Effect of Formulation on Adinazolam Pharmacokinetics and Pharmacodynamics

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Introduction

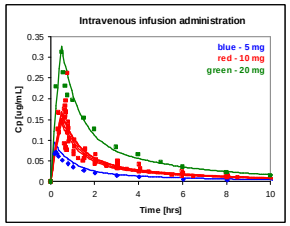
Adinazolam has been reported to have anxiolytic and antidepressant properties [1]. Numerous pharmacokinetic (PK) and pharmacodynamic (PD) studies of immediate release as well as sustained release formulations have been reported in the literature [2-9]. Some of the studies report PK parameters fitted to intravenous or oral doses. One provides an in vivo-in vitro correlation relating the % of drug dissolved in vitro to the % of drug absorbed in vivo [10]. Some PD relationships between the plasma concentration (Cp) and PD effect have been reported as well [9]. However, these models are mostly descriptive in nature and can only be used with difficulties to predict the PK or PD profiles after oral administration of new controlled release formulations. The current study was performed in order to create a comprehensive model for the simulation of the Adinazolam Cp-time profile as well as its therapeutic PD profile as a function of drug release from the formulation, taking into account the physiological parameters of the in vivo system. Such a model can be useful in predicting the PD effect of various Adinazolam formulations or to help in design of formulations with desired strengths and durations of PD effect.

Data

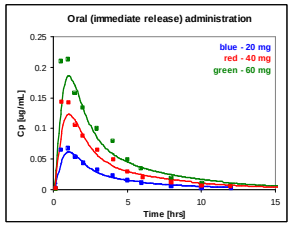
The study was conducted using Cp-time profiles and PD effect (sedation score)-time profiles collected from literature [1-14]. The dataset consisted of multiple PK and PD datasets after *i.v.* and *p.o.* administration. All initial physico-chemical properties are in silico predictions (ADMETPredictor™,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

Methods

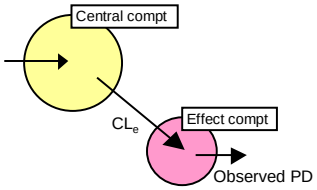
1. GastroPlus™ (Simulations Plus, Inc.) was used to obtain Adinazolam pharmacokinetic parameters. Two-compartmental model was successfully fitted across multiple datasets after IV administration for doses ranging from 5 to 20 mg.



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.

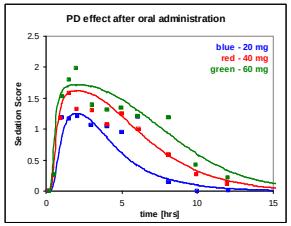


3. The PDPlus module of GastroPlus was then used to fit Pharmacodynamic data. An Indirect – Effect Compartment model explained the sedation score data for the dose range 20 to 60 mg (*p.o.* administration). Six of the immediate release *p.o.* formulations had associated PD data, only three shown in graph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

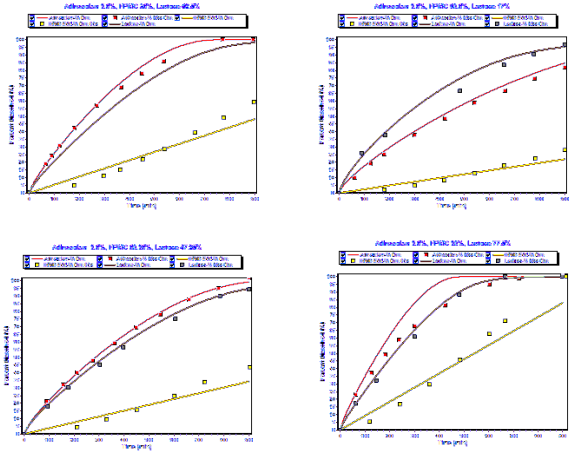


E0	0
E_{max} [a]	1.8
EC50[b] [nM]	***28***
Hill	2
Cle [h^{-1}]	1
Fu[c] [%]	***31***

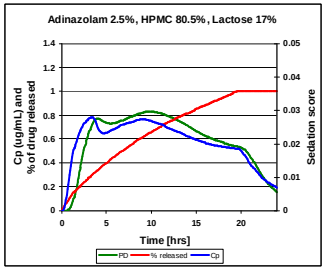
[a] E_{max} may differ between different studies since it is dependent on arbitrarily set scale
[b] corresponds to in vitro measured K_d of GABA-stimulated CL influx into membrane
[c] corresponds to fraction unbound in plasma



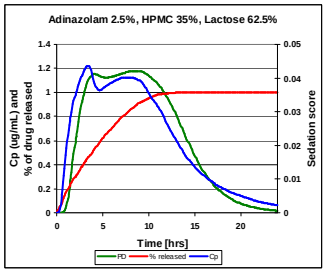
4. DDDPlus™ (Simulations Plus, Inc.) was used to model Adinazolam dissolution/release from swellable polymer matrix tablets based on a dissolution model reported in the literature [16]. The model was able to predict/simulate the release of Adinazolam, HPMC and lactose from several formulations with different ratios of the three ingredients, with HPMC content from 35% up to 80%. As shown in figure D below, the Adinazolam release was significantly overestimated with formulation containing only 20% of HPMC.



5. The dissolution profiles of Adinazolam from polymer matrix tablets simulated in DDDPlus were used as release profiles in GastroPlus simulations to predict the Cp-time profile and Pharmacodynamic response profile (assuming that *in vivo* Adinazolam release is the same as *in vitro* release). The simulation results for the formulations with the lowest and the highest HPMC content are shown below.



High content of HPMC leads to very slow drug release (with all drug being released over ~20hrs). The slow release results in lower but steady Cp and long lasting sedation (sedation score is between 0.5 to 0.9 for about 15 hrs).



Lower content of HPMC leads to much faster drug release (with all drug being released within ~10hrs). This causes the plasma concentration to spike and subsequently decrease much faster. Similarly a sedation with quick onset but short duration is predicted

Conclusions

The fitted model can be used further to optimize the formulation (adinazolam dose and ratio of HPMC and lactose) for desired pharmacodynamic effect -such as a quick onset of effect that wears off quickly or a sustained effect for a longer period of time. This study also provides the protocol for creating similar models for other drugs where less information from clinical studies is available.

References

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