Population PK/PD of Alprazolam in the Attenuation of ACTH Activation Induced by Cognitive Performance in Metyrapone-treated Healthy Volunteers

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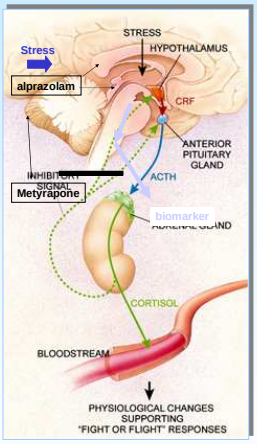
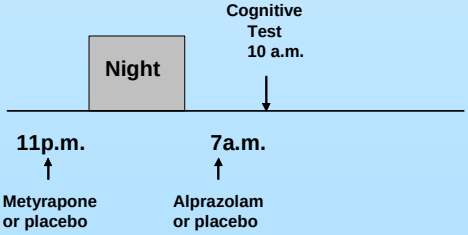
INTRODUCTION



Clinical investigations of patients with Major Depressive Disorders (MDD) and, to a lesser extent, Anxiety Disorders, shown that hypercortisolaemia is the most prominent neuroendocrine abnormality, present in approximately 50 to 60% of patients with MDD.
Hypercortisolaemia appears to be linked to increased ACTH (adrenocorticotrophic hormone) release, produced by a pathologic enhancement of the production of the hypothalamic releasing factor. The control of ACTH release from the pituitary is under hormonal controls. Stimulating effects are produced by the peptide CRH released from the hypothalamus under stress. Inhibiting effects are produced by circulating cortisol, whose release from the adrenal glands is in ACTH-dependent. Metyrapone, an inhibitor of the cortisol synthesis, attenuate the cortisol negative feedback on ACTH release, resulting in an enhanced sensitivity to the stimulating effects of CRH.

STUDY DESIGN

The experimental paradigm chosen is a hypocortisolemia induced by metyrapone producing an enhanced sensitivity of ACTH response via a feedback mechanism. Under this condition the effects of a ACTH realizing test was evaluated: cognitive test (psychological stressor). The inhibitory effect produced by Alprazolam, acting only centrally, was evaluated versus placebo. Two groups of healthy subjects were enrolled in a cross-over design, one group for Part A and one group for Part B. In Part A, subjects were exposed to two dosing sessions (each consisting of 2 consecutive days), with 7day wash-out. Session 1 was without and session 2 was with metyrapone . In part B, subjects were exposed to cognitive test under metyrapone (Session. 1) and with a single dose 0.75mg Alprazolam dose or placebo (session 2).



OBJECTIVES

To investigate the effects of Alprazolam versus placebo on ACTH levels over time and to build a PK/PD model describing the time-course of ACTH response in presence of Alprazolam.

METHODS

The relationship between ACTH and Alprazolam plasma levels was studied using an indirect PD response model. The rate of change of the ACTH response over time with no drug present was described by

$$\frac{dR}{dt} = k_{in} - k_{out} \cdot R$$

kin is the zero-order constant for production and *kout* is the first-order rate constant for loss. The circadian fluctuation of ACTH in the absence of metyrapone was described by a cosine function over a 24h period.

$$h_{in}(t) = h_{out} Ro_{End} \cdot \left(1 + Amplitude \cdot \cos\left[\left(t - t_{\max}\right)\frac{2\pi}{24}\right]\right)$$

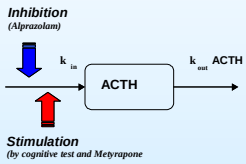
The PK/PD model was developed in a stepwise fashion and described the change in ACTH over time with the effect of cognitive test at 3h post-dose. The final model represents inhibitory processes that operate according to the classical inhibitory function:

$$I(t) = 1 - \frac{C_p}{C_p + IC_{50}}$$

where *Cp* is the Alprazolam plasma levels and *IC50* is the Alprazolam plasma levels producing 50% of maximum inhibition. The rate of change of R was described by

$$\frac{dR}{dt} = k_{in} \cdot I(t) - k_{out} \cdot R$$

A mixed-effect modelling approach (NONMEM) was used to estimate the model parameters.

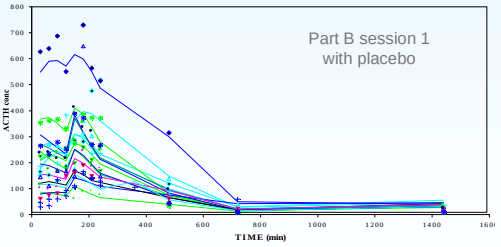


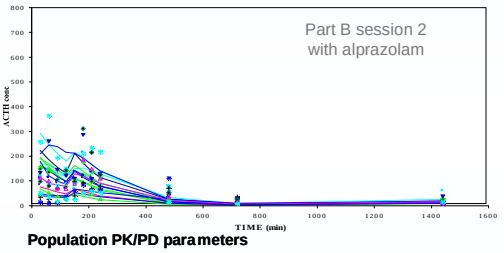
RESULTS

ACTH circadian fluctuation was described by a cosine function over 24h period. The experimental paradigm including a cognitive test was not suitable to describe any further shorter-period fluctuations.
Increase of ACTH over time was produced by metyrapone. No appreciable effect on ACTH plasma levels was observed after cognitive test (indirect and central) without metyrapone whereas ACTH plasma levels in presence of metyrapone were further enhanced by the cognitive test. Individual PK/PD parameters were estimated for ACTH in the basic experimental setting (only cognitive test) and under metyrapone treatment in part A.

RESULTS cont.

Post-hoc individual parameters were estimated for subjects in part B. Alprazolam significantly decreased ACTH plasma levels. The estimated IC50 of Alprazolam was 5.65ng/mL.
Figure 1 and 2 showed the observed plasma concentration over time together with prediction in the metyrapone experimental setting with (2) and without (1) Alprazolam co-administration.

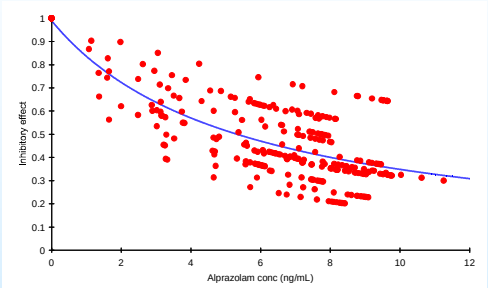




Population PK/PD parameters

Parameter		Estimate	ETA
Fixed Effect Parameter			
θ_1	IC50 (ng/mL)	5.65	0.32 [b]
Random Effect Parameter			
σ^2	Proportional residual error	0.12	
σ^2	Additive residual error	42	

[b] Exponential model



CONCLUSIONS

Metyrapone increases ACTH levels over the 24hour by indirect effect and points out the effect of cognitive test on the ACTH levels. Both effects were attenuated by Alprazolam in exposure-dependent manner, with an IC50 estimated a 5.65 ng/mL. This work indicates the possibility to investigate GABAergic compound using endocrinologic endpoints and PKPD modelling.

REFERENCES

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