BOTULINUM TOXIN FOR THE TREATMENT OF MIGRAINE AND OTHER PRIMARY HEADACHE DISORDERS

Migraine is a disorder that affects 6 - 15% of the world's population. It is the cause of major disability for the sufferer and leads to a significant economic burden to society.

JOHAN A SMUTS
MB ChB, MMed (Neurol)
Private Practitioner
Wilgers Hospital
Pretoria
Part-time Consultant
Department of Neurology
University of Pretoria

Johan Smuts completed his undergraduate and neurology training at the University of Pretoria. His current interests include movement disorders as well as headache. Botulinum toxin has been an area of special interest, with applications in both the above areas, and many research projects and publications have stemmed from this work.

Patients suffering from frequent, disabling or refractory migraine should be considered for treatment with prophylactic agents. There is an ever-increasing list of therapies available for prevention of migraine, but most are associated with the potential for significant side-effects.

Botulinum toxin type A (BoNTA) is a neurotoxin which is effective in the treatment of many disorders of involuntary muscle contraction. These conditions include cervical dystonia, blepharospasm, hemifacial spasm and spasticity.[1] The drug inhibits neuromuscular signals by blocking the release of acetylcholine at the neuromuscular junction.[1] Recent clinical evidence suggests that BoNTA may inhibit pain associated with migraine and other types of headaches. The analgesic effects of BoNTA have been observed in the treatment of dystonia and spasticity. This has led to further investigations of BoNTA as a possible treatment for other painful conditions including migraine and tension-type headaches.

This article aims to describe the potential antinociceptive mechanism of action of BoNTA, to summarise the clinical evidence of efficacy in migraine prophylaxis and to review injection technique in treating headache.

MECHANISM OF ACTION

Botulinum toxins are exotoxins of the anaerobic bacterium *Clostridium botulinum*. There are 7 serotypes that are labelled A - G. The vast majority of clinical experience with botulinum toxin is with the A serotype (BoNTA) which is the only serotype commercially available in South Africa (Botox) – the focus of this article. The toxin is a 150 kilodalton metallo-protein and comprises a light and a heavy chain. The heavy chain binds with high affinity and specificity to the cholinergic, presynaptic membrane of the neuromuscular junction. The toxin is then internalised at the nerve ending where it cleaves an intracellular protein known as SNAP-25, which is involved in the exocytosis of the neurotransmitter acetylcholine. This results in blockade of neurotransmission and inhibition of muscle contraction. The motor endplates regenerate over a number of weeks and full function is usually restored in 3 months.[1]

Although inhibition of neuromuscular activity can explain some of the pain relief in headache disorders it cannot fully explain the analgesic mechanism of BoNTA. Current data suggest that BoNTA may modify the sensory feedback loop to the central nervous system by blocking intrafusal fibres, resulting in decreased muscle-spindle activity. The toxin may also inhibit release of glutamate from primary afferent nociceptive fibres. The reduction in afferent sensory activity from the

pericranial and cervical muscles and inhibition of peripheral and central trigeminal sensitisation can be potential mechanisms for BoNTA's therapeutic effect in headache.

CLINICAL EVIDENCE OF EFFICACY

The original idea that BoNTA may be of value in the treatment of headache came from two observations during studies for the treatment of other conditions. It was noted early on in the treatment of cervical dystonia that not only was the position of the neck corrected, but also the associated pain was often relieved. Also, patients in the initial trials for the treatment of frown lines reported a correlation between pericranial BoNTA injections and improvement of migraine headache symptoms. These findings led to a number of open-label studies of the effect of BoNTA in headache. Initially only the decrease in headache frequency was studied but later also the changes in migraine-related disability. The results of these retrospective reviews and open-label studies supported the beneficial role of BoNTA in the preventive treatment of episodic migraine, chronic tension-type headache and treatment-refractory chronic migraine.[2,3]

Although no large pivotal trials are available yet, at least 2 randomised, controlled studies were published that showed efficacy in the treatment of migraine. These studies observed a significant reduction in the intensity of migraine attacks and in 1 study also in the frequency of attacks. These early studies utilised standardised injection schemes, which often led to treatment administered in clinically inappropriate sites, resulting in a poorer response rate.[4]

In the treatment of tension-type headache the results of studies are more difficult to interpret. A number of reasons for this variation in results may exist, including patient selection, duration of headache, and amount of analgesic used. The injection scheme also plays a role. The best results seemed to be obtained when experienced injectors were treating patients by injecting trigger points. It also appears that higher doses of toxin are needed to obtain results in tension-type headache than when treating pure migraine. When comparing the findings of 6 of the largest studies to date some degree of response was found in almost 80% of patients.[5] Improvement rates rose with multiple treatments, appearing to be progressive and possibly also cumulative.

The onset of effect is usually slow and decline in headache is often noted only after 1 - 2 weeks, but depending on the level of response the relief can be sustained for 16 - 20 weeks.

Because of the cost of treatment, the invasive nature and also the technical difficulty of injection, patient selection is of cardinal importance to ensure good clinical outcome when treating headache patients with BoNTA.

General considerations to take into account include the severity of the headache, duration of the complaint, success or failure of previous prophylactic treatment with other drugs, secondary psychogenic overlay and financial status of the patient. Specific factors relating to a patient can include preference for natural treatment options, absence of systemic side-effects and need for secondary benefits including positive cosmetic effect of treatment.
In our experience patients most likely to benefit from BoNTA treatment are the following: those with a shorter history of headache (< 10 years), a moderate to severe headache pattern, previous prophylaxis which was either partially or very effective but poorly tolerated owing to systemic side-effects, no analgesic misuse with resulting analgesic rebound headache, and those who use triptan therapy frequently.

If BoNTA therapy is reserved only for patients who are refractory to all other forms of treatment overall results may be diminished, since this group of patients generally has only limited treatment success with any form of treatment. Therefore selection of patients who may benefit from this form of treatment is important and worthwhile for both patient and treating physician.

Although BoNTA may be useful in many types of headache disorders, current data support its use only in patients suffering from migraine, chronic migraine, and chronic tension-type headache and possibly in patients in whom headache is part of a more widespread pain syndrome, such as myofacial pain. Some data exist on the use in cluster headache and trigeminal neuralgia, but these are insufficient to advocate use in such conditions. Evidence is very limited and only case reports and small series of open-label treated patients exist. Currently the use of BoNTA in these settings can not be advised outside well-structured research environments.

INJECTION PROCEDURE

Dilution

Standard dilution techniques can be used and this would be 2 - 4 ml of saline to a 100 U vial of Botox (currently the only commercially available botulinum toxin in South Africa).

Where and how to inject

There is no absolute recommendation as to injection sites or dosages. In tension-type headache an individual injection scheme based on the patient's history, pain location (follow the pain) and radiation of pain tends to give the best results. Since a small volume of drug is injected per site a 1 ml insulin syringe is used to ease calculation of dose per site. Thin needles (27 - 30 gauge) are best suited for injection. The use of electromyographic guidance is rarely needed. When injecting in the frontal region take cognisance that the drug has an effect on facial expression and adhere to a

cosmetically acceptable schema and keep a good distance from the muscle levator palpebrae to prevent ptosis. If trigger points can be precisely located and injections are directed at these it leads to better results. Injection technique is mainly determined by surrounding anatomical structure. According to the muscle volume and degree of muscle hyperactivity, 5 - 15 U of Botox per trigger point should be given. The total amount needed to treat tension-type headache varies, but in general 75 - 150 U of Botox are needed.

Directions for injection in migraine (episodic and chronic) are even more difficult to prescribe. Our standard approach is to use a so-called 20:10:20 approach. In the frontal area 20 U of Botox is given in a fixed pattern (Fig. 1), 5 U into each temporal region and 20 U into the 4 posterior regions, 2 sub-occipital and 2 more lateral in the splenius capitis muscle. If more sites are called for, locate and inject trigger areas (Fig. 2). This injection plan causes minimal discomfort and has the added advantage of reducing hyperactive facial lines.

References available on request.

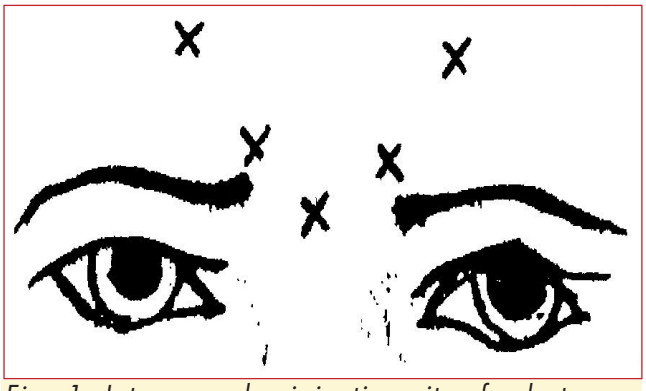

Fig. 1. Intramuscular injection sites for botulinum toxin type A.

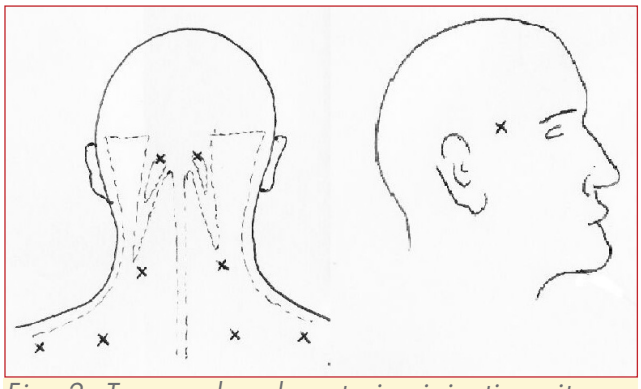

Fig. 2. Temporal and posterior injection sites.

IN A NUTSHELL

Botulinum toxin offers a new treatment option for patients suffering from chronic pain syndromes including migraine and tension-type headache.

Headache patients often suffer greatly as a result of side-effects of the drugs used as prophylactic agents. These can include dizziness, fatigue, weight gain, hair loss and loss of libido. BoNTA does not cause any of these side-effects and to date no organic damage or allergic complications have been reported.

The long duration of action also has the added benefit that patients do not need to take medication on a daily basis.

These factors make this a treatment with a high safety profile and high patient acceptability.

In the treatment of headache there are opinion differences on dosages, areas of injection and patient selection.

Comparative studies with standard treatments are still needed.

Currently therefore the use of BoNTA in the treatment of headache is only justified after all standard therapeutic procedures have been exhausted and only after evaluation in specialist centres.