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Published literature data on D3 and 25OHD3 pharmacokinetics (PK) have shown considerable variability between studies. The developed PK model simultaneously describes parent D3 and its 25OHD3 metabolite, providing an integrated understanding of variability associated with baseline (BL) values, nonlinear (NL) processes, and inter-assay variability.

Objectives
1. To develop a PK parent-metabolite (PM) model for D3 and its 25OHD3 metabolite
2. To investigate non-linearity in D3 and 25OHD3 kinetics
3. To explore the relationship between D3 dosing and 25OHD3 concentration-response
4. To investigate sources of 25OHD3 variability related to BL and assay type

Background
1. D3 and its metabolites maintain bone health by facilitating the absorption of calcium (Ca) from the gut and kidneys. The active form of D3, 1,25(OH)2D3, provides negative feedback for parathyroid hormone (PTH), which regulates bone remodeling and Ca homeostasis (Fig. 1).
2. Clinical assessment of D3 deficiency relies on measurement of 25OHD3. To date, however, there are no published PK models that describe the D3 dosing-25OHD3 response relationship.

Methods

Results: Model Structure

Graphical Data Evaluation
- Prolonged accumulation suggested multi-CMT disposition
- Non-superimposable, dose-normalized (DN) curves indicated NL kinetics for both forms (Fig. 3) [2]
- Fig. 3: DN D3 (left) and 25OHD3 (right) concentration

Results: Diagnostics & Simulation
- Fig. 5: Observed vs. predicted 25OHD3 conc (top) & residuals plots (bottom); pink = indiv, blue = arms
- Fig. 6: Prediction-corrected visual predictive check (pVPC) for indiv (left) and arm (right) level data
- Fig. 7: BL effect on simulated 25OHD3 conc after 1 year of daily D3 dosing (assay = HPLC-MS, CFB = change from BL, log scale on right)
- Fig. 8: Simulated median 25OHD3 conc after one year of daily D3 dosing by assay type (BL = 40 nmol/L)

Conclusions
- Diagnostics indicated D3 & 25OHD3 were well described by 2 CMT models with 1st order oral absorption, with NL parent and linear metabolite CL.
- Simulations of 25OHD3 conc resulting from various D3 doses indicated an inverse relationship between 25OHD3 BL and response [6] [3], as well as a less than proportional 25OHD3 response.
- Simulations of 25OHD3 conc measured by different assays indicated HPLC-MS and RIA assays provided consistent results with one another. CPA and CHESI assays were more biased and estimates related to these assays were less precisely estimated relative to HPLC-MS. Therefore, assay type should be considered when comparing 25OHD3 PK data.

References