Review Article

Pharmacotherapy of Spasticity in Children With Cerebral Palsy

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Spasticity is a common disability in children with cerebral palsy. Pharmacological and non-pharmacological treatments, including physical therapy, occupational therapy, orthotics, rhizotomy, and orthopedic surgery, all play important roles in the management of spasticity. The purpose of this article is to provide an overview of available medications for treatment of spasticity in children with cerebral palsy. Common medications include benzodiazepines, dantrolene sodium, baclofen, tizanidine, botulinum toxins, phenol, alcohol and intrathecal baclofen. In general, oral medications and intrathecal baclofen are used for treating generalized spasticity, whilst chemodenervation agents (botulinum toxins, phenol, and alcohol) are used to treat localized spasticity. There is more sufficient evidence for the recommendation of botulinum toxin A as an effective anti-spasticity treatment in children with cerebral palsy. However, more data concerning safety and long-term effects of botulinum toxin A is needed. Further study is needed to determine which kinds of medications can cause substantial improvement in daily activity, participation level, self-competence, or quality of life in children with cerebral palsy.

Key Words: botulinum toxins, cerebral palsy, pharmacotherapy, spasticity

Cerebral palsy is the most common motor disability in childhood, with a prevalence of 2 to 2.5 per 1000 live births.1 Cerebral palsy describes a group of disorders of movement and posture, causing activity limitations. The activity limitations in cerebral palsy are attributed to non-progressive disturbance that occurs in the developing brain of the fetus or infants. Despite advances in technology, cerebral palsy remains a clinical diagnosis, and the essential findings include delayed motor milestones, abnormal muscle tone, hyperreflexia and absence of regression.2 Cerebral palsy is essentially a movement and balance disorder. Children with cerebral palsy may have muscle weakness, spasticity, loss of coordination, and persistence of primitive reflexes, interfering with the development of normal motor control.3,4

In cerebral palsy, spasticity usually arises from a chronic loss of inhibitory suprasegmental inputs, producing hyperactivity of the alpha motor
neuron. Depending on the injury mechanism, the manifestations of cerebral palsy may be variable, with spasticity as the most common sign. Although spasticity is one important component of the motor disability in cerebral palsy, it may not be the major factor interfering with the function, participation, or activity of children.

Spasticity Evaluation and Management Principles

The treatment program of spasticity begins with careful and detailed evaluation to determine whether muscle overactivity interferes with some aspects of motor function. It should be determined whether the patient’s spasticity is aiding function or not. It may be that reducing such “useful” spasticity would be counterproductive.

Spasticity management techniques used in children with cerebral palsy are determined primarily by clinical findings. The severity and distribution of spasticity is crucial for determination of appropriate management. Spasticity in cerebral palsy can be classified by affected body region to be monoplegia, diplegia, hemiplegia, quadriplegia, and double hemiplegia. It is important to document the particular patterns and severity of spasticity. Evaluation includes not only measurement of tone with the Ashworth scale, but also one or more measures of motor performance, functional ability and health-related quality of life. The treatment plan is to maximize the active function, ease daily care, and minimize secondary problems, such as pain, joint subluxation, and joint contracture. The main goal is to improve motor and self-care ability as much as possible.

Pharmacologic treatment with antispasmodics and non-pharmacologic treatment, such as rehabilitation therapy, have been mainstays in spasticity management. Rehabilitation therapy includes a wide range of techniques, such as Bobath techniques, patterning, conductive education, hippotherapy, aquatics, Vojta techniques, pediatric massage, Adelphi Polish Suit Program, and constraint-induced movement therapy. The essential treatment for spasticity is physical management, and all pharmacological treatment is adjunctive to good physical management.

Children with spastic cerebral palsy may eventually need orthopedic surgery to correct deformity induced by muscle overactivity. However, orthopedic surgery should be delayed until the child’s gait is mature, usually between age 6 and 10 years, when gait analysis and clinical examination can be used to determine the need for surgery. Selective dorsal rhizotomy, a surgical intervention for the treatment of lower extremity spasticity, may reduce the need for subsequent, selected orthopedic interventions.

Various oral, intramuscular, and intrathecal administered medications are available to reduce spasticity in children, which include oral benzodiazepines, dantrolene sodium, baclofen, tizanidine, chemodenervation agents (such as botulinum toxins, phenol and alcohol), and intrathecal baclofen. Oral medications and intrathecal baclofen are used in generalized spasticity while chemodenervation agents are used to treat localized spasticity (Table). In the following sections, we give a short review covering the application of these drugs in spasticity.

Oral Medications

Oral antispasticity medications have the advantage of easy use but have the disadvantage of systemic effects and significant side effects. Thus they are most appropriate for children who need only mild tone reduction, or who have widespread spasticity. Most studies on the efficacy of these medications are old, and did not have good study designs like those used today. Therefore, the choice of different medications is usually based on personal experience or trial and error rather than evidence-based medicine. Most oral medications, including benzodiazepines, dantrolen, baclofen, and tizanidine, can be used in combination with each other. Because of the complexity of spasticity, it is unlikely that one drug can be beneficial.
The reason for combination therapy is to improve the clinical effect and lessen side effects. Oral antispasticity medications can also be used with other treatment, such as neuromuscular blocking agents and intrathecal baclofen. Understanding their mechanisms, side effects and limitations is essential for treatment of spasticity.

**Benzodiazepines**
Benzodiazepines are useful in reducing spasticity because of an inhibitory effect at both the spinal cord and supraspinal levels. However, side effects are important limiting factors for long-term use; a short-term treatment is generally preferred.

**Benzodiazepines**
- **Mechanisms**: Increase the affinity of GABA for GABA<sub>A</sub> receptors; inhibitory effect at both the spinal cord and supraspinal levels. 
- **Major points**: Side effects are important limiting factors for long-term use; a short-term treatment.

**Dantrolene sodium**
- **Mechanisms**: Inhibit release of calcium from sarcoplasmic reticulum in muscle; works at the muscle. 
- **Major points**: General concern regarding its potential frequent and serious side effects; potential for hepatotoxicity in approximately 1% patients.

**Baclofen**
- **Mechanisms**: GABA agonist; binds at the GABA<sub>B</sub> receptor; inhibit release of excitatory neurotransmitters in the spinal cord and supraspinally. 
- **Major points**: Rapidly absorbed after oral administration; level in the CSF are low because of low lipid solubility.

**Tizanidine**
- **Mechanisms**: Centrally acting alpha-2 noradrenergic agonist; inhibit release of excitatory neurotransmitters in the spinal cord and supraspinally. 
- **Major points**: Monitor liver function.

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cord and supraspinal levels. Their effect is mediated by $\gamma$-aminobutyric acid (GABA) via the $\text{GABA}_A$ receptors. Benzodiazepines increase the affinity of GABA for $\text{GABA}_A$ receptors, resulting in pre-synaptic inhibition and a reduction of mono- and polysynaptic reflexes. They bind in both the reticular formation and spinal polysynaptic pathways. Diazepam is a benzodiazepine and the oldest antispasticity medication, with series of trials in the 1960s demonstrating its ability to reduce spasticity. The daily dose of diazepam is usually 0.2 to 0.8 mg/kg, divided into three or four doses. Therapy is initiated as a nighttime dose to help sleep. Benzodiazepines have many potential side effects. Sedation is the most common and may limit the clinician’s ability to increase dose. Ataxia, constipation, urinary retention, and weakness have also been reported, and side effects, such as drowsiness, sedation, hypersalivation, and weakness, are important limiting factors for long-term use. Prolonged use of diazepam may produce physical dependence and cannot be discontinued abruptly. Therefore, it should be considered as a short-term antispasticity treatment in children.

Although diazepam is the most commonly used benzodiazepine, other benzodiazepines are sometimes used in treatment of spasticity. Clonazepam has been used to decrease night spasms.

**Dantrolene sodium**

Dantrolene sodium works at the muscle, inhibiting calcium release from the sarcoplasmic reticulum. Studies have demonstrated that dantrolene can reduce spasticity in children with cerebral palsy. However, it can also lead to global weakness and sedation, despite its peripheral mode of action. Doses of dantrolene sodium in children range up to 12 mg/kg/d. Treatment is generally initiated at a low dose and titrated upward every 5 to 7 days as tolerated. Dantrolene sodium also has the potential for hepatotoxicity in around 1% of patients, and may cause nausea, vomiting, diarrhea or paresthesia. Dantrolene is rarely used in clinical practice due to the limited evidence to support its efficacy and the general concerns about its serious side events.

**Baclofen**

Baclofen is a GABA agonist. It can cross the blood-brain barrier and bind to $\text{GABA}_B$ receptors of laminae I–IV of the spinal cord, where primary sensory fibers end, thereby inhibiting the release of excitatory neurotransmitters and causing presynaptic inhibition of mono- and polysynaptic reflexes. Baclofen can significantly reduce spasticity and improved both passive and active movement. The side effects of baclofen include sedation, confusion, dizziness, ataxia, weakness, nausea, hypotension, and paraesthesia. A typical starting dose is 2.5 mg/day, which can be titrated up gradually to a maximum of 20 to 60 mg/day. However, the tendency to cause confusion and sedation limits their clinical dose. Baclofen must be weaned gradually to avoid a withdrawal syndrome. Acute discontinuation of both oral and intrathecal baclofen may cause signs and symptoms of withdrawal, like spasticity with spasms, hallucinations, confusion, seizures, or temperature elevation.

**Tizanidine**

Tizanidine is a centrally acting alpha-2 noradrenergic agonist, and is as effective as diazepam and baclofen in tone reduction. Alpha 2 adrenergic agonists also have an antinociceptive effect, which may contribute to their tone-reducing abilities, because pain is known to increase spasticity in children. It is possible that this antinociceptive effect is mediated through the release of substance P in the spinal cord. Tizanidine is readily absorbed after oral administration and metabolized in the liver. The half-life of tizanidine is around 2.5 hours, and treatment is usually initiated as a single nighttime dose, gradually titrating upward and adding daytime doses. Sedation and the need for frequent dosing have been limiting factors for tizanidine use. However, the sedative effect can be an advantage when the medication is given at night. The antispasticity effect of tizanidine has been demonstrated in adults with spasticity. However, little information is available to evaluate the effect of this drug in children. Side effects of tizanidine used in adults include
hypotension, sedation, asthenia, dry mouth, dizziness, hallucination, and hepatotoxicity. The incidence of side effects in children has not been studied.28

Neuromuscular Blocking Agents/chemodenervation

Chemodenervation (neurolysis or neuromuscular blockade) usually uses injection therapy to block neuromuscular transmission. Three techniques are currently used, including perineural injection of phenol4,45,46 or ethyl alcohol8,47,48 and intramuscular injection of botulinum toxin.49−52 Injectable neuromuscular blocking agents can balance muscle power across joints by producing selective denervation of muscles and nerves.8 Injection therapy to block neuromuscular transmission is mainly applied for treating focal spasticity. The duration of the effect depends on the agent and sites of injection.

Botulinum toxins A and B

Numerous retrospective or prospective studies have described the potency of botulinum toxin A to reduce the spasticity in children with cerebral palsy.49−53 Botulinum toxin A is a major breakthrough in the treatment of spasticity. It is effective in reducing spasticity and provides a time-limited improvement in motor function of the extremities for children with cerebral palsy.6

Botulinum toxin A works at the neuromuscular junction by inhibiting the release of acetylcholine. It binds, with high affinity and specificity, to presynaptic membranes of cholinergic motor neurons, and is then internalized; thereby preventing the discharge of acetylcholine-containing vesicles.50 For localized spasticity that needs treatment, botulinum toxin A can be injected intramuscularly to produce selective and reversible chemodenervation at the neuromuscular junction. Typically, there is a 3 to 4 month clinical response period requiring repeated injections of the agent. Some studies suggest using the smallest dose of botulinum toxin A and avoiding injections more frequently than every 3 months to minimize the risk of antibody resistance.28 Failure to respond to these injections may indicate the production of antibodies against botulinum toxin A, which may develop in around 5% of patients.25,54 Modifying drug preparations, accurate target muscle injection and combination therapy with other adjunctive therapy have been emphasized for better efficacy and reduction of drug resistance.

Botulinum toxin A has an excellent safety profile with a low incidence of side effects. Commonly reported side effects include muscle soreness, pain, leg cramps, skin rash, fatigue, excessive weakness, calf atrophy, influenza-like symptoms, infection, bleeding and allergic reaction.5,8,55 Systemic effects, such as dysphagia, dysphonia, weakness, dyspnea, or respiratory distress, have also been reported as potential side effects.28

Chemical denervation

Phenol and alcohol are non-selective proteolytic agents and can produce selective denervation when injected into motor nerves or muscles.8 In general, 45−50% of alcohol solution, diluted with normal saline, is used for injection to motor nerves and muscle.47,48 The duration of denervation with alcohol injection is about 3−6 months.8

Phenol is the most commonly used agent to produce chemical neurolysis. The duration of denervation of phenol is about 4−8 months.8 Injections of 3 to 5−6% of phenol solution perineurally promotes denervation via axonal degeneration,4,25 or into motor points of selected muscles produces a sustained reduction in muscle tone.25 The target nerve is usually identified with electrical stimulation, a procedure that may be poorly tolerated in children, requiring sedation or anesthesia.4 Phenol can denature proteins when injected perineurally, disrupting efferent signals from hyperexcitable anterior horn cells by inducing necrosis of the axons.25,56,57 The effect of denervation is not permanent, with functional reinnervation occurring in months to years.4 Studies have demonstrated the benefits of alcohol47,48 and phenol45,46 in treating spasticity in cerebral palsy. Side effects of phenol block include
lethargy and nausea secondary to systemic absorption, dysesthesia due to necrosis of sensory axons, possible permanent muscle fibrosis, and the potential for necrosis of skin at the injection site. Neurolysis may also lead to pain, especially when mixed nerves are treated. Despite these limitations, the low cost of phenol makes phenol injections a good treatment choice in selected patients with focal spasticity. The absence of immunogenicity and the lower cost compared with botulinum toxins make these agents more attractive in some institutes.

**Intrathecal Baclofen**

By contrast to botulinum toxins, intrathecal baclofen and selective dorsal rhizotomy are used to manage more widespread spasticity. Baclofen is hydrophilic and its low lipid solubility limits its transport across the blood-brain barrier. Contrastingly, spinal intrathecal baclofen administration can bypass the blood-brain barrier. By infusing baclofen directly into the subarachnoid space around the spinal cord, the GABA-mediated inhibition of spasticity can be achieved while minimizing the side effects secondary to high level of baclofen in the brain. Baclofen has its effect by binding with GABA receptors in the spinal cord. Since the site of action is in the spinal cord, intrathecal baclofen administration can have a much lower incidence of cerebral side effects and often a higher reduction in muscle tone than when administered orally. The effectiveness of oral baclofen has been limited by its sedating side effect. It has been reported that the intrathecal dose of baclofen is only 1% of the oral dose. The half-life of intrathecal baclofen in the cerebrospinal fluid is about 5 hours. However, the short half-life of the drug means continuous infusion is necessary for better spasticity reduction. Intrathecal baclofen is an effective treatment for severe, generalized spasticity in selected patients with cerebral palsy and movement disorders. However, patients must be of sufficient size to fit the pump, so typically a minimum of 15 kg is needed. As with other implanted devices, complications of intrathecal baclofen administration are possible. These complications may be secondary to surgical complications, human error or device-related complications. Infection rates reported in the literature vary, but may be about 5%. Overdose has been reported, secondary to human errors in programming or refilling pump procedures. Depending on the degree of overdose, respiratory suppression and reversible changes in consciousness may occur. Technical problems related to the infusion system have also been reported to occur around 1% per year of service. The majority of these technical problems involves breakage or disconnection of the catheter. Catheter or pump failure may lead to a sudden withdrawal of medication, causing signs and symptoms of withdrawal. There have been reports of spasticity, hallucination, temperature elevation, confusion, or seizures associated with sudden withdrawal of intrathecal baclofen. Drug-related side effects include changes in bowel or bladder function, impotence, sedation, dizziness, weakness, nausea, and vomiting.

**Conclusion**

Muscle overactivity can be a significant source of functional disability in children with cerebral palsy. Appropriate treatment can improve the function, reduce pain, and prevent or correct deformity. Oral medications, chemodenervation, rhizotomy, intrathecal baclofen, and orthopedic surgery may all play important roles in the properly selected children. Although physical and occupational therapy is central to any treatment plan, oral antispasticity agents have the advantages of easy use but the disadvantages of systemic effects. In general, oral medications have narrow therapeutic windows, and are used when generalized spasticity is noted. However, most studies on the efficacy of oral antispasticity agents are old, and deserve serious research effort. Chemodenervation, including botulinum toxin A, phenol and
alcohol, is the main option for treating focal spasticity. The effect is temporary. However, phenol and alcohol can be used in combination with botulinum toxin A once the maximum dosage of botulinum toxin A is met. There is sufficient evidence to support the use of botulinum toxin A as an effective antispasticity treatment. Intrathecal baclofen is used to manage more widespread spasticity. By considering whether the intervention is focal or generalized in effect and whether the effect is permanent or temporary, appropriate choices of antispasticity treatment can be made. For successful management, the least invasive and most cost-effective treatment should be chosen. More evidence is needed to determine which medications can make substantial improvement in daily activity, participation level, or quality of life in children with cerebral palsy.

References

C.Y. Chung, et al


