

Prolonging the Duration of Effectiveness of Botulinum Toxin Injections

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Botulinum toxin is an effective treatment for benign essential blepharospasm and related focal dystonia disorders. There are two somewhat inter-related issues that unfortunately can limit its long-term effectiveness. First, the duration of effectiveness tends to diminish over time after multiple injection cycles, resulting in the need for reinjection at shorter intervals. Second, there is a group of patients for whom the injections lose effectiveness, and the loss of clinical effectiveness has been linked to the formation of antibodies against botulinum toxin. Thus, there is the potential to decrease the frequency of botulinum toxin injections if the duration of relief from muscle spasms could be increased. Our study attempts to do this.

Botulinum toxin acts by paralyzing the neuromuscular junction, that specialized connection that allows the nerve to communicate with muscles. Very soon after botulinum injections, investigators have looked at changes associated with the return of muscle function. A number of laboratories, including our own, have shown that new nerve fibers begin to sprout from the paralyzed nerves. We have also shown that there is a doubling of the number of neuromuscular junctions on the paralyzed muscles. This increase in sites where sprouting nerves can form connections would increase the speed with which new functional connections can be made - which in turn would result in more rapid return of muscle spasms. We have a number of ideas for co-treatments that might decrease either the nerve sprouting or the new formation of neuromuscular junctions where previously there were none.

Our current study examined several strategies for decreasing the normal doubling of neuromuscular junctions in paralyzed muscle. In a previous study, we showed that excess nerve sprouting that occurs after local tissue injury could be significantly reduced by the co-injection of a drug called corticotropin releasing factor. We hypothesized that the same drug, when injected after botulinum toxin, might prevent the nerve sprouting and new neuromuscular junction formation. Another laboratory showed similar effects on nerve growth with a drug that can bind a factor that normally promotes nerve growth. The drug is an antibody to a growth promoting molecule called insulin growth factor-1.

We have completed the animal testing of these two drugs. As expected, injection of botulinum toxin at a dose similar to that used in patients resulted in a large increase in the number of neuromuscular junctions. When corticotropin releasing factor was

injected after the botulinum toxin treatment, the increase in new neuromuscular junctions was significantly reduced by the combined treatment. The antibody to the insulin growth factor receptor had a similar effect, preventing the increase in neuromuscular junctions observed after botulinum toxin injections alone. We have additional drug candidates to test, but our initial studies are quite promising. While antibody therapy has some associated risks, corticotropin releasing factor is already an FDA-approved drug. While it is beyond the scope of the current study, the next step would be to test these two drugs in a non-human primate. Should these prove as successful as our current studies demonstrate, this could set the stage for a Phase I trial in humans.

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