Case Report

Refractory orthostatic hypotension in a patient with a spinal cord injury: Treatment with droxidopa

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Context: Orthostatic hypotension (OH) is a common complication in patients with a spinal cord injury, mainly affecting complete injuries above neurological level T6. It is generally more severe during the acute phase but can remain symptomatic for several years.

Findings: A 65-year-old male with a grade ASIA A post-traumatic cervical spinal cord injury, at neurological level C4, presenting with symptomatic refractory OH. Increased blood pressure (BP) levels and an overall clinical improvement was observed after administering an increasing dose of droxidopa. Treatment was started at a dose of 100 mg twice daily (bid), one to be taken upon rising in the morning and another one in the afternoon, at least three hours before bedtime. According to the patient's symptomatic response, each individual dose was increased by 100 mg at 48-hour intervals. Both increased mean BP levels and a subjective symptomatic improvement were evidenced at a dose of 300 mg bid.

Clinical relevance: Treatment with droxidopa increases BP levels and improves symptoms related to refractory OH using all physical and pharmacological measures available. It could therefore constitute an effective alternative treatment for OH in patients with a spinal cord injury.

Keywords: Orthostatic hypotension, Blood pressure, Droxidopa, Spinal cord injury, Rehabilitation.

Introduction

Orthostatic hypotension (OH) is defined as a decrease in systolic blood pressure (BP) of more than 20 mm Hg or a decrease in diastolic BP of more than 10 mm Hg with upright posture, or head-up tilt to 60 degrees for at least three minutes.¹ It is a common complication in patients with spinal cord injuries, mainly affecting complete lesions above neurological level T6. It is generally more severe during the acute phase but can remain symptomatic for several years.

OH in patients with a spinal cord injury results from the deafferentation of the sympathetic cardiovascular control and from a decrease in the plasma levels of norepinephrine during the postural change.² When switching to a standing position, an excessive accumulation

of blood in the abdominal viscera and lower limbs occurs as a result of the loss of vasoconstriction and the lack of muscle contraction. This consequently causes a drop in the blood volume of the intrathoracic veins, in cardiac output and in BP levels. This outcome is detected by the aortic and carotid baroreceptors, which, in healthy individuals, activate the sympathetic nervous system. However, given that the efferent sympathetic pathway is interrupted in patients with a spinal cord injury, the sympathetic outflow does not increase (epinephrine and norepinephrine) and no tachycardia or vasoconstriction occurs to compensate the decrease in BP levels.

The symptoms of OH are related to a decrease in cerebral blood flow, rather than to absolute BP levels. Usually, these symptoms resolve over time, presenting themselves as compensatory mechanisms: the onset of postural reflexes of the spinal cord, hypersensitivity of the receptors of the vascular wall, spasticity, improved

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autoregulation of the cerebral blood flow in response to the low perfusion pressures and adaptation of the renin-angiotensin system.³ Its associated symptomatology includes dizziness, lethargy, bradypsychia, fatigue and even syncope, interfering with the rehabilitation program and adversely impacting the patient's quality of life.⁴

Therapeutic measures to control OH include the use of compression measures (abdominal binders, elastic stockings in the lower limbs, orthotics, etc.); kinesiotherapy, tilt table, functional electric stimulation; as for pharmacological treatment, the use of sodium chloride tablets, sympathomimetic drugs (midodrine hydrochloride and etilefrine) and mineralocorticoids (fludrocortisone) has proven to be effective for the treatment of symptomatic OH in some patients. Muneta *et al.*⁵ and Wecht *et al.*⁶ evaluated the effects of droxidopa in patients with a spinal cord injury and symptomatic OH. In February 2014, the Food and Drug Administration (FDA) approved droxidopa, a synthetic amino acid acting as a precursor of norepinephrine for the treatment of OH of neurological nature.⁷

The aim of the present report is to describe our experience using droxidopa in a patient with tetraplegia and refractory OH using all therapeutic measures available.

Case description

A 65-year-old male patient who was admitted to the Intensive Care Unit with polytrauma after being involved in a traffic accident. He presented to the hospital with a head trauma, vertebral fractures (C3 and C6), a post-traumatic disk herniation at the C6-C7 level (Figs. 1A and B), an American Spinal Injury Association Impairment Scale ASIA A, a C4 sensory level, a C5 motor level and a 14/100 motor index. A surgical intervention was carried out within the first 24 hours involving decompression and anterior vertebral arthrodesis with osteosynthesis. The patient required prolonged mechanical ventilation, for which a tracheostomy was performed.

Upon sitting, six weeks after the injury, he experienced severe OH associated with dizziness, fatigue, light-headedness, lethargy and episodes of syncope. His mean BP levels were of 80/51 mm Hg and his mean heart rate (HR) was of 83 beats per minute (bpm), with BP levels as low as 55/33 mm Hg being recorded. Standard physical measures for the treatment of OH were initiated (use of a high back reclining wheelchair, elastic stockings in the lower limbs and abdominal binders) along with pharmacological therapy consisting of etilefrine at a daily dose of 5 mg gradually increased to 15 mg, subsequently adding fludrocortisone at a daily

dose of 0.1 mg until reaching a final dose of 0.2 mg. Despite administering all these therapeutic measures, the patient continued experiencing severe symptoms of OH that prevented the slightest progress in his rehabilitation program.

Based on his poor response to the previous treatment, initiation of treatment with droxidopa was requested and its import as a foreign medication was processed through the hospital's Pharmacy Service.

Treatment with droxidopa was started at a daily dose of 100 mg bid, at 6 A.M. and 3 P.M. (3 hours prior to rising in the morning and afternoon), along with etilefrine and fludrocortisone. Comprehensive controls of the patient's BP levels and heart rate were carried out, including measurements in the supine position, with the headboard at a 30° incline, five minutes after lifting the patient and three hours after administering the medication, concurring with the peak of maximum blood concentration of the drug. After 48 hours, the dose was increased to a dose of 200 mg bid. No signs of hypertension were evidenced when the patient remained in a supine position, although he did experience symptomatic episodes of OH in the morning for which he was prescribed a nightly dose of 100 mg of droxidopa, with gradual increases until reaching a total dose of 300 mg three times daily (tid). Treatment with etilefrine and fludrocortisone was discontinued at that moment.

After beginning treatment with droxidopa, the patient's mean BP levels in the supine position were of 90/57 mm Hg and his mean HR was of 65 bpm, thus involving a 10 mm Hg increase in his systolic BP and of 6 mm Hg in his diastolic BP. Furthermore, five minutes after being lifted, his mean BP levels were of 72/49 mmHg and his mean HR was of 75 bpm, involving that his systolic BP had dropped less than 20 mm Hg and his diastolic BP less than 10 mm Hg when switching from a supine position to a sitting one.

At a dose of 300 mg tid of droxidopa, the patient reported an improvement of his fatigue, of his cognitive function and only reported dizziness upon rising on two occasions with rapid resolution. With regard to the medication's potential side effects, he did not experience hypertension in a supine position nor an increased HR.

Finally, given his good symptomatic response, we decided to progressively decrease his nightly dose by 100 mg every 48 hours until discontinuing it completely. By applying this measure and elevating his headboard 30° to sleep, we contributed to reducing his risk of experiencing hypertension while in a supine position. Two months after initiating treatment, the patient was discharged home with a dose of 300 mg bid, one to be

Figure 1 MRI images of the spinal cord at the level of the lesion.

taken in the morning and the other in the afternoon. He continues to remain asymptomatic.

Discussion

Several drugs have been approved for the treatment of OH. Midodrine activates alpha-adrenergic receptors of the arteriolar and venous smooth muscle, causing an increase in vascular tone and BP. There is level 2 evidence that midodrine increases performance during exercise in some individuals with a spinal cord injury, similarly to the case of other populations with autonomous cardiovascular dysfunctions.^{8,9}

Fludrocortisone is a mineralocorticoid that increases sodium release into the bloodstream, thus increasing blood volume. Although several authors have described the use of fludrocortisone to treat OH in patients with a spinal cord injury, there is level 4 evidence that it is not effective for the treatment of OH in patients with a spinal cord injury.¹⁰

Dihydroergotamine and ergotamine are ergot alkaloids that interact with alpha-adrenergic receptors and have vasoconstricting effects. There is level 5 evidence that ergotamine, combined daily with fludrocortisone, can successfully prevent OH.¹¹

Ephedrine is a non-selective agonist of alpha and beta receptors. Its peripheral actions are partially attributed to the release of norepinephrine and partially to its direct effects on the receptors. There is level 5 evidence that ephedrine can reduce symptoms of OH.¹²

Finally, droxidopa (L-treo-3,4-dihydroxyphenylserine) is a synthetic amino acid that converts into norepinephrine, a strong vasoconstrictor, in the presence of aromatic amino acid decarboxylase and pyridoxal phosphate. It has been available in Japan since 1989 for the treatment of neurogenic OH and was approved in the USA as an oral therapy in February 2014. It is indicated

for the treatment of symptomatic neurogenic OH caused by a primary autonomic failure, a beta-hydroxylase deficiency and a non-diabetic autonomic neuropathy in adult patients.¹³ There are several studies that have demonstrated the efficacy of this medication.^{14–17} Droxidopa is the first medication for OH approved for symptomatic improvement and not only for increasing BP levels when in a standing or sitting position. Evidence on the usefulness of this drug in patients with a spinal cord injury was documented in two published studies. In 1992, Muneta *et al.*⁴ published a clinical case of a patient with a non-traumatic spinal cord injury in which the use of droxidopa with concomitant sodium supplements significantly reduced episodes of syncope and drowsiness associated with OH. Furthermore, in 2013, Wecht *et al.*⁵ carried out a study with 10 patients and found that the use of greater doses of droxidopa (100 mg, 200 mg and 400 mg) in hypotense patients did not cause an excessive increase in BP levels when they were in a supine position. Additionally, they concluded that a dose of 400 mg of droxidopa was effective in increasing BP levels for up to 3 hours when patients remained in a sitting position. The expected drop in BP levels after adopting an orthostatic position was prevented with a dose of 200 and 400 mg. This trial consisted in a level 4 evidence study, for which its results prove that droxidopa is a safe and moderately effective drug for the treatment of OH.

With regard to the treatment of patients with OH, our standard protocol involves the use of conservative measures such as compression stockings, abdominal binders, kinesiotherapy, repeated postural changes on a tilt table and, in some cases, functional electric stimulation. When these measures prove to be ineffective, we begin pharmacological treatment with midodrine, etilefrine and fludrocortisone. Generally, OH is a

complication which tends to resolve during its acute phase by applying standard measures; however, our patient's symptomatology persisted and consequently prevented the rehabilitation program, for which we decided to initiate treatment with a new drug, droxidopa. The prescribed doses were chosen on the basis of the results of previous studies which recommended beginning treatment orally at a dose of 100 mg tid, increasing the dose by 100 mg during each intake, with an interval of at least 24–48 hours having elapsed since the previous modification, until reaching a maximum total dose of 600 mg tid.^{13,18} It is also recommended that the last dose be administered at least 3 hours prior to the patient's bedtime in order to avoid the onset of hypertension while in a supine position.^{13,19,20}

Conclusions

In conclusion, although we did not observe a significant increase in our patient's BP levels, he did report a subjective improvement of his symptoms and he did not experience adverse reactions; therefore, we consider that the treatment was successful. Hence, we believe that droxidopa can be an effective treatment alternative in patients with OH refractory to treatment with standard physical and pharmacological measures after the acute phase of the trauma.

It is possible that not all patients will respond to this treatment and that the doses must be individualized as in the case of all therapies in this patient population. Furthermore, additional long-term studies with a greater number of patients must be carried out in order to determine the persistence of these effects during its chronic use and, in the case of achieving adequate control of the BP levels and an absence of symptoms related to OH, when to discontinue the treatment.

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