PBPK-PD to Examine $1\alpha,25$-Dihydroxyvitamin D$_3$ Concentrations and Vitamin D Receptor Gene Targets

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Purpose
A physiologically-based pharmacokinetic (PBPK) model was found to adequately describe the dose- and route-dependent kinetics of $1\alpha,25$-dihydroxyvitamin D$_3$ [1,25(OH)$_2$D$_3$], the active vitamin D receptor (VDR) ligand and the changes in mRNA relative expression of Cyp27b1, the synthetic enzyme in kidney, and Cyp24a1, the degradation enzyme, in kidney, liver, intestine, and brain, in mice.

The segregated intestinal flow model (SFM) that describes a low and partial intestinal (blood/plasma) flow to enterocytes, was found to be superior to that without segregated flow (the traditional model, TM). Hence, this resultant SFM-PBPK model was utilized to describe VDR-induced pharmacodynamic effects of VDR target genes: induction of renal and brain P-gp for excretion and brain efflux, TRPV5 and 6 (calcium channel) for calcium absorption, and Cyp7a1 (cytochrome 7a-hydrolase), the rate-limiting enzyme, for the metabolism of cholesterol.

Methods
The SFM-PBPK model was used as a platform for the pharmacodynamic modeling of various VDR related activities in C57Bl/6 mice: (a) renal and brain P-glycoprotein (P-gp) in the excretion of $[^3$H]digoxin, (b) intestinal and renal TRPV5 and 6 for increased calcium absorption, (c) induction of Cyp7a1 that lowers plasma and liver cholesterol, and (d) the increased brain P-gp for excretion of human beta amyloids 1-40 and 1-42 in transgenic Tg2576 mice that display human amyloid beta precursor protein (APP) and plaque formation. The indirect response model was applied to fit data on the relative expression of VDR-target genes and the responses using ADAPT5 (BMSR, USC). The goodness-of-fit was examined with observation vs. prediction and residual plots, and the predictivity was validated by calculating percent prediction error [\%PE=(observations-predictions)/observations].

Results
Excellent agreement was obtained between observed and predicted effects. The calculated median %PE values were acceptable with the range of 25-32%. Fitted parameters such as maximal stimulatory effect ($E_{max}$) and turn-over rate constants [zero-order production rate constant ($k_{in}$) and first-order degradation rate constant ($k_{out}$)] for VDR-target genes were estimated with low coefficient of variations.

Conclusion
The developed SFM-PBPK-PD model successfully characterized VDR-activated gene regulation and serves as a useful tool to predict therapeutic effects of 1,25(OH)$_2$D$_3$ or other vitamin D analogs on cholesterol-lowering and in the reduction brain neurotoxic peptides following different dosing regimen and route of administration.

Reference
1. Ramakrishnan et al. 2016 Drug Metab Dispos 44:189-208
5. Durk et al. 2014 J Neurosci 34:7091-7101