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Long-term benefits of botulinum toxin type A (BOTOX) in chronic daily headache: a five-year long experience

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Abstract Botulinum toxin type A (BoNT-A) has been recently suggested as prophylaxis therapy for the treatment of primary headache chronic forms. Several studies on its efficacy are available, but results are often contradictory and not univocal. The effects of BoNT-A on chronic forms of both tension-type headache and migraine have been investigated. In this study we introduce our five-year long experience with BoNT-A (BOTOX, Allergan, Irvine, CA). The employed dosage was 100 U and the Fixed Sites–Fixed Doses (FSFD) protocol was used. The period of study was April 2001 to July 2006. A sum of 1347 patients suffering from chronic daily headache (CDH) were treated. We

registered in these patients the number of headache days per month and observed their reduction in relation to the number of injections. The best results were found after 12 months of treatment, with patients being free of attacks 23 days per month. The BoNT-A treatment was safe and well tolerated, as only 1.6% of patients reported adverse events, and they were all mild and transient. In conclusion, BoNT-A therapy appears to be an efficacious new therapeutic choice in the prophylaxis of CDH, especially for patients not responding to previous prophylactic treatments.

Keywords Botulinum toxin type A • Prophylaxis • Chronic daily headache

Introduction

Headache is among the most common symptoms requiring a physician consultation, and therefore one of the major issues in public health [1]. Approximately 51% of the general population is affected by headache, of which 33% are affected by tension-type headache (TTH), 14% by migraine and 4% by chronic forms (chronic daily headache, CDH). In CDH, attacks occur at least 15 days per month, for three months consecutively. Incidence is higher in women than in men [2].

Reduced work ability and absence from work are reported by a range of 7%–15% of this population. Considering only migraine, the number of lost working days per year varies between 2 and 6 [3].

Patients experiencing medium/high monthly attacks need preventative therapy. Botulinum toxin type A (BoNT-A) has been recently proposed as a new option in this approach. At present, this drug plays a possible role in the treatment of both chronic forms of TTH and migraine [4, 5].

In clinical practice, BoNT-A (BOTOX, Allergan, Irvine, CA) is currently applied to various conditions

including post-stroke disability, cervical dystonia, blepharospasm, regional myofascial pain syndromes like hemifacial spasm, and other disorders involving pathological muscle hyperactivity [6].

Against this background, BoNT-A may be considered as a possible therapeutic choice in TTH management, as suggested by increased muscular tension and tenderness in several TTH patients, together with other factors, both peripheral and central, such as stress and psychopathological factors [7].

Mechanisms of action

BoNT-A is a substance synthesised from the gram-positive anaerobic bacterium *Clostridium botulinum*. It acts by blocking the peripheral release of acetylcholine at the level of peripheral cholinergic nerve endings [8]. In fact, BoNT-A reaches the extra-cellular space through transport in the general vascular circulation. Unfortunately, the mechanism conducting BoNT-A outside the vasculature is unknown. The neuromuscular junction, which constitutes its principal target, is reached in the extra-cellular space. Botulinum toxin also arrests exocytosis in all the peripheral cholinergic sites [9]. At the neuromuscular junction level, BoNT-A blocks spontaneous quantal release of acetylcholine via cleavage of SNAP-25 protein (synaptosomal protein with a molecular weight of 25 kDa), producing muscular relaxation. This mechanism of action is responsible for both the botulism disorder and the use of BoNT-A as a therapeutic agent in clinical practice. Among the seven known serotypes (going from A to G), BoNT-A represents the most investigated in clinical studies. Besides, BoNT-A displays the most sustained action [10]. Major effects can be observed 5 or 6 weeks after the intramuscular injection. Recovery usually occurs 12 weeks after the injection, the required period for the regeneration of the nerve endings [9]. For that reason, in therapeutic programmes injection cycles are repeated every three months. Furthermore, BoNT-A action on pain modulation processes could play a predominant role in the prophylactic treatment of TTH. BoNT-A inhibits the release of calcitonin gene-related peptide (CGRP), as demonstrated by Durham et al. In this study, CGRP was expressed in trigeminal ganglia neurons present in 1–3-day-old cultures, incubated afterwards with toxin. This incubation shows the reduction of the secretory stimulation of CGRP neurotransmitter with respect to control cultures [11]. These data suggest a contribution of CGRP to migraine pathophysiology. CGRP causes, together with other peptides, the release of proinflammatory mediators that increase CGRP synthesis, in correspondence with the duration of a typical migraine episode [12].

Consequently, BoNT-A could be extended also to the treatment of this disorder [13]. Eross et al. demonstrated the efficacy of reducing headache frequency in patients affected by episodic and chronic migraine [14]. Besides, suppressive effects of BoNT-A on intradermal capsaicin-evoked pain and secondary hyperalgesia have been demonstrated, suggesting a local peripheral effect on cutaneous nociceptors [15].

BoNT-A in headache treatment

In the literature, discordant opinions exist concerning BoNT-A therapy in primary headache disorders according to ICDH-II criteria [16]. However, BoNT-A seems particularly useful for CDH. In fact, the treatment of CDH is often still inadequate [17]. There is a need for new effective, safe and manageable prophylactic drugs, rather than the umpteenth triptan [18, 19].

But the debate has seen Blumenfeld defining BoNT-A as a “rational treatment choice” [20] and Welch affirming BoNT-A’s beneficial effects, which remain unproven [21].

The analysis of recent clinical trials with BoNT-A in headache prophylaxis reported diverse information. These studies are often structured quite differently concerning population selection, choice of outcome and study duration. Some studies in favour of BoNT-A are the following. In an 11-month, randomised, double-blind, placebo-controlled study, Dodick et al. enrolled 355 patients affected by CDH, of which 228 were not under prophylaxis treatment. Those patients received three treatment cycles (BoNT-A or placebo) every 90 days. After the first month, BoNT-A consistently reduced headache frequency, and its effect persisted for 2 or 3 months. Headache frequency diminished in over 50% of patients after two BoNT-A injection sessions, and the mean number of headache-free days per month was almost tripled (from 6 to 16 days). Furthermore, drug consumption decreased remarkably [22].

Similar results were shown by Mathew et al. [23]. Patients treated with BoNT-A presented 7 more (1 week) headache-free days with respect to their baseline. The initial difference between the groups consisting in 1.5 headache-free days did not prove to be statistically significant after 180 days.

At the same time, Relja and Telarović included 16 patients with chronic TTH in a prospective double-blind, placebo-controlled, cross-over study and 30 patients in an open-label long-term study, to investigate the role of BoNT-A in prophylaxis. All patients experienced a decrease in headache intensity and pericranial

muscle tenderness, and an increase of headache-free days, statistically significant compared to the placebo group [24].

In a retrospective chart review, Blumenfeld observed a reduction of 56% in the number of headache days per month from 18.9 to 8.3 ($n=256$, $p<0.001$). Two hundred and seventy-one patients were treated with BoNT-A from January 1999 to February 2002 [25].

In contrast, Rollnik et al. [26] registered no significant differences between placebo and BoNT-A after 4, 8, 12 weeks. In this double-blind, placebo-controlled study, with 21 patients affected by TTH, no reduction was observed in terms of attack frequency, analgesics intake, total tenderness score evaluated through palpation and quality of life parameters. However, the great limitation of this pilot study was the unique drug dosage (20 U).

Silberstein et al. evaluated the efficacy of various dosages (50, 100 and 150 U injected in 5 muscle groups and 86 and 100 U injected in three muscle groups). In this study as well, both control and BoNT-A groups were found to be equivalent. For tension headache-free days per month, all groups improved at the day 60 primary endpoint, while after 90 days a 50% decrease in terms of headache days was observed in BoNT-A patients. This suggests the necessity of a longer evaluation period [27].

Evers and Olesen recently predicted “the end of the road” for BoNT-A. After having reviewed the published data they conclude there is no possible role for this treatment [28]. We do not share this opinion [17].

A long list of studies, which cannot be discussed here, represent “pro” and “cons” factions [29–40].

Five-year experience with BoNT-A in CDH

In our five-year-long experience at the Regional Referral Headache Centre of the Sant’Andrea Hospital, BoNT-A has been employed in prophylaxis therapy of CDH. The Fixed Sites-Fixed Doses (FSFD) protocol used considered the following pericranial muscles: *frontalis*, *anterior temporalis*, *occipitalis*, *trapezius*, *semispinalis capitis* and/or *splenius capitis*.

A total dosage of 100 U was administered every three months during the first year of treatment, and afterwards twice a year.

From 2001 to 2006, 1347 patients were treated in our centre in a Day Hospital regimen, with an average of 350 patients per year over the last three years (Fig. 1).

We registered in these patients a frequency reduction of headache days per month, increasing in time. The maximum reduction was reached after 12 months of

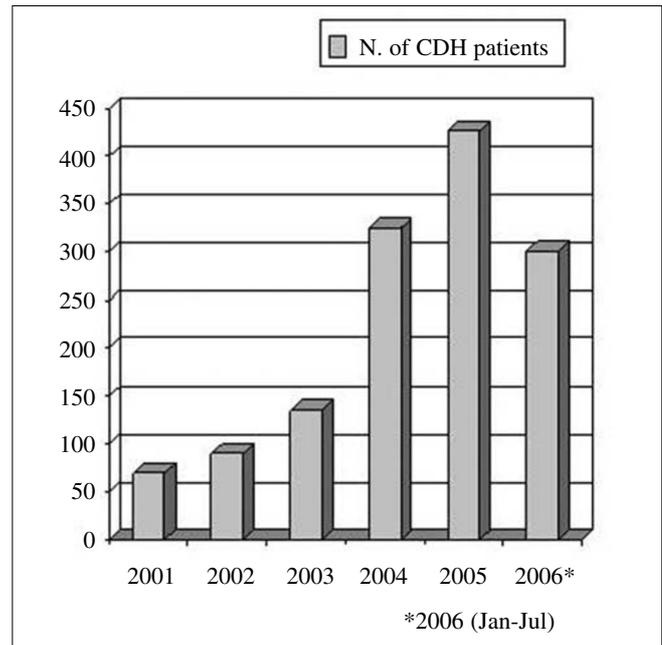


Fig. 1 Number of CDH patients under prophylaxis treatment with BoNT-A

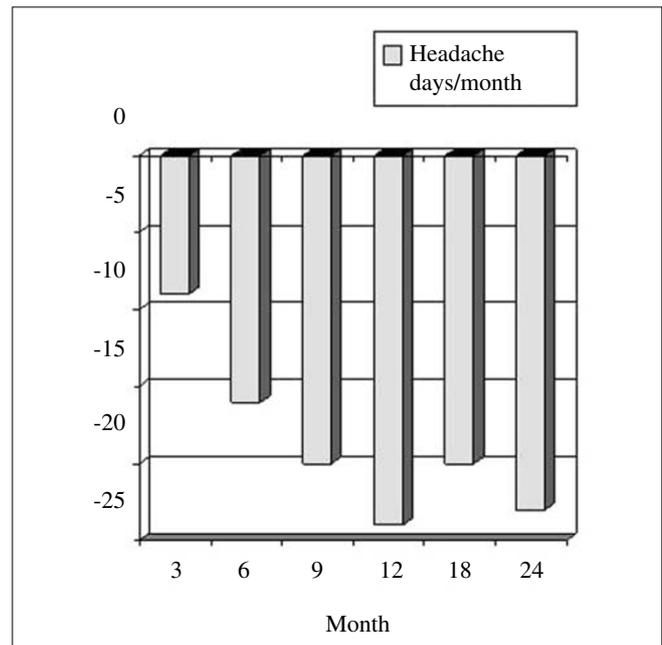


Fig. 2 Headache frequency in CDH patients after BoNT-A administration

treatment, with patients being free of attacks 23 days per month (Fig. 2).

The first three-month cycle accomplished a maximum of 10 headache-free days per month. The improved results after that suggest a major efficacy of a longer treatment (Fig. 2).

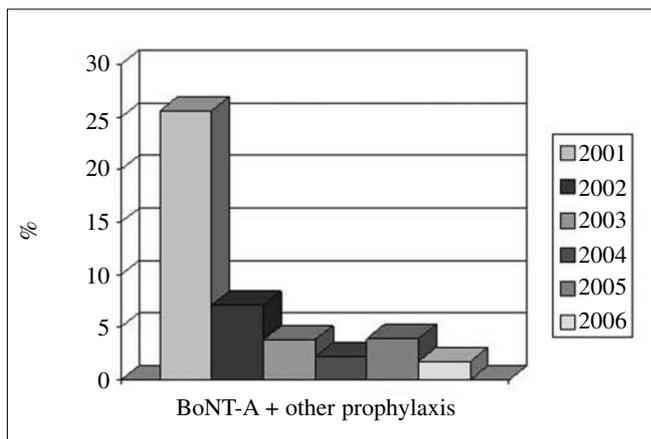


Fig. 3 CDH patients co-treated with additional prophylaxis therapies

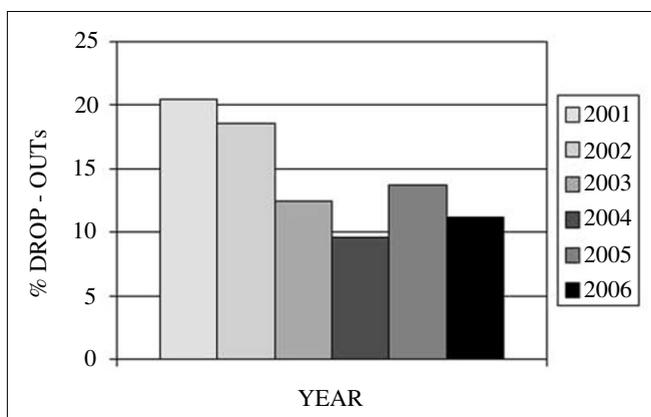


Fig. 4 Total drop-outs in CDH therapy with BoNT-A

In 2001 about 25% of the patients had been undergoing concomitant prophylaxis therapies (myorelaxants, antidepressants, etc.), while in the following years only 5% of the patients were co-treated with an additional prophylaxis therapy (Fig. 3). In the first two years, the number of total drop-outs represented 20%, which was reduced to 12% in 2006 (Fig. 4).

As recorded in the literature the percentage of adverse events is extremely low, BoNT-A appearing to be therefore safe and well tolerated [20–23]. In our data, only 1.6% of patients reported side effects. Forty-two percent of these patients reported pain at the injection site, 41% cutaneous irritation, 6% neck muscle rigidity, 6% nausea, 4% dizziness and 1% ptosis/dysphonia/dysphagia (Fig. 5). All these side effects were mild and transient.

Health economics considerations on BoNT-A use in headache lead us towards interesting views on its savings. One year of in-hospital BoNT-A therapy amounts to €564.00 including pharmaceutical costs, consumable supplies and personnel. The total cost of BoNT-A treatment per patient was €642.00, whilst average costs of previous

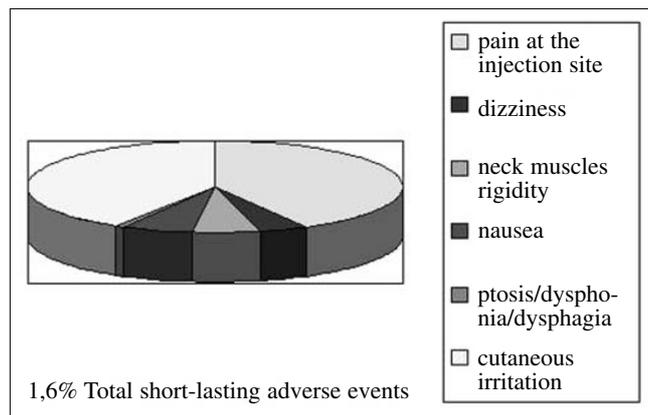


Fig. 5 Adverse events of BoNT-A in CDH

therapies amounted to €853.43 [41, 42]. This can be considered together with a reduction of clinic symptomatology and analgesic intake [43].

Conclusions

On the basis of our clinical experience of BoNT-A off-label application in CDH, the preferred subgroup for BoNT-A application seems to be the non-responder CDH patients. As the majority of these patients come from detoxification procedures, we thought this application could constitute a new option. There is clearly a higher compliance for a prophylaxis therapy using a different method of administration if compared to the traditional treatment *per os*. CDH patients with medication overuse headache (MOH) usually lose perception of the difference between acute or preventative drugs, as they consume an undetermined number of tablets daily. Therefore, the injection approach with BoNT-A was apparently more accepted after detoxification. The role of placebo in this unusual administration pathway should be attentively evaluated. Further studies dealing with this clinical topic in double-blind phase III are *in fieri* and soon we will be able to define BoNT-A's efficacy in CDH patients non-responders to previous therapies.

However, labeled preventative therapy for chronic headaches remains inadequate. The drugs used are old and often produce side effects. The poor efficacy of the available drugs and their unacceptable side effects often create the pathway for abuse of pain-relief drugs and then MOH.

In conclusion, BoNT-A therapy appears to be an efficacious new therapeutic choice in the prophylaxis of CDH, especially for patients not responding to previous prophylactic treatments. New upcoming data will definitively clarify this issue.

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