Ability of Partial Inverse Agonist, Iomazenil, to Block Ethanol Effects in Humans

NCT01590277

June 10, 2022

ABILITY OF PARTIAL INVERSE AGONIST, IOMAZENIL, TO BLOCK ETHANOL EFFECTS IN HUMANS

Principal Investigator: Deepak Cyril D'Souza, MD

Objective: The main objective of this study is to evaluate whether iomazenil can attenuate the affective and cognitive effects of alcohol.

Background: The pathological use of alcohol is a major public health challenge facing VHA. Among soldiers returning from Iraq and Afghanistan, alcoholism is one of the most common initial psychiatric disorders. There is a need to develop effective treatments for alcohol intoxication and alcoholism. The stimulation of extrasynaptic $GABA_A$ receptors by ethanol contributes substantially to its effects at doses associated with human intoxication. Therefore, drugs that could block ethanol actions at $GABA_A$ receptors might play a unique role in the treatment of alcohol intoxication and alcoholism. Preclinical studies suggest that benzodiazepine inverse agonists, but not benzodiazepine antagonists, attenuate the effects of ethanol on many levels.

They attenuate ethanol-stimulated Cl^- influx thereby affecting the rewarding, sedating, ataxic, and amnestic effects of ethanol, the discriminative stimulus effects of ethanol, operant behavior motivated by ethanol and ethanol self- administration. However, this has not yet been shown in humans. This project is evaluating the benzodiazepine partial inverse agonist, iomazenil, as an agent that could reverse alcohol's effects on subjective intoxication, alcohol's effects on driving using a driving simulator and on measures of electrophysiology in the laboratory in healthy subjects.

Research Methodology: We hypothesize that: the $GABA_A$ benzodiazepine partial inverse agonist, iomazenil, will attenuate several measures of ethanol intoxication in healthy human subjects. In a double-blind, placebo-controlled fashion, counterbalanced, within-subjects design, participants will receive an intravenous (IV) infusion of placebo or active ethanol (target BrAc=100mg%) followed by placebo or active iomazenil (3.7 µg/kg) administered intravenously via a separate IV. Subjects will undergo four test days. Subjects will receive the following drug combinations: (1) active ethanol and active iomazenil; (2) active ethanol and placebo iomazenil; (3) placebo ethanol and active iomazenil; and (4) placebo ethanol and placebo iomazenil. Measures of intoxication will be collected before, and several times during and after drug administration. Automobile driving will be assessed using a driving simulator. Cognitive function will be assessed using the visual novelty oddball paradigm. EEG will be recorded during the driving simulator and novelty oddball tasks, allowing for the analysis of ERP components related to making errors (error-related negativity, ERN; driving simulator) and target (P3b)

Innovation and Impact: Although inverse agonists have been shown to attenuate several aspects of ethanol in animals, this has not yet been demonstrated in humans. The innovative elements of the study are:1) the use of the only BZ inverse agonist probe available for use in humans – one that was developed at this center and to our knowledge is not available elsewhere for use at pharmacological doses, 2) the use of event- related potential and event-related oscillations, 3) the use of simulated driving, a functional measure of ethanol effects, and driving error-related potentials, 4) the use of eyeblink conditioning as a biomarker of alcohol's effects on cerebellar function. This study may provide insights into the neurobiology through which iomazenil attenuates features of ethanol intoxication in humans. In so doing, this project may help to advance the exploration of benzodiazepine inverse agonists as ethanol "antidotes" and possible treatments for pathological alcohol use. Characterizing the interplay of iomazenil-ethanol interactions on several overlapping measures will contribute to the rational development of agents similar to iomazenil as antidotes or pharmacotherapies for alcoholism.