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COMMENTARY

Botulinum Toxin A: New Hope for RLS?

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Commentary on Rotenberg JS; Canard K; DiFazio M. Successful treatment of recalcitrant restless legs syndrome with botulinum toxin type-A. J Clin Sleep Med 2006;2(3):275-278.

Dr. Justinus Kerner first studied the effects of botulinum toxin during the Napoleonic Wars when increased deaths attributed to food poisoning were observed in individuals consuming blood sausages.[1] Its first therapeutic use was as a treatment for strabismus and blepharospasm, which was explored in the 1960s and approved by the Food and Drug Administration (FDA) in 1989. Since then, botulinum toxin type A (BTX-A) has been tested in a wide array of potential applications. The FDA approved the use of BTX-A for the treatment of cervical dystonia in 2000 and for the cosmetic improvement of facial wrinkles in 2002.

The new study by Joshua Rotenberg and colleagues explores the use of BTX-A in the treatment of persistent restless legs syndrome (RLS). This case series describes 3 adult RLS patients whose symptoms are refractory to conventional treatment or who refused oral medication. The investigators found that the 3 patients given intramuscular injections of BTX-A had symptom relief, less daytime sleepiness by the Epworth Sleepiness Scale (ESS), and/or reduced their medication use.

Any new therapy or an existing medication used for a new indication (i.e., off-label use of an FDA-approved medication) should always warrant the exploration of several key questions:

Is it safe? Coté et al reviewed the adverse events regarding BTX-A reported to the FDA between 1989 and 2003.[1] The majority of these longitudinal data was related to therapeutic use, with a 33-fold higher proportion of serious adverse events for therapeutic use observed compared with cosmetic use.[1,2] This is not too surprising because patients given BTX-A for therapeutic reasons tend to receive higher doses of BTX-A and are generally less healthy. Of the 406 adverse event reports related to therapeutic use, 217 met the FDA's definition of serious and included a wide spectrum of events, including 28 deaths and 17 seizures.[1] However, of the 28 patients who died, 26 had underlying systemic diseases with elevated risk of mortality, and 15 out of the 17 patients with seizures had either a history of seizures or a preexisting condition that may have elevated their risk for seizures. The majority of the remaining serious adverse events corresponded to potential risks described in the FDA-approved labeling (e.g., dysphagia, muscle weakness).

Is it effective? This study represents the first report of BTX-A in the management of RLS, so it would be a large leap to infer effectiveness of BTX-A in RLS based on this 1 study. Nevertheless, all 3 cases showed RLS improvement, and the clinical response was consistent with the specific muscle groups injected as well as the pharmacologic properties of BTX-A. However, RLS is a disorder that is based on subjective reports of symptoms; thus, a placebo effect is always a consideration, especially in a case series with only 3 patients. In addition, the use of clinical assessment of RLS symptoms, daytime sleepiness by ESS, and/or concurrent medication use as outcome measures in this study differ from those used in other clinical studies of RLS treatments; the most notable absence is that of the validated International Restless Legs Syndrome Study Group Rating Scale[3] that is used to assess RLS severity. The effectiveness of BTX-A in RLS also hinges on the premise that BTX-A affects a presumed pathophysiologic mechanism of RLS. The exact pathophysiology of RLS is unknown, but the leading theories involve dopamine, iron, and endogenous opioids. The mechanism of action of BTX-A is to block presynaptic neurotransmitter and neuropeptide release at peripheral terminals, and the study authors highlight the theory that blocking these substances reduces painful impulses and subsequently reduces c-FOS expression and dorsal horn responses in the spinal cord.[4] Although pain is not always present in RLS patients, Stiasny-Kolster and colleagues demonstrated that sensitivity to pin prick was increased in 11 RLS patients, as compared with control subjects.[5] The issue is further complicated by the complex nature of pain processing involving dopamine and endogenous opioids and the recent finding of a subtype of RLS patients with small sensory fiber loss.[6]

How much does it cost? The approximate retail price of 1 unit of BTXA is $5.35.[7] The BTX-A doses, approximate frequency of dose, and estimated annual costs for the 3 cases in this study were Case 1 (100 units, 2-3 months, $2,140-$3,210), Case 2 (320 units, 3 months, $6,848), and Case 3 (70 units, 3 months, $1,498).

BTX-A therapy comes at a high cost, both literally and figuratively. It is expensive, requires an office visit for administration, and has time-limited effects, and its mechanism of action in RLS patients is largely unknown. On the other hand,

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RLS is a disorder that has been demonstrated to have a substantial impact on sleep, daytime function, and quality of life. BTX-A is an option for RLS patients who have failed other treatments, but it is clear that further work using BTX-A needs to be conducted with controlled trials using large sample sizes because the safety and effectiveness of BTX-A in RLS patients has yet to be established.

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