INTRODUCTION:

Since German physiologist Justinus Kerner first described possible therapeutic applications of Clostridium Botulinum toxin in 1821⁴ there has been an unfailing interest in pursuit of new treatment approaches. In the past several decades the pace of investigating this unusual toxin has been accelerated which result in a neuromuscular blocking effect. This toxin was first used clinically in the 1950s but its usefulness to the medical community became clearly apparent when Alan Scott utilized it in clinical trials in the 1970s. Allergan® purchased the rights to the “A” serotype (BTX-A) and by 1989 Botox® was approved by the FDA. The BTX molecule is synthesized as a single 150kD (dodevalapo, a measure of atomic mass) chain formed in 2 parts connected by a disulfide chain. (See Above) The molecule is further identified by its ‘light’ (50kDa) and heavy (100kDa) parts. Essentially, BTX-A is shown to work through inclusion in the cholinergic nerve endings, cleavage and binding to SNARE (soluble NSF attachment receptor) protein receptors thus preventing acetylcholine release from the nerve terminal. Action of BTX-A is slow and manifestation of its effects may be days or even weeks to arise. Complete recovery and original neuromuscular junction regeneration has been demonstrated. Clinicians also saw effects that could not easily be explained by the accepted model of action. Pain relief was reported that did not coincide in proportion with its activity on muscle.¹ Current research now appears to confirm the findings of Wiegand in 1976¹ suggesting axonal migration and secondary central effects.

RATIONALE:

The growing bodies of data suggest that BTX-A has more diverse effects that pharmacologically go beyond its action on cholinergic motor nerve fibers. Recent studies have shown that BTX-A appears to have an independent anti-nociceptive action.² Investigations suggest that the actions of BTX-A affect glutamate, substance P, calcitonin gene-related peptide (CGRP) as well as acetylcholine. As these elements are key in nociceptive response in peripheral sensitization, which can result in central sensitization in the spinal cord, it follows that a breakdown in peripheral nociceptive cascade may be useful in pain control. Data also exists supporting a central analgesic effect from BTX-A transport to the CNS. In addition to the effects on glutamate, Substance P and CGRP it appears that BTX-A also increases enkephalin release and reduces cholecystokinin (CCK) expression.³ (See Figure 1). While the use of BTX-A in managing pain disorders is still undecided, there are uses in augmenting conventional treatments of TMD and secondary cervical pain. In the typical pain practice patients are seldom seen in the acute phase but routinely treated from a chronic history. In most cases, patients were being treated with one or more regimes including agents to reduce neuropathic pain, headache prophylaxis medications, anti-inflammatories or orthotic stabilization. Some of these agents were tapered where BTX-A had reduced pain severity or frequency. Initial patients in the pain clinic were treated with 25-50 units of BTX-A and 80-100 units in the craniofacial clinic. Then, it was decided to use a uniform dose of 100 units for each subsequent patient. In all cases, BTX-A was given intraorally. In the case of painful cervical spine (and headaches), the skin was shaved in 2-3 areas in both sites. In the case of temporomandibular disorder (TMD), a fixed site injection was utilized, as we are studying this approach to treating TMD in an ongoing manner.

RESULTS:

In the case of painful TMD, all 54 (41♀ and 13♂) patients treated with intradural BTX-A had significant reductions in frequency and severity of pain. Average reductions were 75.2% in severity of painful TMD with muscle spasm of cervical origin, with an average response duration of 9.5 weeks (range 4-21 weeks). In patients with coexistent headaches, there was an 80% reduction in average headache frequency over a period of 8 weeks (range 4-18 weeks). The 21 cases of temporomandibular disorder were also treated with all patients reporting reductions in pain averaging 71.2% with subjective lessening of clenching and bruxism. Maximum pain reduction in responders was 12.5 weeks in duration (range 3-40 weeks), with an average reduction of 68% (See Figure 2) in pain symptoms across all categories of patients.

DISCUSSION:

The results presented in this open-label study administering intradural BTX-A in painful TMD states, suggest an excellent ability of BTX-A to reduce nociceptive symptoms by mechanisms other than motor inhibition of muscle contraction. Using this novel administration of the BTX-A, the toxin fragment presumably interrupts ongoing pain signals that promote central sensitization, windup or long-term potentiation in chronic pain and headache states. Whether blockade of glutamate, Substance P, CGRP or other neuromodulators is primarily involved in this process is not known at this time. There is growing evidence to suggest an interaction of BTX-A with sensory affrements in nociceptive fibers.⁶ With rapid pain reduction onset and control averaging 8.5 weeks, clinicians have ample time to initiate a coordinated approach to long term resolution.¹² Likewise, recent research also demonstrates very positive results with BTX-A injection both into the intra-orcular space and into trigger points.¹³,¹⁴ However, the intradural approach appears to be as effective and has the additional advantage of simplicity.

METHODS:

54 patients with a variety of facial pain disorders were chosen from both a neurology headache practice and craniofacial pain practice for treatment with BTX-A. All were female and 13 were male. Average age was 39.4 years (range = 21-75). In most cases, patients were being treated with one or more regimes including agents to reduce neuropathic pain, headache prophylaxis medications, anti-inflammatory or orthotic stabilization. Some of these agents were tapered where BTX-A had reduced pain severity or frequency. Initially patients in the pain clinic were treated with 25-50 units of BTX-A and 80-100 units in the craniofacial clinic. Then, it was decided to use a uniform dose of 100 units for each subsequent patient. In all cases, BTX-A was given intraorally. In the case of painful cervical spine (and headaches), the skin was shaved in 2-3 areas in both sites. In the case of temporomandibular disorder (TMD), a fixed site injection was utilized, as we are studying this approach to treating TMD in an ongoing manner.

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