Pharmacologic Treatment Tools

Systemic Medications and Toxins, Opportunities, and Pitfalls

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KEYWORDS

• Upper motor neuron syndrome • Spasticity • Muscle overactivity • Treatment
• Pharmacotherapy • Toxins

KEY POINTS

- Treatment of pathologic muscle overactivity associated with upper motor neuron syndrome can be multifaceted.
- One of the initial decisions to be made when formulating an overarching treatment plan is selecting a combination of strategies that is most applicable.
- Strategies may include physical interventions, such as stretching or splinting modalities, or surgery, whereas pharmacotherapeutic strategies encompass oral/systemic medications as well as agents, such as toxins and alcohols, used for focal chemodenervation.

INTRODUCTION

Treatment of pathologic muscle overactivity associated with upper motor neuron (UMN) syndrome can be multifaceted. One of the initial decisions to be made when formulating an overarching treatment plan is selecting a combination of strategies that is most applicable. Strategies may include physical interventions such as stretching or splinting modalities or surgery, whereas pharmacotherapeutic strategies encompass oral/systemic medications as well as agents, such as toxins and alcohols used for focal chemodenervation. This article reviews the oral/systemic therapies as well as toxins that are used focally. Although medication can also be administered via intrathecal pumps, this treatment approach is discussed elsewhere.

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SYSTEMIC PHARMACOTHERAPY

Oral medications are frequently started as one of the initial treatments for muscle overactivity related to UMN syndrome. The use of these medications, as is discussed later, has significant associated risks. It must be emphasized that hypertonia not contributing to decreased function, pain, or increased burden of care need not be suppressed. Clinicians should always have a clear, goal-oriented approach for prescribing. Exacerbating factors such as visceral distension or other noxious stimuli should be identified and limited as much as possible before initiation of treatment. Most of the oral medications are likely to cause some degree of sedation so timing and environmental context of treatment are important considerations.

Baclofen

Baclofen is the most commonly known and used oral medication to inhibit muscle overactivity. It binds to gamma-aminobutyric acid (GABA)-B receptors, inhibiting calcium influx that would otherwise allow release of excitatory neurotransmitters.[1] It is thought to have postsynaptic effects at the GABA-B receptor through multiple pathways and decreases activity of both the gamma motor neuron and intrafusal spindle muscles.[2–4] Both monosynaptic and polysynaptic reflexes are inhibited by baclofen.[5] Animal studies have also shown a possible mechanism for analgesic properties via reduction of substance P from nociceptive afferent nerve terminals.[6] Baclofen is mostly excreted through the kidneys (a small amount is metabolized by the liver) and has a short half-life of approximately 3.5 hours.

Baclofen has been studied most extensively in patients with spinal cord injury and those with multiple sclerosis and has been shown to reduce spasticity as well as painful flexor spasms in these populations.[7,8] There is less evidence supporting benefit in patients with spasticity of cerebral origin. Like many other oral medications for spasticity, there is no established evidence that baclofen alone can improve independence with mobility or activities of daily living. It has been used for more than 40 years and has a generally low incidence of drug tolerance and/or side effects.[9]

Side effects of baclofen include gastrointestinal upset, sedation, confusion, dizziness, insomnia, muscle weakness, euphoria, depression, and dyskinesia.[10] Baclofen can lower the seizure threshold in patients with epilepsy and decrease alertness in elderly patients with acquired brain injury.[11] Patients should be tapered appropriately off baclofen because of risk of seizures, temporarily increased spasticity, confusion, and hallucinations.[12]

Diazepam

Like baclofen, benzodiazepines are a commonly known and used class of medications to treat spasticity. Benzodiazepines indirectly work through the GABA-A receptor by neuronal membrane hyperpolarization via increased chloride influx once GABA is already bound.[13] This presynaptic inhibition enhances the efficacy of GABA binding at spinal and supraspinal sites, which reduces both monosynaptic and polysynaptic reflexes at the spinal level.[14,15]

Diazepam, a long-acting benzodiazepine, has been used to treat spasticity in patients with spinal cord injury for more than 40 years and is the most commonly used drug for this purpose in its class.[16] However, because of its deleterious effects on attention and memory, it is not commonly used for spasticity in patients with acquired brain injury, although it has been shown to improve athetosis in addition to spasticity in patients with cerebral palsy.[17] Diazepam is metabolized by the liver and its half-life can be from 20 to 50 hours, with active metabolites lasting up to 100 hours.[18]