Adverse Effects Evaluation of Pharmaceutical Grade Botulinum Type B (BTX B) Toxin After Intracerebroventricular Administration
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Hypothesis: Slight penetration of BTX B into CSF from brain parenchyma during therapeutic infusion is not likely to cause adverse effects to entire central nervous system.

Proposed research to accomplish: New evidence has suggested that BTX B can inhibit neurotransmitter release from neurons within the brain, specifically the release of excitatory neurotransmitter such as glutamate. This may allow for the silencing of a region of the brain responsible for seizures. Using the relatively new technique of convection-enhanced delivery to deliver an anticonvulsant toxin directly to the specific region of the brain may provide an alternative for resection in epileptic patients. In the event of leakage within the brain parenchyma and possible entrance to the cerebrospinal fluid (CSF), the entire central nervous system will be exposed to the neurotoxin. This study investigated the adverse effects of neurotoxin delivery to the CSF in order to determine the safety of this alternative treatment. Eventually, the anticonvulsant potential of BTX B will be tested using the kindling model of epilepsy in the basolateral amygdala of the rat.

Rats for intraventricular infusion had a guide cannula assembly implanted at the stereotaxic coordinates with respect to bregma of AP - 0.90 millimeters; ML - 1.4 millimeters; and DV - 3.0 millimeters. Three concentrations of two different formulations were infused into the right lateral ventricle of the rats. Animals were closely monitored for 1 hour and monitored daily for at least 3 days for any signs of distress (3 days is approximately equivalent to 7 half lives of BTX B in CSF). If the animals did not show any changes in behavior after single infusion, the procedure was repeated with a higher concentration of BTX B. Since a single dose of BTX B did not cause any behavioral changes, the double amount of the highest concentration was infused and animals were observed for changes in behavior. For repeated infusion, animals were closely monitored for 1 hour and monitored daily for at least 3 days for any signs of distress. If the animals did not show any behavioral changes after previous infusion, the procedure was repeated with the same concentration and amount of BTX B. This was repeated until changes in behavior were observed.

Results: Single intraventricular administration of 5000 U of BTX B caused significant changes in behavior and weight loss in experimental animals. All infusion amounts of BTX B preceding 5000 U (25, 250, and 2500 U) did not cause any weight loss or alter behavior. Repeated intraventricular administration of 2500 U of BTX B significantly influenced weight and behavior of treated animals after two infusions. A single infusion of 2500 U did not affect the rat in a significant manner. Thus, slight penetration of BTX B into CSF from brain parenchyma during therapeutic infusion is not likely to cause adverse effects to entire central nervous system.