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Towards flexible and tailored botulinum neurotoxin dosing regimens for focal dystonia and spasticity – Insights from recent studies

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ABSTRACT

Botulinum neurotoxin (BoNT) is an effective, well-tolerated, and well-established option for the treatment of dystonic and spastic movement disorders. However, a single approach does not suit all patients, even within one disease indication. The degree of flexibility in treatment protocols is determined by individual product licenses, which often lag behind real-world clinical experience. A number of patient/practitioner surveys conducted recently have highlighted a desire for greater flexibility than that currently approved, both in BoNT doses and in the intervals between consecutive doses. New evidence arising from research conducted during the last few years has opened new avenues for tailoring BoNT treatment to patients' needs. Data suggest that escalating incobotulinumtoxinA doses enables treatment of a greater number of spasticity patterns than current dose limitations allow, without compromising safety or tolerability. Similarly, in patients with cervical dystonia (CD), repeated injections of incobotulinumtoxinA at intervals as early as 6 weeks after a previous treatment, based on individual patient need, were effective and well tolerated. Here, the BoNT doses and dosing intervals currently indicated in the USA and European Union are reviewed, together with the use of BoNT for the treatment of spasticity, CD, and blepharospasm. Opportunities for tailored BoNT therapy are also discussed.

1. Introduction

Botulinum neurotoxin type A (BoNT-A) injection is the recommended first-line treatment for focal hyperkinetic movement disorders such as cervical dystonia (CD) and blepharospasm (BSP) (Albanese et al., 2015; Simpson et al., 2016), and is recommended as an effective part of multi-modal treatment for focal and segmental upper- and lower-limb spasticity in adults (Baker and Pereira, 2013; Esquenazi et al., 2017; Simpson et al., 2016; Wissel et al., 2009). Usually botulinum neurotoxin (BoNT) can be used for the focal treatment of muscles involved in focal dystonia in close anatomical proximity in the face, arm, or neck region (Albanese et al., 2015; Hallett et al., 2009) and, in the treatment of focal or segmental spasticity, at one-to-three movement segments in limbs, such as the hand, forearm, and shoulder, or the foot, ankle, and knee (Simpson et al., 2017; Wissel et al., 2009). A wealth of clinical experience has demonstrated that BoNT is very much a long-term and individualized treatment (Kaňovský et al., 2009, 2011; Kessler et al., 1999; Mohammadi et al., 2010; Schramm et al., 2014). By modifying the target muscles for therapy, the BoNT dose (per session, per muscle, and/or per injection site), the interval between treatments (Albanese et al., 2015) and the number of target sites (single joint vs multiple movement segments) (Wissel et al., 2009), focal and segmental BoNT treatment can be tailored to individual patients' symptoms. However, muscle selection and dosing are based on the clinical experience of the treating physician (Albanese et al., 2015), and a single approach does not suit all patients, even within one disease indication.

Although BoNT is an effective treatment option for many movement disorders, and studies show that BoNT treatment reduces symptom burden and disability, thereby increasing patient participation in daily activities and improving quality of life (Dressler et al., 2015b; Hefter et al., 2013; Rychlik et al., 2016), the degree of flexibility in treatment protocols is determined by individual product licenses, which often lag behind experience from real-world clinical practice (Schramm et al., 2014) and in the context of clinical studies (Hyman et al., 2000; Pittock et al., 2003; Poewe et al., 1998; Wissel et al., 2017). Several patient/practitioner surveys and an online discussion forum conducted during the last few years have highlighted a desire for more tailored treatment options and more flexibility in dose and/or injection intervals than

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Abbreviations

BoNT	botulinum neurotoxin
BoNT-A	botulinum neurotoxin type A
BSP	blepharospasm
CD	cervical dystonia
UMNS	upper motor neurone syndrome

those currently approved (Bensmail et al., 2014; Poliziani et al., 2016; Sethi et al., 2012). However, despite more than 25 years of clinical experience and numerous guidelines, product licenses, and recommendations for dosing and intervals, there is insufficient evidence from well-designed clinical trials to support higher-than-labelled doses of BoNT per treatment session and individualized treatment intervals, or to inform changes to product licenses (Simpson et al., 2016). Here, the BoNT doses and dosing intervals currently indicated in the USA and European Union are reviewed, together with the use of BoNT for the treatment of spasticity, CD, and BSP, and the opportunities for tailoring BoNT therapy to meet individual patients' needs for these conditions are discussed.

2. BoNT mechanism of action in dystonic and spastic movement disorders

Dystonia is a movement disorder characterized by slow, typically patterned, twisting, repetitive movements or abnormal postures that are often accompanied by pain and tremor, and are caused by involuntary muscle contractions (Albanese et al., 2013). There are many types of dystonia with differing and overlapping pathophysiologic features, and clinical diagnostic criteria to characterize the individual subtypes remain an unmet need (Albanese, 2017). The most common focal dystonia is CD (Epidemiological Study of Dystonia in Europe [ESDE] Collaborative Group, 2000), also known as spasmodic torticollis (Chan et al., 1991). CD is characterized by abnormal head, neck, and shoulder posture caused by contraction of the cervical muscles, which may be accompanied by involuntary movements that are sometimes tremulous (Albanese et al., 2015; Chan et al., 1991), and the diagnosis of CD is considered an easy one, based on clinical experience (Albanese, 2017). The second most frequent focal dystonia is BSP (Epidemiological Study of Dystonia in Europe [ESDE] Collaborative Group, 2000), a cranio-facial dystonia characterized by repetitive, bilateral, involuntary contraction of the orbicularis oculi, resulting in spasmodic eyelid contraction, which forms the basis of diagnosis (Defazio et al., 2013).

Spasticity, defined by Young in 1994 (Young, 1994), is only one component of the upper motor neurone syndrome (UMNS) (Wissel et al., 2009). UMNS occurs following a lesion in the cerebrum or spinal cord that alters sensorimotor structures, and can be caused by stroke, spinal-cord injury, brain injury, or other neurologic conditions and neurodegenerative diseases (Wissel et al., 2009). In everyday clinical use, the term “spasticity” collectively describes a combination of clinical signs and was originally defined by J.W. Lance in the 1980s as, “*a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks, resulting from hyper excitability of the stretch reflex, as one component of the UMNS*” (Lance, 1980). In 2005, Pandyan et al. redefined spasticity as, *“disordered sensori-motor control, resulting from an UMN lesion, presenting as intermittent or sustained involuntary activation of muscles”*, focusing on the positive features (characterized by increased levels of involuntary motor activity) of the UMNS, while excluding the negative features (characterized by reduced levels of voluntary motor activity) of the syndrome and the biomechanical alterations in joints and soft tissue (Pandyan et al., 2005).

The clinical features and changing understanding of dystonia (Albanese et al., 2013; Albanese, 2017; Phukan et al., 2011) and spasticity (Trompetto et al., 2014; Wissel et al., 2009) have been reviewed extensively in the literature. Although distinct conditions, dystonia and spasticity have common traits, including the characteristic involuntary muscle hyperactivity and co-contractions that may lead to disturbed movement performance, involuntary movements, spasms, and altered joint positions due to imbalance of antagonistic muscles, resulting in disfigurement and pain. Muscle hyperactivity can be effectively targeted by BoNT therapy through acetylcholine blockade at the neuromuscular junction with blockade of the extra- and intra-fusal muscle fibers and nerve terminals, as reviewed by Dressler and Adib Saberi (2005) and Kumar et al. (2016). However, the effects of BoNT treatment are temporary, which may be attributed to the re-establishment of synaptic contacts with the denervated muscle through a proposed mechanism of motor-neurone sprouting (de Paiva et al., 1999). The duration of BoNT treatment effect varies from patient to patient, from 9–10 to over 17 weeks (Marsh et al., 2014; Sethi et al., 2012) with a mean duration of 13.2–13.5 weeks in patients with CD (Marsh et al., 2014) and a mean (standard deviation) duration of 9.3 (4.0) weeks in patients with post-stroke spasticity (Bensmail et al., 2014). Dose-dependent effects of BoNT treatments have also been documented, with increasing doses of BoNT being associated with the greatest effects on muscle tone in patients with post-stroke spasticity (Pittock et al., 2003; Yablon et al., 2011).

Common adverse events associated with BoNT treatment include injection-site pain and diffusion of the toxin from the injection site into neighbouring muscles causing inadvertent weakness, with symptoms including: dysphagia, following injection of the neck muscles; ptosis, following injection of the orbicularis oculi; and weakness of adjacent muscles, following injection of the limb muscles (Allergan Inc., 2017; Ipsen Biopharm Ltd, 2017; Merz Pharmaceuticals LLC, 2015; Solstice Neurosciences Inc, 2009). However, a wealth of clinical evidence is accumulating to show that BoNT treatment is well tolerated, and typically associated with few adverse events, which are generally transient and mild-to-moderate in severity (Dong et al., 2017; Naumann and Jankovic, 2004).

3. BoNT treatment of dystonia and spasticity

Licensed indications for BoNT treatment, dosing, and injection intervals are influenced by the regulatory authorities in different countries. Three BoNT-A formulations (onabotulinumtoxinA, Botox®, Allergan Inc; abobotulinumtoxinA, Dysport®, Ipsen Biopharm Ltd; incobotulinumtoxinA, Xeomin®, Merz Pharmaceuticals GmbH) and one BoNT type-B formulation (rimabotulinumtoxinB, Myobloc®/NeuroBloc®, Solstice Neurosciences Inc/Eisai Ltd) are currently approved in the USA and European Union for the treatment of dystonia and/or spasticity. Table 1 provides a snapshot of the current US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approval (focusing on UK approval as an example) for these formulations as they relate to the treatment of dystonia and spasticity in adults. Similarities and differences in clinical indications, BoNT doses, and dosing intervals between regions and formulations are highlighted. The level of clinical evidence referred to in currently available US and European guideline recommendations is included in Table 1 for comparison. There are several national and international guidelines and consensus statements relating to the use of BoNT in spasticity and dystonia, which are based on clinical evidence and

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