EFFECTS OF A SMALL DOSE OF TRIAZOLAM ON COGNITIVE FUNCTION AND RESTING EEG


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INTRODUCTION

EEG recording is a validated and flexible technique for investigating on line the neural electrophysiological activity. It can provide objective, quantitative, non-invasive and reliable information on brain activity. Wide availability, relatively low costs and high time resolution are additional features.

The last decades have provided standardized data not only for the resting EEG activity but also data about the modification induced by exogenous stimulations (i.e.: visual, olfactory, auditory, EEG) and the late signal components (event related potential, ERP) to evaluate also some aspects of the cognitive process.

Triazolam (TRZ) is a widely used benzodiazepine (BDZ). It is the best specific BDZ because of its quick action, short half-life and reduced side effects.

The study of Lantieri et al. shows that a low dosage of TRZ can reduce slightly BDZ typical alterations in EEG (only the beta band power value was significantly elevated after TRZ administration if compared to placebo) and the BDZ typical alterations in P300 (prolongation in latency and reduction of amplitude) without distinct general sedation and subjective sleepiness.

TRZ can be used to demonstrate the effectiveness of the technique to discriminate electrophysiological alteration in resting EEG and P300 when compared to placebo and to verify the hypothesis that low dose of TRZ may produce cognitive impairment before inducing sleepiness.

OBJECTIVES

• Set up resting EEG and auditory P300 recording
• Evaluate the effects of a single dose of Triazolam on resting EEG and auditory P300
• Investigate the reproducibility of the EEG and auditory P300 recording

MATERIALS & METHODS

1.1. Study Design

Study Population

Healthy male volunteers, from 18 to 35 years old

Free from any kind of psychoactive drugs for at least 3 months

Normal acoustical function

Right-handed subjects

This is a double-blind, randomized, placebo-controlled, 3 period cross-over study to evaluate resting EEG and auditory P300 under oral placebo in 9 healthy young subjects. Subjects will attend the Glaxo GSK Verona Clinical Pharmacology Unit in three different occasions at least 3 days apart.

A resting EEG and auditory P300 will be recorded before the drug administration. EEG and P300 will be recorded 2, 4 and 8 hours after the administration of 0.125mg of Triazolam single dose or Placebo (in two occasions).

A blood sample for the evaluation of pharmacokinetic concentration of Triazolam, will be taken pre-dose and 0.5, 1, 2, 4, 6, 7 and 8 hours after the drug administration.

NEUROPHYSIOLOGICAL MONITORING: in all patients we recorded resting EEG, P300 ERPs.

P300: auditory oddball paradigm (OB); two stimuli are presented in a random series with one of the two occurring relatively infrequently and rarely (target stimulus is set at 20% and the non-target or standard stimulus at 80% with an interstimulus interval of 2-3 s). The subjects is required to discriminate between the two stimuli by responding to the target. The auditory version of this paradigm uses two different tones with mentally counting and not responding to the other.

The recording were performed on 2 channels (Cz, Pz referenced to the linked ears; analysis time 1 sec, bandpass 0.5-10 Hz).

Each subject will receive a single dose of 0.125mg of TRZ and placebo (in two occasions), in accordance with the randomisation list. There will be a washout of at least 3 days between each study occasion.

Pharmacodynamics

Absence of relative power data and percent of alfa-activity and beta-activity

Global EEG spectrum power and mean frequency

Latency and amplitude of P300 wave in Cz and Pz

Absolute and relative power data and percent of alfa activity and beta activity

Safety

Full medical history, physical examination, laboratory safety screen, acoustic function with acoustic threshold evaluation, resting EEG and auditory P300 parameters, blood tests for HIV and hepatitis B and C, 12-lead ECG and urine drug screen will be performed within 3 weeks of the first study day. During the study adverse event enquire will be made prior to dosing, at scheduled time-points up to 24 hours after dosing and in the post-dose assessment.

Pharmacokinetic measurements

Blood samples for determination of Triazolam plasmaic levels will be taken pre-dose and 0.5, 1, 2, 4, 6, 7 and 8 hours after each dose. Pharmacokinetic parameters will be calculated using standard non-compartmental analysis.

RESULTS

After TRZ we found in EEG a significant decrease of alpha (8-12Hz) absolute power in Cz at 2 and 4 h (Cz: 28%, p: 0.05; 27%, p: 0.014), in Pz (32% p: 0.02 at 4 h) and of alpha relative power in Cz at 2h (TRZ: 0.06, p: 0.02) with a significant increase of beta activity (more than 12 Hz) mean frequency at 4 h in Cz (23% p 0.025); we didn't found a significant changes about P300 (mean latency increased at 2 h and mean amplitude decreased 4 h).

Pharmacokinetic measurements

Tmax (mean: 3 h; range: 1-5 h)

Cmax (mean: 0.94 ng/ml; range: 0.5-2.8 ng/ml)

AL/Clast (mean: 3.22 ng/ml)

CONCLUSIONS

TRZ causes a significant modification of ERP parameters with sedative changes observed in spectral EEG analysis without alteration of ERP under simple auditory task.

The EEG data showed a decrease of alpha band (4-8 Hz) with a decreased of alpha activity before increased in beta band (4 h) in according to pharmacokinetic parameters of a time to maximum observed serum concentrations (Tmax of 1 h) (max 0.5-2).

The cognitive impairment of TRZ is reflected by the latency and decrease the amplitude of P300 in normal subjects probably associated with hypnosis in the cognitive process; in recent studies these results are confirmed for low dose of TRZ (0.125 mg) too without any significant ERP changes.

In our study, after low dose drug’s administration we detected sedative changes in the EEG spectral analysis without any significant changes in P300 latency and amplitude. We think that the P300 modifications are secondary to a general sedation or sleepiness rather than a direct effect of drug on cognitive system, possibly only for higher doses.

REFERENCES

