PK/PD modeling of Adinazolam – effect of variability of absorption, PK and PD parameters on variability in PD response

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Purpose: Develop a model for prediction of the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of Adinazolam from IV, immediate release oral, and controlled release oral formulations. Estimate the effects of variability in absorption, pharmacokinetic and pharmacodynamic parameters on PD response

Methods: The PKPlus™ module of GastroPlus™ (Simulations Plus, Inc.) was used to fit PK parameters for Adinazolam from observed plasma concentration-time (Cp–time) profiles after intravenous administration of different doses [1-4]. Oral solution [1,5] and immediate release tablet [2,4] doses were then used to fit the absorption model for Adinazolam in human. The PDPlus™ module of GastroPlus was used to find the relationship between therapeutic PD response (mean sedation score) and the Cp-time profiles of Adinazolam. GastroPlus was then used to run virtual trial simulations to estimate the variability in PD response.

Results: Cp-time profiles after various levels of intravenous and oral doses (immediate as well as sustained release) were successfully simulated with a single fitted model (PK parameters were fitted to IV doses, Peff and first pass extraction were fitted to immediate release oral doses). Similarly, the therapeutic PD response-time profiles were modeled for several different immediate release oral doses (20, 30, 40 and 60mg). For one of these doses (40mg), multiple PD response-time profiles were available from literature. The virtual trial simulations successfully reproduced the variability in observed mean sedation scores for this dose.

Conclusions: A predictive PK/PD model of Adinazolam in human was calibrated. This model accurately predicts the pharmacokinetic and pharmacodynamic behaviors of Adinazolam for several different dose levels and dosage forms. The model can be used to evaluate the changes in PK/PD upon changes in immediate release formulations as well as to predict variabilities in PK/PD due to variabilities in formulation parameters.

References:

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