Statistical Analysis Plan

Modulation of GABA-A Receptors in Parkinson Disease-Flumazenil Arm

NCT03462641

05/31/2022

In this proposal, the investigators present data suggesting that flumazenil (FMZ) administration leads to a decrease in postural instability and gait disorder (PIGD) symptoms of Parkinson's Disease (PD). Further association is made between treatment effectiveness and GABA-A receptor FMZ PET thalamic binding at baseline.

Study participants were pseudo-randomly assigned into A and B sequences, and came in for two visits, with sequence A participants receiving FMZ infusion on the first visit and sequence B participants receiving saline infusion (placebo) on the first visit. The other treatment was given on the subsequent day for participants in both sequences. Detailed motor examination including modified UPDRS was conducted on both days prior to infusion and at 60-90 minutes postinjection. UPDRS PIGD motor subscale score was computed as our primary outcome measure. FMZ PET imaging was done to collect data for the test of interaction between treatment and GABA-A receptor availability.

A paired samples t-test was conducted for each participant's pre and post infusion PIGD score for the flumazenil pharmacological injection treatment only to test whether FMZ pharmacological injection appears to have any effect on PIGD score in a univariate comparison. A repeated measures ANOVA model was used to test the significance of interaction between treatment (FMZ pharmacological injection vs. placebo) and time of administration (pre-infusion vs. post-infusion), with additional three-way interaction term between treatment, time of administration, and sequence (A vs B) included to account for potential confounding effect of sequence. Lastly, a mixed linear model comparison was conducted between the random intercept model and FMZ PET by treatment interaction model, to test the hypothesis that the effect of flumazenil pharmacological i.v. treatment on change in PIGD scores depends on baseline GABA-A FMZ PET receptor availability in the thalamus. Bilaterally averaged thalamic FMZ PET distribution volume ratio (DVR) by treatment (FMZ pharmacological therapy injection vs placebo) was used for the interaction term, and difference between PIGD scores (post – pre) infusion were used as a response variable for that model.