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 devices can provide standardised data not only for the resting EEG activity but also data about the modification induced by exogenous stimulations (evoked potentials) and the late signal components (event related potential, ERP) to evaluate also some aspects of the cognitive process.

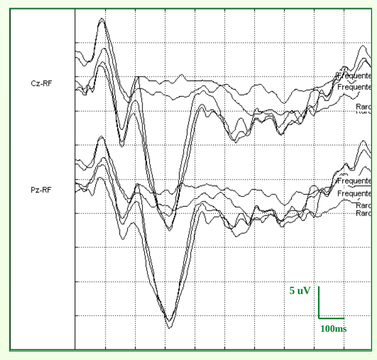
Triazolam (TRZ) is a widely used benzodiazepine (BDZ). It is the best ipnotic BDZ because of its quick action, short half-life and reduced side effects.

The study of Urata et al. shows that a low dosage of TRZ can induce slight BDZ tipical alterations in EEG (only the beta band power value was significantly elevated after TRZ administration if compared to placebo) and the BDZ tipical alterations in P300 (prolungation in latency and reduction of amplitude) without distinct general sedation and subjective sleepness.

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 psycoactive drugs for at least 3 months

Normal acoustic function

Right-handed subjects

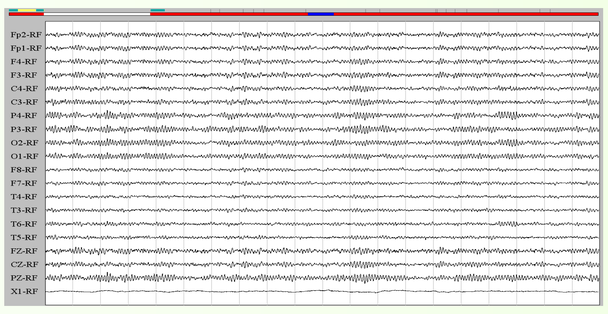
This is a double blind, randomised, placebo-controlled, 3 period cross-over study to evaluate resting EEG and auditory P300 under odball paradigm in 9 healthy young subjects. Subjects will attend the Glaxo GSK Verona Clinical Pharmacology Unit in three different occasion at least 3 days apart.

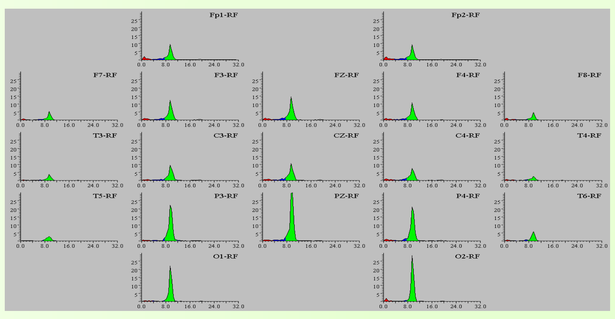
A resting EEG and auditory P300 will be registered before the drug administration. EEG and P300 will be recorded 2, 4 and 8 hours after the administration of 0.125mg of Triazolam single dose or Placebo (in two occasions).

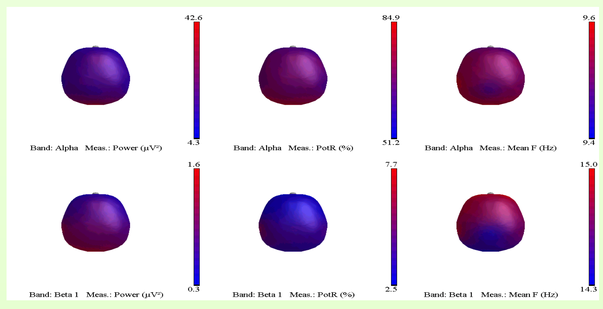
A blood sample for the evaluation of plasmatic concentration of Triazolam will be taken pre-dose and 0.5, 1, 2, 4, 6, 7 and 8 hours after the drug administration.

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

EEG: electrodes Fp1 - Fp2 - F3 – F4 – F7 - F8 -C3 – C4 - P3 - P4 - T3 – T4 – T6 - T5 - FZ - CZ - PZ - O1 – O2 (10-20 International System) with linked-ear reference and X1 for eye movements .







P300: auditory oddball paradigm (OP): 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 nontarget or standard stimuli at 80% with an interstimulus interval 2-3 s). The subjects is required to distinguish between the two tones by responding to the target. The auditory version of this paradigm uses two different tones with mentally counting and not responding to the standard..

The recording were performed on 2 channels (Cz, Pz referenced to the linked ears; analysis time 1sec, bandpass 0.5-30 Hz).

1.2. Control Group(s)

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

Pharmacodynamics

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

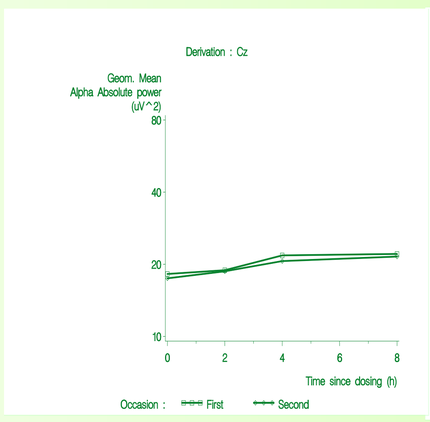
Global EEG spectrum power and mean frequency

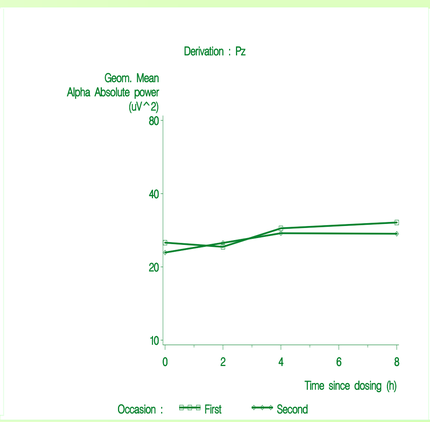
Latency and amplitude of P300 wave in Cz and Pz

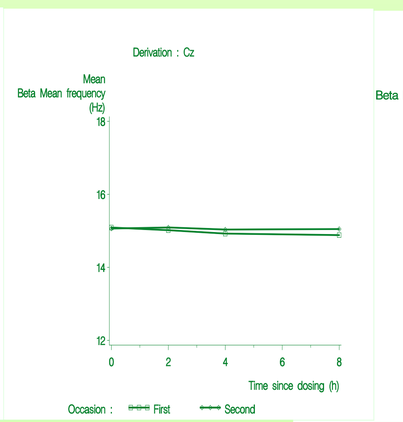
Pharmacokinetics

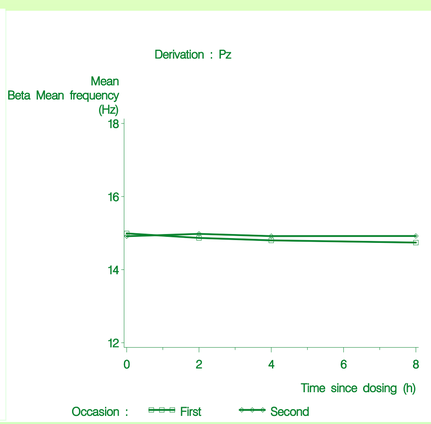
Triazolam plasma concentrations and main pharmacokinetic parameters following single oral 0.125mg dose administration: AUC_{last} , $AUC_{¥}$, C_{max}, and $t_{max.}$

Plot of Resting EEG parameters by Placebo Occasion and Time









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 enquiries will be made prior to dosing, at scheduled time-points up to 24 hours after dosing and in the post-dose assessment.

Laboratory safety screens

These will be performed prior to and 4-10 days after the last session.

Pharmacokinetic measurements

Blood samples for determination of Triazolam plasmatic 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 at EEG a significant decrease of alpha (8-12Hz) absolute power in Cz at 2 and 4 h (Cz: 26%, p 0.05; 27%, p 0.014), in Pz (32% p 0.022 at 4 h) and of alpha relative power in Cz at 2 h (TRZ-PL 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 at 4 h).

Pharmacokinetic measurements

Tmax (median): 1 hour (min - max 0.5-2)
Cmax (geometric mean): 0.94 ng/ml
AUClast (geometric mean): 3.22 ng.h/ml

Summary of Results of Statistical Analysis of Differences from Pre-dose values of Auditory P300 parameters

Parameter : Latency (ms)

Derivation	Planned Relative time	LSmean Triazolam	LSmean Placebo	Difference Triazolam - Placebo	Lower 95% CI Difference	Upper 95% CI Difference	p-value
Cz	2h	18.5	8.0	10.5	-9.3	30.3	0.249
	4h	1.3	9.0	-7.8	-42.1	26.6	0.610
	8h	-6.8	6.4	-13.1	-49.0	22.7	0.415
Pz	2h	14.7	7.1	7.6	-15.9	31.1	0.468
	4h	-0.7	2.9	-3.6	-27.6	20.4	0.731
	8h	-3.0	5.0	-8.0	-39.6	23.6	0.568

Parameter : Amplitude (uV)

Cz	2h	-0.949	-0.349	-0.600	-2.185	0.985	0.408
	4h	-1.408	0.673	-2.081	-4.743	0.582	0.109
	8h	-0.884	-0.123	-0.761	-3.277	1.755	0.505
Pz	2h	0.183	-0.536	0.719	-0.658	2.097	0.263
	4h	-0.763	0.868	-1.632	-4.164	0.900	0.176
	8h	-0.392	0.533	-0.926	-3.800	1.948	0.479

Summary of Results of Statistical Analysis of Log-transformed Differences [*] from Pre-dose values of Resting EEG parameters for each Derivation

Parameter : Alpha Absolute power (uV^2)

Derivation	Planned Relative time	Geometric LSmean Triazolam	Geometric LSmean Placebo	Ratio Triazolam / Placebo	Lower 95% CI Ratio	Upper 95% CI Ratio	p-value
Cz	2h	0.775	1.053	0.74	0.54	1.00	**0.050**
	4h	0.865	1.188	0.73	0.58	0.92	0.014
	8h	1.046	1.222	0.86	0.70	1.04	0.106
Pz	2h	0.704	1.026	0.69	0.45	1.05	0.075
	4h	0.797	1.173	0.68	0.50	0.93	0.022
	8h	1.051	1.202	0.87	0.67	1.14	0.275

Parameter : Beta Mean frequency (Hz)

Cz	2h	0.082	-0.022	0.104	-0.076	0.285	0.218
	4h	0.082	-0.097	0.179	0.079	0.280	0.003
	8h	-0.042	-0.111	0.069	-0.119	0.256	0.421
Pz	2h	0.043	-0.029	0.073	-0.160	0.306	0.491
	4h	0.020	-0.093	0.113	-0.037	0.264	0.120
	8h	-0.029	-0.122	0.093	-0.074	0.260	0.236

[*] : Differences expressed as Ratio of Geom. mean to Pre-dose

CONCLUSIONS

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

The EEG data showed a variation of alpha band (2- 4 h) with a decreased of alpha activity before than increased in beta band (4 h) in according to pharmacokinetic parameters of a time to maximum observed serum concentrations (T_{max}) of 1 hour (min-max 0.5-2).

Therapeutic doses of BDZ are reported to prolong the latency and decrease the amplitude of P300 in normal subjects probably associated with hypofunction in the cognitive process; in recent studies these results are confirmed for low dose of TRZ (0.125 mg) too without any significant EEG sedations.

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, possible only for higher doses.

REFERENCES

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