

Botulinum toxin type A for migraine headaches

MIGRAINE HEADACHES CAN BE DEBILITATING, AND ARE ASSOCIATED with significant economic burden due to both direct medical costs and indirect costs (i.e., reduced productivity or missed workdays).¹ Those who are afflicted by migraines generally experience between 1 and 4 attacks per month; the duration of each ranges from 4 to 72 hours.¹ While conventional treatments (acute and/or prophylactic) offer substantial relief for many, there is still a significant proportion of patients who do not respond adequately.^{1,2}

Botulinum toxin type A (BTX-A) is approved in Canada for use in several conditions associated with muscular spasm (e.g., cervical dystonia, blepharospasm), and for the treatment of upper facial wrinkles.³ The efficacy of BTX-A has also been assessed in a variety of off-label uses, including migraine headache. Given the prevalence of patients with migraines who do not respond to traditional therapies, it is possible that many pharmacists will receive questions about BTX-A for this use.

Case

Jill is a 34-year-old female who is well known to your pharmacy. She comes in regularly to refill her prescription for sumatriptan. Today, Jill presents you with a prescription from a neurologist for BTX-A injection. She explains to you that her migraines have been increasing in frequency. You know that she has been on several preventive medications in the past, including amitriptyline, propranolol, and verapamil, with little success. Jill tells you that she thought the drug was just for wrinkles, and was hoping you could provide her with some information regarding its use to decrease the frequency of her migraine headaches.

Mechanism of action

The primary effect of BTX-A is to inhibit acetylcholine release at the neuromuscular junction, resulting in local, temporary paralysis.^{3,4}

In the treatment of migraine headaches, which result from a pathophysiology that is not fully understood, it has been pos-

BTX-A may be considered for migraine sufferers who require prophylactic therapy, but who are refractory to traditional therapies or do not tolerate them

tulated that BTX-A may produce effects by inhibiting overactive peripheral neurons, sensory trigeminal nerve endings, or extracranial inflammatory pathways that could contribute to migraine symptoms.¹ In patients whose migraines are associated with increased muscle tension, BTX-A may exert effects by decreasing this tension.²

Efficacy

Several randomized, placebo-controlled trials⁵⁻⁸ have evaluated the use of BTX-A in the prophylaxis of migraine headache; one of the trials⁶ included patients with chronic tension-type headache and those with migraine headache. Most of the trials, but not all, reported some degree of benefit with BTX-A.

In one trial ($n = 123$),⁵ the outcome measures used included migraine frequency and severity, migraine-associated vomiting, and use of acute drug treatment; at 3 months after treatment, all were reduced significantly from baseline in patients who received 25 units of BTX-A (divided among multiple frontal muscle sites), but not in those who received 75 units. The authors suggested that the lack of efficacy seen with the 75 unit dose could be related to a lower baseline incidence of migraines in that treatment group compared with the other groups.

In a second trial⁶ that included patients with chronic tension-type headache as well as those with migraines (chronic tension-type headache, $n = 46$; migraine, $n = 14$), BTX-A treatment (200

units divided among multiple individual sites) resulted in a significant improvement in headache-free days from post-injection weeks 8 to 12, as compared with placebo.

A third trial ($n = 60$),⁷ which assessed the use of 16 units of BTX-A injected into frontal muscles or 100 units of BTX-A injected into frontal and neck muscles, found no significant results for migraine frequency, severity, or acute medication use in either active treatment group.

A fourth trial ($n = 56$),⁸ which was published in abstract form only, also reported positive effects of BTX-A on migraine pain.

Safety

BTX-A appears to be relatively well tolerated when used for the prevention of migraine headache. Serious adverse events were not reported in randomized controlled trials, although cases of reversible ptosis (eyelid drooping), diplopia (double vision), and injection site weakness did occur.^{1,2}

Unanswered questions

There are several limitations of current data regarding the use of BTX-A for migraine headache. Future study is required to help determine the optimal dose, frequency, and sites of administration for BTX-A, as well as how to identify ideal candidates for

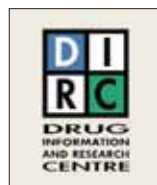
therapy.² Cost effectiveness and long-term safety and efficacy should also be assessed.¹

Place in therapy

Based on available evidence, BTX-A may be considered for migraine sufferers who require prophylactic therapy, but who are refractory to traditional therapies or do not tolerate them.^{1,2}

Pharmacist's role

Explain to Jill that although BTX-A is best known for its cosmetic uses, it is also used in a variety of other conditions, including migraine headache. Tell her that there is some evidence that the drug can decrease both the frequency and severity of headaches, and that she is a reasonable candidate for such therapy given her lack of response to previous treatments. Advise Jill that the drug is generally well tolerated, but has been associated with reversible effects such as eyelid droop and injection site reactions. ■



This article was written by Simmi Sidhu and Brent Ruddock, both of whom are drug information pharmacists with the Ontario Pharmacists' Association Drug Information and Research Centre.

References

1. Chilson CN, Brown SJ. Role of botulinum toxin type A in the prophylactic treatment of migraine headaches. *Ann Pharmacother* 2005;39(12):2081-5.
2. Loder E, Biondi D. Use of botulinum toxins for chronic headaches: a focused review. *Clin J Pain* 2002;18(6 Suppl):S169-76.
3. Repchinsky C, editor. *Compendium of pharmaceuticals and specialties*. Ottawa: Canadian Pharmacists Association; 2006.
4. Cheng CM, Chen JS, Patel RP. Unlabeled uses of botulinum toxins: a review, part 1. *Am J Health Syst Pharm* 2006;63(2):145-52.
5. Silberstein S, Mathew N, Saper J, Jenkins S. Botulinum toxin type A as a migraine preventive treatment. For the BOTOX Migraine Clinical Research Group. *Headache* 2000;40(6):445-50.
6. Ondo WG, Vuong KD, Derman HS. Botulinum toxin A for chronic daily headache: a randomized, placebo-controlled, parallel design study. *Cephalalgia* 2004;24(1):60-5.
7. Evers S, Vollmer-Haase J, Schwaag S, et al. Botulinum toxin A in the prophylactic treatment of migraine — a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2004;24(10):838-43.
8. Brin MF, Swope DM, O'Brien C, et al. Botox for migraine: double-blind, placebo-controlled, region-specific evaluation [abstract]. *Cephalalgia* 2000;20:421-2.



The 5th Canadian Cochrane Symposium Knowledge for Health

February 12-13, 2007
Crowne Plaza Hotel, Ottawa

- * Learn how to access and use systematic reviews
- * Attend workshops on systematic review methods
- * Network with other health care providers

Join us in Ottawa and experience
the fun of Winterlude!



For details see: www.cochrane.uottawa.ca/symposia.asp

Canadian Adverse Reaction Newsletter

Highlights from the October 2006 issue of Health Canada's *Canadian Adverse Reaction Newsletter*, Volume 16, Issue 4

- BioGlue: Chronic inflammation and foreign-body reactions
- New tool for reporting adverse reactions at www.healthcanada.gc.ca/medeffect
- Physician reporting of adverse reactions
- Case presentation: Atomoxetine and tics
- Summary of advisories at www.hc-sc.gc.ca/dhp-mpps/medeff/advisories-avis/index_e.html

For further information, go to
www.hc-sc.gc.ca/dhp-mpps/medeff/bulletin/index_e.html