J Neural Transm (2007)
DOI 10.1007/s00702-007-0832-3
Printed in The Netherlands

Journal of Neural Transmission

Evidence based medicine on the use of botulinum toxin for headache disorders

W. J. Schulte-Mattler, E. Leinisch

Department of Neurology, University of Regensburg, Regensburg, Germany

Received 25 August 2007; Accepted 23 September 2007; Published online 12 November 2007

Summary. Botulinum toxin blocks the release of acetylcholine from motor nerve terminals and other cholinergic synapses. In animal studies botulinum toxin also reduces the release of neuropeptides involved in pain perception. The implications of these observations are not clear. Based on the personal experiences of headache therapists, botulinum toxin injections have been studied in patients with primary headaches, namely tension-type headache (TTH), chronic migraine (CM) and chronic daily headache (CDH). So far, the results of randomized, double-blind, placebo controlled trials on botulinum toxin in a total of 1117 patients with CDH, 1495 patients with CM, and 533 patients with TTH have been published. Botulinum toxin and placebo injections have been equally effective in these studies. In some of the studies, the magnitude of this effect was similar to that of established oral pharmacotherapy. This finding may help to explain the enthusiasm that followed the first open-label use of botulinum toxin in patients with headache. However, research is continuing to determine the efficacy of botulinum toxin in certain subgroups of patients with CM or CDH.

Keywords: Botulinum toxin; headache; pain; evidence based medicine

Introduction

Botulinum toxin is the most toxic agent known (Gill 1982; Arnon et al. 2001). Botulinum toxin acts by inhibiting the release of acetylcholine at neuromuscular junctions, which causes a flaccid paralysis of affected muscles. This action accounts for its toxicity and formed the basis for its initial clinical use. Botulinum toxins are a group of proteins produced by the bacterium *Clostridium botulinum*. Seven different serotypes are known, which vary in the animal species that they affect and both the severity and the duration of the paralysis that they evoke (Schiavo et al. 2000). To date, the serotypes A and B both have been used therapeutically, with a clear predominance of botulinum neurotoxin type A (BoNT/A).

Several distinct formulations of BoNT/A are marketed. It is not clear how or even whether the pharmacological properties of the formulations compare to one another (Rosales et al. 2006). Thus, it is important to take into consideration which formulation was used when study results or patient's outcomes are evaluated.

The first therapeutic use of botulinum toxin was in 1980 in patients with strabismus. Since then, botulinum toxin has been found to be beneficial in an increasing number of diseases or conditions in which unwanted muscular hyperactivity plays a role. These include blepharospasm, dystonias, spasticity of various causes, detrusor-sphincter dyssynergia, and the cosmetically use for facial wrinkles (Hallett 1999). It was noted that patients treated with botulinum toxin for these conditions often reported a substantial reduction of the pain that accompanied their primary disorder (Tsui et al. 1986; Brin et al. 1987).

Mechanism of action of BoNT/A

To produce its pharmacological action in a motor nerve terminal, a BoNT/A molecule must be actively taken up by that nerve terminal. This process is coupled to the neuron's activity (Dong et al. 2006; Mahrhold et al. 2006). Inside the nerve terminal the BoNT/A molecule is split into two parts. The smaller part produces the intrinsic effect of BoNT/A by irreversibly binding to one molecule of the protein complex necessary for the fusion of synaptic vesicles with the cell membrane (SNARE complex). The release of acetylcholine is blocked until a new SNARE complex is formed. Thus, the effect of BoNT/A is long-

Correspondence: Wilhelm J. Schulte-Mattler, MD, Department of Neurology, University of Regensburg, Universitätsstr. 84, 93053 Regensburg, Germany
e-mail: wilhelm.schulte-mattler@klinik.uni-regensburg.de

lasting. In muscle nerve endings, this drug effect reaches its maximum after 100 h post injection, and the restoration of function begins after 8 weeks (Wohlfarth et al. 1997).

BoNT/A not only affects motor nerve endings, but other cholinergic synapses as well, such as in the salivary glands (Mancini et al. 2003) and the sweat glands (Schnider et al. 1997). To explain a potential analgesic effect of botulinum, several groups have examined the influence of botulinum toxin on other types of neurons, namely those involved in pain perception. In vitro studies, botulinum toxin consistently lowered the extracellular concentrations of the neuropeptides substance P (Yokosawa et al. 1994; Ishikawa et al. 2000; Welch et al. 2000) and calcitonin gene related peptide (CGRP) (Durham et al. 2004; Rapp et al. 2006), which both are involved in pain perception. In contrast, no analgesic effects of BoNT/A were found in a total of 137 healthy humans in whom intracutaneous injections of BoNT/A were compared with saline in a double-blind fashion (Blersch et al. 2002; Kramer et al. 2003; Voller et al. 2003; Sycha et al. 2006; Schulte-Mattler et al. 2007). In a recent double-blind study BoNT/A was compared with saline in 32 healthy men (Gazerani et al. 2006). Injections were made into pericranial muscles in a way that had been proposed for the treatment of migraine. Significant suppressive effects of BoNT/A on capsaicin induced pain and hyperalgesia area were reported, but it was not reported in how far an accidental unblinding of the study subjects or the investigators due to the muscular effects of BoNT/A had occurred, which may have confounded this study's results.

Rationale for the use of BoNT/A in headache disorders

Tension-type headache, migraine, and trigemino-autonomic headache are the most common primary headaches. The latter term denotes headaches that are not the symptom of any underlying disorder. The pathophysiology of the primary headaches is complex and still a focus of research.

Among other factors, an increased tension of pericranial muscles and active myofascial trigger points may play some role in tension-type headache (Sakai et al. 1995; Fernandes-de-las-Penas 2007). The well established potency of BoNT/A to lower increased muscle tension, and the well known pain reduction in patients who have had received BoNT/A for that purpose, both were the initial motivations to study BoNT/A in tension-type headache (Zwart et al. 1994; Schulte-Mattler et al. 1999).

The motivation to study BoNT/A in migraine and in trigemino-autonomic headache is less clear. The neuropeptides CGRP and substance P are released in migraine and involved in so-called neurogenic inflammation and vasodilatation (Goadsby et al. 1990; Lee et al. 1994; Phebus et al. 1997; Edvinsson 2001). However, their pathogenic role is not known in detail. Thus, the animal data on BoNT/A in relation to these neuropeptides cannot be taken as evidence for an influence of BoNT/A on migraine. Accordingly, the first studies of BoNT/A were not driven by pathophysiologically oriented reasoning but by the personal experiences of physicians who successfully had given BoNT/A to individuals with migraine.

Clinical data on botulinum toxin in patients with headache disorders

Literature scan

A MEDLINE search (August 23rd, 2007) for articles containing ''botulinum'' and one of the words ''headache'', ''pain'', or ''migraine'' resulted in 932 articles, 277 of which were marked as review articles. We have personally reviewed these results and have limited them to reports of prospective, randomized, placebo-controlled trials (RCTs) on primary headache disorders only. These reports are summarized in Tables 1–3. We used the scale of the Therapeutics and Technology Assessment (TTA) subcommittee of the American Academy of Neurology (Edlund et al. 2004) to evaluate these studies.

Tension type headache

Rollnik et al. (2000) and Schmitt et al. (2001) studied patients with tension-type headache and neither found any significant difference between patients treated with BoNT/A and patients treated with placebo. Probably because of their entirely negative results they did not report if they defined a primary efficacy criterion, thus the studies had to be rated class II.

These articles of episodic migraine and tension-type headache stimulated a discussion as to how and whether the method of botulinum toxin application may influence its efficacy (Blumenfeld et al. 2003). It was argued that results of the above-mentioned studies were negative, because BoNT/A was given to the patients into predetermined fixed sites (FS); and that instead injections should be made individually in each patient, depending on the location of the patient's pain – thus named ''follow the pain'' (FTP) approach. This hypothesis was not supported by the class I trial of Padberg et al. (2004), who used an FTP approach in 40 patients with tension-type headache and found no significant difference between BoNT/A and placebo.

Table 1. *Controlled studies on botulinum toxin in patients with tension-type headache*

Refs.	No. of patients	Dose [units]; distribution; formulation of BoNT/A	Rating of study (evidence class)	Result*	SAE
Rollnik et al. (2000)	21	200; FS; Dysport®	II	–	0
Schmitt et al. (2001)	60	20; FS; Botox®	II	–	0
Padberg et al. (2004)	40	100; FTP; Botox®	I	–	0
Schulte-Mattler et al. (2004)	112	500; FS; Dysport®	I	–	0
Silberstein et al. (2006)	300	50, 86, 100, 150; FS; Botox®	I	–	0

FTP Variable injection sites, ''follow the pain approach''; *FS* fixed injection sites.
SAE Number of patients in that study with any serious adverse event related to botulinum toxin treatment.
* Results were judged as positive (+) only if the prospectively defined efficacy criterion was met.

Subsequent larger class I trials of BoNT/A in a total 412 patients with tension type headache were also negative (Table 1).

Chronic daily headache

Chronic daily headache (CDH) is a term that generally includes chronic tension type headache, chronic daily migraine, new daily persistent headache and hemicrania continua. Ondo et al. (2004) reported on their RCT in which an FTP approach was employed in patients with CDH. The study did not meet its a priori significance criterion. It is here rated class II because the inclusion/exclusion criteria are not clearly indicated.

Subsequent larger class I trials of BoNT/A in a total of 1057 patients with CDH failed to reach prospectively defined primary endpoints (Table 2).

Migraine

In the RCT of Silberstein et al. (2000), patients with migraine were randomized to receive either 25 units, or 75 units of BoNT/A, or placebo (saline) injections into fixed sites. The primary efficacy criterion was the change from baseline in the frequency of moderate-to-severe migraines, but it was not defined prospectively which post-treatment time interval had to be compared with baseline. Thus, this study here is rated as class II. All patients improved, and

Table 2. *Controlled studies on botulinum toxin in patients with chronic daily headache*

Refs.	No. of patients	Dose [units]; distribution; formulation of BoNT/A	Rating of study (evidence class)	Result*	SAE
Ondo et al. (2004)	60	200; FTP; Botox®	II	–	0
Mathew et al. (2005)	355	200; FTP; Botox®	I	–	0
Silberstein et al. (2005)	702	75, 150, 225; FS; Botox®	I	–	0

FTP Variable injection sites, ''follow the pain approach''; *FS* Fixed injection sites.
SAE Number of patients in that study with any serious adverse event related to botulinum toxin treatment.
* Results were judged as positive (+) only if the prospectively defined efficacy criterion was met.

Table 3. *Controlled studies on botulinum toxin in patients with migraine*

Refs.	No. of patients	Dose [units]; distribution; formulation of BoNT/A	Rating of study (evidence class)	Result*	SAE
Silberstein et al. (2000)	123	25, 75; FS; Botox®	II	–**	0
Barrientos and Chana (2003)	30	50, FS; Botox®	III	–***	0
Evers et al. (2004)	60	16, 100; FS; Botox®	I	–	0
Elkind et al. (2006)	418	7.5, 25, 50; FS; Botox®	II	–	0
Relja et al. (2007)	495	75, 150, 225; FS; Botox®	I	–	0
Aurora et al. (2007)	369	110–260; FTP; Botox®	I	–	0

FTP Variable injection sites, ''follow the pain approach''; *FS* fixed injection sites.
SAE Number of patients in that study with any serious adverse event related to botulinum toxin treatment.
* Results were judged as positive (+) only if the prospectively defined efficacy criterion was met.
** Significant effect only in the 25 U group but not in the 75 U group.
*** No outcome criterion was defined prospectively.

the improvement in the 25 units group was superior to placebo, while the response in the 75 units group was equal to placebo. The differences between 25 units and placebo were significant only at month 2 and 3 ($p \leq 0.042$), but not at month 1 after the treatment.

Barrientos and Chana (2003) studied a relatively small number of patients with migraine, but did neither prospectively define an outcome criterion nor exact inclusion/exclusion criteria thus, their study is rated as class III.

Subsequently, larger trials of BoNT/A in a total of 1342 patients with migraine were published, three studies were of class I and one study was of class II (Table 3). Prospectively defined primary endpoints were not reached.

These results were not in accord with the positive personal experiences of headache specialists who had been treating migraine patients with BoNT/A (Blumenfeld 2004). To explain these experiences, it was hypothesized that the experiences were mainly the result of a pronounced placebo effect of BoNT/A injections. Earlier, this hypothesis was denied (Blumenfeld 2004), but is supported by the data from the more recent RCTs (Mathew et al. 2005; Silberstein et al. 2005; Aurora et al. 2007; Relja et al. 2007), in which patients from both the BoNT/A and the placebo groups benefited equally from the injections they received. The magnitude of that benefit was similar to that of approved migraine treatments, such as divalproate sodium or topiramate.

Despite the overall negative results from randomized, controlled trials, research into the effects of botulinum toxin in the treatment of primary headache disorders is continuing. Some authors have suggested that specific features of the randomized, controlled trials may have confounded the results (Dodick et al. 2005). For example, the studies of chronic daily headache patients included patients who were treated concomitantly with other headache prophylactics (Mathew et al. 2005; Silberstein et al. 2005). One of these studies was followed by a subanalysis that only included patients who did not receive concomitant prophylaxis (Mathew et al. 2005; Dodick et al. 2005). In this subanalysis, BoNT/A showed statistically significant reductions in headache-free days and headache frequency compared with placebo (Dodick et al. 2005). Whether these results will be borne out in randomized, controlled trials is, as yet, unknown.

Conclusion

So far, the results of class I and class II studies on botulinum toxin in a total of 1117 patients with CDH, 1495 patients with CM, and 533 patients with TTH have been published. Prospectively defined primary outcome criteria were not met, but secondary outcomes were positive in some of the studies. According to the TTA quality of evidence scale, the treatment effectiveness is considered ''unproven'' (U). Studies are ongoing for an evaluation of some subgroups of patients with possible benefit from botulinum toxin treatment.

References

Arnon SS, Schechter R, Inglesby TV, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, Fine AD, Hauer J, Layton M, Lillibridge S, Osterholm MT, O'Toole T, Parker G, Perl TM, Russell PK, Swerdlow DL, Tonat K (2001) Botulinum toxin as a biological weapon: medical and public health management. JAMA 285: 1059–1070

Aurora SK, Gawel M, Brandes JL, Pokta S, Vandenburgh AM (2007) Botulinum toxin type a prophylactic treatment of episodic migraine: a randomized, double-blind, placebo-controlled exploratory study. Headache 47: 486–499

Barrientos N, Chana P (2003) Botulinum toxin type A in prophylactic treatment of migraine headaches: a preliminary study. J Headache Pain 4: 146–151

Blersch W, Schulte-Mattler WJ, Przywara S, May A, Bigalke H, Wohlfarth K (2002) Botulinum toxin A and the cutaneous nociception in humans: a prospective, double-blind, placebo-controlled, randomized study. J Neurol Sci 205: 59–63

Blumenfeld A (2004) Botulinum toxin type A for the treatment of headache: pro. Headache 44: 825–830

Blumenfeld AM, Binder W, Silberstein SD, Blitzer A (2003) Procedures for administering botulinum toxin type A for migraine and tension-type headache. Headache 43: 884–891

Brin MF, Fahn S, Moskowitz C, Friedman A, Shale HM, Greene PE, Blitzer A, List T, Lange D, Lovelace RE, et al (1987) Localized injections of botulinum toxin for the treatment of focal dystonia and hemifacial spasm. Mov Disord 2: 237–254

Dodick DW, Mauskop A, Elkind AH, DeGryse R, Brin MF, Silberstein SD (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: 315–324

Dong M, Yeh F, Tepp WH, Dean C, Johnson EA, Janz R, Chapman ER (2006) SV2 is the protein receptor for botulinum neurotoxin A. Science 312: 592–596

Durham PL, Cady R, Cady R (2004) Regulation of calcitonin gene-related peptide secretion from trigeminal nerve cells by botulinum toxin type A: implications for migraine therapy. Headache 44: 35–42

Edlund W, Gronseth G, So Y, Franklin G (2004) Subcommittee for the Quality Standards Subcommittee and the Therapeutics and Technology Assessment Subcommittee. Clinical practice guideline process manual. Minneapolis: American Academy of Neurology, www.aan.com/globals/axon/assets/2535.pdf

Edvinsson L (2001) Sensory nerves in man and their role in primary headaches. Cephalalgia 21: 761–764

Elkind AH, O'Carroll P, Blumenfeld A, DeGryse R, Dimitrova R (2006) A series of three sequential, randomized, controlled studies of repeated treatments with botulinum toxin type A for migraine prophylaxis. J Pain 7: 688–696

Evers S, Vollmer-Haase J, Schwaag S, Rahmann A, Husstedt IW, Frese A (2004) Botulinum toxin A in the prophylactic treatment of migraine – a randomized, double-blind, placebo-controlled study. Cephalalgia 24: 838–843

Fernandes-de-las-Penas C, Cuadrado ML, Arendt-Nielsen L, Simons DG, Pareja JA (2007) Myofascial trigger points and sensitization: an updated pain model for tension-type headache. Cephalalgia 27: 383–393

Gazerani P, Staahl C, Drewes AM, Arendt-Nielsen L (2006) The effects of botulinum toxin type A on capsaicin-evoked pain, flare, and secondary hyperalgesia in an experimental human model of trigeminal sensitization. Pain 122: 315–325

Gill MD (1982) Bacterial toxins: a table of lethal amounts. Microbiol Rev 46: 86–94

Goadsby PJ, Edvinsson L, Ekman R (1990) Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. Ann Neurol 28: 183–187

Hallett M (1999) One man's poison – clinical applications of botulinum toxin. N Engl J Med 341: 118–120

Ishikawa H, Mitsui Y, Yoshitomi T, Mashimo K, Aoki S, Mukuno K, Shimizu K (2000) Presynaptic effects of botulinum toxin type A on the neuronally evoked response of albino and pigmented rabbit iris sphincter and dilator muscles. Jpn J Ophthalmol 44: 106–109

Kramer HH, Angerer C, Erbguth F, Schmelz M, Birklein F (2003) Botulinum toxin A reduces neurogenic flare but has almost no effect on pain and hyperalgesia in human skin. J Neurol 250: 188–193

Lee WS, Moussaoui SM, Moskowitz MA (1994) Blockade by oral or parenteral RPR 100893 (a non-peptide NK1 receptor antagonist) of neurogenic plasma protein extravasation within guinea-pig dura mater and conjunctiva. Br J Pharmacol 112: 920–924

Mahrhold S, Rummel A, Bigalke H, Davletov B, Binz T (2006) The synaptic vesicle protein 2C mediates the uptake of botulinum neurotoxin A into phrenic nerves. FEBS Lett 580: 2011–2014

Mancini F, Zangaglia R, Cristina S, Sommaruga MG, Martignoni E, Nappi G, Pacchetti C (2003) Double-blind, placebo-controlled study to evaluate the efficacy and safety of botulinum toxin type A in the treatment of drooling in parkinsonism. Mov Disord 18: 685–688

Mathew NT, Frishberg BM, Gawel M, Dimitrova R, Gibson J, Turkel C (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: 60–65

Padberg M, de Bruijn SF, de Haan RJ, Tavy DL (2004) Treatment of chronic tension-type headache with botulinum toxin: a double-blind, placebo-controlled clinical trial. Cephalalgia 24: 675–680

Phebus LA, Johnson KW, Stengel PW, Lobb KL, Nixon JA, Hipskind PA (1997) The non-peptide NK-1 receptor antagonist LY303870 inhibits neurogenic dural inflammation in guinea pigs. Life Sci 60: 1553–1561

Rapp DE, Turk KW, Bales GT, Cook SP (2006) Botulinum toxin type a inhibits calcitonin gene-related peptide release from isolated rat bladder. J Urol 175: 1138–1142

Relja M, Poole AC, Schoenen J, Pascual J, Lei X, Thompson C (2007) A multicentre, double-blind, randomized, placebo-controlled, parallel group study of multiple treatments of botulinum toxin type A (BoNTA) for the prophylaxis of episodic migraine headaches. Cephalalgia 27: 492–503

Rollnik JD, Tanneberger O, Schubert M, Schneider U, Dengler R (2000) Treatment of tension-type headache with botulinum toxin type A: a double-blind, placebo-controlled study. Headache 40: 300–305

Rosales RL, Bigalke H, Dressler D (2006) Pharmacology of botulinum toxin: differences between type A preparations. Eur J Neurol 13 (Suppl 1): 2–10

Sakai F, Ebihara S, Akiyama M, Horikawa M (1995) Pericranial muscle hardness in tension-type headache. A non-invasive measurement method and its clinical application. Brain 118(2): 523–531

Schiavo G, Matteoli M, Montecucco C (2000) Neurotoxins affecting neuroexocytosis. Physiol Rev 80: 717–766

Schmitt WJ, Slowey E, Fravi N, Weber S, Burgunder JM (2001) Effect of botulinum toxin A injections in the treatment of chronic tension-type headache: a double-blind, placebo-controlled trial. Headache 41: 658–664

Schnider P, Binder M, Auff E, Kittler H, Berger T, Wolff K (1997) Double-blind trial of botulinum A toxin for the treatment of focal hyperhidrosis of the palms. Br J Dermatol 136: 548–552

Schulte-Mattler WJ, Krack P (2004) Treatment of chronic tension-type headache with botulinum toxin A: a randomized, double-blind, placebo-controlled multicenter study. Pain 109: 110–114

Schulte-Mattler WJ, Wieser T, Zierz S (1999) Treatment of tension-type headache with botulinum toxin: a pilot study. Eur J Med Res 4: 183–186

Schulte-Mattler WJ, Opatz O, Blersch W, May A, Bigalke H, Wohlfahrt K (2007) Botulinum toxin A does not alter capsaicin-induced pain perception in human skin. J Neurol Sci 260: 38–42

Silberstein S, Mathew N, Saper J, Jenkins S (2000) Botulinum toxin type A as a migraine preventive treatment. For the BOTOX migraine clinical research group. Headache 40: 445–450

Silberstein SD, Stark SR, Lucas SM, Christie SN, Degryse RE, Turkel CC (2005) Botulinum toxin type A for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. Mayo Clin Proc 80: 1126–1137

Silberstein SD, Gobel H, Jensen R, Elkind AH, Degryse R, Walcott JM, Turkel C (2006) Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicentre, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia 26: 790–800

Sycha T, Samal D, Chizh B, Lehr S, Gustorff B, Schnider P, Auff E (2006) A lack of antinociceptive or antiinflammatory effect of botulinum toxin a in an inflammatory human pain model. Anesth Analg 102: 509–516

Tsui JK, Eisen A, Stoessl AJ, Calne S, Calne DB (1986) Double-blind study of botulinum toxin in spasmodic torticollis. Lancet 2: 245–247

Voller B, Sycha T, Gustorff B, Schmetterer L, Lehr S, Eichler HG, Auff E, Schnider P (2003) A randomized, double-blind, placebo controlled study on analgesic effects of botulinum toxin A. Neurology 61: 940–944

Welch MJ, Purkiss JR, Foster KA (2000) Sensitivity of embryonic rat dorsal root ganglia neurons to Clostridium botulinum neurotoxins. Toxicon 38: 245–258

Wohlfarth K, Goschel H, Frevert J, Dengler R, Bigalke H (1997) Botulinum A toxins: units versus units. Naunyn Schmiedebergs Arch Pharmacol 355: 335–340

Yokosawa N, Suga K, Kimura K, Tsuzuki K, Fujii N, Oguma K, Yokosawa H (1994) Exogenous zinc ion is required for inhibitory activity of botulinum neurotoxin C1 against norepinephrine release and its endopeptidase activity toward substance P. Biochem Mol Biol Int 32: 455–463

Zwart JA, Bovim G, Sand T, Sjaastad O (1994) Tension headache: botulinum toxin paralysis of temporal muscles. Headache 34: 458–462