Model-based Meta-analysis for Development of a Population-Pharmacokinetic (PPK) Model for Vitamin D3 and its 25OHD3 Metabolite

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Purpose

Published literature data on D3 and 25OHD3 pharmacokinetics (PK) have shown considerable variability between studies.The developed PK model simultaneously described 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 dosage 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.

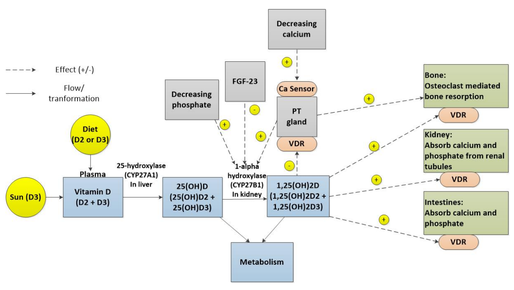


Fig. 1: Metabolism of Vitamin D and its role in Ca homeostasis [4]

References

[1] Jae Eun Ahn and Jonathan L French. Longitudinal aggregate data model-based meta-analysis with nonmem: approaches to handling within treatment arm correlation. *J Pharmacokinet Pharmacodyn*, 37(2):179–201, Apr 2010.

[2] Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. *Dietary Reference Intakes for Calcium and Vitamin D*. National Academies Press, 500 Fifth Street, N.W. Wasington, DC 20001, 2011.

[3] S Harris and B Dawson-Hughes. Plasma vitamin d and 25ohd responses of young and old men to supplementation with vitamin d3. *Journal of the American College of Nutrition*, 21(4):357–362, 2002.

[4] P Lips. Vitamin d physiology. *Prog Biophys Mol Biol*, 92:4–8, 2006.

[5] R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria, 2014.

[6] H Trang, D Cole, L Rubin, A Pierratos, S Siu, and R Vieth. Evidence that vitamin d3 increases serum 25-hydroxyvitamin d more efficiently than does vitamin d2. *Am J Clin Nutr*, 68:854–8, 1998.

Methods

Meta-analysis data search-strategy

- *Data*: public source PK data (D3 & 25OHD3) in healthy or osteoporotic populations were mined from literature (individual (indiv) & arm-level data)
- *Three study types*: (1) **D3-25D3** = D3 administered, 25OHD3 concentrations (conc) reported; (2) **25D3-25D3** = 25OHD3 administered, 25OHD3 conc reported; or (3) **D3-D3** = D3 administered, D3 conc reported

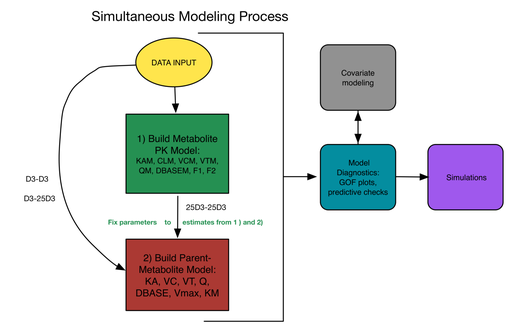
Graphical Data Evaluation

- Consider dispositional characteristics (e.g., 1- or 2-compartmental (CMT))
- Visual inspection of time-course (stationarity) and dose-proportionality (linear vs NL)

Model-development process

- Mass transfer using ordinary differential equations (ODEs)
  - 1- and 2-CMT models
  - Linear and NL clearance (CL)

Fig. 2: Model-development process



Variance Models

All models were run with the first order conditional estimation with interaction (FOCE-I) method. Separate random effects were included for indiv and arms.

Proportional (prop) inter-unit variance structure for PM models:

$P_i = \theta_k exp(\frac{\eta_{kui}}{\sqrt{nOBS_{ij}}})$

where P_i is the estimated parameter value for the ith unit, θ_k is the typical population value of parameter k, η_{kui} are the inter-unit random effects for unit i and parameter k, u is an indicator for whether the data unit is an indiv or arm, and $nOBS_{ij}$ is the size of unit i at time-point j [1]

Prop residual variance structure for PM models:

$C_{obs,ij} = C_{pred,ij} exp(\frac{\epsilon_{uij}}{\sqrt{nOBS_{ij}}})$

where $C_{obs,ij}$ is the observed conc in unit i at time-point j, $C_{pred,ij}$ is the unit-predicted conc, ϵ_{uij} is the prop residual random error

Software Nonlinear Mixed Effects Modeling (NONMEM®) software, v 7.2 (ICON Development Solutions, Hanover, MD); data processing and graphics: R [5]

Results: Model Structure

Literature Search

Table 1: Summary of literature data (SD = single dose; MD = multiple dose)

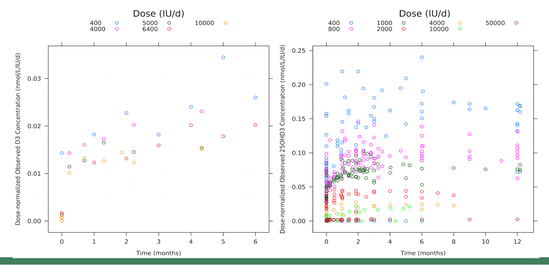
Treatment	Endpoint	Doses	Route/Regimen	Individuals	Arms	Total Subjects	Studies
25OHD3	25OHD3	15-100 µg/d	IV, PO/ SD, MD	11	7	65	5
D3	D3	400-100,000 IU/d	PO/SD, MD	0	12	168	7
D3	25OHD3	400-300,000 IU/d	PO/SD, MD	14	103	5173	53
Totals				25	111*	5406	57*

*Some studies/arms included more than one end-point

Graphical Data Evaluation

- Prolonged accumulation suggested multi-CMT disposition
- Non-superimposable, dose-normalized (DN) curves indicated NL kinetics for both forms (Fig. 3) [2]

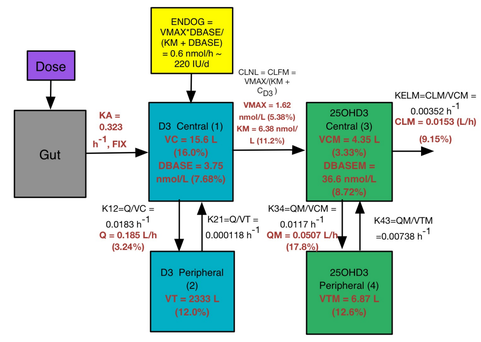
Fig. 3: DN D3 (left) and 25OHD3 (right) concentration



Pharmacokinetic Analysis

- 2-CMT disposition models with inter-unit random effects on VMAX, KM, CLM, DBASE, and DBASEM (Fig. 4)

Fig. 4: Final compartmental PK model for D3 and 25OHD3 [a] [b]



[a] All parameter estimates are relative to bioavailability (F) of parent and metabolite

[b] The following are % coefficients of variation (CV%) and % relative standard errors (%RSE) for inter-unit and residual random effects, weighted by median sample size n = 19 (D3-D3, D3-25D3) and n = 1 for 25D3-25D3: $\omega^2_{DBASE,arm}$: 67.8, 21.7; ω^2_{DBASEM}: 45.5, 40.8; ω^2_{CLM}: 5.57, 458; $\omega^2_{Vmax,indiv}$: 13.0, 70.5; $\omega^2_{Vmax,arm}$: 33.6, 20.3; $\omega^2_{Dbase-Vmax,arm}$: 16.7, 164; $\sigma^2_{25OHD3,prop,indiv}$: 16.7, 7.14; $\sigma^2_{25OHD3,prop,arm}$: 10.0, 10.0; $\sigma^2_{D3,prop,SD}$: 53.8, 8.4; $\sigma^2_{D3,prop,MD}$: 12.6, 31.2.

Results: Diagnostics & Simulation

Fig. 5: Observed vs. predicted 25OHD3 conc (top) & residuals plots (bottom); pink = indiv, blue = arms

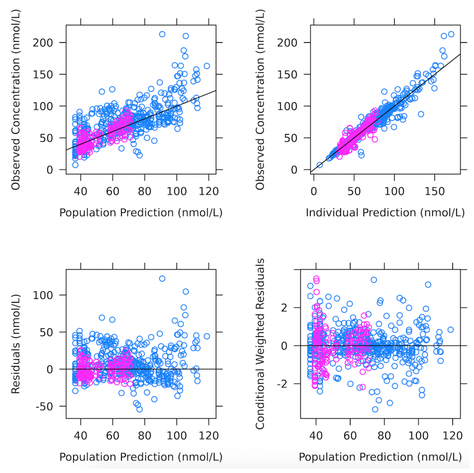
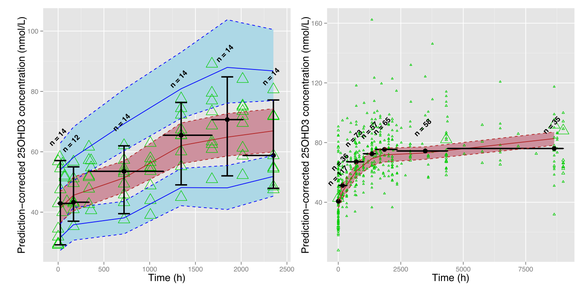


Fig. 6: Prediction-corrected visual predictive check (pcVPC) for indiv (left) and arm (right) - level data [a]



[a] red line = simulated (sim) median (med); blue lines = sim 5th & 95th percentiles (perc); red band = sim 90% confidence interval (CI) around med; blue bands =sim 90% CI around the 5th & 95th perc; black dots = observed med at given time bin; black vertical bars = observed 5th & 95th perc of the observed data; black horizontal bars = time bin range; green triangles = observed 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)

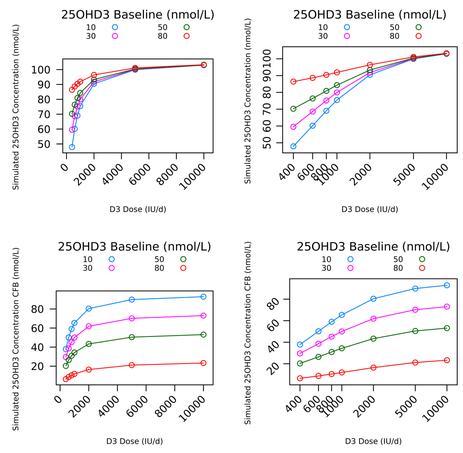
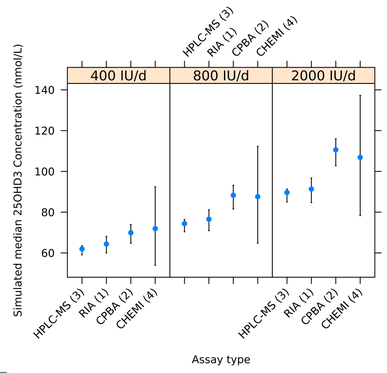


Fig. 8: Simulated median 25OHD3 conc after one year of daily D3 dosing by assay type (BL = 40 nmol/L)



Conclusion

- 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; CPBA and CHEMI 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.