Pharmacotherapy of Spasticity: Some Theoretical and Practical Considerations

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ABSTRACT: The availability of new antispasticity agents has greatly extended the therapeutic arm of the neurologist and has obviated the need for destructive neurosurgical procedures in many instances. Baclofen remains the single most useful agent, but in certain circumstances, benzodiazepines and dantrolene sodium are useful alternative or adjunctive treatments. Tizanidine has been recently introduced, and early experience with this agent appears to be favourable. A variety of new drugs are awaiting further evaluation. The effective use of these agents demands an understanding of their principal mechanisms of action, knowledge of their predictable side effects, and a familiarity with the underlying neurological disorders. The monitoring of clinical efficacy is difficult and is often dependent upon subjective evaluation. The application of electrophysiological studies might facilitate the monitoring of treatment and the prediction of optimum treatment strategies for individual patients. The use of these pharmacological agents, from the perspective of a clinician, will be discussed.

RÉSUMÉ: Pharmacothérapie de la spasticité: considérations pratiques. La disponibilité de nouveaux agents agissant contre la spasticité a considérablement étendu l'éventail des armes thérapeutiques que possède le neurologue et a paré, dans bien des cas, au besoin de procéder à des interventions neurochirurgicales destructrices. Le baclofen demeure l'agent thérapeutique le plus utile, mais dans certaines circonstances, les benzodiazépines et le dantrolène sodique sont utiles comme alternative à la thérapie avec le baclofen ou en association avec celui-ci. La tizanidine a été introduite récemment et les premières expériences avec cette substance semblent favorables. Une panoplie de nouveaux médicaments est prête à être évaluée. On doit comprendre leur principal mode d'action, connaître leurs effets secondaires prévisibles et être familier avec les affections neurologiques sous-jacentes pour pouvoir les utiliser efficacement. Le monitorage de l'efficacité clinique est difficile et dépend souvent d'une évaluation subjective. L'application d'études électrophysiologiques pourrait faciliter le monitorage du traitement et la planification d'une stratégie de traitement optimale pour chaque patient. Nous discutons, du point de vue du clinicien, du l'utilisation de ces agents pharmacologiques.

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The physiology of spasticity has been thoroughly reviewed at this symposium, and elsewhere.[1] The pharmacological approaches, in both theoretical and practical terms, will be reviewed here.

Theoretical Mechanisms of Action of Antispasticity Drugs

Etymologically, spasticity derives from the Greek word spastikos, which means to draw or tug. Spasticity is a specific type of hypertonia in which there is an increased, velocity-dependent, resistance to passive movement of muscles.[2] Spastic muscles have an elastic or spring-like quality which is abruptly terminated when they are stretched beyond a certain point ("clasp knife" phenomenon). Spasticity can be accompanied by weakness, augmented tendon reflexes, clonus and the Babinski sign. It is frequently compounded by flexor or extensor spasms.[2] In brief, this occurs because the stretch reflex arc is deprived of its normal supraspinal modulation. For reasons which are incompletely understood, alpha motoneurons become abnormally excitable. The principal abnormality appears not to lie in the muscle spindle, as previously thought.[3] Integrity of the segmental reflex arc is necessary for its expression.

Theoretically, within the reflex arc, there are many loci at which pharmacological agents might be used to decrease spasticity. Because the ultimate mediator of spasticity is the extrafusal muscle, drugs which depress its activity should be useful. Dantrolene sodium, which decreases the release of calcium ions from the sarcoplasmic reticulum, can be used effectively to weaken the excitation-contraction coupling mechanism.[4] Muscle strength would obviously be diminished by blockade of transmission across the neuromuscular junction by agents such as curare. This kind of pharmacological intervention would be attended by weakness. Section of motor nerves is

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undesirable because of the ensuing wasting. The contribution of primary afferent fibres (Ia) to the gain of the reflex arc could be diminished in two ways. The dorsal roots can be damaged by injections of alcohol or phenol into the spinal subarachnoid space. This chemical "section" of dorsal roots would result in transient reduction in spasticity, but experimental dystonic states cannot be abolished permanently by section of the dorsal roots, implicating significant alpha motoneuron hyperactivity.[5] A better strategy would be to block the release of excitatory transmitters from the primary afferent fibres. Baclofen has proved to be a useful agent in this regard. Although the mechanisms of action are not completely understood, it probably interferes with the release of excitatory transmitters from the terminals of large primary afferent fibres, which release glutamic acid, and of excitatory interneurons, which release aspartic acid.[6] Increasing presynaptic inhibition of the primary afferent input would be another logical pharmacological intervention. This can be done by potentiating the effect of GABA, which is a central mediator of inhibitory postsynaptic potentials. This can be done effectively by benzodiazepines, which probably facilitate the inhibition mediated by GABA at the post-synaptic level. One could theoretically increase the activity of Renshaw cells, which directly inhibit alpha motoneuron excitability. An agent like glycine might be useful in this context.[8] If excessive gamma motoneuron activity were contributing to spasticity, this could be blocked by inhibiting the action of descending noradrenergic fibres, which exert powerful facilitatory actions on the discharge of fusimotor neurons. Activity in these descending fibres can be blocked by phenothiazines and other alpha adrenergic receptor blockers.[9]

It would be useful to know the precise physiological disturbance responsible for spasticity in any particular patient. Electrophysiologists have made progress in determining the primary derangement in individual patients and this has allowed some logical inferences about drug choice.[10] There are several electrophysiological indicators of the physiological perturbations in spasticity. Unfortunately, the clinical assessment of the resistance of the limb to movement can only be used to approximate the severity of spasticity. This was demonstrated in a recent clinical trial in which clinical scales of spasticity proved to be poor indicators of ultimate treatment preference.[11]

A measure of alpha motoneuron excitability can be derived from the ratio of the amplitude of the H-reflex to that of the M-reflex or by the ratio of the T-max to the M-max.[12] However, the correlation of these two parameters and clinical efficacy is weak.[10] Vibration inhibition of the soleus monosynaptic reflex is mediated by presynaptic inhibition exerted upon Ia fibres.[13] This is commonly decreased in spasticity. Delwaide was able to use this technique to show that diazepam and tizanidine reinforced vibration inhibition in spastic patients.[10] The inhibition of the H reflex produced by antidromic conditioning stimulation of motoneurons is considered to be a measure of inhibition of motoneurons mediated by the discharge of Renshaw cells and other interneurons.[14] In patients with spasticity, there is a loss of this inhibition, which suggests a loss of recurrent inhibition or of other kinds of interneuronal inhibition. Baclofen has been shown to modify this response.[10]

The application of these electrophysiological techniques might predict which antispasticity agents would prove most beneficial to certain patients with different kinds of spasticity and furthermore, might help monitor drug efficacy in clinical trials.

Practical Considerations

Much can be done to help patients with spasticity before drugs are considered. Unfortunately there is little at present that can be done to prevent spasticity after central nervous system damage. Many factors can contribute to spasticity in a given patient. Nociceptive stimuli tend to exacerbate spasticity and commonly provoke flexor spasms. This can be helped by expeditiously treating urinary tract infections, constipation, decubitus ulcers, toe nail infections, deep venous thrombosis, and by avoiding constrictive garments. These simple measures, in conjunction with physiotherapy, should be mainstays of treatment.

After these measures have been undertaken there are several considerations which pertain to all drugs. Spasticity is generally a chronic problem and treatment is inherently protracted. The dosage of any drug should be the lowest that produces an optimal therapeutic response without major side effects. Treatment should be continued only if benefit is derived. It is often difficult to evaluate subjective impressions of improvement. It is occasionally advantageous to withdraw a drug periodically to determine whether spasticity worsens. Abrupt withdrawal of any of these drugs can exacerbate spasticity and produce a variety of withdrawal symptoms.

A major problem with almost all of these agents is their tendency to aggravate weakness. For each patient one must determine whether reduction of muscle tone will help or hinder ambulation. Many patients are dependent upon spasticity for transfers. Reduction of spasticity in these instances would jeopardize functional ability.

Patients with different kinds of nervous system lesions differ in their response to various medications. For instance, patients with spastic and dystonic hemiplegias from cerebral lesions are less commonly helped by these drugs. With electrophysiological testing, it might be possible to predict which patients will respond to a given treatment. It is important to anticipate side effects and to learn how these can be controlled. Physicians who prescribe antispasticity drugs should be familiar with the management of acute overdosage and it should be emphasized that none of these medications has been proven safe in pregnancy.

Finally, it should be realized that not all of these medications have been thoroughly studied in well designed, prospective, randomized clinical trials. The physician generally tries a series of medications, titrating each drug to the maximum tolerated dose before other drugs are tried.

Baclofen

Baclofen is a depressant of neuronal activity, mediating its effects predominantly by the suppression of excitatory neurotransmitter release. Its effect might be potentiated by its ability to inhibit the release of substance P and possibly by some direct GABAergic activity. It probably works both directly on the spinal cord and more rostrally.[6]

This is probably the most effective antispasticity drug. It is very useful in patients with spasticity secondary to spinal cord lesions and it is particularly effective in patients with severe flexor spasms. Baclofen is commonly initiated at 5 mg twice daily and increased every 3 or 4 days to a maximum of 80 mg daily. Rarely do patients require more than this. Weakness is by far the commonest side effect, and this is reported by at least one third of patients.[11] Central nervous system depressant effects

include sedation, somnolence, ataxia and respiratory depression, but these are uncommon. Confusional states are more prone to occur in patients with cerebral lesions. Exacerbation of seizure frequency is rare. Abrupt withdrawal can worsen the severity of flexor spasms, and in a few patients may precipitate a temporary hallucinosis.

Benzodiazepines

Benzodiazepines, such as diazepam, appear to interact with an allosteric protein modulator of the GABA receptor to increase receptor affinity for GABA. This increases chloride conductance and presynaptic inhibition.[7] The effect appears to be mediated principally at the postsynaptic side of GABAergic synapses. Although other mechanisms might be involved, the chief antispasticity effect appears to be related to GABAergic activity. This antispasticity effect is probably mediated both centrally and directly in the spinal cord, evidenced by the fact that the drug is more effective in patients with partial spinal cord transections.[15,16] Many drug trials have compared the efficacy of diazepam to baclofen. Both appear to be superior to placebo, but there are few demonstrable differences between the two.[6] Sedation appears to be more common with diazepam. Neither drug is particularly helpful in patients with spasticity from cerebral lesions. Both drugs are useful in patients with painful spasms.

Dosage is commonly introduced at 1 or 2 mg twice daily and increased gradually. Few patients require more than 20 or 30 mg daily. Common side effects include sedation, weakness, fatigue, dizziness, and ataxia. Sedative effects are compounded by alcohol and other centrally acting drugs. Particular care must be taken in the elderly. Greater potential for abuse is afforded by diazepam than with the other medications. Caution is advised in the setting of depression.

Dantrolene Sodium

This agent has a unique mechanism of action.[4] It acts peripherally in muscles to decrease calcium influx from the sarcoplasmic reticulum after membrane depolarization, thereby decreasing excitation-contraction coupling. It works essentially because it weakens muscle.[6] The drug is useful in treatment of spasticity. There are remarkably few comparative studies of dantrolene, baclofen, diazepam and placebo in the control of spasticity. Clinicians find it particularly useful in the management of the most severely spastic patients who are no longer ambulatory. It makes patients comfortable and facilitates nursing care. The drug is helpful in patients with spasticity from both spinal cord and hemispheric lesions. When compared to diazepam alone, it appears to have comparable efficacy with less sedation. Dosage is commonly introduced at 25 mg daily, and increased by 1 or 2 capsules a week. Few patients require more than 400 mg daily. If a response has not been achieved before this dosage is reached, the drug should be withdrawn.

Weakness is the commonest side effect. The drug should be given only with extreme caution to patients with chronic obstructive lung disease and congestive heart failure. An idiosyncratic drug-related hepatitis is the most dramatic complication and this occurs in 0.35-0.5%. In two-thirds of patients, the hepatitis is preceded by a recognizable prodrome of anorexia, nausea, vomiting and abdominal discomfort. Increased risk for dantrolene hepatitis occurs in women, patients older than 35, and in those receiving other drugs, particularly estrogens. Risk is increased in patients who have had intermittent short courses of high dose dantrolene treatment and in patients who have received more than 300 mg for longer than 2 months. Gastrointestinal irritability, manifested by diarrhea, can be controlled to some extent by titrating the dosage increment.[4]

Tizanidine

Tizanidine is a newly available centrally acting muscle relaxant. The mechanism of action is not known. It potentiates vibration inhibition of the Hoffmann reflex, which suggests an ability to reinforce presynaptic inhibition, similar to benzodiazepines.[10] The drug has been studied in double blind trial against placebo, baclofen and diazepam. Previous trials have suggested that it is as effective as baclofen and diazepam.[17-19] We recently compared tizanidine to baclofen in a double-blind cross-over trial in patients with multiple sclerosis. A favourable response was obtained in over 50%. The drug was comparable in efficacy to baclofen. The introductory dose was 2 mg, and most patients could tolerate 16 mg. It was well tolerated. The major side effects were weakness, somnolence and xerostomia.[11]

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