Botulinum neurotoxin A for chronic migraine headaches

does it work and how?

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EDITORIAL

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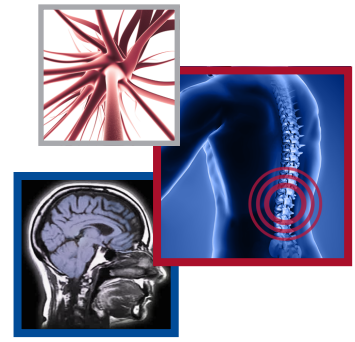

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Does it work?

In 2010, botulinum neurotoxin A (BoNTA) was approved to prevent headaches in adult patients with chronic migraine. The approval was based on the outcomes of two multicenter clinical trials (PREEMPT 1 & 2) that tested the efficacy and safety of BoNTA [1,2]. In PREEMPT 1, the primary efficacy end point, which was the average number of headache episodes, was similar for BoNTA and placebo. However, the number of headache days was reduced in the BoNTA group [1]. In the PREEMPT 2, the primary efficacy end point was the mean change from baseline in headache days from 21–24 weeks post-treatment and was found to be significantly lower in the BoNTA treatment group [2]. A planned pooled analysis of all patients included in PREEMPT 1 and 2 showed significant improvements in all secondary end points with BoNTA compared with placebo [3]. BoNTA was well tolerated, but adverse events including neck pain, muscle weakness, headache and migraine led to withdrawal of a small number of patients in these studies. However, a high placebo effect combined with concerns about inability to blind patients to the paralytic effects of BoNTA and the heterogeneity of the study participants in terms of headache diagnosis, have lead to lingering questions about the efficacy of BoNTA for migraine prophylaxis.

A recent high quality meta-analysis to assess the effects of BoNTA for prophylactic treatment of headaches that included 27 placebo-controlled and four active-controlled trials has addressed questions about efficacy [4]. This analysis found that BoNTA injections significantly reduced the frequency of chronic daily headache and chronic migraine when compared with placebo, but did not have any significant effect on episodic migraines or chronic tension headaches. However, patients who received BoNTA had more adverse events than had been previously recognized and a large placebo effect was identified. Thus, while BoNTA appears to be effective for chronic migraine and chronic daily headache, more evidence-based data is needed to provide reliable information for or against the use of BoNTA in other types of headaches, which include cervicogenic or cluster headaches [5].

KEYWORDS

• chronic migraine • clinical trials • glutamate • headache • muscle • neurotoxin • neurotransmitter release • nociceptor • prophylaxis

"This analysis found that botulinum neurotoxin A injections significantly reduced the frequency of chronic daily headache and chronic migraine when compared with placebo..."

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The findings of these studies provide insight into which headache types might respond to BoNTA, but definitive predictors of individual patient response have not yet been identified. A single study reported a higher response rate to BoTNA when migraine patients who reported 'imploding' headaches, where pain is perceived as emanating from external pressure and includes a significant ocular component, were compared with those reporting 'exploding' headache, where pain is perceived to come from inside the head [6]. Chronic migraine is also more prevalent in women, but whether response to BoNTA differs in a sex-related manner is not known. Migraine aura might also be a predictor of response. While it is clear that additional work is needed to improve identification of best candidates for, and optimal route, location and dose of administration of BoNTA [7], there is general agreement that both fixed-site/fixed-dose and 'follow-the-pain' paradigms are effective for headache prophylaxis [5]. Future clinical trials may also reveal whether other botulinum neurotoxins (e.g., BoNTB) have comparable safety and efficacy profiles to BoNTA.

How does it work?

BoNTA is made up of a light chain, which contains a zinc protease component, connected by a disulfide bridge to a heavy chain that facilitates uptake of the toxin into the peripheral endings of nerve fibers [8]. The toxin rapidly enters the axon terminal by binding to receptors expressed on the membrane [8,9]. In the cytosol, the disulfide bond between the heavy and light chain is broken and the two chains separate. The light chain of BoNTA binds to and cleaves SNAP-25, part of the structure responsible for vesicular docking to the membrane that permits neurotransmitter release [10]. This results in a long lasting, reversible inhibition of neurotransmitter release from the terminal due to the stability of the BoNTA light chain in the cytosol [11]. As a result, injected BoNTA blocks neurotransmission from motor and autonomic nerve terminals, leading to muscle paralysis and inhibition of autonomic function, respectively [12]. It also reduces the sensitivity of sensory afferent fibers to noxious stimulation and inhibits neurogenic inflammation.

For migraine prophylaxis, BoNTA is injected into craniofacial muscles including the temporalis muscle. BoNTA has been found to decrease the mechanical sensitivity of nociceptors that innervate these muscles as well as the underlying periosteum, within 3 h of injection [13,14]. One important determinant of muscle nociceptor mechanical sensitivity is the concentration of the amino acid glutamate in the interstitial space [15]. Intramuscularly injected BoNTA has been shown to significantly decrease muscle interstitial glutamate concentration [14,15]. BoNTA may also block the normal cycling of receptors (e.g., glutamate receptors) from inside the axon to the axon membrane surface [11]. Through these mechanisms, BoNTA would directly attenuate nociceptive input from the muscles. It has recently been found that some nociceptors that innervate the dura, which is proposed to be a principal source of pain in migraines, have extracranial projections to the periosteum underlying the temporalis muscle [13,16]. Thus, it is possible that injection of BoNTA into the temporalis muscle also acts on these extracranial branches of dural nociceptors to lower nociceptive input [13].

It has also been proposed that BoNTA injected peripherally can access the CNS where it could act to decrease synaptic transmission in pain pathways. It has been known for some time that injected radiolabeled BoNTA can be transported through sensory (and motor) axons as far as the CNS [9,11]. Indirect evidence based on immunohistochemical detection of the cleaved form of SNAP-25 has recently suggested that functional BoNTA not only reaches the central endings of nociceptor axons but may act on neurons in the CNS [11]. If confirmed, this evidence would suggest that part of the analgesic action of BoNTA is due to central mechanisms [9,11].

In addition to preclinical work, the analgesic effect of BoNTA in experimental models of pain in healthy humans has also been investigated. BoNTA injection into the human temporalis muscle was found to significantly reduce glutamate-evoked pain and vasomotor responses beginning 3 h after injection and lasting for at least 7 days [17]. These findings suggest a relatively short onset of analgesic effect when BoNTA is injected intramuscularly. It has subsequently been shown that BoNTA decreased pain and cutaneous glutamate release provoked by capsaicin plus mild heat application to the volar forearm, which suggests that attenuation of tissue glutamate concentrations also contributes to the mechanisms of BoNTA analgesia in humans [18].

So, why do these actions of BoNTA decrease migraine headache duration and severity? It

is thought that sustained input from tender craniofacial muscles increases the sensitivity of trigeminal sensory neurons in the brainstem and activates non-neuronal glial cells to contribute to central sensitization; a state of pain hypersensitivity. BoNTA, through its proposed peripheral and central mechanisms, decreases central sensitization and this raises the threshold for headache initiation [10]. Evidence in support of this concept comes from reports that single local anesthetic nerve blocks or even trigger point injections, which provide comparatively short periods of analgesia, also appear to provide long lasting relief from headache in some migraine patients [19]. It is possible that the quick onset of muscle analgesia after BoNTA injection may be as, or even more, important than a long duration of action in terms of decreasing headache frequency. Based on this mechanism, the variability in effectiveness of BoNTA to decrease headache frequency would not be due to a failure of BoNTA to produce muscle analgesia *per se*, but rather to the fact that in certain migraine sufferers, mechanisms other than sustained painful input from craniofacial muscles are responsible for maintaining central sensitization. This may explain the observation that BoNTA is more effective at preventing 'imploding' headaches, which are proposed to be generated by extracranial pain input. It may also explain why subcutaneous injections of BoNTA have also been reported to be effective for headache prophylaxis in certain patients.

Research is currently underway to produce the next generation of botulinum neurotoxins that will be engineered for increased duration of action and improved proteolytic activity. In addition, toxin formulations and novel methods of toxin delivery (e.g., topical) are being investigated as a way to improve efficacy and safety. One interesting direction has involved the creation of a composite protein of the BoNTE protease moiety with BoNTA to produce a toxin that has a more rapid onset of effect, like BoNTE, but lasts six-times longer than this short acting neurotoxin. In a related approach, substance P has been conjugated to the light chain of BoNTA. The conjugated protein was endocytosed by trigeminal ganglion neurons in culture and retained its protease activity against SNAP-25 [20]. This approach could be used to selectively target BoNTA to nociceptors and could one day help answer whether muscle paralysis is important for BoNTA's prophylactic effect against migraine. The ultimate goal is to introduce selective, specific and potent botulinum neurotoxin products to yield unique antinociceptive activity where it is needed.

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