Protocol Synopsis

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

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Axial motor impairments represent a significant cause of disability in Parkinson disease (PD), which is mainly explained by a lack of efficacy of dopaminergic treatments of these symptoms. Treatment approaches to reduce balance problems and falls have been recently identified as the number 1 research priority in PD. Postural instability and gait difficulties (PIGD) motor features are mediated by widespread neural networks that extend well beyond the nigrostriatal system. There is increasing interest in dysfunction of non-dopaminergic neurotransmitters to better understand the complexity of the multisystem nature of mobility impairments in PD. Flumazenil is a short-acting intravenously administered modulator of the γ-aminobutyric acid-A (GABA-A) receptor benzodiazepine binding site, which has shown to rapidly improve motor impairments in PD. Based upon current basal ganglion models in PD, flumazenil could normalize neuronal signaling of hyperGABA-ergic activity in PD.

We have preliminary data that reduced cerebral GABAA receptor availability (likely reflecting increased synaptic or extracellular GABA-ergic activity) as determined by [11C]flumazenil PET imaging has most robust association with axial compared to other cardinal motor impairments in PD. Although flumazenil therapy has been shown to improve motor symptoms in PD, its practical limitation is that it can only be effectively and reliably given intravenously. The overarching goal of this project is to perform biomechanistic GABAA receptor target engagement studies to investigate the effects of GABAA receptor modulation to motor impairments in PD, including PIGD features using i.v. flumazenil vs placebo in a cross-over study design to be correlated to pretreatment C11-flumazenil PET thalamic binding. Our main hypothesis is that negative allosteric modulation of cerebral GABAA receptor activity improves dopamine-resistant PIGD features.