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Drugs Used to Treat Spasticity

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Contents

Abstract

Spasticity is a common and disabling symptom for many patients with upper motor neuron dysfunction. It results from interruption of inhibitory descending spinal motor pathways, and although the pathophysiology of spasticity is poorly understood, the final common pathway is overactivity of the alpha motor neuron. Therapy for spasticity is symptomatic with the aim of increasing functional capacity and relieving discomfort. Any approach to treatment should be multidisciplinary, including physical therapy, and possibly surgery, as well as pharmacotherapy. It is important that treatment be tailored to the individual patient, and that both patient and care giver have realistic expectations. Pharmacotherapy is generally initiated at low dosages and then gradually increased in an attempt to avoid adverse effects. Optimal therapy is the lowest effective dosage. Baclofen, diazepam, tizanidine and dantrolene are currently approved for use in patients with spasticity. In addition, clonidine (usually as combination therapy), gabapentin and botulinum toxin have shown efficacy, however, more studies are required to confirm their place in therapy. Intrathecal baclofen, via a surgically implanted pump and reservoir, may provide relief in patients with refractory severe spasticity.

Spasticity, a clinical sign of upper motor neuron dysfunction, results from interruption of inhibitory descending spinal motor pathways. As observed in numerous neurological disorders such as cerebral palsy, spinal cord injury, stroke, and multiple sclerosis (MS), spasticity is defined as a velocity-dependent increase in tonic stretch reflexes,[1] where faster passive movements meet with increasing resis-

tance. A clasp-knife phenomenon may be seen with dissipation of resistance during stretch. Additional signs associated with spasticity include weakness, increased muscle tone, impaired dexterity and coordination, hyper-reflexia, extensor plantar responses, spontaneous muscle spasms, and contractures.[2] Spasticity worsens in the setting of noxious stimuli such as infection, urolithiasis, urinary or faecal retention, decubitus ulcers, tight or misfitting clothing or misfitting orthotics. The symptoms of spasticity can greatly interfere with a patient's functional capacity.

1. Pathophysiology

The pathophysiology of spasticity is poorly understood but the final common pathway underlying the mechanism is overactivity of the alpha motor neuron. Descending spinal pathways (corticospinal, reticulospinal, vestibulospinal) exert control over alpha motor neurons via mono- and poly-synaptic pathways.

The muscle spindle is the complex sensory structure of the muscle conveying information about muscle length. Spindles lie in parallel with extrafusal fibres (large muscle fibres that effect gross movement), so when the muscle is lengthened, the spindle is stretched causing Ia afferent fibres to send impulses to the spinal cord. Shortening of the extrafusal muscle results in shortening of the spindle and silencing of the Ia afferents. The intrafusal muscle fibres of the spindle complex are innervated by gamma motor neurons in the anterior horns of the spinal cord, which act to increase the tension of the intrafusal fibre when it is shortened. This resets the spindle after shortening so it is again sensitive to changes in muscle length.

When the muscle is lengthened by tendon tap or stretch, Ia afferents produce excitatory postsynaptic potentials (EPSPs) on agonist motoneurons. Although this monosynaptic connection plays a role in the reflex, most excitatory activity in the stretch reflex is mediated by oligosynaptic and polysynaptic pathways.[2] Interneurons play a major role in the reflex arc. Antagonist muscle spindles also send Ia afferents to produce EPSPs on agonist interneurons which subsequently produce inhibitory postsynaptic potentials (IPSPs) on motoneurons. The firing of the motoneuron depends on the summation of EPSPs and IPSPs. Additional inhibitory interneurons act on Ia afferents to produce a presynaptic inhibition of the afferent signal. γ-Aminobutyric acid (GABA) is the neurotransmitter involved in this selective presynaptic inhibition.

Thus, the spinal segmental reflexes require the participation of muscle spindles, fusimotor innervation (gamma motor neurons), Ia primary afferents, and alpha motor neurons, as well as Renshaw recurrent inhibition, disynaptic reciprocal inhibition, nonreciprocal autogenic Ib inhibition, presynaptic inhibition and remote inhibition/excitation of alpha motor neurons.[2] Spasticity results from a prolonged disinhibition of components of this system but the exact mechanism remains unclear.

2. Rationale for Treatment

The goal of therapy is to increase functional capacity and relieve discomfort. Before initiating treatment one must first evaluate the functional consequences of reducing spasticity. For some patients with proximal leg weakness, increased extensor tone in the legs offers necessary stability and support during transferring and walking. For other patients, hyper-reflexia and clonus interfere with normal ambulation. In non-ambulatory patients, flexor spasms may be painful and debilitating. Patients with spasticity may exhibit further increase in tone or spontaneous spasm in the setting of an underlying infection, such as a urinary tract infection, or other noxious stimulus. These secondary causes should be ruled out before altering a given therapeutic regimen. The approach to treating spasticity should be multimodal. Physical therapy is an essential component of antispasticity regimens and in the most patients with refractory spasticity, surgical intervention (e.g. posterior rhizotomy or tendon release procedures) may be beneficial. In this review we will focus on pharmacological treatment of spasticity.

3. Pharmacotherapies

Medications frequently used in the treatment of spasticity include baclofen, benzodiazepines, tizanidine, clonidine, dantrolene, gabapentin, and botulinum toxin. Of these, only baclofen, diazepam, tizanidine and dantrolene are approved for the treatment of spasticity. A general rule is to initiate treatment at low dosages and to increase them gradually to avoid adverse effects. The lowest dosage that proves to be effective for an individual patient is considered optimal. Table I outlines the use of frequently used oral antispasticity agents.

3.1 Baclofen

Baclofen is a structural analogue of GABA, and inhibits monosynaptic and polysynaptic spinal reflexes. It binds to the $GABA_B$ receptor which is coupled to calcium and potassium channels, and occurs both pre and postsynaptically.[3] By binding at the presynaptic site the membrane is hyperpolarised, and influx of calcium into presynaptic terminals is restricted resulting in a decrease in neurotransmitter release in excitatory spinal pathways and a decrease in alpha motor neuron activity.[4] In addition, postsynaptic binding on the Ia afferent terminal increases potassium conductance, hyperpolarising the membrane and enhancing the presynaptic inhibition. Activation of $GABA_B$ receptors may also result in inhibition of gamma motor neuron activity and decreased muscle spindle sensitivity.[5]

Several trials have examined the efficacy of baclofen in patients with spasticity secondary to MS and spinal cord pathology.[6-14] In the patients with MS, baclofen has been found to be effective in reducing spasticity, decreasing frequency and severity of sudden painful spasms, and improving the range of joint movement. However, increased weakness was a common complaint. In patients with spinal cord injuries, baclofen has been reported to be particularly helpful in reducing flexor spasms. In post-stroke patients, it appears to be less beneficial.[15,16] Specifically, patients were found to have a modest decrease in muscle tone which was interpreted subjectively as only a slight improvement

Table I. Oral agents commonly used to treat spasticity

Agent	Starting dosage	Maximum recommended dosage	Adverse effects	Monitoring	Special attention
Baclofen	5 mg/day increasing to 15 mg/day in 3 divided doses	80 mg/day in divided doses	Muscle weakness, sedation, fatigue, dizziness, nausea	Periodic liver function tests	Abrupt cessation associated with seizures
Diazepam	2 mg/day bid or 5 mg qhs	40-60 mg/day in divided doses	Sedation, cognitive impairment, depression	Dependence potential	Withdrawal syndrome
Tizanidine	2-4 mg/day	36 mg/day in divided doses	Drowsiness, dry mouth, dizziness, reversible dose-related elevated liver transaminases	Periodic liver function tests	Not to be used with antihypertensives or clonidine
Clonidine	0.1 mg/day	Not approved for spasticity; in patients with hypertension, doses as high as 2.4mg in divided doses have been studied but rarely employed; Usual dose in hypertension 0.2-0.6 mg/day	Bradycardia, hypotension, dry mouth, drowsiness, constipation, dizziness, depression		Add-on agent Hypotension may result Not to be used with tizanidine
Dantrolene	25 mg/day	400 mg/day in divided doses	Hepatotoxicity (potentially irreversible), weakness, sedation, diarrhoea	Periodic liver function tests	Hepatotoxicity
Gabapentin	100mg tid	3600 mg/day in divided doses	Stomach upset		

bid = twice daily; **qhs** = at bedtime; **tid** = three times daily.

in the feeling of stiffness. No effect was noted on hyper-reflexia or clonus.[16]

Baclofen is rapidly absorbed after oral administration but CNS penetration is relatively limited. The mean half-life is fairly short with an average of approximately 3.5 hours. Because it is partially metabolised by the liver (15%) and excreted by the kidney, the dosage should be decreased in patients with known hepatic or renal impairment. There have been reports of elevated liver enzyme levels in patients receiving baclofen. As such, screening liver function tests should be performed when initiating treatment with baclofen and every 6 months thereafter. Treatment is often initiated at 5mg once daily increasing to 3 times daily as tolerated. Thereafter, the dosage can be increased slowly at increments of 5mg/day as needed. It may be helpful to initiate treatment and increments at night to minimise adverse effects. The highest recommended dosage is 80mg daily in divided doses, but for some patients, this dosage may not be sufficient to relieve symptoms. Higher dosages should be prescribed with caution as adverse effects are likely to be more prominent.

Typical adverse effects are related to CNS depression and include drowsiness, fatigue, weakness, nausea, and dizziness. Abrupt cessation of sustained treatment should be avoided because sudden withdrawal of baclofen has been associated with hallucinations and seizures.

3.2 Diazepam

The action of the benzodiazepines is mediated by the coupling of the benzodiazepine-$GABA_A$ receptor-chloride ionophore complex.[17] Binding of benzodiazepine to the $GABA_A$ receptor increases chloride conductance resulting in presynaptic inhibition in the spinal cord.[18,19] Diazepam is the most commonly used benzodiazepine in the treatment of spasticity. Early trials have demonstrated efficacy in treating spasticity in patients with spinal cord injury, hemiplegia, and MS.[20-23] From and Heltberg[24] studied 17 patients with MS in a double-blind, crossover trial with baclofen and diazepam. Each patient received 4 weeks therapy with each drug. No differences were seen in efficacy of reducing spasticity, clonus, flexor spasms, or improvement in gait or bladder function. The adverse effect profiles differed slightly, with more patients reporting sedation while receiving diazepam, but the severity of adverse effects was similar in both groups. When patients, still masked to treatment assignment, were asked which agent they preferred, baclofen was significantly favoured.[24] Other studies have confirmed comparable antispasticity effects of baclofen and diazepam in reducing muscle tone and frequency of spasms. However, baclofen was not necessarily favoured by patients over diazepam.[25,26] In clinical practice, diazepam is frequently used as an adjunct to baclofen in treating spasticity,[27] and is less commonly used as a single agent.

Diazepam is well absorbed after oral administration and reaches a peak concentration after approximately 1 hour. It is 98% protein-bound and is metabolised by the liver to active compounds nordazepam and oxazepam. In patients with hepatic dysfunction, initial dosages should be titrated carefully. Total half-life can range between 20 and 80 hours. Treatment may be initiated at 2mg twice daily increasing as needed to obtain a desired effect. Alternatively, single 5mg doses at night may be effective for nocturnal symptoms. Adverse effects include sedation and cognitive impairment, and there is a potential for dependence. A withdrawal syndrome is associated with the benzodiazepines and abrupt cessation of diazepam has been associated with seizures.

3.3 Tizanidine

Tizanidine is an imidazole derivative and is a centrally acting α_2-adrenergic agonist which inhibits the release of excitatory amino acids in spinal interneurons. It may also act by facilitating the action of glycine. Tizanidine has demonstrated potent muscle relaxing properties in animal models of spasticity,[28] and it was found to suppress the polysynaptic reflex in the spinal-transected cat.[29,30] In addition, tizanidine has been shown to enhance vibratory inhibition of the H-reflex in humans and

reduces abnormal co-contraction which may also, in part, contribute to antispasticity effects.[31] In placebo-controlled trials, tizanidine has been shown to reduce muscle tone and frequency of muscle spasms in both patients with MS and spinal cord injury.[32-34] Similar efficacy was noted when tizanidine open-label was tested in patients who had experienced a stroke.[35] Although tizanidine was found to reduce spasticity without altering muscle strength, it has shown no consistent positive effect on functional measures, such as timed ambulation, upper extremity function or activities necessary in activities of daily living (ADLs).[32] When compared with baclofen or diazepam in early trials, tizanidine demonstrated similar efficacy and better tolerability.[30,33,36-43] When compared with baclofen, night-time insomnia was reported more frequently with tizanidine, and weakness was also reported but less frequently than with baclofen.[36] There have been no controlled trials investigating the use of tizanidine in combination with baclofen.

Tizanidine undergoes first-pass hepatic metabolism and is subsequently eliminated by the kidney. Its half-life is approximately 2.5 hours and the peak effect is seen 1 to 2 hours after administration. Liver function tests should be checked at baseline, months 1, 3 and 6 of treatment, and periodically thereafter. Treatment is initiated at 2 to 4 mg/day, increasing every 3 days by 2 to 4 mg/day. The total dosage should not exceed 36 mg/day in 3 divided doses. There is little experience with single doses greater than 8mg. Adverse effects include dry mouth (45%), drowsiness (54%) and dizziness, and were seen primarily when dosages exceeded 24 mg/day. Visual hallucinations (3%) and elevated liver function tests (5%) were reversible with dosage reduction.[32] Tizanidine has not been found to have consistent effects on blood pressure, but because of its central α_2-adrenergic activity and risk of potential hypotension, concomitant use of antihypertensives, especially clonidine, should be avoided.

3.4 Clonidine

Clonidine is a centrally acting α_2-adrenergic agonist that is frequently used to treat hypertension as well as opiate withdrawal. The central α-adrenergic activation is thought to decrease sympathetic outflow. Clonidine has been shown to decrease the vibratory inhibition index in patients with spinal cord injury,[44] to reduce muscle tone in patients with brain injuries (stroke, trauma, haematoma, cerebral palsy),[45] and has shown modest benefit as a supplement to baclofen.[46] Clonidine is rarely used as a single agent in the treatment of spasticity. It is available in 0.1mg tablets, but the patch formulation (0.1mg and 0.2mg) is designed to deliver the specified dose daily and must be changed every 7 days. Adverse effects include bradycardia, hypotension, dry mouth, drowsiness, constipation, dizziness, and depression.

3.5 Dantrolene

Dantrolene is a hydantoin derivative. It acts directly on muscle contractile elements decreasing the release of Ca^{2+} from skeletal muscle sarcoplasmic reticulum, which interferes with excitation-contraction coupling that is necessary to produce muscle contraction.[47-49] The effect is most pronounced on extrafusal fibres, but there is a minor effect on intrafusal fibres as well. Whether this effect may alter spindle sensitivity is unclear.[50] Dantrolene has a greater effect on fast-twitch fibres (those that produce rapid contraction and high tension, but fatigue relatively easily) than on slow-twitch fibres (those that contract tonically, producing less tension, but are more resistant to fatigue).[51]

Placebo-controlled trials of dantrolene have demonstrated effective reduction of muscle tone and hyper-reflexia.[49,52-54] When dantrolene was compared with diazepam in a double-blind, crossover designed trial in 42 patients with MS, both drugs were found to decrease spasticity, clonus and hyperreflexia, as well as diminish muscle stiffness and cramping.[55] Similar trials have been performed in children with cerebral palsy[56] and in patients with spasticity secondary to varying causes of cerebral and spinal disorders.[57] Spasticity was slightly better controlled with dantrolene than with diazepam and adverse effects were reported to be more tolerable with dantrolene.

The half-life for oral dantrolene is approximately 15 hours, with peak concentrations occurring within 3 to 6 hours. It is metabolised largely by the liver. Dantrolene therapy is initiated at 25 mg/day and slowly titrated upwards by increments of 25 mg/day every 5 to 7 days, with a recommended maximum of 400 mg/day in divided doses. Because its site of action is peripheral, the most common adverse effect of dantrolene is weakness. For this reason, dantrolene may be most appropriate for those patients who are non-ambulatory with severe spasticity. Other adverse effects include drowsiness, diarrhoea and malaise. Hepatotoxicity, which can be irreversible, is the major concern with dantrolene and those patients who are being considered for therapy should have liver function tests checked prior to initiating therapy and on a regular basis (every 3 months) thereafter.

3.6 Gabapentin

Gabapentin was first introduced in 1994 as a new treatment option for patients with partial seizures.[58] It is structurally similar to GABA, exerting GABAnergic activity by binding receptors in the neocortex and hippocampus. However, it does not bind conventional $GABA_A$, $GABA_B$, glycine, glutamate, benzodiazepine or N-methyl aspartate receptors.[59,60] It is easily absorbed, reaching peak plasma concentrations in 2 to 3 hours, it is not protein bound, does not undergo metabolism, and is excreted unchanged in the urine. It is well tolerated in dosages up to 3600 mg/day.[61] Recent studies and reports have suggested it might be effective as another tool in treating spasticity[61,62] but further studies will be necessary to confirm efficacy.

3.7 Botulinum Toxin

Botulinum toxin is a product of *Clostridium botulinum*, and ingestion of the organism or its spores results in botulism. Botulinum toxin blocks presynaptic release of acetylcholine from the nerve terminal. Seven immunologically distinct toxins (type A through G) have been purified. Local intramuscular injection of botulinum toxin A has been approved for the treatment of strabismus and blepharospasm associated with dystonia. When injected, the agent spreads through muscle and fascia approximately 30mm, binding presynaptic cholinergic nerve terminals, resulting in a chemical denervation.

Botulinum toxin injection has been studied as a treatment for severe spasticity caused by stroke, traumatic brain injury and other causes,[63-66] and has been found to be effective in reducing muscle tone and spasms. Snow et al.[67] studied botulinum toxin A in 9 patients with advanced MS (wheelchair- or bed-bound) in a randomised, crossover, double-blind study. Muscle tone, frequency of spasms and hygiene/self-care scores were used to assess efficacy. Botulinum toxin injection produced a significant reduction in spasticity and improvement in ease of nursing care, with no adverse effects.[67] Botulinium toxin injection was found to be a promising therapy for the treatment of spasticity in children with cerebral palsy.[68,69] Judicious use of botulinum toxin may permit surgery to be delayed until children reach a more suitable age.

Although botulinum toxin injection is off-label for treatment of spasticity, it may be an appropriate option for selected patients with severe localised spasms. Physicians using botulinum toxin should be trained in its use with attention to relevant topical anatomy and kinesiology. Onset of focal muscle fibre paralysis begins in 24 to 72 hours with a maximal effect seen at 5 to 14 days. The paralysis is transient lasting 12 to 16 weeks. Localising specific muscles with electromyographic guidance may be necessary to produce optimal effects. Injection site reactions can occur and antibodies may develop to specific immunological strains, thus limiting efficacy. Because the delivery of toxin is not entirely contained, the paralysis of muscles may not be exact. Excessive weakness, though ultimately reversible, may result.

3.8 Intrathecal Baclofen

When treatment with oral medication fails in a patient with persistent severe spasticity, intrathecal administration of baclofen should be considered. A pump with reservoir is surgically implanted in the

subcutaneous tissue of the abdominal wall. A catheter is threaded into the subarachnoid space allowing delivery of baclofen directly into the CSF. This allows as much as 4 times the concentration of drug to be delivered at only 1% of the oral dosage, without concomitant elevation of serum concentrations, and thereby reducing unwanted cerebral adverse effects.[70] Penn et al.[70] conducted a double-blind, placebo-controlled, 3-day crossover study in 20 patients (10 with MS and 10 with spinal cord injury). All patients had decreased muscle tone and frequency of spasms while treated with baclofen. All patients were subsequently enrolled in a long term nonblind trial of continuous infusion, with a mean follow-up period of 19 months. Using the Ashworth scale[71,72] (a standardised scale to assess muscle tone), all patients exhibited normal tone and spasm frequency was diminished to the point that there was no interference with ADLs. Seven of 8 patients also experienced improvement in bladder function.[70] Others have found equally dramatic results.[73-75] Well tolerated and effective long term follow-up has been reported in patients up to 84 months.[76]

Pump implantation is considered only after a patient undergoes a trial of intrathecal baclofen to establish responsiveness. Treatment is started at a dosage of 25 μg/day, increasing up to an average of 400 to 500 μg/day, although dosages as high as 1500 μg/day have been reported.[77] The half-life of intrathecal baclofen is approximately 5 hours. Many patients require increased dosages during the first 6 months' treatment and tolerance has been reported.[71,78] Most adverse effects tend to occur during the titration phase and include drowsiness, headache, nausea, weakness, and hypotension. Reversible coma has been reported in baclofen overdosing.[79] Other complications may be due to mechanical problems (dislodgment, disconnection, kinking, blockage), pump failure or infection. Intrathecal baclofen is a costly treatment and although useful, should only be considered in patients with severe functional limitations who have not responded satisfactorily to other treatments.

4. Conclusion

As with any symptomatic therapy, the treatment of spasticity should be individualised. Goals for therapy and realistic expectations should be established by both care provider and patient. Conservative measures should be incorporated into treatment regimens for spasticity. Stretching, massage and passive range of motion exercises are extremely important in preventing muscle shortening and the formation of contractures. Guidance on proper positioning and posture, as well as how to avoid specific positions that may elicit clonus or spasms, can result in increasing functional. Patients should also be evaluated for adaptive equipment such as ambulatory aids, reachers and other devices, and be instructed on the appropriate use of these tools. Direct effects of muscle relaxation from physiotherapy are often short-lived and for many patients, these conservative measures alone are insufficient to treat their symptoms. Most patients experience symptomatic improvement with physiotherapy in combination with one or more antispasticity agents. Patients refractory to these treatment options may respond to intrathecal baclofen. An understanding of the mechanism of action of these therapies should aid in developing individualised regimens for patients.

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