Toxicon 107 (2015) 72–76

Contents lists available at ScienceDirect

Toxicon

journal homepage: www.elsevier.com/locate/toxicon

Review

Is it time for flexibility in botulinum inter-injection intervals?

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ARTICLE INFO

Article history:
Received 30 June 2015
Received in revised form
7 July 2015
Accepted 30 September 2015
Available online 9 October 2015

Keywords:
Shortened intervals
Flexible inter-injection intervals
Botulinum toxin
Cervical dystonia
Blepharospasm

ABSTRACT

Based largely on old retrospective reports, the recommendation of injecting BoNT as infrequently as possible, with the lowest possible dose, was formed. While BoNT is inherently immunogenic, with improved production, most patients no longer develop immune resistance and poor response to BoNT is often due to other factors.

In a randomized controlled trial (RCT) using abobotulinumtoxinA for cervical dystonia (CD) by the German Dystonia Study Group, half of the patients treated with 250 and 500 U, and 39% in the 1000 U group required retreatment after 8 weeks. In a RCT comparing onabotulinumtoxinA and incobotulinumtoxinA for CD by Benecke et al., waning of effect was noted in 70 days for both toxins. Finally, two long-term prospective trials employing flexible intervals, with reinjections based on patient's request, have been performed using incobotulinumtoxinA. In the CD study, 22.5% were re-injected in <10 weeks and 24.6% between 10 and 12 weeks. In the blepharospasm study, the median injection interval was 6–10 weeks for 23.7% and 10–12 weeks for 32.3%)

While long-term studies utilizing flexible/shortened intervals, with vigilance over immunogenicity are needed, the majority of current evidence no longer support the very stringent adherence to strict 90-day BoNT injection intervals.

Contents

1. Background

Botulinum toxin (BoNT) injections are now approved for the treatment of many neurological and non-neurological conditions. BoNT is the treatment of choice for focal (and segmental) dystonias, including cervical dystonia and blepharospasm (Albanese et al., 2006; Benecke and Dressler, 2007; Simpson et al., 2008; Albanese

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http://dx.doi.org/10.1016/j.toxicon.2015.09.037
0041-0101/

et al., 2011). The different strains of Clostridium botulinum bacteria produce 7 antigenically different strains of toxins labeled from A – G. However, only 2 serotypes of BoNT are currently in use clinically – serotype A [3 brands – abobotulinumtoxinA (Dysport), incobotulinumtoxinA (Xeomin) and onabotulinumtoxinA (Botox) and serotype B [rimabotulinumtoxinB (Myobloc or Neurobloc)]. There are additional brands available in other geographical regions especially in Asia and South America.

In the USA, the FDA-approved indications in the field of movement disorders differ slightly for the different toxin serotypes (e.g., onabotulinumtoxinA is approved for cervical dystonia, blepharospasm, chronic headache and upper limb spasticity; incobotulinumA is approved for adult cervical dystonia and blepharospasm; abobotulinumtoxinA and rimabotulnumtoxinB are approved for use in cervical dystonia). Because focal dystonias are chronic disorders, BoNT injections need to be given repeatedly over long periods of time (many times over years) to maintain clinical benefit (Brashear et al., 2000; Brin et al., 2008).

Despite more than 25 years of use, some aspects of BoNT injection therapy have yet to be standardized across clinical practice; especially the inter-injection or treatment interval, optimal dosing and choice and number of injection sites. This is partly because of factors that affect successful outcome, such as injector experience (e.g., correct diagnosis, muscle identification and injection technique), patient feedback (e.g., realistic expectations, perception of benefit) and the development of secondary non-response, which was previously thought to be primarily due to the formation of neutralizing (also known as 'blocking') antibodies.

The current accepted standard among physicians regarding inter-injection interval is generally 12 weeks or more. This recommendation is also underscored in all the BoNT product inserts, and in the United States and other countries, it is strongly enforced by third party payors. However, this gold standard practice was primarily based from prior studies using an old BoNT-A toxin (Botox) formulation that carried higher antigenic properties than the present day BoNT formulations. Whether this standard is still applicable today with improvements in the quality of BoNT production is debatable. This review intends to bring forward available recent evidence to support the consideration of flexible inter-injection intervals when using BoNT injections.

2. Secondary non-response in chemodenervation with BoNT

Secondary non-response (SNR) occurs during the course of therapy when a previously effective toxin treatment no longer produces significant clinical benefit. Sometimes SNR may be due to a placebo effect of the first series of treatment. Some disorders worsen over time and can be exacerbated by stress, giving a clinical picture of SNR. In addition, the despondency caused by a chronic debilitating condition can result in symptom deterioration such that a previously efficacious dose now induces a subclinical response. However, an important reason for secondary treatment failure of any therapeutic protein is its neutralization by antibodies, where the clinical effect may wane gradually, eventually leading to complete treatment failure.

The non-toxic clostridial proteins, also known as complexing proteins or neurotoxin-associated proteins (NAPs), protect the neurotoxin against degradation in the acidic conditions of the host gastrointestinal tract (particularly in the stomach) (Ohishi et al., 1977; Chen et al., 1998). These NAPs are integral in the production of old BoNT formulations. In onabotulinumtoxinA and abobotulinumtoxinA preparations, the complexing proteins have a molecular weight of 300kDA, while in botulinutoxin B preparations the molecular weight of the NAPs is 150kDA. Under physiologic pH conditions, these complexing proteins dissociate almost completely from the toxin following injection into target tissue (Eisele and Taylor, 2008). Therefore, complexing proteins are not expected to play a meaningful role in the clinical efficacy of BoNTs. However, while specific antibodies generated against the complexing proteins are termed 'non-neutralizing', complexing proteins increase the bacterial protein load and can thus, in theory, potentially increase the immunogenic risk of neutralizing antibody formation.

3. Reports of antibodies and initial studies' influence on injection frequency recommendation

The initial recommendations on BoNT dosing and inter-injection interval were based on the defining studies on the efficacy of BoNT and these were done utilizing the first formulation of botulinum toxin in the United States (lot 79–11), first known as Oculinum and then Botox, which had a higher percentage of complexing proteins; 25 ng per 100 ml of toxin compared with the current 5 ng per 100 ml of onabotulinumtoxinA preparation (Aoki, 2001). The studies also used fixed dosing and schedules.

The development of antibodies and the phenomenon of BoNT resistance or SNR was first described in the 1990s (Zuber et al., 1993; Greene et al., 1994; Kessler et al., 1999). Greene et al. (1994) reported the occurrence of antibodies to the old BoNT-A (Botox) formulation and the occurrence of SNR in a review of 559 cervical dystonia patients injected at their center between 1984 and 1992. Twenty four patients with serological evidence of antibodies to this original BoNT-A formulation were found. However, not all patients were tested for the presence of the antibodies. The decision to test for the presence of antibodies to BoNT was based on the physician's assessment of a lack of response or a loss of previous response. The prevalence of antibodies to BoNT in their cohort was estimated at 7.1%, which the authors describe as an underestimate in view of the fact that not all the patients were tested for presence of antibodies. The authors also retrospectively assessed the risk for developing resistance by looking at a cohort of 76 patients who had been receiving injections since 1988 – 8 of whom had developed BoNT resistance (SNR) by 1992 giving a frequency of 10.5%. These BoNT-resistant patients had received higher doses of BoNT-A per treatment, and had more frequent injections especially booster doses (which were typically being given 2 – 3 weeks following injection treatment). Based on these findings, the investigators recommended using the lowest possible dose of toxin and to avoid injecting more frequently than every 3 months. These findings were supported by outcomes from a study by Kessler et al. (1999) who prospectively followed 616 cervical dystonia patients receiving BoNT-A at their center. Because their study focused on long-term effects of BoNT, patients who received less than 6 injection series were excluded as well as patients with incomplete datasets (n = 313). Out of the remaining 303 studied, 17 developed clinical evidence of SNR with only 9 demonstrating presence of neutralizing antibodies in their serum. In determining the frequency of SNR due to presence of antibodies, the authors used a denominator of 357 subjects (303 analyzed plus 54 dropouts) giving a frequency of 2.5%. As with the previous study by Greene et al. (1994), their patients with SNR and presence of antibodies received higher doses of BoNT per session compared with controls, had shorter injection intervals and received a higher number of 'booster injections'. In addition, their antibody-positive SNR cohort had a younger age of onset of their dystonia symptoms when compared to the responder group.

The development of SNR with presence of antibodies was also reported in other studies (Duane et al., 1995; Jankovic and Schwartz, 1995). Although these studies reiterated the recommendation by Greene et al. to use lowest possible dose and give