

Review of botulinum toxin type A for the prophylactic treatment of chronic daily headache

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Abstract: Botulinum toxin A is increasingly used in the treatment of idiopathic and symptomatic headache disorders. However, only few controlled trials are available and many trials can hardly be compared to each other because of different endpoints and different trial designs. In particular chronic daily headache, which is defined as an idiopathic headache occurring on more than 15 days per month for at least 3 months and a daily duration of at least 4 hours, is considered as a headache disorder with possible efficacy of botulinum toxin A. For the prophylactic treatment of chronic tension-type headache and chronic migraine, no sufficient positive evidence for a successful treatment can be obtained from randomized, double-blind, and placebo-controlled trials to date. For the treatment of chronic daily headache including medication overuse headache, there is some positive evidence for efficacy in a subgroup of patients. To date, the majority of double-blind and placebo-controlled studies do not suggest that botulinum toxin A is efficacious in the treatment of chronic idiopathic headache disorders. However, it is possible that some subgroups of patients with chronic daily headache will benefit from a long-term treatment with botulinum toxin A.

Keywords: botulinum toxin A, chronic daily headache, chronic tension-type headache, chronic migraine

Introduction

After the first case reports, open studies, and preliminary reviews on the efficacy of botulinum toxin in pain therapy, the use of this substance for the treatment of headache disorders has been discussed widely (Mathew and Kaup 2002; Argoff 2003; Dodick 2003; Evers 2004; Blumenfeld et al 2004). However, the interpretations of the findings in trials and case series are conflicting and inconsistent. In this paper, the published evidence based on the placebo-controlled, double-blind trials for the prophylaxis of chronic daily headache with botulinum toxin A will be analysed. This analysis is based on literature research in medical databases (Medline, Embase, Current Contents, Science Citation Index) from 1995 to 2007 and on published congress reports of the relevant headache and pain congresses. Key words were botulinum and chronic headache.

Chronic daily headache is defined as headache occurring on at least 15 days per month for at least three months and with a daily duration of at least four hours a day (Silberstein and Lipton 2000). Per definition and per classification of the IHS, the following four entities are differentiated: chronic migraine, chronic tension-type headache, hemicrania continua and new onset daily persistent headache. These types can occur with and without medication overuse. This means that medication overuse headache is not separately considered in the classification system of chronic daily headache.

Only studies on the prophylactic treatment of headache were considered. As recommended by the International Headache Society (IHS), headache frequency was regarded the most important primary endpoint (Schoenen 1995; Tfelt-Hansen et al 2000). The diagnosis of cervicogenic headache and studies on patients with different coexisting or with other headache diagnoses were not considered.

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Table 1 Randomized, double-blind, placebo-controlled studies on botulinum toxin in the prophylactic treatment of tension-type headache

Reference	Indication to treatment	Number of patients	Results compared with placebo
Göbel et al 1999	chronic tension-type headache	10	No significant reduction of pain intensity, headache hours, or use of analgesics
Smuts et al 1999	chronic tension-type headache	41	Significant reduction of headache intensity and pain-free days in month 3 compared with baseline data in group with botulinum toxin but not in placebo group
Rollnik et al 2000	chronic tension-type headache	21	No significant differences between botulinum toxin and placebo in all headache parameters
Burch et al 2001	episodic and chronic tension-type headache	41	No significant difference in headache frequency
Schmitt et al 2001	chronic tension-type headache	59	No significant differences between botulinum toxin and placebo in all headache parameters
Schulte-Mattler and Krack 2004	chronic tension-type headache	113	No significant reduction in all efficacy endpoints
Ka et al 2004	chronic tension-type headache	40	No significant reduction of headache frequency; significant reduction of pain intensity
Padberg et al 2004	chronic tension-type headache	40	No significant results
Empl et al 2005	chronic tension-type headache	125	No significant results
Silberstein et al 2006	chronic tension-type headache	300	No significant difference in headache frequency (primary endpoint) for all treatment groups (treatment with 150 U was significantly inferior to placebo); significant increase in percentage of responders for three treatment groups

Trials on headache treatment

In Table 1, the studies on botulinum toxin in the prophylactic treatment of chronic tension-type headache (one trial also with episodic tension-type headache) according to the IHS criteria are listed. Ten randomized, double-blind, and placebo-controlled studies on patients suffering from tension-type headache were included (Göbel et al 1999; Smuts et al 1999; Rollnik et al 2000; Burch et al 2001; Schmitt et al 2001; Schulte-Mattler and Krack 2004; Kokoska et al 2004; Padberg et al 2004; Empl et al 2005; Silberstein et al 2006). Apart from one, all these studies were negative for the primary endpoint and did not show any efficacy of botulinum toxin in reduction of headache frequency or intensity. The only study with a significant reduction of headache days in the treatment group but not in the placebo group, however, did not perform a formal statistical comparison between the two groups (Smuts et al 1999). In one long-term blinded and placebo-controlled study, the efficacy of botulinum toxin was maintained over a year in some patients (Relja and Klepac 2001). In some secondary endpoints such as headache intensity or headache duration, a positive trend or significant subgroup analysis could be observed. In particular, patients

with mixed headache and migrainous headache showed benefit. The studies used different doses (25 to over 100 IU Botox® and up to 240 IU Dysport®) and injection sites making a direct comparison difficult. The design of these studies mainly followed the guidelines of the IHS for studies on tension-type headache (Schoenen 1995) including the diagnosis according to the first (Headache Classification Committee 1988) and the second (Headache Classification Committee 2004) version of the IHS criteria for chronic tension-type headache (dull, bilateral, moderate headache on more than 15 days per month).

In summary, all but one randomized, double-blind, and placebo-controlled studies on botulinum toxin in the prophylactic treatment of chronic tension-type headache showed negative results for the primary endpoint.

In unspecific chronic daily headache, very recently larger studies have been performed since it has been suggested from observational studies that these patients might show the most benefit from botulinum toxin. The randomized, double-blind, and placebo-controlled studies on this headache type are listed in Table 2. Three different studies (Ondo et al 2004; Silberstein et al 2005; Mathew et al 2005; Freitag et al 2006)

Table 2 Randomized, double-blind, placebo-controlled studies on botulinum toxin in the prophylactic treatment of chronic daily headache

Reference	Indication to treatment	Number of patients	Results compared with placebo
Ondo et al 2004	chronic daily headache	60	No significant reduction but trend ($p = 0.07$) in primary endpoint (days with headache)
Silberstein et al 2005	chronic daily headache	702	No significant reduction of headache frequency
Mathew et al 2005	chronic daily headache	355	Primary endpoint (reduction of headache free days) negative; secondary endpoint (percentage of patients with reduction $>50\%$) positive
Dodick et al 2005	chronic daily headache	228	Significant reduction of headache frequency in patients not receiving other prophylactic drugs (subanalysis of Mathew et al 2005)
Elkind and Turkel 2005	chronic migraine	355	Significant reduction of migraine frequency for all treatment arms (105–260 U Botox®) as compared to placebo (subanalysis of Mathew et al 2005)
Freitag et al 2006	chronic migraine	60	No significant reduction in migraine days ($p = 0.18$)

showed a negative result for the primary endpoint. However, preplanned subgroup analyses of one study (Mathew et al 2005) showed significant improvements for patients with no other prophylactic treatment and for patients with chronic migraine with or without medication overuse (Dodick et al 2005; Elkind et al 2005).

There are no published controlled trials on the use of botulinum toxin A in the treatment of hemicrania continua and of new onset daily persistent headache.

Conclusion

In this review, the current published data on botulinum toxin in the treatment of chronic daily headache was analysed regarding all published double-blind and placebo-controlled trials. This analysis showed that a general efficacy of this therapy cannot be postulated to date. After a period of very optimistic case series and open studies, we are now able to analyse placebo-controlled and double-blind studies. This evidence-based approach gives us a more pessimistic picture showing no consistent efficacy of botulinum toxin in idiopathic headache disorders. For chronic tension-type headache, nearly all randomized, double-blind, placebo-controlled trials showed negative results. In summary, pure idiopathic headache disorders cannot be regarded as an indication for botulinum toxin to date.

For chronic daily headache, no consistent results can be obtained from randomized, double-blind, and placebo-controlled trials. However, analysing subgroups of these studies enables the identification of patients who might benefit from botulinum toxin. It is likely that those patients with chronic

daily headache (with or without medication overuse) who are severely impaired (ie, highest loss of productivity) and who are not receiving any other prophylactic treatment are the appropriate group of patients with a benefit from botulinum toxin. Since this total patient group shows a prevalence of up to 4% in population based epidemiological studies (Stovner et al 2006), it is warranted to further elucidate the clinical efficacy of botulinum toxin in this subgroup. In this context it should be noted that a subgroup of patients with exploding headache quality (in contrast to imploding or ocular headache quality) showed a good response to botulinum toxin suggesting that allodynia is an important predictor for the probability that botulinum toxin is efficacious (Jakubowski et al 2006).

References

- Argoff CE. 2003. The use of botulinum toxins for chronic pain and headaches. *Curr Treat Options Neurol*, 5:483–92.
- Blumenfeld AM, Dodick DW, Silberstein SD. 2004. Botulinum neurotoxin for the treatment of migraine and other primary headache disorders. *Dermatol Clin*, 22:167–75.
- Burch CM, Kokoska MS, Glaser DA, et al. 2001. Treatment of frontal tension headaches with botulinum toxin A. *Cephalalgia*, 21:489.
- Dodick DW. 2003. Botulinum neurotoxin for the treatment of migraine and other primary headache disorders: from bench to bedside. *Headache*, 43 (Suppl 1):25–33.
- Dodick DW, Mauskop A, Elkind AH, et al. 2005. Botulinum toxin type A for the prophylaxis of chronic daily headache: subgroup analysis of patients not receiving other prophylactic medications: a randomized double-blind, placebo-controlled study. *Headache*, 45:315–24.
- Elkind AH, Turkel CC. 2005. Botulinum toxin type A for the prophylaxis of headache in migraineurs with 16 days or more days of headache per 30 days: effect on frequency of all headache attacks and headaches of >4 hours in duration (randomised, double-blind, placebo-controlled study). *J Neurol*, 252:II/60.

- Empl M, Ceballos-Baumann A, Tölle T, et al. 2005. Treatment of chronic tension-type headache with botulinum toxin A (Dysport®): a double-blind multicentre study. *J Neurol*, 252 (Suppl 2):II/61–II/62.
- Evers S. 2004. Botulinum toxin and the management of chronic headaches. *Curr Opin Otolaryngol Head Neck Surg*, 12:197–203.
- Freitag FG, Diamond S, Diamond M, et al. 2006. Botulinum toxin type A (BnTxA) in the treatment of chronic migraine. *Headache*, 46:849.
- Göbel H, Lindner V, Krack P, et al. 1999. Treatment of chronic tension-type headache with botulinum toxin. *Cephalalgia*, 19:455.
- Headache Classification Committee of the International Headache Society. 1988. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia*, 8 (Suppl 7):1–92.
- Headache Classification Committee of the International Headache Society. 2004. International classification of headache disorders 2nd ed. *Cephalalgia*, 24 (Suppl 1):1–160.
- Jakubowski M, McAllister PJ, Bajwa ZH, et al. 2006. Exploding vs imploding headache in migraine prophylaxis with Botulinum Toxin A. *Pain*, 125:286–95.
- Kokoska MS, Glaser DA, Burch CM, et al. 2004. Botulinum toxin injections for the treatment of frontal tension headache. *J Headache Pain*, 5:103–9.
- Mathew NT, Kaup AO. 2002. The use of botulinum toxin type A in headache treatment. *Curr Treat Options Neurol*, 4:365–73.
- Mathew NT, Frishberg BM, Gawel M, et al. 2005. Botulinum toxin type A (Botox®) for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. *Headache*, 45:293–307.
- Ondo WG, Vuong KD, Derman HS. 2004. Botulinum toxin A for chronic daily headache: a randomized, placebo-controlled, parallel design study. *Cephalalgia*, 24:60–5.
- Padberg M, de Bruijn SFTM, de Haan RJ, et al. 2004. Treatment of chronic tension-type headache with botulinum toxin: a double-blind, placebo-controlled clinical trial. *Cephalalgia*, 24:675–80.
- Relja MA, Klepac N. 2001. Botulinum toxin A as prophylactic treatment in chronic tension-type headache: long-term follow-up study. *Neurology*, 56 (Suppl 3):A349–50.
- Rollnik JD, Tanneberger O, Schubert M, et al. 2000. Treatment of tension-type headache with botulinum toxin A: a double-blind, placebo-controlled study. *Headache*, 40:300–5.
- Schmitt WJ, Slowey E, Fravi N, et al. 2001. Effect of botulinum toxin A injections in the treatment of chronic tension-type headache: a double-blind, placebo-controlled trial. *Headache*, 41:658–64.
- Schoenen J. 1995. Guidelines for trials of drug treatments in tension-type headache. First edition: International Headache Society Committee on Clinical Trials. *Cephalalgia*, 15:165–79.
- Schulte-Mattler W, Krack P, BoNTTH study group. 2004. Treatment of chronic tension-type headache with botulinum toxin A: a randomized, double-blind, placebo-controlled multicenter study. *Pain*, 109:110–4.
- Silberstein SD, Lipton RB. 2000. Chronic daily headache. *Curr Opin Neurol*, 13:277–83.
- Silberstein SD, Stark SR, Lucas SM, et al. 2005. Botulinum toxin type A for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc*, 80:1126–37.
- Silberstein SD, Göbel H, Jensen R, et al. 2006. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicenter, double-blind, randomized, placebo-controlled, parallel-group study. *Cephalalgia*, 26:790–800.
- Smuts JA, Baker MK, Smuts HM, et al. 1999. Prophylactic treatment of chronic tension-type headache using botulinum toxin type A. *Eur J Neurol*, 6 (Suppl 4):99–102.
- Stovner LJ, Zwart JA, Hagen K, et al. 2006. Epidemiology of headache in Europe. *Eur J Neurol*, 13:333–45.
- Tfelt-Hansen P, Block G, Dahlföf C, et al. 2000. Guidelines for controlled trials of drugs in migraine: second edition. *Cephalalgia*, 20:765–86.