PK/PD Modeling of Adinazolam

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Abstract:

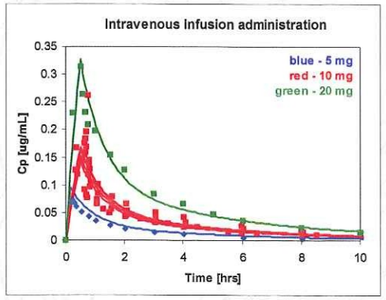
Purpose: Develop a model for prediction of the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of Adinazolam from IV, immediate release oral, and controlled release oral formulations. Estimate the effects of variability in absorption, pharmacokinetic and pharmacodynamic parameters on PD response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

Data

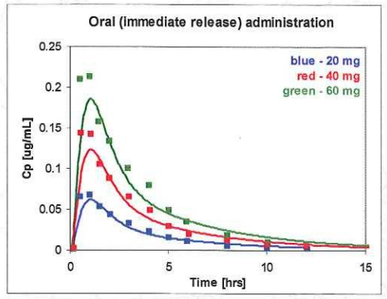
The study was conducted using Cp-time profiles and PD effect (sedation score)-time profiles collected from literature [1-14]. The dataset consisted of multiple PK and PD datasets after *i.v.* and *p.o.* administration. All initial physico-chemical properties are *in silico* predictions (ADMETPredictor™, Simulations Plus, Inc.). Fraction unbound in plasma (Fup) and blood plasma concentration ratio are experimental values reported by Fleishaker [2].

Methods

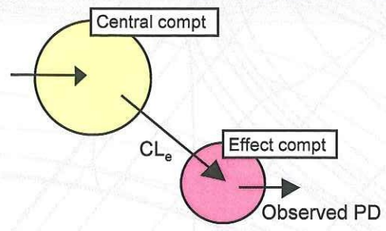
1. GastroPlus was used to obtain Adinazolam pharmacokinetic parameters. A two-compartmental model was successfully fitted across multiple datasets after IV administration for doses ranging from 5 to 20 mg.



2. Oral immediate release formulations were used to optimize the permeability and first pass extraction (FPE). The same model was able to explain the dose range 10 to 60 mg (for picture clarity only 3 doses shown). Fitted FPE (69%) was in good agreement with experimental value (~ 62%). Experimental FPE was calculated from AUC after *p.o.* and *i.v.* dosing. AUC for *p.o.* doses represents an average of the dose normalized AUC values from 14 datasets across doses 10 to 60 mg. AUC for *i.v.* doses represents an average of the dose normalized AUC values from 7 datasets across doses 5 to 20 mg.

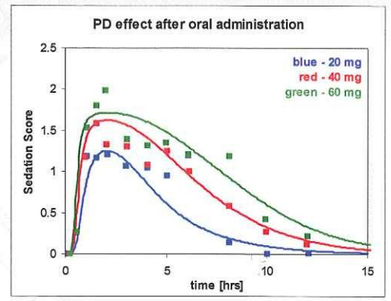


3. The PDPlus module of GastroPlus was then used to fit pharmacodynamic data. An Indirect – Effect Compartment model explained the sedation score data for the dose range 20 to 60 mg (*p.o.* administration). Six of the immediate release *p.o.* formulations had associated PD data; only three are shown in the graph for clarity. *In vitro* Kd, measured as GABA-stimulated CL influx into membrane [15], was used directly for EC50; Fu was estimated by Fup. All parameters from PD model are as shown in the table to the right:

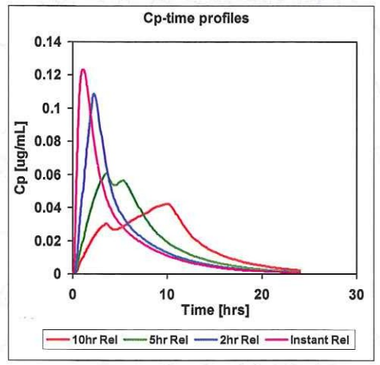


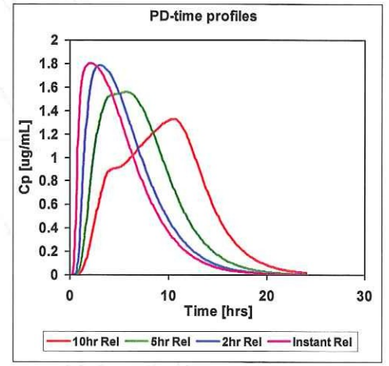
E0	0
E_{max} [a]	1.8
EC50 [b] ***[nM]***	***28***
Hill	2
Cle [h^{-1}]	1
Fu [c] *[%]*	*31*

[a] E_{max} may differ between different studies since it is dependent on arbitrarily set scale
[b] ***corresponds to in vitro measured K_d of GABA-stimulated CL influx into membrane***
[c] corresponds to fraction unbound in plasma

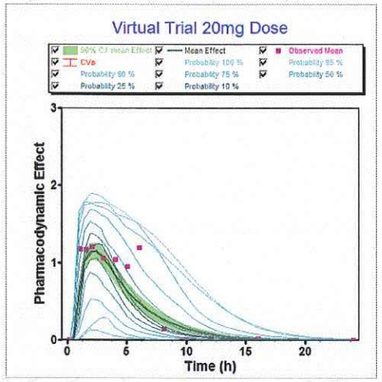


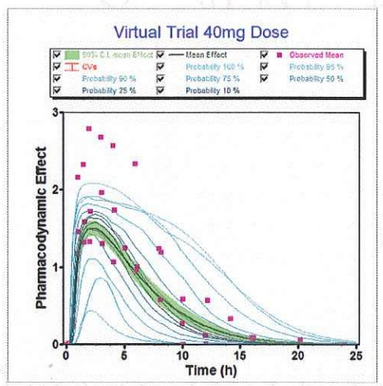
4. The effect of different dissolution rates on the pharmacokinetic and pharmacodynamic profiles of Adinazolam was explored. Cp-time and PD-time profiles were simulated for formulations with a linear drug release, with release time ranging from zero to 10hr. The rate of release greatly affects the onset of drug appearance in plasma, maximum plasma concentration, and the time during which the drug can be detected in plasma. In terms of pharmacodynamic effect, the release rate has high impact on the onset and duration of the effect but not so much on the maximum effect.

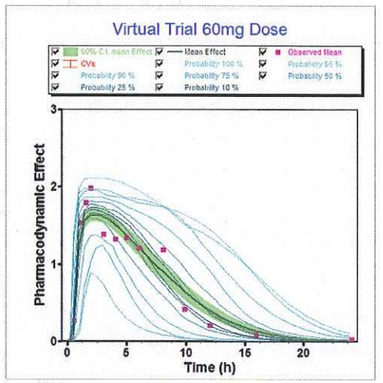




5. Virtual Trial simulations were used to estimate the expected variability in pharmacodynamic response in a population of 50 subjects. A cross-over trial design was used for these simulations so any differences between observed variability in the three dose levels are caused only by differences in the variability of formulation parameters.







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