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A Triphasic Physiologically Based Pharmacokinetic Model of Vitamin D3 and Metabolites in Vitamin D Insufficient Patients

Colton W. Sawyer
Southern New Hampshire University, c.sawyer1@snhu.edu

Stacey M. Tuey
University of Colorado, Skaggs School of Pharmacy and Pharmaceutical Sciences, stacey.tuey@cuanschutz.edu

Raymond E. West III
University of Pittsburgh, School of Pharmacy,, raymond.west@pitt.edu

See next page for additional authors

Presenter Information

Colton W. Sawyer, Stacey M. Tuey, Raymond E. West III, Thomas D. Nolin, and Melanie S. Joy

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Presenter: Dr. Colton W Sawyer, Southern New Hampshire University

Abstract: A physiologically based pharmacokinetic (PBPK) model of vitamin D_3 and metabolites was developed to model patients with vitamin D insufficiency status ($25(OH)D_3$ concentrations below 30 ng/ml) in a triphasic study design where patients moved between three vitamin D sufficiency states (insufficient, replenishing, sufficient). In this study, vitamin D insufficient patients were provided with a single dose of 125 ug cholecalciferol, followed for 14 days, and then provided with daily supplementation of 125 ug cholecalciferol for up to 16 weeks until vitamin D replete (plasma concentrations of $25(OH)D_3$ above 30 ng/ml). Stimulatory and inhibitory effects of $1,25(OH)_2D_3$ were incorporated using fold-changes in the primary metabolic enzymes CYP27B1 and CYP24A1. The induction rate of each enzyme was allowed to vary based on total $1,25(OH)_2D_3$ concentration in target tissues, namely the liver, kidney, brain, or intestine. Measures of model predictions agree well with data from metabolites, with 85%-97% of data falling within 2-fold of unity for metabolites. This PBPK model could be a useful tool for understanding connections between vitamin D and its metabolites under a variety of clinical situations.