CASE REPORT

Preliminary evidence of safety following administration of L-DOPA and buspirone in an incomplete monoplegic patient

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Study design: Case report.

Objectives: To report a case where a monoplegic patient received L-DOPA and/or buspirone. These compounds, normally used in the treatment of Parkinson's disease and anxiety respectively, were recently shown to induce spinal locomotor network activity and reflex stepping-like movements in animal models of spinal cord injury (SCI). However, the safety of these drugs as potential treatments for Central Pattern Generator (CPG) activation in paralyzed individuals remain unclear.

Setting: St-Jean-Chrysostome, Quebec, Canada.

Method: The acute effects induced by these compounds were qualitatively assessed by the patient, a 38-year-old man who underwent surgery 17 years ago to remove an intracavernous angioma located at the mid-thoracic level (T5–T6) of the spinal cord.

Results: Self-administration every 2 days of L-DOPA (200, 400 and 600 mg, p.o.) and buspirone (5, 10 and 15 mg, p.o.) either separately or combined led to no atypical side effects (that is, occasional sleepiness, nervousness, insomnia or mild headaches). No movement was induced ipsilaterally although some sensations referred to by the patient as an increased blood flow in the lower back and upper leg regions were reported shortly after administration of the combined treatment.

Conclusion: The results show no significant side effects following acute administration of L-DOPA and/or buspirone. This constitutes the first report providing preliminary evidence of safety following administration of these drugs in incompletely paralyzed individuals. The sensations of increased blood flow ipsilaterally with the combined treatment may also suggest that the dose regimen was not optimal or sub-threshold for inducing detectable CPG-mediated leg movements.

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Introduction

As with traumatic spinal cord injuries (SCI), intracavernous angiomas lead generally to an irreversible loss of motor control and sensations below the injured level. Increasing evidence suggests that exercise training can contribute to prevent or reverse many of the secondary health consequences and complications associated with chronic paralysis and immobility.¹ A novel class of drug treatments aimed at promoting exercise training after chronic SCI by re-activating spinal locomotor networks (often referred to as Central Pattern Generator (CPG)) is currently in development.² Families of compounds tested in animals as CPG-activating drugs (for example, L-3,4-dihydroxyphenylalanine (L-DOPA) and 5-HT_{1A/7} agonists such as 8-OH-DPAT or buspirone)

are well-known Food and Drug Administration-approved molecules in the treatment of Parkinson's disease and anxiety, respectively.^{3,4} However, there is no published report of their therapeutic use either separately or combined in paralyzed individuals. It remains, therefore, unclear whether these drugs are safe in this particular population of patients (that is, monoplegic, hemiplegic, paraplegic or tetraplegic individuals).

Methods

We reported observations made by a monoplegic patient, a 38-year-old man diagnosed 17 years ago with an intracavernous angioma located at the thoracic level (T5–T6). The patient underwent surgery to remove the angioma that left him with an incomplete monoplegia on the left side (that is, a near complete loss of sensations and motor control in the left leg with moderate muscle wasting and spasticity). During the first week, the patient was asked to take (self-administration) oral tablets of 5, 10 or 15 mg buspirone hydro-

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chloride (Novo-buspirone, Novopharm, Ontario, Canada) every second day. During the second week, he took oral tablets of 200, 400 or 600 mg L-DOPA (Apo-Levocarb, Apotex, Ontario, Canada) every second day. Finally, he was asked to proceed subsequently with self-administration of both compounds simultaneously (5 mg buspirone + 200 L-DOPA, 10 mg buspirone + 400 mg L-DOPA, 15 mg buspirone + 600 mg L-DOPA) every 48 h. Each session of observation following administration was performed in a seated position or lying down on a bed for 45 min. The patient reported sensations, feelings and involuntary movements that may have occurred during testing.

Results

Following self-administration of either 5, 10 or 15 mg buspirone, the patient reported no particular effect other than mild somnolence during the time period assessed (that is, 45 min post-administration). Following self-administration of either 200, 400 or 600 mg L-DOPA, he reported having once a mild headache at 200 mg. He also noted a reduction of tremor in his ipsilateral leg. No headache was found at 400 or 600 mg although some aggressiveness was reported. Although not systematically assessed, the patient also noticed mild nervousness and insomnia when going to sleep a few hours after buspirone administration. The day after, he reported (approximately 12 h after drug administration) mild stiffness in the ipsilateral leg. Following administration of 5 mg buspirone + 200 mg L-DOPA or 10 mg buspirone and 400 mg L-DOPA, the patient reported increased sleepiness and mild depression-like effects (anti-anxiety-like). Finally, the patient reported having felt some warmth in his lower back and upper leg muscles as if a sudden increase in blood flow occurred ipsilaterally. However, as no movement was induced *per se* with this dose regimen, the patient decided not to proceed with the last dose regimen (15 mg buspirone + 600 mg L-DOPA).

Discussion

The results show no atypical side effects, thus providing the first preliminary evidence of safety for the therapeutic use of

these drugs in incompletely paralyzed individuals. The sensation reported as presumed blood flow increase in the lower back and left leg may be taken as preliminary signs of efficacy. However, the fact that no movement was induced may have been due to CPG neurons and pools of motoneurons that were insufficiently activated to generate movements *per se* in the paralyzed muscles. As administered in an incompletely injured patient, these drugs may have also acted indirectly upon CPG neurons via descending commands from supraspinal centers which may also explain why no leg movement was found (that is, many descending systems inhibit spinal networks). A clear assessment of safety and efficacy will require formal Food and Drug Administration-approved trials (for example, $\geq$ PI/IIa) with more sophisticated measurements and testing conditions to be undertaken. If safety and efficacy were to be demonstrated, such pharmacological approaches may, thus, eventually contribute to the development of a first-in-class therapeutic capable of preventing or reversing immobility-related secondary health complications (for example, cardiovascular problems, type II diabetes, osteoporosis, muscle wasting, immune system deficiency and so on)⁵ by inducing reflex stepping and treadmill training in chronically paralyzed patients.

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