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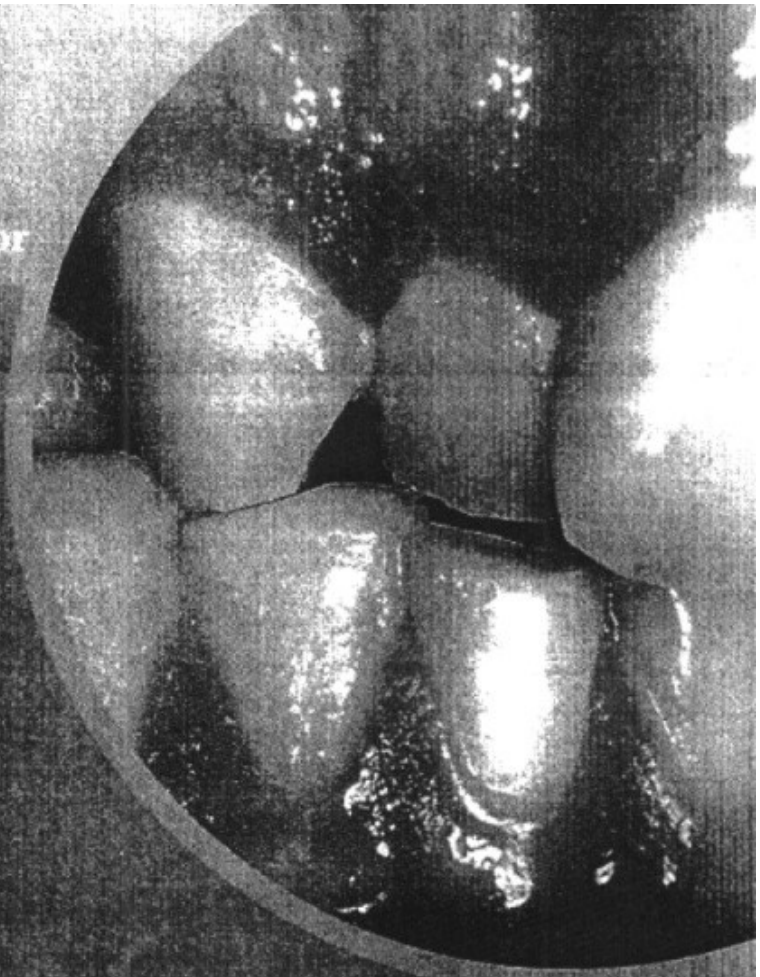

BRUXISM
Theory and Practice

Contributors:

Monica Andersen | Taro Arima | Lene Baad-Hansen
Marta M. Barreiro | Gunnar E. Carlsson
Fernando Cifuentes | Sergio Foster | Jorge Mario Galante
Carlos Gianoni | Fernando Goldberg | Hans L. Hamburger
Faramarz Jadidi | Anders Johansson | Ann-Katrin Johansson
Takafumi Kato | Marcelo Kreiner | Stephanos Kyrkanides
Frank Lobbezoo | Ricardo L. Macchi | Daniele Manfredini
Arturo E. Manns Freese | Machiel Naeije
Luca Guarda-Nardini | Ridwaan Omar | Claudia Restrepo
Xiomara Restrepo-J. | Andres R. Sanchez
Guillermo Schimmi | Teresa Cristina Barros Schütz
José T. T. de Siqueira | Peter Svensson | Ross H. Tallents
Sergio Tufik

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Botulinum Toxin in the Treatment of Bruxism

Daniele Manfredini and Luca Guarda Nardini

Introduction

Botulinum toxin is a neurotoxin produced by *Clostridium botulinum*, a Gram-positive spore-forming anaerobic bacterium, which is responsible for botulism. Botulism is a potentially lethal disease, whose signs include limb paralysis, facial weakness, ophthalmoplegia, dysphagia, dysarthria, constipation (progressing to ileus), dyspnea (progressing to respiratory arrest), and urinary retention.[1] Botulism can occur following ingestion of contaminated food, from colonization of the infant gastrointestinal tract, or from a wound infection. Fortunately, both prevalence and mortality of botulism have markedly decreased in recent years.[2]

Research studies have identified seven neurotoxic types (BTX-A, B, C1, D, E, F, G) of botulinum toxin, of which the first two are primarily responsible for human intoxications.[3]

Botulinum toxins cause a prolonged inhibition of neurotransmitter release at peripheral cholinergic nerve terminals at both neuromuscular junctions and autonomic sympathetic and parasympathetic nerve terminals. The discovery of these properties has been the basis for hypotheses involving therapeutic use of botulinum toxin and, nowadays, this potentially dangerous poison has been transformed into a widely used drug that is useful for the management of several muscle disorders associated with an excessive cholinergic activity.[4]

Indeed, the purification of botulinum toxin at basic research levels has allowed its adoption in the treatment of spasticity,[5] blepharospasm,[6,7] spasmodic dysphonia,[8–10] and cervical dystonia.[11–13]

History of Botulinum Toxin as a Therapeutic Drug

Botulinum toxins are produced by *C. botulinum*, an anaerobic bacterium whose spores are commonly located within the soil. The bacterium grows in a pin-like form within the food only if the contact between the food and the spore occurs under deter-

mined conditions (absence of oxygen, temperature <10°C, acidic conditions). In such an environment, *C. botulinum* can grow and release new spores; ultimately it implodes, thus destroying the cell membrane and releasing its powerful neurotoxins. The seven types of botulinum toxins are actually the most powerful and dangerous among known neurotoxins; and even though they probably have different biochemical properties, they share similar effects on muscle activity – which have been described in detail for the serotype BTX-A.

Studies on BTX-A biochemistry date back to the 1920s, with the first attempts at purifying the toxin. The efforts of Sommer and other pioneering researchers laid the basis for successive studies from Schantz who, in 1946, obtained a purified crystalline form of botulinum toxin, thus improving the quality of future research. Later in the 1950s, Brooks described a temporary paralysis following BTX-A injection in a hyperactive muscle. This effect was described as a consequence of the inhibition of acetylcholine release at motor nerve terminals, and obviously led to a growing interest in the potential therapeutic use of botulinum toxin. A decade later, Scott provided animal experimental models supporting the usefulness of a purified version of BTX-A to correct strabismus (an ophthalmic dystonia) in monkeys. In 1978, Scott obtained US Food and Drug Administration (FDA) approval to begin studies on the effects of botulinum toxin on strabismus in human volunteers. In 1989, botulinum toxin was definitively introduced in the market under the trade name Oculinum, with FDA-labeled indications in the treatment of strabismus and blepharospasm; also included was facial nerve paralysis. Later, a pharmaceutical company, Allergan, bought the BTX-A licence, and changed its trade name to Botox, which is now currently used for a number of muscle hyperactivity disorders. In 2000, both BTX-A and BTX-B (MyoBloc) were approved by the FDA for cervical dystonia; and in 2002 Botox was approved by the FDA for the treatment of glabellar lines, and most recently for primary axillary hyperhydrosis. Thus, from the time of its clinical debut, reports on the indications of BTX have been growing in number and fields of application.

The type-A botulinum toxin has high affinity for the neuromuscular junction and causes a long-lasting inhibition of neurotransmitter release at peripheral cholinergic nerve terminals at both neuromuscular junctions and autonomic sympathetic and parasympathetic nerve terminals.

Like many other biologic and pharmaceutical agents, Botox is produced via a process of fermentation and purification, and available information about its structures and properties will be discussed here.

Mechanism of Action

The size of the structural complex of the different botulinum toxins varies among serotypes, ranging from 300 to 900 kDa. The purified BTX-A has a molecular weight of 900 kDa and includes three proteins: the neurotoxin (made up of a heavy and a light chain for a total 150 kDa molecular weight), a non-hemagglutinin protein, and a hemagglutinin protein (associated with the toxin with the aim to protect it from degradation and combining for about 750 kDa).[14]

The heavy chain of the BTX-A is responsible for binding to its serotype specific receptor/acceptor on the target cell and mediates translocation, allowing for the expression of the light chain outside of the cholinergic vesicle, while the effect of BTX-A depends on the enzymatic action of the light chain (very specific peptidase with a specific target – this region is unique for each serotype).

Once active, the toxin produces a muscle relaxant effect that is local – effective within a predictable radius at the site of injection, and temporary – lasting up to 3–6 months. Muscle relaxation is the result of the block of acetylcholine release at the endplate of the motor neuron.[15]

From a molecular viewpoint, the current hypothesis for its motor mechanism of action in skeletal muscle provides that, at the nerve terminal, botulinum toxin type A induces a temporary chemodenervation through the following steps.[16,17]

The toxin binds to acceptors (yet to be identified) on cholinergic terminals.

The molecule is internalized into the nerve ending by endocytosis.

Once inside the nerve ending, botulinum toxin interferes with the exocytosis of cholinergic vesicles. This leads to chemo-denervation and reduced muscular contractions.

Over time, terminal sprouting occurs.

Finally, the original functional endplate is reestablished and sprouts regress. At this point symptoms may return in some patients.

Fields of Application

In 1990, the National Institutes of Health Consensus Development Conference Statement recommended that botulinum toxin therapy was safe and effective for treating strabismus, blepharospasm, hemifacial spasm, adductor spasmodic dysphonia, jaw-closing oromandibular dystonia, and cervical dystonia;[18] it also stated that BTX is not curative in chronic neurologic disorders. Since that time, clinical and research experience of the use of BTX to treat these disorders has been intense, and BTX-A is currently available under the trade names Botox (Allergan, Irvine, CA, USA) and Dysport (Speywood Pharmaceuticals, Maidenhead, UK) in the USA and Europe, respectively. A purified version of BTX-B has been approved for the treatment of cervical dystonia and is available on the market under the names Neurobloc (Elan Pharmaceuticals, Shannon, Co. Clare, Ireland) and MyoBloc (Elan Pharmaceuticals, San Diego, CA, USA).

A National Library of Medicine's PubMed database search performed with the keyword "botulinum toxin" identified over 8,000 articles, more than half of which regarded the clinical use of botulinum toxin as a therapeutic drug. Along with studies lending support to the above-described indications, research were performed on the use of botulinum toxin in a number of minor disorders related to muscular hyperactivity.

Those so-called emerging applications included treatment for conditions associated with pain (e.g., tension headache, migraine headache, cervicogenic headache, cluster headache, myofascial pain, chronic low back pain, tennis elbow), hypersecretion of glands (e.g., hyperhydrosis, sialorrhea, crocodile tear syndrome, intrinsic rhinitis), excessive or dyssynergic muscle contraction (e.g., myokymia, bruxism, anal fissure, anismus, vaginismus, detruso-sphincter dyssynergia, sphincter of Oddi dysfunction, esophageal spasm, laryngeal and pyloric spasm, achalasia), and for cosmetic use.[19,20]

Promising data have emerged for all of these indications and, even though the quality of published papers has not been excellent so far, thus needing to be consistently improved before definitive confirmation of results, it appears that botulinum toxin may find increasing application in the future.

Safety of Botulinum Toxin Treatments

Botulinum toxin therapy is effective for several of the disorders described above, and has a good safety level. The only absolute contraindications to its use are allergy to the drug and infection/inflammation at the site of the injection; safety for use during pregnancy, lactation, and childhood has not been assessed. Diseases of neuromuscular transmission, coagulopathy, and inability of the patient to cooperate are relative contraindications.[18]

Nonetheless, therapeutic administration of botulinum toxin must be performed by skilled practitioners, possibly within a skilled interdisciplinary team, owing to the risk of side-effects and complications.

Side-effects are usually transitory and well tolerated. They are mainly related to diffusion of the

drug into the nearest muscular groups, thus being different in dependence of the target muscles and the type of the treated disorder. Systemic complications and side-effects, such as generalized weakness or severe electromyographic abnormalities, are rare.

A small percentage of patients develop antibodies to the toxin and, even though the mechanism leading to the development of antibodies is unknown, this may be a main reason to explain therapeutic failure.

Orofacial Pain Relief

Once the use of botulinum toxin was settled as a possible therapeutic approach to muscle hyperactivity-related disorders, research began to support its use as a pain relief drug as well. Indeed, in most patients pain relief exceeded the benefits related to the reduction of muscle activity, as observed with electromyographic (EMG) recordings. These observations were mostly valid for cervical dystonia[21,22] and were the basis for successive studies on the usefulness of botulinum toxin in the treatment of orofacial painful disorders.

There is a limited amount of literature suggesting that the analgesic effect of BTX-A is related to reduction of the local release of nociceptive neuropeptides from either cholinergic neurons or from other nerve terminals in vivo, which would prevent the local sensitization of nociceptors and thus reduce the perception of pain.[23,24] This mechanism of action appears to be independent of the reduction of muscular hyperactivity, and is in line with current theories supporting a non-linear relationship between pain and EMG signs of neuromuscular activity.[25,26] BTX-A hence found applications in a number of orofacial pain disorders, such as various types of headache and temporomandibular disorders.

Botulinum toxin was introduced in the treatment of tension-type headache owing to the supposed role of muscle activity in its pathogenesis.[27] Nonetheless, there is a paucity of literature on this issue, and findings are not consistent among the different studies.[28-31] This suggests that larger sample investigations are needed, with a well-defined and homogeneous study protocol with regard to the dose and site of BTX-A injections in these patients.[30]

In contrast, botulinum toxin has been found effective in the treatment and prophylaxis of migraine headache, as measured on subjective rating scales, on the basis of currently available clinical trials.[32,33] With regard to cervicogenic and cluster headaches, only pilot data have been published so far, and they are mainly based on case reports, so they need to be further assessed.[34,35]

Temporomandibular Disorders

Interestingly, botulinum toxin has shown good therapeutic efficacy in the approach to some forms of chronic myofascial pain, a term which is used here in its wide definition of being a localized musculoskeletal pain with tenderness in association with trigger points. Given the inconsistent findings reported by the literature on the use of non-steroidal anti-inflammatory drugs, steroids, antidepressants, and other drugs in the treatment of these disorders – and considering that corticosteroids, which are the currently adopted first-choice drugs to treat chronic myofascial pain, may produce undesired systemic and side-effects – some trials have assessed the analgesic efficacy of BTX-A in such patients.[36-38]

Literature findings are generally supportive of an efficacy of botulinum toxin in the treatment of these disorders, being superior to both placebo saline solution and methylprednisolone injections. However, all the research on the therapeutic use of botulinum toxin has a common limitation – the difficulty in patient recruitment and selection for studies of "off-label" drug use, to the point that this basic consideration must be kept in mind before generalizing positive results from preliminary small-sample studies. Nonetheless, it seems

that the potential of BTX for achieving muscle relaxation and analgesic effects in many muscular disorders is well-evidenced, and this led to a search for new therapeutic applications.

The adoption of botulinum toxin in temporomandibular disorder (TMD) patients is a consequence of these considerations, given the high rate of comorbidity of TMD with some forms of headache[39,40] and the common uncertainties about the pathophysiology of both disorders, which force clinicians and researchers to adopt a symptomatic therapeutic approach in both cases.[41-43]

In 2004, at the time of a systematic review of the literature on the usefulness of BTX-A in the treatment of head and neck muscle disorders,[44] only one study satisfied the authors' qualitative criteria to be included in the review. In that study, which tested a small sample of highly selected patients with muscular TMD treated with a crossover protocol (BTX-A vs. placebo), the dropout rate was up to one-third of participants, due to either pain increase (treatment inefficacy) or muscle paralysis (side-effect of the treatment). No significant differences in pain improvement were observed between the two treatments, thus not providing support for the efficacy of BTX-A in muscular TMD.[45]

Similar conclusions emerged from a systematic review in 2007 on the potential therapeutic effects of botulinum toxin in orofacial pain disorders, which claimed that literature findings are not so promising for orofacial pain, except for migraine prophylaxis.[46] In contrast, two other reviews, one descriptive[47] and one systematic,[48] partly revisited the earlier conclusions and tried to provide a rationale for using BTX-A in TMD patients. Nonetheless, there is a general consensus that the quality of the literature on the therapeutic effects of botulinum toxin in TMD patients is currently poor, and further studies are strongly needed.

A PubMed search performed with the key terms "botulinum toxin" and "temporomandibular disorders" yielded 36 references many of which were single-patient case reports on off-label uses of BTX-A within the orofacial region, such as in the case of masseter hypertrophy,[49] TMJ anterior disc displacement,[50] TMJ disc disfigurement,[51] and chronic or recurrent TMJ dislocation.[52-56] Apart from studies on these particular applications, most clinical data on the use of type-A botulinum toxin to treat facial pain has come from case series on TMD patients.

An uncontrolled preliminary investigation by Freund and co-workers[57] found that the injection of 150 units of BTX-A (50 U within each masseter and 25 U within each temporalis muscle) provided a significant reduction in both objective (mouth opening) and subjective (pain, function, tenderness) jaw function in a sample of 15 subjects with non-homogeneous TMD over an 8-week period. Similar findings were reported by the same group of researchers in a successive case series study on a larger sample,[58] and by Von Lindern,[59] who reported encouraging findings with the injection of 200 U of BTX-A per side in a sample of 41 patients with muscular TMD over a 6-month span.

Botox and Bruxism

Myofascial pain of the masticatory muscles has a strong epidemiologic relevance, affecting from 38% to 75% of patients with signs and symptoms of TMD in Caucasian populations[60,61] and about 30% Asian patients.[62] Therefore, despite the fluctuating and self-limiting nature of these disorders,[63] efficacious first-step symptomatic therapies are requested to reduce their psychosocial impact. There is a complex pathogenesis which is often the expression of a multifactorial etiology, with a number of systemic and local risk factors.[64]

Some similar epidemiologic and psychosocial characteristics have been described for bruxism as well, which is a parafunctional activity strongly detrimental for all the stomatognathic structures.[65] In particular, despite a lack of demonstration of its causal role for TMD,[66] and doubts existing about

the etiology of both awake and sleep bruxism,[67-70] a clinical association between bruxism and myofascial pain has been reported in several works.[71,72] Many therapies have been proposed to treat bruxism-related muscle hyperactivity, but published data have not been conclusive so far.[73-76]

Similarly, uncertainty about the etiopathogenesis of myofascial pain has led to the proposal of several treatment approaches for this condition, among which are occlusal splints,[77,78] physical therapy,[79] behavioral and physical treatments,[80] and drugs.[81-83]

These considerations, which support the need for a symptomatic management approach to these disorders in the absence of a specific causal therapy to achieve muscle relaxation, along with the above-described attempts of introducing botulinum toxin in the treatment of myofascial TMD, have led to hypotheses on the possible efficacy of BTX-A to reduce muscle activity in bruxers. However, studies are complicated by the difficulty of obtaining objective data on the severity of bruxism and on the different patterns of parafunctional activity (clenching or grinding).

At the time of writing there are no studies assessing the polysomnographic activity of bruxers before and after a botulinum toxin injection, and the simplest approach to the evaluation of a treatment for bruxism appears to be clinical assessment.

Tan and Jankovic[84] assessed the efficacy of BTX-A injections (25–100 MU per masseter muscle) in a sample of 18 subjects with severe long-term bruxism. The efficacy of treatment was assessed with a combination of patients' self-perception of improvement and their partners' interviews. The mean duration of response was about 6 months, and the mean peak effect was 3.4 on a scale of 0 to 4, in which 4 is equal to total abolishment of grinding. Only one subject (5.6%) reported having experienced dysphagia.

Self-report perception of efficacy was also reported by a patient affected by amphetamine-induced bruxism treated with BTX-A,[85] and clinical improvement was shown in a 7-year-old child who exhibited teeth clenching and grinding as a consequence of a post-traumatic brain injury.[86]

At present, the only available randomized clinical trial on the use of botulinum toxin in bruxers is a preliminary double-blind, placebo-controlled investigation with a 6-month follow-up period, aiming to assess the efficacy of type-A botulinum toxin to treat myofascial pain symptoms and to reduce muscle hyperactivity in bruxers.[87] Twenty subjects with a clinical diagnosis of bruxism and with myofascial pain of masticatory muscles were randomly enrolled and included either within a treatment group (BTX-A injection) or a control group (saline placebo injections). A number of objective and subjective clinical parameters were assessed at baseline, and at 1-week, 1-month, and 6-month follow-up appointments. The parameters were: pain at rest and at chewing; mastication efficiency; maximum unassisted and assisted mouth opening, protrusive, and laterotrusive movements; functional limitation during usual jaw movements; subjective efficacy of the treatment; and tolerability of the treatment. Interestingly, improvements in both objective and subjective clinical outcome variables were higher in Botox than in placebo patients. Besides, patients treated with BTX-A reported a higher subjective improvement with time in their perception of treatment efficacy than did the placebo patients. According to the authors, the differences were not significant in some cases owing to the small sample size. Nonetheless, the findings supported the efficacy of BTX-A to reduce myofascial pain symptoms in bruxers, thus providing pilot data that have to be confirmed by further research on larger samples.

Taken together, this scarce literature suggests that BTX-A studies in bruxers have suffered from the same methodologic concerns as other investigations on bruxism, such as the issues of clinical evaluation and quantification of the disorder. The study by Guarda-Nardini and co-workers[87] is an example of the difficulties of identifying which

part of a patient's symptoms improved. Is pain relief a direct consequence of bruxism reduction, or is it due to the analgesic/muscle relaxant properties of botulinum toxin?

Conclusion

The reliability of clinical diagnostic criteria for bruxism is much debated.[86,89] When assessing the efficacy of a therapeutic modality, the clinician must be conscious that pain in the masticatory muscles might be a spurious outcome variable, being the expression of concurrent disorders as well.

Evidence-based knowledge on bruxism characteristics and effects is mostly based on findings from studies of sleep bruxism, which is more suitable for a reliable diagnosis in a scientific research setting. Unfortunately, PSG studies are expensive and adequately equipped sleep laboratories are not numerous. The problem of patient recruitment affects experimental studies on bruxism treatments, including investigations on botulinum toxin efficacy.

Nonetheless, the generally positive findings suggesting that botulinum toxin may provide potential for minor neuromuscular conditions, along with the number of neuromuscular disorders for which BTX-A represents a first-choice option (e.g., blepharospasm, cervical dystonia, and several other focal dystonias), seem to justify further investigations of its efficacy in bruxers.

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