The Diagnosis and Treatment of Spasticity

The Diagnosis and Treatment of Spasticity:

A Practical Guide

Edited by

Ivano Dones and Vincenzo Levi

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CHAPTER 1

SPASTICITY

IVANO DONES

Introduction

The term spasticity comes from the Greek word ‘spasmos’ meaning cramp and it was first introduced in English by Good in 1829 and then by Little in 1843 to define a syndrome in which a marked increase in muscle tone occurs together with spasms. The clinical picture of spastic paraplegia was then described together with symptoms of multiple sclerosis by Charcot in 1868.[1]

The latter and universally adopted definition of spasticity by Lance (1980) is ‘a motor disorder characterised by velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex as one component of the upper motor neuron syndrome’ and, although there have been several more recent attempts to rename spasticity as the result of spastic muscle overactivity, the concept of a velocity-dependent increase in muscle tone remains the core meaning of the term spasticity.[2] From the clinical viewpoint spasticity is a disabling neurological clinical sign observed in many neurological disorders and characterised by muscular velocity-dependent hypertonus, osteotendinous hyperreflexia, presence of abnormal spinal reflexes such as the Babinski sign and clonus. These signs frequently come together with muscle spasms and pain localised at the most involved body segments.

Spasticity has long been considered as an incurable condition that only motor rehabilitation and orthopaedic procedures might correct by improving the patient’s consequent motor disability. Moreover, unfortunately, spasticity, as a clinical sign frequently causing severe motor impairment,

[1] Rowland, Pedley, and Kneass, *Merritt’s Neurology.*
[2] Lance, ‘Symposium Synopsis’.

has always been underestimated. That is why spasticity as a disabling trait has always been mostly considered, both by general practitioners and neurologists, as something to live with without any attempt to improve the spastic trait thus improving both motor performance and quality of life in a spastic patient. Weakness, always present together with spasticity, is usually the major problem when dealing with the effort to improve motor performance in a patient affected by spasticity. It is frequently worth treating in order to give the patients an improvement of their motor performance and of their quality of life as well. While a separation between spasticity of cerebral and spinal origin still exists in the literature, a more helpful distinction between focal and diffuse spasticity is worth considering for practical use when planning its possible treatment. Moreover, an additional distinction must be made between spasticity in patients who are bedridden or in a wheelchair and patients who, despite their spasticity and motor impairment, are still able to move autonomously even with a cane or crutches.[3] Spasticity may have different aetiologies. The associated spinal and cerebral forms of spasticity are frequently due to the development of multiple sclerosis. Patients who underwent a spinal cord injury due to a trauma will soon develop spasticity. Spinal cord neoplasms, transverse myelitis, different myelopathies due to spondylosis may present together with a relevant and progressive clinical picture of spasticity (30% of patients). Cerebral palsy (70% of patients), cranial traumas with brain injury, brain bleeding or strokes and degenerative disorders at the brain level may as well be the cause of a stable clinical picture of diffuse or focal spasticity (50% of patients).[4] Spasticity can show both positive and negative clinical signs together with some alterations of the skeletal muscle occurring on a long-term history of spasticity. The positive clinical signs are the increase of muscle tone, increased tendon reflexes, stretch reflex spread to extensors and repetitive stretch reflex discharges and clonus. Negative signs are the loss of motor dexterity, weakness and slow movements. Muscle alterations are stiffness, contracture, fibrosis and atrophy appearing in the long term **(Table 1).**

The large diffusion of spasticity as caused by such a great variety of diseases can give an idea of the high number of patients that are affected by spasticity all over the world. From the early orthopaedic and rehabilitating approaches to treating spasticity, the medical sciences moved forward to the introduction of many pharmacological, surgical and neuromodulation procedures to adequately treat spasticity regardless of its

[3] Daroff and Bradley, 'Bradley's Neurology'.
[4] Daroff and Bradley; Albright, 'Spasticity and Movement Disorders'.

aetiology. These present different therapeutic strategies are described in this handbook.

Table 1: Positive signs, negative signs and muscle alterations associated with spasticity

Positive signs	**Negative signs**	**Muscle alterations**
Increased muscle tone	Loss of motor dexterity	Stiffness
Increased tendon reflexes	Weakness	Contracture
Stretch reflex spread to extensors	Slow movements	Fibrosis
Repetitive stretch reflex discharges and clonus		Atrophy

Diagnosis

Spasticity, as defined by Lance in 1980, is a clinical sign characterised by a velocity-dependent increase in muscle tone involving both agonist and antagonist muscles together with increased osteotendinous reflexes as a consequence of the hyperexcitability of stretch reflexes. It largely interferes with the normal motor function of many body segments and almost every time it is accompanied by muscle weakness and loss of motor dexterity.

It can be considered part of the first motor neuron syndrome.[5] Spasticity is a predominant positive clinical sign of the upper motor neuron syndrome although it is often able to decrease motion, thus bringing it to relative disability. Its negative signs are weakness and loss of dexterity.

The increased excitability of the group of alpha-motor neurons at the segmental spinal level or the increase of afferent excitatory inputs coming

[5] Brooks and Stoney, 'Motor Mechanisms'.

from the motor cortex to the second motor neuron are the causes of spasticity.

Whatever the cause, the final result is an imbalance between the gamma-aminobutyric acid (GABA) mediated inhibitory afference on the second motor neuron and the glutamate mediated excitatory afference on the same neurons, with the excitatory afference prevailing.

Moreover, the decrease in the inhibitory GABA-mediated afference, in the first motor neuron syndrome, occurs together with a decrease of dendrites from descending fibres from the motor neurons to the dorsal roots and the concomitant collateral sprouting of nerve fibres, causing an increase in the excitatory afference on the second motor neuron thus increasing muscle tone[6] **(Figure 1-1).**

It is present in many clinical pictures as a predominant sign of different neurological disorders such as multiple sclerosis (around 34% of cases) with both brain and spinal localisation of demyelinating areas, degenerative brain disorders, brain bleeding or ischaemia, spinal cord injury or myelopathies from different causes. Thus, it may affect a wide range of patients at different ages.

The most frequent causes of spasticity are reported in **Table 2** together with the site of the lesion responsible for spasticity and the dedicated tests that are needed to ascertain the disease.

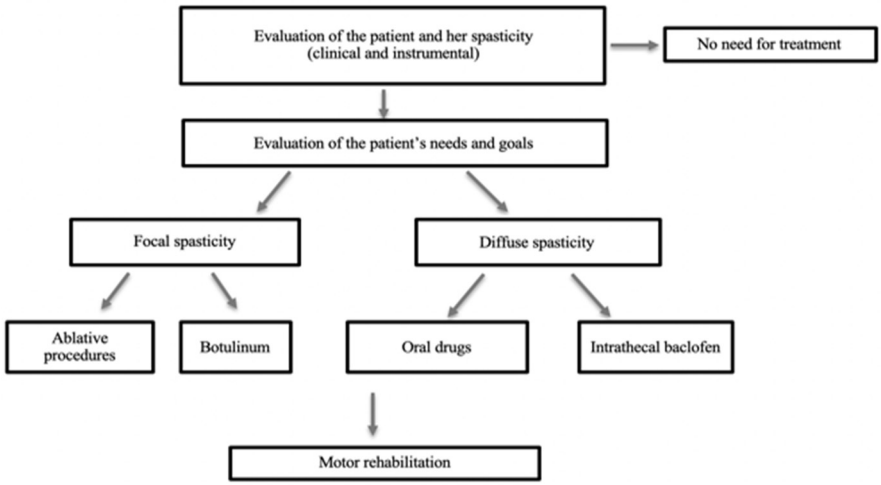

Figure 1-1 *Spasticity treatment flowchart*

[6] Akert et al., 'Motor Performance'; Ashby et al., 'Pyramidal and Extrapyramidal Control'.

Table 1 Neurological disorders causing spasticity. *A careful clinical assessment is always mandatory

Name of the disease	Site of lesion	Tests needed *
Infantile cerebral palsy	Brain	Brain MRI
Myelopathies	Spinal cord	CSF test, spinal MRI
Leukoencephalopathies	Brain	brain MRI, biochemistry
Primary lateral sclerosis	Brain	Brain MRI, MEP
Sjogren-Larsson syndrome	Brain	Brain MRI, biochemistry
Familial spastic paraplegia	Brain	Brain MRI, molecular bio
Infantile cervical malformations	Atloccipital	Atlooccipital CT and MRI
Spinal cord trauma	Spinal cord	Spinal cord MRI, SSEP
Multiple sclerosis	Brain, spinal cord	Spinal and brain MRI, CSF
Acute myelitis	Spinal cord	Spinal cord MRI, CSF
Brain trauma	Brain	Brain CT and MRI, MEP
Spinal cord injury	Spinal cord	Spinal cord MRI, SSEP
Amyotrophic lateral sclerosis	Brain, spinal cord	Cervical MRI, EMG, MEP
Cervical myelopathy	Spinal cord	Cervical MRI, SSEP
Spinal cord tumours	Spinal cord	Spinal cord MRI
Adrenoleukodystrophy	Brain	Biochemistry
Joseph disease	Brain	Brain MRI

Due to its appearance when a pyramidal injury is observed, spasticity as a compensatory trait originated by the central nervous system is considered as a positive sign although it is always matched to the negative sign of an associated muscle weakness. However, spasticity has been considered a parapyramidal clinical sign of dysfunction as it refers to both an impairment of the pyramidal corticospinal pathway, an involvement of the brainstem to spinal cord circuitry and the system of gain-setting originating from the inferior brainstem nuclei under limbic control. That is the reason why when a pure pyramidal lesion occurs the loss of muscle strength and dexterity appear without spasticity that, on the contrary, will occur later in the progression of the pyramidal disorder as a compensatory involvement of the parapyramidal system originating at the brainstem and controlled by an excitatory afference coming from the cortical pre-motor

and supplementary motor areas of the brain cortex. Moreover, a lesion in these latter circuits will produce spasticity although the involvement of the pyramidal tract is poor. Rigidity, contracture, muscle atrophy and fibrosis may then, in the long term, interfere with the pathological regulatory mechanisms by hampering the normal control of limb position in space and movement. Thus, when assessing a spastic patient, the proper distinction between the resistance to movement caused by spasticity and the resistance due to rheologic changes is important to tailoring the proper treatment. In this regard, diagnostic nerve blocks and dynamic EMG are used to separate those two causes of rigidity.[7]

Co-activation of agonist muscles and abnormal activation of antagonist muscles are one of the elements causing muscle weakness together with weakness originating from a poor signal from the motor cortex both decreasing the net force at a joint and impairing movement. The clinical evaluation of a patient with spasticity should include the complete assessment and scoring according to the common scales internationally used for spasticity, together with the general neurological evaluation of the patient. Muscle tone is assessed by having the patient completely relaxed while the examiner moves each patient's body segment to full flexion and extension. By increasing the passive movements of these body segments the examiner appreciates a progressive increase in the muscle tone proportional to the speed of passive movement. A comparison is carefully made of both sides of the body. In a completely relaxed non-spastic patient, no increase in resistance is felt at the wrist, elbow, knee and ankle while in a spastic patient the 'clasp-knife phenomenon' is felt proportional to the speed of the passive movement. Pain and joint fixations can confuse the examination of the resistance due to spastic hypertonus. Active movements are then made to assess muscle strength. The flexor reflex (Babinski sign), indicating an alteration of the descending projections from the first cortical and brain stem motor neurons and the alpha and gamma motor neuron in the spinal cord, is always present in a patient affected by upper motor neuron syndrome.

The Ashworth scale is used at the different body segments, to score spasticity according to five degrees of muscle tone. From 0 as a condition of normal muscle tone, to 5 as no movement can be induced even passively due to a very severe muscle tone on both agonist and antagonist muscles. **(Table 3)**

[7] Dones, Nazzi, and Broggi, 'Guidelines for the Diagnosis'.

Table 2 The Ashworth scale to score spasticity

Grade	Condition
1	Normal tone
2	Slight increase in muscle tone with easy flexion and extension and initial 'clasp-knife' phenomenon
3	Marked increase in muscle tone but flexion and extension easily possible
4	Severe increase in muscle tone with difficulties in passive movements
5	Total rigidity both in extension and flexion

An additional scale to grade spasticity in a more dynamic context, is the Tardieu scale which quantifies spasticity through the assessment of the muscle response to stretch applied at different velocities at each limb with a constant position of the body. **(Table 4)**

There are two more scales to grade spasticity. The first is the scale for osteotendinous reflexes and the second is the scale for muscle spasms. **(Tables 5-6)** The FIM (functional independence measure) and the index Index complete the scoring of a spastic patient by measuring their autonomy in the conventional actions of daily living. The evaluation of the quality of life of a spastic patient together with the knowledge of their social environment is helpful in tailoring a bespoke treatment for their spasticity.

Motor impairment due to increased muscle tone is the consequence of enhanced motor neuron activity, co-activation and increased stretch reflexes together with enhanced postural reflex activity even in children affected by cerebral palsy. Spastic still-ambulant patients need a computerised gait analysis to record both the gait trait and the EMG activity of different muscles during gait in order to evaluate the opportunity of possible combined treatments for both diffuse and focal spasticity to optimise the patient's motor performance.[8]

[8] Dones et al., 'A Neurophysiological Method'.

Table 3 The Tardieu scale

This scale quantifies muscle spasticity by assessing the response of the muscle to stretch applied at specified velocities. Grading is always performed at the same time of day, in a constant position of the body for a given limb. For each muscle group, reaction to stretch is rated at a specified stretch velocity with two parameters, x and y.

VELOCITY TO STRETCH	
V1	as slow as possible
V2	speed of the limb segment falling
V3	as fast as possible
QUALITY OF MUSCLE REACTION	
0	no resistance throughout passive movement
1	slight resistance with no clear catch at a precise angle
2	clear catch at a precise angle followed by release
3	fatigable clonus (< 10/sec) occurring at a precise angle
4	indefatigable clonus (>10/sec) occurring at a precise angle
5	immobile joint
ANGLE OF MUSCLE REACTION	
Measure relative to the position of minimal stretch of the muscle (corresponding to angle)	
SPASTICITY ANGLE	
R1	Angle of catch seen at velocity V2 or V3
R2	Range of motion achieved when muscle is at rest and tested at V1 velocity

Table 4 The scale of osteotendinous reflexes

0	Absent
1	Hyporeflexia
2	Normal
3	Hyperreflexia
4	Extinguishable clonus
5	Unextinguishable clonus

Table 5 Penn's scale of muscle spasms

Penn's scale of muscle spasms	
0	No spams
1	Absence of spontaneous spasms. A relevant sensory or motor stimulation provokes spasms
2	Occasional spontaneous spasms
3	Hourly spontaneous spasms
4	More than 10 spasms per hour

In the correct assessment of a patient affected by spasticity, it is mandatory to decide whether patients actually need their spasticity to be treated. In fact, there are many conditions where spasticity must be preserved in order to help the patient in keeping their standing position or to use their spasticity to keep a desired posture.

Treatment

Spasticity, as a clinical sign of upper motor neuron syndrome, may variously interfere with any motor function. To plan any possible treatment of spasticity a few concepts have to be considered: severity of spasticity, its chronicity, extension throughout the body, the level of lesion in the central nervous system responsible for its appearance, co-morbidities, the availability of social support from both the family and centres of motor rehabilitation, and the real goal of treatment that should be clearly explained to the patient. The treatment of spasticity is aimed to improve motor performance, patient's comfort and nursing, decrease pain and prevent fixed abnormal postures and joint blockade. In fact, spasticity must be treated only if it severely interferes with motor performance or positioning, care and comfort.

As spasticity is one of the prevailing clinical signs as a consequence of stroke, brain injury, spinal cord injury of different origin, neurodegenerative disorders, cerebral palsy and multiple sclerosis, it is frequently associated with other clinical signs and symptoms such as sensory disturbances, perception abnormalities, cognitive impairment, and additional motor disturbances such as dystonia and extrapyramidal rigidity that always appear together with muscle weakness, spasms and loss of dexterity. Spasticity can even increase the energy a patient must spend to move as it hampers both agonists and antagonists, thus braking any voluntary movement. It usually limits the fitting of orthotic devices including a real limitation in even using exoskeletons and it can lead to pressure sores,

contractures and related pain. All these additional signs and symptoms create a general state of inadequacy in performing even simple daily motor tasks. Thus, when explaining any antispastic treatment to a patient, we must be careful in depicting any miraculous future scenario obtainable with the antispastic treatment alone.

Spasticity can give many different motor patterns: co-contractions of agonist and antagonist muscles with limitation of extremity movements and poor agonist activation together with other overactive agonist muscles, with a resulting limited ability to voluntarily contract single muscles. Moreover, muscle tone varies according to the state of movement or rest. Thus, the patient must be carefully evaluated during activity and at rest. Standard electromyography (EMG), dynamic EMG and quantitative gait analysis together with a careful clinical examination are helpful tools to draw an accurate clinical picture of the spastic patient.

In addition, evaluating and treating a patient affected by spasticity is a matter of multidisciplinary interaction between neurosurgeons, neurologists, rehabilitation physicians, physiotherapists, nurses, urologists, psychologists and, sometimes, orthopaedic specialists. Motor rehabilitation, wherever indicated, must be mandatory to obtain the maximal effect of any treatment together with a careful analysis of the social environment of the patient.

The type of treatment of spasticity is indicated not only by the degree of spasticity, but also by using a scale of invasiveness of any treatment ranging from oral drug therapy to dorsal root entry zone lesions at the spinal cord. It is often a multimodal treatment consisting of non-pharmacological and pharmacological approaches associated with physical therapy.[9]

Finally, as already mentioned, focal and diffuse spasticity must have different treatments. It is then worth separating spastic patients into two different groups: the first being bedridden or wheelchair patients and the second of still-ambulatory patients as the spasticity assessment tools and the goal of any treatment are different in the two groups. **(Table 7)**

Oral drugs

The pharmacological treatment of chronic spasticity is mainly a symptomatic treatment, which is rarely able to solve the chronic degenerative disease of the central nervous system that causes spasticity.

[9] Dimitrijevic and Sherwood, ‘Medical and Surgical Treatment’.

As spasticity is variously present in many neurological diseases, the common goal of any of its treatments is the relief of subjective discomfort, improvement in patient care, and occasionally in the patient's functional performance and prevention of long-term complications due to prolonged excessive muscle tone such as joint ankylosis, tendon retractions and skeletal muscle fibrosis.

While spasticity can be improved by the drug treatment, the coexisting loss of dexterity and weakness cannot be treated, thus implying a limitation of the outcome of any drug treatment presently available.

Mephanesin was the first drug, introduced in 1946, to treat spasticity by blocking spinal interneurons. Since then, a large variety of antispastic agents have been developed. Most of them can even be used in combination. Unfortunately, they show relevant efficacy in only a small percentage of cases and in some of them the antispastic effect comes together with the onset of undesired side effects.[10]

When observing a lack of effect or a loss of effect of these drugs even at their highest daily dosage, a further treatment must be thought of and set, and the oral treatment consequently withdrawn accordingly.

These drugs are part of the two groups GABAergic and central alpha2-adrenergic, acting on the inhibitory afference of the second motor neuron at different levels. GABA agonists are diazepam (maximal daily dosage 60 mg), clonazepam (maximal daily dosage 3 mg) and baclofen (maximal daily dosage 75 mg) while central alpha2 adrenergic agonists are tizanidine (maximal daily dosage 36 mg) and clonidine (maximal daily dosage 3 mg). Dantrolene as a calcium channel blocker at the muscle fibre not only always gives muscle weakness but it is even hepatotoxic, thus it should not be considered as a useful drug for spasticity.[11]

The fact that all drugs, when orally administered, distribute everywhere in the central nervous system and not only at the spinal cord level, where their concentration is needed to decrease spasticity, is responsible for the occurrence of undesired side effects due to their action on analogous receptors that, at the brain level, are not strictly connected to the control of muscular tone.

Benzodiazepines

The antispastic effect of benzodiazepines is mediated by a functionally coupled benzodiazepine-GABA-A receptor chloride ionophore complex.

[10] Young and Delwaide, 'Drug Therapy: Spasticity'.
[11] Elovic, 'Principles of Pharmaceutical Management'.

They have no primary presynaptic GABA-mimetic effect but an indirect postsynaptic action only in the case where GABA action is functional. Benzodiazepines are largely metabolised by the liver and they differ in long-acting and short-acting molecules. They cross the placental barrier and are secreted into breast milk.[12] Diazepam is the oldest drug used to decrease spasticity: this molecule has great affinity for the GABA-A receptors thus give an increase in the presynaptic inhibition and a decrease of mono and polysynaptic reflexes excitability. Diazepam overdose may bring the patient to CNS depression and coma. Its effect on spasticity is often hampered by the onset of side effects such as somnolence, light-headedness, fatigue, muscular weakness, dizziness, ataxia, vertigo and addiction. Drug tolerance to diazepam may occur in the long term.

Anxiety, agitation, irritability, increased tremor, muscular fasciculations and twitching, nausea, insomnia, psychotic manifestations and death can be experienced in case of rapid or abrupt withdrawal of diazepam administration.

The action of diazepam on spasticity has been reported in double-blind studies on spastic patients of both spinal and cerebral origin. Sedation has been observed more frequently than during baclofen treatment although side effects and their efficacy in reducing spasticity were equally observed with the oral administration of both molecules.[13]

It is always advisable to begin treatment with diazepam with a bedtime dose of 5 mg and extending its use at daytime with 2 mg twice/day progressively reaching a maximum of 60 mg per day when needed. Control studies on the use of diazepam in spastic patients ceased in 1991. Besides its well-known anticonvulsant action, clonazepam can also decrease rigidity and muscle spasms similarly to baclofen but with higher sedation and muscle weakness.[14] It is primarily used for the suppression of night-time spasms.

Baclofen

The drug used the most to treat spasticity is a GABAb agonist, inhibiting spinal mono and polysynaptic reflexes. It was first synthesised in the 1960s as a GABA agonist for the treatment of epilepsy. Its anti-epileptic effect was poor, while a marked antispastic effect was observed.[15] It is able to decrease spasticity and muscle spasms but, when

[12] Young and Delwaide, ‘Drug Therapy: Spasticity’.
[13] Cocchiarella, Downey, and Darling, ‘Effect of Diazepam’.
[14] From and Heltberg, ‘A Double-Blind Trial’.
[15] Van Hemert, ‘Comparison of Baclofen’.

given orally, its response can be interfered with by undesired side effects related to central depression such as confusion, sedation, drowsiness, fatigue and coma, due to its concentration at the GABA receptors in the brain. Therefore, patients must be cautioned about any activity made hazardous by decreased alertness (above all, driving). In this regard it is always advisable to begin baclofen by prescribing one single dose at night and then increase the dosage and spread the administration evenly in the morning and at lunch time.

Baclofen is believed to exert a major action on spasticity of spinal origin and not on the one of brain origin although the decrease in spasticity on patients affected by cerebral palsy has been observed.[16] Baclofen might even cause lack of memory and attention in elderly and brain-injured patients. An excess daily dosage of baclofen may cause trunk hypotonia, altering posture in patients in wheelchairs. In patients who are still able to walk despite their spasticity, baclofen might induce muscle weakness by an independent peripheral mechanism, thus reducing their walking ability.[17]

Spastic patients affected by asthma should be carefully evaluated before the use of oral baclofen as it increases airway bronchial constriction responsiveness. Cough reflex is also inhibited. Moreover, patients who are additionally affected by epilepsy should be monitored as baclofen can interact with anti-epileptic drugs, thus losing seizure control. Possible interaction of baclofen with pregnancy is largely unknown. Baclofen withdrawal syndrome appearing with the abrupt decrease or discontinuation of baclofen is characterised by seizures, confusion, rebound muscle activity and hypertonia, hallucinations and fever.[18] Patients experiencing oral baclofen overdosage may present with hypoventilation, low blood pressure, small pupils, hypothermia and bradycardia and, occasionally, unresponsiveness. Baclofen oral daily dosage ranges from 10 to 75 mg with increases of 10 mg every 10 days if needed.

Tizanidine

Tizanidine is an alpha-2 adrenergic central agonist that interferes with the release of excitatory amino acids (aspartate and glutamate) from the presynaptic endplates of spinal internuclear neurons and enhances the action of glycine as an inhibitory neurotransmitter. Its antispastic action is

[16] Pedersen, Arlien-Soborg, and Mai, ‘The Mode of Action’.
[17] Hulme et al., ‘Elderly Stroke Patient’.
[18] Garabedian-Ruffalo and Ruffalo, ‘Baclofen Withdrawal’.

mediated by the increase of the noradrenergic presynaptic inhibition. The antinociceptive effect is due to the inhibition of the synaptic transmission of nociceptive stimuli in the spinal pathways through an alpha-2 adrenergic receptor – mediated action was reported by Davies in 1984.[19]

Its use at 6–36 mg/day has been found equal or superior to baclofen in reducing passive stretch responses in patients affected by stroke, spinal cord lesions or multiple sclerosis although no differences between the two molecules were observed in gait and functional measures.

Moreover, there is a discrepancy in the findings on a large cohort of patients on tizanidine and placebo in two reports, one a UK study reporting a significant reduction in muscle tone with tizanidine, while in the other, a US study, no differences in response were found between patients on tizanidine and on placebo. [20] A transient increase in hepatic transaminase levels restored after discontinuation of treatment with tizanidine was reported.

Clonidine

Clonidine is an alpha2 noradrenergic agonist having both hypotensive and antispastic properties. It is rarely used due to the frequent appearance of low blood pressure, bradycardia and somnolence. About half of its dosage is metabolised in the liver while the other half is excreted in the urine as an unchanged drug. Autoradiographic studies of clonidine demonstrate its binding not only in the brain but even at the dorsal horns of the spinal cord.

In spinalised animals, clonidine was reported to induce a reduction in motoneuronal excitability. The antispastic effect of clonidine in humans affected by spinal cord injury was ascribed to an enhancement of alpha-2 mediated presynaptic inhibition of sensory afferents.

Bradycardia, hypotension, depression, constipation and dry mouth are relevant undesired side effects of clonidine. Blood pressure and pulse must be periodically monitored. Main side effects such as syncope seizures, cerebrovascular accidents, deep vein thrombosis, nausea, vomiting and autonomic hyperreflexia have also been reported.[21]

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[19] Davies et al., ‘Tizanidine (DS103-282)’.
[20] Kamen, Henney, and Runyan, ‘Overview of Tizanidine Use’.
[21] Elovic, ‘Principles of Pharmaceutical Management’.

Dantrolene

The use of dantrolene as an inhibitor of calcium release at the sarcoplasmic reticulum of muscle fibres in the skeletal muscle has been mostly withdrawn due to its hepatotoxicity and poor action on spasticity. Together with a relevant decrease in muscle strength and motor performance, dantrolene is also sedating and can cause lethargy, drowsiness, malaise, nausea, vomiting, diarrhoea and paraesthesia. Its weakening effect can cause postural complications. Its use as an antispastic should not be encouraged at present.[22]

[22] Ward, Chaffman, and Sorkin, 'Dantrolene. A Review'.

CHAPTER 2

THE TREATMENT OF FOCAL SPASTICITY: THE BOTULINUM TOXIN

GRAZIA DEVIGILI

Introduction

The use of botulinum neurotoxins (BoNTs) is a well-established treatment in the management of focal spasticity, both for the lower and upper limbs. There is now consistent knowledge about its indications, effects and safety in clinical practice. The BoNTs are neurotoxins produced by neurotoxigenic strains of anaerobic bacteria of the genus Clostridium, that cause the flaccid paralysis of botulism by inhibiting the neurotransmitter release mainly at the peripheral cholinergic nerve terminals at the neuromuscular junction. [1] This causes a reversible reduction in muscle contraction and a dose-dependent reduction in muscle strength. There is also some evidence for other sites of action including the cholinergic autonomic terminals, and the more recently discovered inhibition of the release of peripheral neurotransmitter and inflammatory mediators in the nociceptive system.[2] The mechanism of action consists of the high-affinity binding to a receptor of the presynaptic membrane of peripheral cholinergic nerve terminals, and its entry into their cytosol where they cleave the SNARE proteins (VAMP/synaptobrevin, SNAP-25, and syntaxin) thus blocking the neurotransmitters' release.[3] The clinical effect is temporary, as the BoNTs degrade and become inactive in 48 hours and the neuromuscular junctions regenerates with sprouting within a

[1] Burgen, Dickens, and Zatman, 'The Action of Botulinum'; Rossetto, Pirazzini, and Montecucco, 'Botulinum Neurotoxins'; Pirazzini et al., 'Biology, Pharmacology, and Toxicology'.
[2] Pirazzini et al., 'Biology, Pharmacology, and Toxicology'; Luvisetto, Vacca, and Cianchetti, 'Analgesic Effects of Botulinum'.
[3] Rossetto, Pirazzini, and Montecucco, 'Botulinum Neurotoxins'.

few weeks. Generally, the muscle weakness and hypotrophy regress over three to five months. The BoNTs have been traditionally classified into seven serotypes, from A to G. However, there are many variants for each serotype and some chimeric BoNTs were also identified, i.e. BoNT/CD, BoNT/FA and BoNT/DC. Several BoNT preparations were licensed for clinical use. They are nearly all based on serotype A1, with only one on serotype B1. Details are summarised in **Table 7**. The duration of clinical effects varies between different serotypes, animal species and kind of cholinergic terminals, e.g. in humans the duration of action is three times longer than in mice, and the skeletal muscles recover about three times faster than autonomic nerve terminals. The BoNTs are potent and neurospecific drugs, and when they are correctly injected they show limited diffusion; their effect is reversible over time. For all these reasons BoNT/A1 is considered as the safest and most efficacious treatment for a variety of human syndromes characterised by hyperfunction of selected nerve terminals, including spasticity.

Botulinum as treatment of spasticity

Several open and placebo-controlled studies reported the efficacy and safety of local botulinum toxin injections in reducing spasticity.[4] Recent systematic reviews have concluded that BoNT/A1 injections have to be considered as the pharmacological treatment of choice in focal spasticity to improve limb mobilisation and posture and functional ability, and to reduce pain, whereas limited data are still available on the effectiveness of BoNT/B1 on spasticity.[5]

The principal goal of BoNT/A treatment of spasticity is to reduce motor overactivity to improve movement without worsening weakness. BoNTs treatment can reduce muscle tone, improving function and pain due to shortening of muscle fibres and ligaments, and ameliorate nursing. However, this treatment should be included in a multidisciplinary approach where all physical, medical and surgical treatments need to be combined.

[4] Elia et al., 'Post-Stroke Spasticity'; Hara et al., 'Botulinum Toxin A.'; Hara et al., 'Therapy and Multidisciplinary Rehabilitation'; Kaji et al., 'Botulinum Toxin Type A'.

[5] Esquenazi et al., 'Evidence-Based Review'; Zakin and Simpson, 'Evidence on Botulinum Toxin'; Bentivoglio et al., 'Clinical Differences between Botulinum'.