Simulation of Sublingual and Gastrointestinal Absorption of Nifedipine

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Abstract

Purpose: To develop an integrated model for drug absorption from the oral cavity. The model simulates combined absorption of a drug from both the oral cavity and the gastrointestinal tract.

Methods: GastroPlus® 5.3 with the PBPKPlus™ Module (Simulations Plus, Inc., Lancaster, CA) was used to simulate adult human plasma concentration time (Cp-time) profiles of nifedipine when administered as a 1 mg intravenous (IV) infusion, 10 mg oral capsule (PO), 10 mg oral solution held sublingually (SL) for 7 min and then swallowed, and 10 mg oral solution held sublingually for 20 min and expectorated. A physiologically-based pharmacokinetic model (PBPK) based on adult human physiology was used in all simulations. Tissue/plasma partition coefficients were calculated using in silico physicochemical properties (ADMET Predictor™, Simulations Plus, Lancaster, CA) combined with in vitro measured values where available. Cp-time data from an IV infusion dose were used to fit the systemic clearance model, which was then used in all PO and SL dose simulations. Cp-time profiles after expectorated SL and PO doses were used to calibrate the absorption and first pass extraction of drug from the oral cavity and the gastrointestinal tract, respectively. The combination of these absorption parameters was then used to simulate the SL dose swallowed after 7 min.

Results: The Cp-time profiles for all the dosage forms were successfully modeled with a single absorption-PBPK model incorporating sublingual and gastrointestinal absorption with physiologically-based pharmacokinetics.

Conclusion: The developed generic model can be used for simulation of a variety of dosage forms that deliver drug into the oral cavity. Integration of the new model with the well-established gastrointestinal absorption model (ACAT) provides a mechanistic interpretation of complex formulation issues.

References

7. van Harten J., Lancet 1987, 1363-1364

Conclusions:

Sublingual dosage forms are usually developed to combat problems of standard oral dosage forms – late onset of action and/or high first pass extraction. This would not be the case for nifedipine where the standard PO solution results in a faster onset of action as well as higher bioavailability. Nifedipine seems to have low sublingual absorption and undergoes significant first pass metabolism in the oral mucosa. The final calibrated model was able to correctly predict the sublingual administration with swallowing of unabsorbed amount after 7 minutes with respect to lower bioavailability (~70%), lower Cmax (~130ng/mL) and delayed Tmax (~45 min).