Anti-spasticity medications

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ABSTRACT

Spasticity is common in patients with a variety of central nervous system disorders. It can lead to significant disability or cause complications that may result in severe morbidity. In such patients, treatment of spasticity is warranted. Several oral and parenteral medications are available for use in the treatment of spasticity. This article reviews the pharmacological properties and therapeutic effectiveness of these medications to provide a practical objective guide for physicians who may be involved in the management of spasticity.

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Spasticity was defined by Lance in 1980 as a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex which is as one component of the upper motor neuron syndrome.[1] It is a common clinical problem in patients with a variety of central nervous system disorders such as multiple sclerosis, strokes, brain and cord injuries and cerebral palsy.[2,3] It has some advantages in some patients as it substitutes for strength, thus facilitating transfer, standing and ambulation. The resultant increase in muscle tone may help prevent muscle atrophy, decrease edema, and prevent deep vein thrombosis as well as reduce the risk of osteoporosis. Conversely, spasticity has many negative aspects. These include interference with functional mobility and activities of daily living. It may also cause painful spasms, result in fractures, interfere with sleep or increase the risk of bed ulcers. The treatment of spasticity therefore is warranted under these circumstances. Varieties of oral and parenteral medications are available for the treatment of spasticity. These include tizanidine, baclofen (oral and intrathecal), diazepam, dantrolene and botulinum toxin.[1-3] All these have different modes of action and clinical efficacy, and their different side effects can limit their use. This article reviews the mechanism of action, efficacy and side effects to provide practical guidelines for physicians who may be involved in the management of patients with spasticity.

Oral medications. Tizanidine is a centrally acting alpha-2-adrenergic agonist.[4,5] It has been shown to decrease polysynaptic reflex activity probably by reducing release of excitatory neurotransmitters from presynaptic neurons.[6-8] As an alpha-2 adrenergic agonist, tizanidine can cause hypotension. The reduction in muscle tone following therapeutic doses of tizanidine without a reduction in muscle strength was not associated with a desirable outcome.[6,7] Therefore, tizanidine may be the drug of first choice in the treatment of spasticity in patients who have marginal strength, and in whom using other antispasticity drugs may cause sedation. Tizanidine occasionally causes slight elevation of liver enzymes, which usually normalize with dose reduction or discontinuation of therapy.[9] Monitoring of liver enzymes is recommended during the first 6 months of therapy and the drug should be avoided in patients with liver disease. Other side effects of tizanidine include sedation, hallucination, asthenia, dry mouth and dizziness. It should therefore be used with caution in patients receiving other concurrent antihypertensive agents because of its hypotensive effect and not prescribed in combination with other alpha-2-adrenergic agonists. It has been found to be effective in the treatment of spasticity of both cerebral and spinal origin.[5,9,10] A meta-analysis of

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controlled clinical trials comparing tizanidine with baclofen and diazepam showed that although all 3 drugs were effective against spasticity, tizanidine was better than the other 2.[11] Aside from its primary use as an anti-spasticity agent, other uses of tizanidine are being evaluated especially in the treatment of neuropathic pain, tension type headache, acute low back pain, and addition in combination with dextromethorpan.[12-14] Tizanidine is usually started as single dose of 2-4 mg and slowly titrated upward in 2-4 mg increments of divided doses every 3-4 days to a maximum of 36 mg/day.

Baclofen acts centrally like most anti-spasticity medications. It binds to gamma amino butyric acid (GABA) receptors and inhibits spinal reflexes.[15] It reduces calcium influx to the presynaptic nerve terminal of the corticospinal tract thus inhibiting the release of excitatory neurotransmitters, and decreases their effects post-synaptically when given at high doses.[16] After its oral dose, baclofen is rapidly absorbed and excreted unchanged primarily by the kidney. Baclofen has been shown to be effective in the treatment of spasticity and associated painful spasms.[17,18] Its use is limited by several side effects which include sedation, muscle weakness, dizziness, fatigue, headache, confusion, hallucination, ataxia, dyskinesia, hypotension, and respiratory depression.[16,17,19] It should be used with caution in patients with epilepsy as it may provoke seizures in such patients.[20] The usual starting dose is 5-10 mg twice a day (bd) or 3 times a day (tid) and increased slowly as clinically required to a maximum of 120 mg/day divided doses.

Benzodiazepines result in enhanced presynaptic and postsynaptic inhibition by binding to GABA receptors. Benzodiazepine binding sites are contained within the GABA-A receptor complex in the central nervous system.[15] Besides their uses as anticonvulsants, sedatives and anxiolytics, benzodiazepines have been shown to be effective in reducing spasticity of both cerebral and spinal origin.[3,17,21] Although their efficacy is similar to baclofen, benzodiazepine use is limited by side effects particularly habituation and sedation.[17] Therefore, they are probably appropriate for patients with nocturnal spasms, or for those who can benefit from the additional sedative and anxiolytic effects.[3]

Diazepam is the most widely used benzodiazepine for the treatment of spasticity. It is lipid soluble and rapidly absorbed after oral administration. Its half-life varies from 20-70 hours. It is highly protein bound (98%), metabolized to oxazepam, which is the active metabolite and excreted in urine. The recommended initial dose is 2-4 mg daily with a maximum dose of 60 mg/day in divided doses.

Dantrolene sodium acts directly on the skeletal muscle by inhibiting the release of calcium from the sacroplasmic reticulum, thus interfering with the excitation-contraction coupling.[22] The absorption of dantrolene after oral administration is incomplete and slow but consistent. The mean biologic half-life is 8 hours. Hepatic microsomal enzymes metabolize it. As its mechanism of action is peripheral, dantrolene is probably appropriate for patients who cannot tolerate the cognitive side effects of the centrally acting antispasticity medications. It is effective in controlling spasticity associated with a variety of cerebral and spinal disorders.[22] However, its use is limited by its effect on muscle strength. Therefore, its use is probably justified in severely affected quadriplegic patients. The most frequently occurring side effects of dantrolene include dizziness, general malaise, weakness, headache, and diarrhea. These are generally transient and can be obviated by slow upward titration of the dose, there is 1% risk of hepatotoxicity.[22] Therefore, liver function tests should be monitored periodically early in the treatment. Dantrolene is started at 25-50 mg/day and slowly increased up to 400 mg/day in divided doses.

Other medications. Clonidine is an alpha-2 adrenergic agonist similar to tizanidine.[3] It was shown to reduce spasticity and control spasms.[23] Its use is limited because of the orthostatic hypotension side effect. The usual starting dose is 0.05 mg bd increasing by 0.1 mg/day weekly up to a maximum of 0.4 mg/day.

Gabapentin, a structural analogue of GABA, has been shown to reduce spasticity associated with multiple sclerosis and spinal cord injuries.[24] Its side effects include dizziness, fatigue, headache and weight gain. The usual dose is 400 mg tid which can be titrated upward to a maximum of 1800 mg/day.

Vigabatrin is one of the new antiepileptic drugs that have been studied for the treatment of spasticity. Its mechanism of action is irreversible inhibition of GABA-transaminase, which is responsible for the catabolism of GABA. A double blind, cross over study comparing vigabatrin and baclofen in patients with multiple sclerosis and spinal cord lesions showed that improvement in spasticity was similar with both drugs.[25] Its side effects include sedation, dizziness, confusion, ataxia, depression and visual fields defect.[26]

Phenothiazines have been shown to reduce spasticity, most probably by blocking the alpha-adrenergic pathway.[3] However, their use is limited by their serious side effects particularly extrapyramidal features.

Cyproheptadine has been shown to have an anti-spasticity effect.[27] Its main side effects include sedation, dry mouth and increased appetite.

Valproic acid has been reported to reduce spasticity.[28] However, there is no strong evidence to support such beneficial side effects.

Intrathecal medications. Spasticity is not adequately controlled by oral medications in one-third of patients. Some of these medications, such as baclofen, do not cross the blood-brain barrier effectively and the need to use higher doses to achieve desired efficacy can result in serious side effects. Intrathecal administration of lower doses of drugs such as baclofen or morphine is an alternative for such patients. Several studies have shown that intrathecal baclofen is effective in controlling spasticity and painful spasms.[29-32] If

intrathecal baclofen pump placement is being considered, the patient should undergo a screening trial of a test dose administered intrathecally through a lumbar puncture. If the trial dose is effective, implantation of the intrathecal pump can then be performed and the pump dose adjusted according to the clinical response. Side effects of intrathecal baclofen include orthostatic hypotension, sedation, loss of penile erection, local infection, cerebrospinal fluid leak and pump or catheter malfunction.[33]

On rare occasions, morphine may be administered intrathecally for patients with refractory spasticity. It has been shown to be effective in reducing pain and spasticity associated with spinal cord injuries.[34] However, respiratory depression may be a limiting factor.

Botulinum toxin injections. Botulinum toxin is a neurotoxin derived from the anaerobic bacteria, *Clostridium botulinum*. It acts on the neuromuscular junction at the presynaptic site by inhibiting the release of acetycholine, thus leading to muscle weakness and reduced muscle tone.[35] It has been shown to be effective in controlling spasticity, particularly if this is focal.[36,37] Electromyographic guidance facilitates injection of botulinum toxin when a specific muscle(s) is (are) considered for this therapy. The local effect is usually demonstrated within 2-3 days of injection and lasts for 2-6 months. Therefore, a repeat injection is recommended every 3 months or more. Side effects include local skin reaction and spread of weakness to the adjacent non-injected muscles. Contraindications to botulinum toxin include pregnancy, lactation, neuromuscular junction disorders and concurrent use of aminoglycosides.

In conclusion, several anti-spasticity medications have been shown to be effective and safe in the treatment of disabling spasticity (**Table 1**). Tizanidine efficacy and its advantages of lack of effect on muscle power make it probably the drug of first choice for treatment of generalized spasticity. Baclofen is effective particularly for spasticity associated with spinal cord disorders including multiple sclerosis. However, under special circumstances, small doses of baclofen administered intrathecally are justified when large oral doses are required as this route eliminates the side effects that would result. Dantrolene is probably appropriate when the cognitive side effects of the centrally acting drugs are not tolerated. Benzodiazepine use is limited by their side effects, however, their use is justified for patients with nocturnal painful spasms or

Table 1 - Summary of the characteristics of orally administered antispasticity drugs.

Drug	Mechanism of action	Site of action			Side effects	Adult dose/ Route of administration	Practical Usefulness
		Cerebral	Spinal	Muscle			
Tizanidine	Decreases polysynaptic reflex	+++	+++	-	Hypotension; elevated liver enzymes; sedation; hallucination; dry mouth	Start dose: 1-4 mg daily. Increase by 2-4 mg daily to maximum total dose of 36 mg/day in divided doses	Cerebral/spinal cord lesions with spasticity and associated marked muscle weakness
Baclofen	Inhibits GABA receptors, inhibits spinal reflexes	++	+++	++	Sedation; muscle weakness; confusion; hallucination; dyskinesia; epileptogenic	Start dose: 5-10 mg bd and tds. Increase slowly to a maximum total dose of 120 mg/day in divided doses	Spinal cord lesions with spasticity particularly where muscle weakness is not very severe
Diazepam	Inhibits GABA receptors; inhibit presynaptic and polysynaptic reflex	++	++	±	Sedation; habituation	Start dose: 2-4 mg daily. Increase by 2-5 mg to a maximal total daily dose of 60 mg in divided doses	Painful spasms and spasticity particularly when present at night
Dantolene sodium	Inhibits calcium release and interferes with excitation-contraction coupling	-	++	+++	Weakness; diarrhea, hepatotoxic	Start dose: 25-50 mg daily. Increase gradually to a maximum of 400 mg daily in divided doses	Severe muscle spasms and spinal cord lesions with spasticity
Clonidine	Decreases polysynaptic reflexes	+	+	-	Hypotension	Start dose: 0.05 mg bd. Increase by 0.1 mg/day to a maximum of 0.4 mg daily in divided doses	Spasticity when associated with difficult to control hypertension
Gabapentin	Unknown: GABA analogue	+	+	-	Sedation; confusion; weakness; fatigue; weight gain	Start dose as for seizures and gradually build up to a maximum tolerated dosage with optimal benefit	Cerebral lesions with spasticity and associated seizures if uncontrolled with regular monotherapy

GABA = gamma amino butyric acid; bd = 2 times a day; tds = 3 times a day; + = positive; - = negative; ± = mixed

when their anxiolytic effect is needed. Botulinum toxin is an effective antispasticity therapy, particularly focal spasticity. The benefit of many other antispasticity medications particularly the newer antiepileptic drugs need to be confirmed in large clinical trials.

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