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Botulinum toxin type-A therapy in cluster headache: an open study

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Abstract The objective of this open single-centre study was to evaluate the efficacy and tolerability of botulinum toxin type-A (BTX-A) as add-on in the prophylactic treatment of cluster headache (CH). Twelve male patients with episodic (n=3) or chronic (n=9) CH, unresponsive to common prophylactic medications, were treated with a cumulative dose of 50 International Units (IU) BTX-A according to a standardised injection scheme into the ipsilateral pericranial muscles. One patient with chronic CH experienced a total cessation of attacks and in 2 patients attack intensity and frequency improved. In another patient with chronic CH typical attacks were not influenced, but an ipsilateral continuous occipital headache significantly improved. Patients with episodic CH did not benefit from BTX-A treatment. Tolerability was excellent. These findings provide evidence that BTX-A may be beneficial as an add-on prophylactic therapy for a limited number of patients with chronic CH.

Keywords Cluster headache • Botulinum toxin-A • Headache/drug therapy • Treatment outcome

Introduction

Cluster headache (CH) is a severe pain syndrome associated with autonomic symptoms. Its prevalence is estimated to be relatively low (<0.4%) [1]. Some prophylactic treatment options have been established, for example verapamil, lithium or topiramate [2]; however, there is still a relevant need for new therapeutic options due to resistance and tolerability problems in a subgroup of these patients.

Botulinum toxin type-A (BTX-A) is a muscle-relaxing agent [3] that has long been used for the treatment of disorders associated with increased muscle tone. It has also been reported to be effective in the therapy for migraine [4, 5] or chronic migraine [6–8]. On analogy to migraine, during CH attacks an activation of the trigemino-vascular system and an elevation of calcitonin gene-related peptide (CGRP) in the jugular venous blood [9] have been observed. These suspected similarities in pathophysiology were the rationale to investigate the use of BTX-A for CH therapy. Single case reports have implicated that the injection of 24–100 IU of BTX-A into the ipsilateral pericranial muscles is beneficial

[10–12]. To systematically evaluate the usefulness and tolerability of BTX-A in CH prophylaxis, we performed an open clinical trial using a cumulative dose of 50 IU of BTX-A (Botox®, Allergan Inc.) in the largest series of patients with CH to date.

Patients and methods

This study was performed as an open, non-randomised, single-centre study. Twelve patients fulfilling the International Headache Society criteria [13] for episodic (n=3) or chronic (n=9) CH were enrolled. Exclusion criteria were the standard ones for BTX therapy (e.g., generalised muscle weakness, myasthenia gravis, gravidity or known antibodies against botulinum toxin). All patients gave their written consent and the local ethics committee approved the study.

The patients were males, with a mean age of 42±11 (mean±SD) years. The mean duration of disease was 6 years. Table 1 lists the patient characteristics, disease history and prophylactic medication at the time of BTX-A treatment; the outcome of the patients responding to BTX-A is described in Table 2.

BTX-A was given as add-on therapy. Prior prophylactic medication was continued without changes in most patients. Attempts to reduce the dose of prophylactic therapy were made in 2 patients (Table 2, Patients 11a and 12a). Otherwise in one case (Patient 12b), with respect to only a transient response to BTX-A, the dose of pro-

Table 1 Patient characteristics, history and outcome before BTX-A treatment

No.	Age	Diagnosis	CH side	CH duration (years)[a]	No. of attacks	Attack duration (min)	Mean duration of prior bouts	Duration of bout at injection	Current daily prophylaxis with verapamil (mg)/ prophylactic drugs	
No benefit from BTX-A therapy										
1	31	epi	r	7	3–4	120–180	3 m	6 w	480	
2	42	epi	l	7	1	60–90	3 w	6 m[b]		Methysergide (4 mg)
3	36	epi	l	4	0.5	120	4 w	3 m[b]	600	
4	50	ch pr	r	2	2	35–60			480	Lithium (36.6 mmol)
5	44	ch pr	l	6	2	45–120			160	
6	64	ch sec	l	15/12	1	30–90			720	
7	29	ch sec	r	5/3	1–2	60			520	
8	42	ch sec	r	6/3	1–2	120				
Improvement after BTX-A therapy										
9[c]	34	ch pr	l	2	1	180			720	
10a	53	ch sec	r	4/2	1–2	60–120			480	
10b[d]					1				240	Topiramate (50 mg)
11a	28	ch sec	r	10/2	4–6	120–180			720	Valproate (600 mg), Lithium (48.8 mmol
11b[d]					3–4					Lithium (97.6 mmol)
12a	50	ch sec	l	5/1.5	0.5	180			600	
12b[d]					1–2				480	

no., patient number; *epi*, episodic; *ch pr*, chronic, primary; *ch sec*, chronic, secondary; *w*, weeks; *m*, months; *r*, right-sided; *l*, left-sided

[a]In case of secondary CH the time since the episodic form has turned into the chronic form is listed after the slash.

[b]BTX-A was injected at a time when the duration of the bout was much longer compared to prior bouts.

[c]No improvement of the patient's typical CH, but decrease of a continuous ipsilateral headache.

[d]Reinjection of BTX-A 10 (Patient 10b), 7 (Patient 11b) and 3 (Patient 12b) months after BTX-A injection.

phylactic medication was enhanced later on. The usual attack treatment (e.g., oxygen or nasal/subcutaneous sumatriptan) was allowed. According to a standardised injection protocol, a cumulative dose of 50 IU Botox® (dissolved in 2 ml 0.9% NaCl) was injected into the temporalis (10 IU), frontalis (10 IU), splenium capitis (10 IU) and trapezius (20 IU) muscle ipsilateral to the headache site. Patients with a positive response to Botox® were reinjected 3–10 months after the first setting due to recurrence of attacks. A positive response was defined as at least 50% reduction of pain intensity and/or attack frequency.

Patients were asked to keep a standardised diary about headache properties including the pain localisation and duration, pain intensity (measured on a visual analogue scale (VAS) ranging from 0/10 to 10/10), concomitant symptoms, attack treatment, concomitant therapy and any side effects of treatment. The screening visit (day –14) was followed by the visit for injection (day 0) and 3 follow-up visits on days +7, +30 and +90. Primary efficacy variables were the number of attacks per day; secondary variables were the duration and pain intensity of the attacks and daily analgesics or oxygen consumption.

Results

Benefit from BTX-A therapy was observed in 4/9 patients with chronic CH. Typical CH was positively influenced in 3 of these patients. One patient experienced improvement of a continuous ipsilateral occipital headache, while CH attacks remained unchanged. Response to BTX-A occurred within the first week after injection and according to the half-life time of BTX-A lasted for 2–3 months. One patient became completely attack-free (Patient 12a), but efforts to reduce verapamil beyond doses of 240 mg/day resulted in attack recurrence. Three months after the first injection, attacks recurred and BTX-A was reinjected. A 2-week period of complete relief was followed by the recurrence of attacks, which were of lower intensity (VAS 8/10) and occurred less frequently (1×/day) compared to attacks prior to the second setting (Patient 12b). Attacks ceased when verapamil was increased to 600 mg/day. The second patient (Patient 11a) experienced a 6-week improvement of attack intensity, reduction of frequency and better response to oxygen. Then valproate was stopped due to side effects. Six weeks after BTX-A injection, lithium was also dropped, but as severe attacks recurred, it had to be restarted. After another 4 weeks CH attacks returned to the level prior to BTX-A injection. In the following months, periods with severe cluster attacks changed with intervals of spontaneous partial remissions. During a period of exacerbation and 7 months after the first setting, BTX-A was reinjected; improvement of CH was reproducible and again limited to a 10-week period (Patient 11b). In the third patient (Patient 10a) the intensity and frequency of attacks decreased after BTX-A injection and the response of CH attacks to oxygen increased. This was limited to a time interval of 10 weeks. Reinjection of BTX-A 10 months later during a period with only one severe attack per week was without any further effect (Patient 10b). In the fourth patient (Patient 9) a concomitant and permanent ipsilateral occipital pain improved after BTX-A injection, whereas cluster attacks were not influenced. The intensity of this concomitant pain initially was moderate (VAS 6/10) and was lessened by 50% (VAS 3/10) over a time period of 11 weeks. The patient reported that the first manifestation of this ipsilateral accompanying headache was not before chronic CH started; this continuous headache associated with CH is mentioned also by other patients with chronic CH and we suspect it to be part of the CH syndrome. BTX-A was well tolerated in all but one patient, who reported mild neck muscle weakness for 8 weeks.

Table 2 Patients responding to BTX-A: influence on cluster attacks and response to attack therapy

No.	CH intensity (VAS 1–10)		CH attack frequency		Latency of response to acute therapy (min)	
	p_0	$p_{BTX\text{-}A}$	p_0	$p_{BTX\text{-}A}$	p_0	$p_{BTX\text{-}A}$
9[a]	10	10	1×/d	1×/d	20	20
10a	8	3	1–2×/d	0.5–1×/d	20	5
10b	8	8	1×/w	1×/w	20	20
11a	10	5	4–6×/d	1×/d	60	10
11b	10	5	3–4×/d	1×/d	60	10
12a	10	0	0.5×/d	0	20	–
12b[b]	10	0	1–2	0	20	–

No., patient number; $p_0/p_{BTX\text{-}A}$, before/after BTX-A therapy;

[a]Only influence on a continuous, ipsilateral headache, no effect on cluster attacks

[b]Attack-free not before increase of verapamil dose to 600 mg/d

Discussion

The efficacy of BTX-A as CH prophylaxis has so far been studied in single case reports only. Now in a descriptive study we applied BTX-A to a group of 12 CH patients following a standardised injection scheme and considering potential influencing parameters. Due to the rarity of CH and severity of its clinical picture, an open design was chosen. Using 50 IU of BTX-A, we observed improvement of the primary study end point – reduction of attack frequency – in 25% (3/12) of all study patients and in 33% (3/9) of patients with chronic CH. Concomitant prophylactic medication could not be stopped in any patient without recurrence of attacks. In an earlier report on 4 patients with chronic CH [12], complete relief was observed in one patient and reduction of attack frequency in another one. Also 3 patients with episodic CH received BTX-A and 2 of them experienced a cessation of the cluster bout, but data on the time point of injection with relation to the duration of the cluster period are lacking. Spontaneous remission also cannot be ruled out in the case reports of Freund and Schwartz [10], who observed a total remission in two cluster patients. Smuts and Barnard reported a favourable response to BTX-A in 2 of 4 CH patients [11], but more detailed information is also missing in their study. We observed positive effects of BTX-A only in patients with chronic CH. In this form of CH spontaneous remission occurs very seldom. The positive effect of BTX-A was only partially reproducible in the patients. In Patient 12 after reinjection of BTX-A a longer cessation of attacks was not seen before the dose of verapamil was increased. Patient 10 received BTX-A for the second time without benefit, but at that time the attack frequency was much lower compared to the situation at the first injection of BTX-A and also the prophylactic therapy had changed. Besides, interpretation of reproducibility in Patient 11 is limited due to the spontaneous reduction of attacks between the treatments. We also observed in our study that patients who suffered from the chronic form of CH for a shorter period (1.5–2 years) in the majority responded better to BTX-A than patients with a longer duration of chronic CH (3–12 years). Improvement of a permanent ipsilateral occipital headache in one patient leaving the typical retroorbital CH unaffected may be explained by influences of BTX-A on occipital afferences to the trigeminal network. We consider this permanent headache to be part of the cluster syndrome. This assumption is based on the clinical experience that some patients with CH suffer from accompanying nuchal pain features [14] and that a lower syndrome of CH with attacks confined to occipital regions or the neck has been described [15].

The aetiology and pathophysiology of CH is still not completely understood. The vascular hypothesis proposes inflammation of the ipsilateral sinus cavernosus. Accordingly, increased venous blood pressure in the sinus would directly cause the attack by temporarily increasing the pressure on sympathetic fibres running in the neighbourhood with the carotid artery [16]. Alternatively, evidence from PET studies [17, 18], voxel-based morphometry [16] and stereotactic hypothalamic deep brain stimulation [20–22] suggests that there is a dysfunction of the ipsilateral posterior hypothalamus in CH, which causes a secondary activation of the trigemino-autonomic brainstem pathways [23]. This secondary activation elicits neurogenic inflammation of the large dural vessels, a mechanism that is similar to that during migraine attacks.

The question arises as to how BTX-A interferes with CH pathophysiology and whether it is responsible for the positive effects observed in our study. A primary effect on the muscles with a secondary influence on central trigger mechanisms in CH is possible, but may not solely explain the action of BTX-A. Alternatively, it is discussed that BTX-A may reduce or even prevent sensitisation of peripheral trigeminal afferents, which through attenuation of the nociceptive input may also result in inhibition of central sensitisation [24]. In the context of neurogenic inflammation, there is evidence that BTX-A is retrogradely transported into the CNS [25] and modulates the release of neurotransmitters such as substance P [26] or CGRP [27] in the trigeminal terminals.

Limitations of this study arise from its open design. Placebo response was not considered and effects of concomitant preventative therapy cannot be excluded. The efficacy of prophylactic CH therapy has rarely been evaluated in controlled studies. In a placebo-controlled trial on the suboccipital injection of steroids no placebo response was noticed, just like in five studies on the efficacy of oral drugs in prophylactic CH therapy [28]. Two studies, which described placebo rates of 14–42%, included only patients with episodic CH [29, 30]. Concerning the acute treatment of CH, the response to hyperbaric normoxic placebo was just as high as to hyperbaric 100% oxygen (25% in chronic and 83% in episodic CH patients). Therefore the hyperbaric condition alone might have some effect on the reduction of CH attack severity and frequency and may not be interpreted as a real placebo [31]. In a recent study on the usefulness of intranasal zolmitriptan the placebo response was 21% in the whole study population [32], but higher values were described for patients with episodic (30%) compared to chronic CH (14%). Thus there may be a relatively mild placebo response in chronic compared to episodic CH.

For the interpretation of our results, the natural course of CH should be considered also. The strongest argument for the efficacy of BTX-A in chronic CH is that spontaneous remissions or the transition from the chronic to the episodic course are rare. In our small group of patients with episodic CH BTX-A was not effective.

In conclusion, our data suggest that the injection of BTX-

A into the pericranial muscles ipsilateral to the headache site could be beneficial as add-on in some patients with otherwise drug refractory chronic CH. But usefulness of BTX-A as a new alternative therapeutic tool in the treatment of chronic CH has to be confirmed in double-blind, randomised, controlled studies. Especially the influence of the placebo response has to be established, patient characteristics that predict benefit from BTX treatment should be identified, and the effects of recurrent applications and concomitant therapy must be investigated.

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