 hours. Both arms had similar parent baselines. The population predicted maximum concentration for this latter dose was 168 nmol/L. It’s possible that the peak concentration in the Armas et al study was missed during the 24 hour period between the bolus dose and the first post-baseline measurement.

The single dose, individual-level data in the D3-25D3 dataset from the Jetter et al [5] study was also suspect. Metabolite concentrations continued to rise after the initial peak, leading to suspicion that additional amounts of D3 were being ingested or large amounts of endogenous D3 were being produced. The study was conducted between January and July 2008 in Zurich,
Switzerland. If the bolus doses were given in the spring or summer months then this might explain the secondary large rise in concentration >= 48 hours post-dose.

There is a general under-prediction of the metabolite data, especially at higher concentrations (Figure 3). This is because of an asymmetrical distribution of observed metabolite baselines for different subsections of the data. The 11 arms of data that have both parent and metabolite concentration measurements (PM1) have observed parent and metabolite baselines between 2-10 nmol/L and 60-85 nmol/L, respectively. The average observed metabolite baseline in PM1 is relatively high at 71 nmol/L. The 106 IDs in the D3-25D3 dataset that have only metabolite measurements (PM0) have 25OHD3 baselines between 7-90 nmol/L with a much lower average baseline of 42 nmol/L. The typical value estimate of DBASE is 3.75 nmol/L, making the average metabolite baseline estimate ~ 40 nmol/L. Therefore, the model is favoring the majority of the data (PM0), which has a typical observed metabolite baseline of 42 nmol/L, making the data with higher baselines (and subsequently higher post-baseline concentrations) slightly under-predicted. As a result, the present model’s use is more reliable for metabolite concentrations between 20-50 nmol/L, as that is where the majority of the data lie. This is also in the range of typical clinical concentrations of 25OHD3. In order to better characterize the kinetics of D3 and 25OHD3 at higher concentrations, consideration of data with higher average baselines and subsequent concentrations is necessary.

References


