

Management of spasticity with onabotulinumtoxinA: practical guidance based on the Italian real-life post-stroke spasticity survey

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Summary

The present paper provides practical guidance on the management of adult spasticity with OnabotulinumtoxinA. Advisory Board members reviewed the available evidence and discussed their personal experiences in order to address the unmet needs in the management of spasticity with botulinum toxin type A identified by the recent Italian Real-Life Post-Stroke Spasticity Survey.

Stroke patients should be referred to spasticity services that have adequate facilities and multidisciplinary teams with the necessary training, competence and expertise. The current literature shows a strong correlation between the development of post-stroke spasticity and the degree of central sensorimotor system destruction/disorganization. Use of tools such as the Poststroke Checklist may help clinicians in the long-term follow-up of stroke patients. The maximum dose of onabotulinumtoxinA – according to the current literature this ranges from 300U to 400U for upper limb and from 500U to 600U for lower limb aggregate postures – should be re-considered. In addition, there is a need for future consensus (also based on pharmacoeconomic considerations) on consistent clinical care models

for the management of patients with post-stroke spasticity.

KEY WORDS: botulinum toxins, disease management, muscle spasticity, rehabilitation.

Introduction

Stroke is a leading cause of disability in Europe (about half of stroke survivors are left with some degree of physical or cognitive impairment) (Benjamin et al., 2017). Damage to the descending tracts and sensorimotor networks results in the positive and negative signs of upper motor neuron syndrome (Veerbeek et al., 2011; Picelli et al., 2017b). Spasticity is a “positive” sign of the upper motor neuron syndrome – the so-called positive symptoms also include clonus and spasms –, and it develops in up to 40% of patients with stroke (Wissel et al., 2013; Li and Francisco, 2015). Spasticity has been defined as a state of increased muscle tone with exaggerated reflexes characterized by a velocity-dependent increase in resistance to passive movement (Lance, 1980). Even though the timing of its post-stroke development varies widely (Wissel et al., 2013; Li and Francisco, 2015), in most cases spasticity emerges between one and six weeks after the onset of stroke (Balakrishnan and Ward, 2013). Early recognition of post-stroke spasticity could result in earlier treatment and possibly better outcomes (Wissel et al., 2015).

Botulinum toxin type A is a first-line treatment for post-stroke spasticity (Simon and Yelnik, 2010). Currently, three brands of botulinum toxin type A are marketed in Italy: onabotulinumtoxinA (Allergan, Botox[®], Irvine, CA, USA), abobotulinumtoxinA (Ipsen, Dysport[®], Boulogne-Billancourt, France) and incobotulinumtoxinA (Merz, Xeomin[®], Frankfurt am Main, Germany) (Albanese, 2011). With regard to adult patients, abobotulinumtoxinA, incobotulinumtoxinA and onabotulinumtoxinA are established as safe and effective for the reduction of upper limb spasticity and should be offered (Level A recommendation) as treatment options (Simpson et al., 2016). In addition, onabotulinumtoxinA has been recommended (Level B) as a treatment option before tizanidine for treating adult upper extremity spasticity (Simpson et al., 2016). Furthermore, abobotulinumtoxinA and onabotulinumtoxinA are established as safe and effective for the reduction of adult lower limb spasticity and should be offered (Level A recommendation) as treatment options (Simpson et al., 2016).

On these bases, and considering that onabotulinumtoxinA is the brand with the widest range of licensed indications in Italy (upper and lower limb spasticity associated

with stroke in adults, focal spasticity associated with cerebral palsy, cervical dystonia, blepharospasm and hemifacial spasm, primary axillary hyperhidrosis, chronic migraine, overactive bladder and neurogenic detrusor overactivity), we conducted a national observational survey of current daily practice (Picelli et al., 2017a), which highlighted a practical need to optimize our treatment paradigms in terms of muscles/limbs/doses, taking into account published clinical evidence and consensus, and clinical experience showing a good safety profile of botulinum toxin type A with both short- and long-term use (Naumann et al., 2006; Ghasemi et al., 2013).

The present paper provides practical guidance on the management of adult spasticity with OnabotulinumtoxinA, based on the unmet needs in the management of spasticity with botulinum toxin type A identified by the Italian Real-Life Post-Stroke Spasticity Survey (Picelli et al., 2017a).

Materials and methods

The present Authors (members of the Italian Real-Life Post-Stroke Spasticity Survey Advisory Board) reviewed the available evidence and discussed their personal experience in order to address the unmet needs identified by the Italian Real-Life Post-Stroke Spasticity Survey (Picelli et al., 2017a). A summary of the findings and conclusions was submitted to all the Board members for approval.

Results

Pathophysiology of post-stroke spasticity

The main features of motor impairment in patients with post-stroke spasticity include paresis (a reduced ability to voluntarily recruit skeletal motor units to generate torque or movement) and muscle overactivity (a reduced ability to relax muscle) (Gracies, 2005; Wissel et al., 2015). Post-stroke paresis of the affected muscles (together with the immobilization of the paretic body part that is commonly imposed as part of the current care protocols) may cause soft tissue contracture (with adaptive muscle shortening and joint contracture) that, over time, leads to chronic disuse, further aggravation of the initial paresis, and progressive development of abnormal responses to muscle stretch (Gracies, 2005; Li and Francisco, 2015; Wissel et al., 2015). Thus, motor impairment in patients with post-stroke spasticity can be described as a cycle of overactivity – contracture – overactivity evolving in parallel with the continuum of paresis – disuse – paresis (Wissel et al., 2015).

Time course of post-stroke spasticity

The rate of post-stroke spasticity has been reported to be 4 to 27% during the first six weeks after onset, 19% at three months, 21.7 to 42.6% at four and six months, and 17 to 38% at 12 months (Wissel et al., 2015).

The variability in estimates of the prevalence of post-stroke spasticity may be explained by the fact that the mechanisms underlying the pathophysiology of post-stroke spasticity may not remain constant over time

(Opheim et al., 2015; Wissel et al., 2015). Indeed, on the basis of its time course, post-stroke spasticity may be divided into three main stages: acute/post-acute phase (less than one month from the onset of stroke); sub-acute phase (between one month and six months from the onset of stroke); and chronic phase (more than six months from the onset of stroke).

Predictors of post-stroke spasticity

Post-stroke spasticity may impact significantly on a patient's functioning profile (i.e., personal hygiene, domestic and workplace activities) and quality of life, both as a direct consequence of the increased muscle tone and, indirectly, as a result of limitations of activities and participation due to physical impairments (Wissel et al., 2015). Early identification of high-risk patients and early diagnosis of post-stroke spasticity are essential to ensure optimal treatment and thus allow better long-term outcomes (Brainin et al., 2011; Opheim et al., 2015; Wissel et al., 2015).

The degree of paresis at any time after the onset of stroke is a consistent predictor of the development of spasticity in affected limbs (Leathley et al., 2004; Sommerfeld et al., 2004; Lundström et al., 2010; Urban et al., 2010; Wissel et al., 2010; Wissel et al., 2013; Picelli et al., 2014c; Opheim et al., 2015; Wissel et al., 2015). More generally, low Barthel Index and sensorimotor function scores in the acute/post-acute disease phases have been found to be related to the development of post-stroke spasticity (Leathley et al., 2004; Ryu et al., 2010; Urban et al., 2010; Wissel et al., 2010; Opheim et al., 2015; Wissel et al., 2015). Increased muscle tone at the level of the affected limbs in the acute/post-acute and sub-acute phases has also been identified as risk factor for the development of permanent post-stroke spasticity (Sommerfeld et al., 2004; Wissel et al., 2010; Opheim et al., 2015). Furthermore, stroke-related pain (i.e. hemihypesthesia) and sensory deficits may be additional risk factors associated with the development of post-stroke spasticity (Lundström et al. 2009; Urban et al., 2010; study), while a younger age at onset of stroke has been described as a predictor of the development of upper limb spasticity (Welmer et al., 2010; Picelli et al., 2014c; Opheim et al., 2015). Other factors found to be related to the development of post-stroke spasticity are left-sided weakness, a history of smoking, low quality of life, manual activities before stroke, a previous history of stroke, and extensive lesions (Leathley et al., 2004; de Cássia do Reis Moura et al., 2009; Urban et al., 2010). Lastly, lesion mapping-based analysis of the association of post-stroke spasticity with stroke lesions showed involvement of the insula, thalamus, basal ganglia and white matter tracts (internal capsule, corona radiata, external capsule, superior longitudinal fasciculus) (Picelli et al., 2014d).

Follow-up of post-stroke spasticity

To date, there exists no standardized process of long-term post-stroke follow-up care (Ward et al., 2014; Paolucci and Smania, 2015). The Global Stroke Community Advisory Panel developed a tool called the Post-stroke Checklist, aimed at helping clinicians standardize the process for identifying long-term problems and pro-

pose appropriate treatment procedures (Smania et al., 2010; Philp et al., 2013). In Italy, a national panel developed the Italian version of the Poststroke Checklist (Paolucci and Smania, 2015). A recent study on use of the web version of the Italian Poststroke Checklist for assessing the needs of patients with stroke after their discharge home showed high compliance and satisfaction (Iosa et al., 2017).

Management of spasticity with OnabotulinumtoxinA

Considering the most common upper limb aggregate postures in patients with post-stroke spasticity, the recommended starting doses of onabotulinumtoxinA, proposed in the literature, are: 300U for adducted shoulder + flexed elbow + pronated forearm + flexed wrist + clenched fist; 300U for flexed elbow + pronated forearm + flexed wrist + clenched fist; and 200U for flexed wrist + clenched fist (Simpson et al., 2017). With regard to the most common lower limb aggregate postures in patients with post-stroke spasticity, the recommended starting doses of onabotulinumtoxinA are: 400U for equinovarus foot + flexed toes; 400U for extended knee + plantar flexed foot/ankle; and 300U for plantar flexed foot/ankle + flexed toes (Esquenazi et al., 2017). The dose and/or the number of muscles treated should be increased in the event of a suboptimal response to onabotulinumtoxinA (Esquenazi et al., 2017; Simpson et al., 2017). Consensus has been reached on a total maximum dose per aggregate posture; this ranges from 300U to 400U for the upper limb and from 500U to 600U for the lower limb (Esquenazi et al., 2017; Simpson et al., 2017). An onabotulinumtoxinA dilution of 50 U/mL (2:1 dilution ratio) has been considered most appropriate (Simpson et al., 2017).

Impact of post-stroke spasticity

Spasticity is associated with a negative impact on the quality of life of stroke survivors, with statistically and clinically meaningful differences being found between patients with and without spasticity (Gillard et al., 2015). Furthermore, the impaired ability of patients with post-stroke spasticity to perform activities of daily living places a considerable burden on caregivers, leading, among other things, to depression, anxiety and low health-related quality of life (Zorowitz et al., 2013). In addition, the indirect costs to caregivers of patients with post-stroke spasticity, in terms of impaired productivity (as measured by absenteeism, presenteeism, work productivity, and activity limitation), have been found to be high (monetization of the costs associated with lost productivity was reported to be >\$10,000/year for each employed caregiver) (Ganapathy et al., 2015).

Discussion

In accordance with the aims of this work, the Authors of the present paper reviewed the current literature in order to address the unmet needs in the management of spasticity with botulinum toxin type A identified by the Italian Real-Life Post-Stroke Spasticity Survey (Picelli et al., 2017a).

To determine the best practice in the management of

post-stroke spasticity with onabotulinumtoxinA, the panelists discussed their personal experiences in light of the available evidence and agreed as follows.

Early detection of post-stroke spasticity

The variability in the epidemiology of post-stroke spasticity is due to the mechanisms underlying its pathophysiology, which may not remain constant over time (Wissel et al., 2013; Ward et al., 2014). The panelists agreed that stroke patients need timely follow-up according to their degree of central sensorimotor system destruction/disorganization. In particular, those patients in the acute/post-acute and sub-acute phases of the illness with severe initial paresis, a low functional profile, stroke-related pain and sensory deficits at the level of the affected limbs require close monitoring. Accordingly, all the members of the stroke care team, i.e. not just stroke physicians (neurologists, physiatrists) but also other healthcare professionals (physical therapists, occupational therapists, nurses), should be aware of the early predictors of post-stroke spasticity and of the patient characteristics suggesting the need for its early treatment (see below). The panelists suggest that awareness could be promoted through periodic meetings and training courses for the staff of the (Stroke and Neurorehabilitation) Unit.

The panelists agreed that widespread diffusion and use of the Poststroke Checklist may allow early detection of post-stroke spasticity, assist in the early management of disability and in rehabilitation planning, support realistic goal setting, and help patients to improve their quality of life (Smania et al., 2009; Hesse et al., 2012; Rosales et al., 2012; Fietzek et al., 2014; Iosa et al., 2017). In particular, with regard to the care of patients in the sub-acute and chronic phases of the illness, use of the Poststroke Checklist should be extended to general practitioners, who should also be aware of early predictors of post-stroke spasticity.

The panelists agreed that information about the risk of developing post-stroke spasticity should be provided by hospital physicians in the discharge letter to general practitioners, who should also be involved in specific training courses on post-stroke spasticity management. Furthermore, stroke patients themselves and their caregivers should be informed, prior to the discharge from hospital, about early predictors of post-stroke spasticity, to help them promptly identify the development of any spasticity and other disabling symptoms needing rehabilitation treatment during follow-up in the sub-acute and chronic phases.

Early treatment of post-stroke spasticity: patient characteristics

The panelists agreed about the need to treat patients early after the onset of stroke. Considering the predictors of spasticity development described so far, and on the basis of the current literature, patients in the acute/post-acute, sub-acute and chronic phases of the illness presenting with low-functional affected limbs, scant volitional muscle activity in the affected limbs, and starting to show muscle stiffness (Modified Ashworth Scale score of 1 or 1+) should be considered for toxin injection (Hesse et al., 2012).

Management of post-stroke spasticity

Setting

Specialist spasticity services operating within the neurorehabilitation setting have an advantage over ad hoc arrangements, in that the healthcare professionals working in these services have experience and expertise in guiding patients towards realistic goals, so as to achieve optimal outcomes (Wissel et al., 2009). Thus, the panelists agreed that patients with post-stroke spasticity should be referred to spasticity services, essentially services with adequate facilities (i.e. space and equipment) and clinicians with the necessary training, competence and expertise (Wissel et al., 2009; Smania et al., 2010; Franceschini et al., 2014).

Assessment of post-stroke spasticity

Several tools for assessing post-stroke spasticity have been developed and validated. However, in order to account for common daily clinical practice, and therefore for patients at all phases of the disease, the panelists agreed that their proposal should be harmonized to the lowest common denominator, as reported below. First of all, clinical evaluation of the affected limbs should include description of posture and examination of (passive and active) joint range of motion, volitional muscle activity, sensitivity and reflexes. The Modified Ashworth Scale and the Modified Tardieu Scale are suggested for assessing the degree and angle of muscle contraction and, in the event of retraction, the amplitude of the movement possible (Thibaut et al., 2013). From a functional point of view, the use of walking tests (2-minute and 10-meter) together with the Functional Ambulation Category, the Timed Up & Go test and the Disability Assessment scale may provide useful information for planning post-stroke spasticity rehabilitation management and evaluating its effects (Brashear et al., 2002; Mehrholz et al., 2007). Furthermore, the panelists suggest filming patients during reaching and walking activities. All in all, patients with stroke should be evaluated according to the "Protocollo di Minima" defined by the Italian Society of Physical and Rehabilitation Medicine for all the phases of the illness (www.simferweb.net).

Organizational care model

With regard to people in the acute/post-acute phase of stroke, the panelists agreed that early predictors of spasticity (see above) should be evaluated within a few days of the onset of stroke, and reported in the letter of discharge from the Stroke Unit. Subsequently, during their stay in the Neurorehabilitation Unit, patients showing characteristics predictive of post-stroke spasticity should undergo a weekly follow-up to allow early detection of any spasticity and initiation of appropriate (pharmacological and rehabilitation) management. Along the same lines, these patients should undergo monthly follow-ups in the sub-acute phase. In addition, a follow-up evaluation every 4-6 months is suggested for these patients during the chronic phase of stroke.

The panelists agreed that a multidisciplinary team should undertake the management of post-stroke spasticity (Wissel et al., 2009). In particular, onabotulinum-

toxinA should be administered to patients with post-stroke spasticity as a part of an integrated rehabilitation treatment program (Wissel et al., 2009; Smania et al., 2013; Franceschini et al., 2014). Accordingly, in order to evaluate the effects of (combined pharmacological and rehabilitation) treatment on post-stroke spasticity, each patient should undergo a follow-up evaluation within 3-5 weeks of onabotulinumtoxinA injection. Moreover, these patients should perform an additional follow-up evaluation three months after onabotulinumtoxinA administration, in order to further evaluate the effects of treatment and decide about possible re-injection. The panelists agreed that the goals of post-stroke spasticity treatment should be defined before treatment and verified at each follow-up evaluation according to the goal attainment scaling approach (Turner-Stokes, 2009).

OnabotulinumtoxinA dose for the management of post-stroke spasticity

The findings of the Italian Real-Life Post-Stroke Spasticity Survey (Baricich et al., 2015) indicated a need to re-consider the dose of onabotulinumtoxinA administered per single treatment. The average onabotulinumtoxinA doses agreed by the panelists are reported in Table I.

OnabotulinumtoxinA injection technique for patients with post-stroke spasticity

In line with growing evidence of the usefulness of electrical stimulation/electromyography and ultrasonography guidance, the panelists agreed that localization techniques are essential for onabotulinumtoxinA treatment of all postures due to post-stroke spasticity (Picelli et al., 2012a; Picelli et al., 2012b; Picelli et al., 2014a; Picelli et al., 2014b; Grigoriu et al., 2015; Esquenazi et al., 2017; Simpson et al., 2017).

Burden of post-stroke spasticity: impact of treatment

Long-term care patients are often inadequately served as a consequence of limited resources (Lam et al., 2012). Spasticity can lead to chronic disability with a negative impact on the quality of life of patients and caregivers (Zorowitz et al., 2013; Gillard et al., 2015). Botulinum toxin has been found to significantly decrease carer burden in long-term care stroke patients with spasticity, mainly owing to its effects in terms of reducing limb spasticity and improving the joint range of movement of the affected limbs (Lam et al., 2012). Usual (rehabilitation) care combined with onabotulinumtoxinA has been found to allow cost-effective improvement of disability due to post-stroke spasticity (taking into account the reduction of the total, society-wide cost of managing patients, including the impact of caregiver burden) (Doan et al., 2013). On these bases, and considering that early botulinum toxin treatment in severely affected stroke patients may prevent disabling spasticity in the chronic phase of the illness (Hesse et al., 2012; Rosales et al., 2012), the panelists agreed on the need for early detection and management of post-stroke spasticity, according to the predictors and patient characteristics mentioned herein, in order to reduce the human and eco-

Table I - OnabotulinumtoxinA average dose per muscle.*

Pectoralis major	Latissimus dorsi	Subscapularis	Teres major	Biceps brachii	Brachioradialis	Brachialis	Pronator teres	Pronator quadratus
75 U	75 U	50 U	35 U	75 U	50 U	70 U	40 U	30 U
Flexor carpi ulnaris	Flexor carpi radialis	Flexor digitorum superficialis	Flexor digitorum profundus	Flexor pollicis longus	Adductor pollicis	Flexor pollicis brevis	Lumbricales	
50 U	50 U	55 U	55 U	35 U	20 U	20 U	35 U	
Adductor longus	Adductor magnus	Gracilis	Iliopsoas	Rectus femoris	Medial hamstrings	Lateral hamstrings	Quadriceps femoris	Gastrocnemius
75 U	90 U	60 U	75 U	75 U	100 U	80 U	100 U	75 U
Soleus	Tibialis posterior	Tibialis anterior	Extensor hallucis longus	Flexor hallucis longus	Flexor digitorum longus	Flexor digitorum brevis		
75 U	75 U	60 U	50 U	45 U	55 U	30 U		

* Italian onabotulinumtoxinA labeling for the treatment of post-stroke spasticity recommends a maximum dose of 250U for the upper limb and a maximum dose of 300 U for the lower limb.

nomie burden of post-stroke spasticity in patients and their caregivers. The panelists suggest that post-stroke spasticity patients in the chronic phase of stroke should continue with the (pharmacological and rehabilitation) treatment until benefits are observed. Anecdotal, unpublished, 10-year follow-up observations showed that a tendency to increase botulinum toxin doses over time was paralleled by a tendency of patients to be more satisfied (Picelli et al., 2017a).

The practical guidance suggested by this paper is limited by the absence of an established clinical pathway for post-stroke spasticity and by the different regional laws that exist in Italy. There is a need for future consensus (also based on pharmacoeconomic considerations) on consistent clinical care models for the management of patients with post-stroke spasticity.

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