Pharmacologic Management of Spinal Spasticity

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Pharmacologic management of spasticity of spinal origin is determined in part by several factors: 1) evidence of a spasticity-related dysfunctional profile, 2) acknowledgement of the clinical effectiveness and side effects of commonly utilized pharmacologic agents, 3) pathophysiologic mechanisms and spinal plasticity (neuronal excitability, anatomical and biochemical reorganization), 4) pharmacokinetics and subject compliance, and 5) unique methods of drug administration. Presently, preferred agents include systemically administered substances, which presumably act at the level of segmental and intersegmental interneuronal circuitry—e.g. baclofen or clonidine, and at the level of muscle contractile tissue—e.g. dantrolene sodium. This paper also describes the action of intrathecally administered morphine on spinal spasticity in subjects resistant to the action of oral agents. Keywords: Spinal spasticity, intrathecal infusion, pharmacotherapy, spinal reflexes.

Spasticity of spinal origin is a manifestation of a chronic suprasacral spinal cord lesion ("chronic spinal lesion") such as that seen in spinal cord injury and multiple sclerosis. When sufficiently severe, it can interfere further with the individual's quality of life by adversely affecting such functional behaviors as sitting posture, mobility, transfers, and comfort, and by generating limb and trunk deformities such as contractures (1). Conversely, spasticity may support or enhance function; thus, inappropriate assessment and/or treatment may lead to further diminution of performance. When pharmacologic management is warranted, the rationale for treatment should be based upon pathophysiologic principles.

Spinal spasticity appears to be an expression of spinal cord plasticity, e.g. an unmasking or release of spinal neuronal excitability and/or anatomical and biochemical reorganization of spinal cord pathways (for review, see below and Herman, ref. 25). Enhanced segmental and intersegmental visceral and somatic spinal reflexes, features of spinal spasticity (2,3), may be characterized by 1) spontaneous, phasic, flexor-extensor motor contractions of proximal (including trunk) and distal muscle groups, e.g. the intersegmental "mass reflex", often referred to as flexor spasms; 2) segmental and intersegmental phasic reactions (e.g., flexor reflexes) evoked by cutaneous (nociceptive and non-nociceptive) and passive limb (single- and multijoint) stimulation; 3) movement-dependent (velocity and nonvelocity) flexor-extensor muscle reactions to periodic limb motion which are also manifest within the induced muscle spasm (4–6); 4) augmented motor discharges sensitive to vesical (bladder) stimulation, 5) intersegmental motor discharge patterns occurring spontaneously or upon perineal stimulation, frequently producing a strong phasic rise in intravesical pressure, a "somatovesical reflex" (7,8); and 6) hyperactive volume-induced micturition reflexes associated with a low threshold of reflex contraction, uninhibited detrusor contractions, vesicoexternal sphincter.
dyssynergia (coupled or uncoupled with enhanced limb reflexes) and, consequently, further somatosensory reflex activation. The net clinical outcome of such somatosensory reflex excitability may be incontinence with a forceful flow and a delimited maximum bladder capacity, requiring frequent catheterizations.

Transsection of the spinal cord in decerebrate animal and man leads to increased sensitivity of the stretch reflex, and spinal reflex excitability to flexor reflex afferent (FRA) stimulation (1,3,6,9–14). Measurements of the excitability (threshold, latency, and amplitude) of stretch- and electrocutaneous-induced reflex reactions following a spinal cord lesion suggest that reflexes dominated by proprioception, which prevail in cerebral spasticity (1), are replaced by those dominated by cutaneous stimulation (9). Such changes in reflex behavior may be attributed to changes in neuronal excitability (15–17) and/or anatomical reorganization of spinal cord circuitry (18–20). Removal of descending inhibition from supraspinal and intraspinal (propriospinal) sites is evidenced by enhanced spontaneous discharges and increased sensitivity of segmental and ascending tract neurons to nociceptive and non-nociceptive peripheral stimulation. Neurons may also “switch” function, e.g. proprioceptive neurons become sensitive to cutaneous stimulation, and low threshold mechanoreceptor neurons responding to non-noxious stimulation exhibit multireceptive properties, i.e. neurons now discharge upon nociceptive and non-nociceptive afferent stimulation (15,21).

The propriospinal system is also an important feature of spinal spasticity (2). Under normal conditions, ascending and descending propriospinal tracts interconnect the spinal segments and enable the spinal cord to integrate supraspinal and peripheral afferent influences (22,23). For example, the ascending intersegmental or propriospinal system inhibits reflex activity in spinal paths rostral to the site of stimulation. In our view, it is the release of spinal reflexes from intersegmental inhibitory control and from direct tonic inhibition from supraspinal centers that contributes to the wide profile of flexor and extensor or irradiating motor discharges (often comprising the mass reflex reaction). However, increased levels of neuronal excitation may not persist in the chronic spinal state. Under such circumstances, enduring enhancement of spinal reflexes may be ascribed to structural reorganization, e.g. intraspinal sprouting of primary afferent terminals (18–20).

Thus, plasticity of spinal reflexes should be interpreted in terms of interruption of descending modulatory mechanisms, i.e. an unmasking or release of spinal reflex inhibition and expansion and reorganization of afferent projections. Furthermore, immunohistochemical studies have demonstrated increased concentrations of neuropeptides such as vasoactive intestinal polypeptide (VIP), substance P (SP), and enkephalin (ENK) in the spinal cord of chronic spinal animals para passu with anatomical changes (20).

Pharmacologic management

It is often argued that baclofen (Lioresal®) is “probably the drug of choice in the spinal forms of spasticity”, and dantrolene sodium (Dantrium®) “may be a useful adjunct to the treatment of spinal forms of spasticity” (see Katz, this issue). When administered orally, baclofen, the prototypic GABA<sub>ß</sub> receptor agonist, suppresses spasticity in patients with both complete and incomplete spinal lesions, suggesting that its antispasticity action is mediated by receptors located in the spinal cord (24). There is a clear preferential action on segmental reflexes elicited by muscle afferent stimulation (e.g., tendon tap, “H” reflex, manual muscle stretch), whereas intersegmental reflexes such as flexor spasms, occurring spontaneously or evoked by cutaneous stimulation, are relatively less sensitive to baclofen (25). Such effects support the concept that monosynaptic excitation of motor neurons by primary muscle afferent signals is more sensitive to baclofen than polysynaptic excitation responding to nociceptive and non-nociceptive primary afferent stimulation (26). These actions distinguish the effects of baclofen from other centrally acting agents such as diazepam (27) and morphine (8,28), which cause a potent depression of polysynaptic activity without altering monosynaptic reflexes substantially. However, when oral baclofen is ineffective, its continuous intrathecal (i.t.) infusion (see below) can produce considerable suppression of hypertonia and flexor spasms and, hence, functional benefit to the patient (29).

Spinal lesions, particularly incomplete ones, can also be associated with ‘central pain states’ (30,31), featured at least in part by function-limiting dysesthesia and paroxysmal pain, the latter often coupled to muscle spasms. Among a population of patients with multiple sclerosis, baclofen may demonstrate a potent analgesic action (25,32) by reducing both spasm-related pain and dysesthesia. Baclofen is also effective in reducing or preventing the painful paroxysms of trigeminal and facial postherpetic neuralgia (33). Baclofen’s action in the treatment of the paroxysmal pain of trigeminal neuralgia resembles that of other substances, such as the anticonvulsants carbamazepine and phenytoin, which depress excitatory
transmission and facilitate segmental inhibition in the spinal trigeminal nucleus of cats (34,35). Olpe and Schmutz (36) suggest that stabilizing effects are achieved by reduced cell excitability, both pre- and postsynaptically, and by diminished release of excitatory neurotransmitters such as glutamate.

The antispasticity and analgesic effects of baclofen are produced by the (–) isomer of the racemic mixture, i.e. Lioresal®; the (+) isomer of the racemic mixture causes its side-effects, including lethargy, dizziness, and weakness, and antagonizes the depressant activity of the (–) isomer (37). Furthermore, the pharmacokinetics of the racemic substance supports our view that Lioresal® should be administered 4 times daily (total dose = 20–80 mg) to prevent undue drug holidays and, hence, to attain a more uniform plasma concentration. This concept also applies to the administration of dantrolene sodium (see below).

In patients with spinal lesions, function-limiting spasticity (1) may be effectively managed by oral administration of dantrolene sodium (Dantuzum®), particularly when reflexes dominated by muscle stretch (hypertonia) are considered mild-to-moderate, and widespread muscle contractions (spasms), occurring spontaneously or elicited by cutaneous stimulation, are not profound (1). As previously suggested (see Mayer, Katz in this issue), dantrolene sodium is a novel substance whose antispasticity action is achieved by depressing the excitation-coupling reaction of skeletal muscle (38). Investigations regarding its mechanisms of action and efficacy by Herman and his colleagues (39–42) demonstrated that dantrolene causes: 1) a dissociation between voluntary/reflex-induced electromyographic (EMG) activity and muscle force; 2) an inverse relationship between impulse frequency and force; 3) preferential action on the rate of force development rather than on the magnitude of force; 4) reduction of rapid, phasic, contractions produced by a tendon tap and clonus at low doses; 5) attenuation of mild (group II) hypertonia (1), but weaker action on moderate-to-severe hypertonia and spasms at high dose; and, 6) altered perception of ground contact forces leading to postural imbalance during early and relatively ‘high-dose’ administration of dantrolene. Consequently, we at the Institute advise:

1. Initial delivery of 25 mg or less for 2–3 days;
2. Progressive increases in dosage to 25 mg, 4 times daily;
3. A maximum daily dosage of 200–300 mg to gain maximal clinical effectiveness and to minimize the potential for hepatotoxicity;
4. That baclofen is the drug of choice in patients with spinal spasticity when both spasms and hypertonicity impair function; however, we have found that dantrolene sodium can be an effective adjunct to baclofen therapy under these conditions and efficacious alone when mild hypertonicity is the principle clinical observation.

Substances acting on monoaminergic mechanisms, such as cyproheptadine, a nonselective serotonergic (5-HT) antagonist, and clonidine, the prototypic alpha2 adrenergic agonist, have been used with some clinical success, particularly when administered to patients with incomplete lesions (43–45). Results derived from animal experiments show that 5-HT increases excitability of spinal motor neurons (46,47), enhances spontaneous hindlimb EMG responses and neuronal activity (48), and produces exaggerated responses to muscle stretch. Barbeau et al (43) presented evidence to suggest that cyproheptadine (peak daily dose = 24 mg in 3 divided doses) reduced clonus and muscle spasms in patients with spinal cord injuries, while producing a mild decrease in dynamic muscle strength. These actions were associated with improvement in the spastic gait of these patients (49,50). Presumably, cyproheptadine was effective because spasticity reflected, in part, the denervation supersensitivity of postsynaptic 5-HT receptors, located on or near large motor neurons in the ventral horn (48).

Like cyproheptadine, clonidine does not lose its potency in producing inhibition of spinal reflexes after spinal cord lesions (3,51,52) despite depletion of the principle neurotransmitter (norepinephrine) and altered viability of presynaptic alpha2 receptors. In fact, inhibitory action may be augmented, suggesting that spinal lesions lead to supersensitivity of postsynaptic alpha2 receptors, purportedly due to increased density of these receptors in the spinal cord (51). By binding to alpha2 adrenergic receptors located on interneurons in the spinal dorsal horn (3), clonidine’s antispasticity action may be attributed to a depressive action on polysynaptic reflexes. However, it may cause a greater reduction in spinal reflexes related to micturition control; clonidine depresses urethral EMG activity and pressure, and diminishes detrusor contraction during bladder filling. The apparent sensitivity of vesicourethral motility to systemic clonidine may indicate that it also binds to alpha2 receptors located in the ventral horn (53). Thus, clonidine may be an effective agent in altering muscle hypertonia and vesicourethral motility in patients with spinal spasticity. However, side effects such as hypotension and sedation may limit its clinical usefulness.

The combined use of cyproheptadine and...
clonidine may be more effective than either agent administered alone. Fung et al (54) demonstrated that such a treatment strategy could lead to substantial reduction in spasticity and to enhanced locomotor recovery.

In recent years, we have concerned ourselves with the pharmacologic management of subjects who do not reveal functional benefit with commonly utilized, systemically administered, agents. Our interests have focused upon a group of neurotransmitter-like substances, e.g. enkephalergic (morphine), alpha-adrenergic (clonidine), and GABAergic (baclofen) substances. When administered intrathecally (i.t.), these substances markedly depress hyperactive visceralosomatic reflexes (8,55-64), principally due to two factors: 1) ready penetration of the blood brain barrier (BBB) by substances that do not effectively penetrate when administered orally (e.g., morphine, baclofen) (65) and 2) increased sensitivity of spinal cord receptors to intraspinal agents following spinal cord lesions (60,66).

Morphine (MOR) is an opium alkaloid that, when administered epidurally or intrathecally in normal humans, produces profound analgesia and suppresses evoked nociceptive motor reflexes without causing sensory (e.g., discrimination of non-nociceptive stimuli) or motor (e.g., voluntary contraction) deficits (67-71). These actions are purportedly mediated by binding to the µ opiate receptor, located on neurons and/or afferent terminals in segmental and ascending paths in the spinal cord (72,73).

Morphine's potent action on spinal cord circuitry is evident in animals with acute and chronic spinal lesions (74-76), in which systemic morphine markedly suppresses the amplitude of the nociceptive flexor reflex. Similarly, systemic MOR suppresses nociceptive flexor reflexes in patients with chronic spinal lesions (28). Willer and Bussel (28) reported that, among normal subjects and those with chronic spinal lesions, comparable i.v. doses of MOR produce greater suppression of nociceptive flexor reflexes in those with chronic lesions (see also ref. 60).

The action of intraspinal MOR on human spinal spasticity was described by Strupppler et al (64), who demonstrated that reflexes elicited by stimulating flexor reflex afferents were markedly suppressed by epidural MOR. In a broader range of experiments by Herman and his colleagues (8,57,59,60), i.t. MOR (50-400 µg) produced a naloxone-sensitive depression of segmental and intersegmental discharges, occurring spontaneously or elicited by stimulation of cutaneous afferents of the foot. Their results clearly revealed that, in the presence of a chronic spinal lesion, i.t. MOR 1) nonselectively suppresses motor discharges evoked by cutaneous stimulation of the foot; 2) abolishes late flexion reflex activity and increases the motor threshold of the early flexion reflex (13); 3) has greater potency on intersegmental, irradiating reflex reactions than on segmental responses; and 4) markedly suppresses spontaneous motor contractions. While cutaneous evoked reflexes are suppressed for 20-60 hours, the inhibition of spontaneous motor contractions endures for 40-60 hours. In contrast, the resistance of lower limb muscles to passive stretch is not altered, as determined by clinical examination. Unquestionably, i.t. MOR has potent antispasticity action, ameliorating disabling motor discharges which occur spontaneously or following cutaneous stimulation.

References

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