Clinical Protocol: Influence of Rosiglitazone on Cognitive Function in Patients Convalescing from Traumatic Brain Injury

Introduction

After recovery from traumatic brain injury (TBI), cognitive dysfunction commonly limits return of recovering patients to their previous level of function and employment. Thornhill et al. found that more than three-quarters of patients recovering from severe TBI and more than half of patients recovering from mild or moderate TBI had moderate or severe disability, frequently attributable to memory and learning deficits. To date, despite great progress in physical and psychosocial rehabilitation of these patients, there is no pharmacologic treatment that improves cognitive function.

One likely contributing factor to cognitive impairment after TBI may be chronically increased brain glucocorticoid concentrations. In rats, chronic administration of the glucocorticoid corticosterone impairs memory performance in behavioral tests. In the hippocampus as well as other parts of the brain, circulating inactive forms of glucocorticoids (cortisone in humans and dehydrocortisone in rats and mice) are converted into active glucocorticoids (cortisol in humans and corticosterone in rats and mice) by 11β-hydrosteroid dehydrogenase 1 (11β-HSD1). In healthy elderly men and type 2 diabetics, inhibition of brain 11β-HSD1 with carbenoxolone improved verbal fluency and verbal memory {27009}. Despite the short-term efficacy of carbenoxolone, the drug is unsuitable for long-term administration because it is associated with hypertension, hypokalemia and sometimes severe sodium retention {29258, 29247, 29260, 29264, 29271, 29141, 29142}. Although these side effects can to some extent be controlled with diuretics, they are sufficiently severe that carbenoxolone, despite more than thirty years of clinical use in Europe, has never been approved by the FDA for its originally intended indications of treatment of duodenal and gastric ulcers.

A promising, safer pharmacologic alternative to carbenoxolone is rosiglitazone, a peroxisome proliferator-activated receptor gamma (PPARγ) agonist that has recently been shown to improve delayed recall and selective attention in 20 patients with early Alzheimer disease and amnestic mild cognitive impairment in comparison to a control group treated with placebo. Rosiglitazone is an FDA-approved, commercially available drug that is used alone or in combination with other agents to improve insulin sensitivity in patients with type 2 diabetes mellitus. In a large study of working memory in 145 adults with type 2 diabetes, both rosiglitazone ($p < 0.001$) and glyburide ($p = 0.017$) improved working memory in addition to improving glycemic control. In mice, rosiglitazone also attenuated learning and memory deficits in transgenic Tg2575 mice, a standard animal model of Alzheimer disease.

The cognitive improvement induced by rosiglitazone may be mechanistically related to the improvement associated with inhibition of 11β-HSD1. Inhibition of 11β-HSD1 leads to activation of PPARγ, which may explain both the neuroprotective effects and cognition-enhancing effects of PPARγ agonists. In addition, rosiglitazone down-regulates

expression of mRNA for 11β-HSD1, thereby inhibiting generation of cortisol from cortisone.

The safety profile of rosiglitazone has been well established in the course of its approval for treatment of diabetes mellitus. Rosiglitazone has been extensively tested in diabetic subjects and has few side effects, limited to mild sodium retention, mild weight gain and mild peripheral edema in less than five percent of treated patients; mild fluid retention can be easily managed by reducing the dose of rosiglitazone or adding a diuretic. There is, however, an increased incidence of cardiovascular disease in individuals on chronic rosiglitazone. Although rosiglitazone improves insulin sensitivity, hypoglycemia occurs in fewer than five percent of patients, even when rosiglitazone is combined with metformin.

In summary, rosiglitazone is a safe, highly investigated drug that is approved for the indication of enhancing insulin sensitivity in type 2 diabetics, has a low risk of associated hypoglycemia and that improves cognitive function in type 2 diabetics, mirroring the effects of carbenoxolone, which has far more severe side effects and is commercially unavailable. Consequently, rosiglitazone is well suited for testing as an intervention for improving cognitive function in patients recovering from TBI.

Participants

Participants will be adults who have suffered moderate to severe TBI. They will be recruited from the population of patients who have been treated at the Transitional Learning Center in Galveston, TX, although patients who have not been treated at the Transitional Learning Center will be eligible if they meet the inclusion and exclusion criteria. All subjects will provide written informed consent for the study.

Inclusion Criteria

- Age between 18-55 years
- Ability to consent to the study
- Documented moderate to severe TBI, defined by *one or more* of the following:
    - Glasgow Coma Scale (GCS) score of 3-12 at the time of admission to the hospital after TBI
    - Loss of consciousness ≥30 minutes
    - Posttraumatic amnesia ≥24 hours
    - Positive neuroimaging findings
- Injury at least 6 months prior to admission
- Ability to speak and read English fluently

Exclusion Criteria

- History of glucocorticoid therapy for more than one week in the previous 6 months
- History of congestive heart failure or evidence of congestive heart failure on physical examination
- Diabetes mellitus requiring insulin therapy
- Abnormal renal, liver, and thyroid function tests on screening

- Alcohol intake exceeding an average of two mixed drinks or two beers per day
- Physical limitation, e.g., bilateral paralysis/paresis, aphasia, severe oral apraxia, vision or hearing deficit, that precludes completion of neuropsychological measures
- Neuropsychological evaluation conducted within 6 months that included any of the study measures
- Ongoing medical condition other than TBI that would be expected to affect cognition

Study Design

Randomized, double blinded, placebo-controlled study comparing the PPARγ agonist rosiglitazone (4 mg, orally, twice per day for 12 weeks) with placebo.

Procedure

- Individuals who meet inclusion and exclusion criteria for entry in the study will be asked to grant informed consent.
- Individuals who grant consent will be randomized to one of the two possible treatments – rosiglitazone or placebo. Randomization of the treatments will be coordinated by the central pharmacy of The University of Texas Medical Branch (UTMB), and no staff members in contact with participants during the study will be informed as to the treatment status of the participant until the participant has completed all phases of the study.
- Placebo pills will be prepared by an outside pharmacy.
- On enrollment into the study, all participants will complete a comprehensive neuropsychological evaluation that includes all of the aforementioned measures. This initial evaluation will also include a measure of overall intellectual functioning (Wechsler Adult Intelligence Scale—Third Edition) and a measure of academic achievement (Wide Range Achievement Test—Third Edition).
- Each treatment will last twelve weeks. Individuals in the treatment group will be administered the PPAR agonist rosiglitazone 4 mg, orally, twice per day.
- At examinations at baseline and at intervals of four weeks (end of weeks 4, 8 and 12), a fasting venous blood sample will be taken (≈8:00 a.m.) for measurement of plasma glucose, serum sodium, potassium, chloride and bicarbonate and also serum cortisol, AST, ALT.
- Blood pressure and blood tests will be monitored at baseline and at four-week intervals thereafter.
- Participants will be asked to report unexpected weight gain or peripheral edema to the investigators.
- At the end of twelve weeks, each patient will undergo a battery of tests of different domains of cognition and mood. The tests will take approximately 90 minutes to complete and testing sequences will include rest intervals.

Measures

Baseline

Dementia Rating Scale-2
National Adult Reading Test
Token Test
Visual Form Discrimination Test

Test Battery

Hopkins Verbal Learning Test – Revised (multiple forms)
Brief Visual Memory Test – Revised (multiple forms)
Symbol Digit Modality Test (written and oral versions)
Brief Test of Attention (letters and numbers)
Randt Repeating Numbers (multiple forms) – digit span forward and backward
Hopkins Verbal Learning Test – Revised Delay
Brief Visual Memory Test – Revised Delay
Controlled Oral Word Associated (PRW, FAS, CFL)
D-KFS Category Fluency (alternate forms)
Stroop Color Word Interference Test
Beck Depression
Beck Anxiety

At the end of the study, each participant will be debriefed and have the opportunity to have his/her questions about the study answered.

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Power Analysis

Published studies of the effect of rosiglitazone 2 mg twice daily on cognitive functioning were conducted by Watson et al. in patients with early Alzheimer disease and amnestic cognitive impairment. In that study, which also used a randomized, parallel-group, placebo-controlled design, the influence of rosiglitazone on verbal memory was significant with a sample size of 20 in the treatment group and 10 in the control group. Using a two-sample, two-sided t-test, a sample size of 32 per group in the present study would be needed to have power of 0.8 to detect a similar difference. The larger study of Ryan et al. provides data that suggest an effect of similar magnitude and similar power with the numbers of subjects proposed.

Pilot Data / Power Analysis for TBI Patients

The Rey Auditory-Verbal Learning Test (RAVLT) is a memory test in which the participant is asked to learn a list of 15 unrelated words over five learning trials. The total words recalled over these five trials is a measure of learning. After the 5th learning trial, an interference trial is presented, after which the individual is again asked to recall the original list (short delay free recall; SDFR). After a 20-30 minute delay, the participant is again asked to recall the original list (long delay free recall; LDFR). Below are the means and standard deviations for normal adults for these three variables:

Learning	SDFR	LDFR
53.0 (7.8)	11.2 (2.6)	11.0 (2.8)

Below are the means and standard deviations for eight individuals with postacute TBI recently seen at TLC:

Learning	SDFR	LDFR
35.3 (5.9)	6.6 (1.8)	5.8 (2.3)

Thus, a one SD difference between the treatment and placebo group would be the equivalent of recalling six more words across the five learning trials, or just over one word per trial, and short- and long-delay recall of approximately two more words than the control group. Given the difference in average performance between normals and patients, achieving these gains appears to be psychometrically reasonable.

Data Analysis

Results will be expressed as means ± SD. Appropriate inferential statistics will be conducted based on the nature of the data.