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Case Report

Midodrine hydrochloride and the treatment of orthostatic hypotension in tetraplegia: two cases and a review of the literature

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Study Design: A report of two cases of orthostatic hypotension in acute tetraplegia that were resistant to classic treatment interventions.
Objective: To discuss the use of midodrine hydrochloride for the treatment of orthostatic hypotension in early tetraplegia.
Setting: Department of Rehabilitation Medicine, The University of Texas Health Science Center at San Antonio, Texas, USA.
Methods: Presentation of two cases.
Results: Midodrine hydrochloride successfully treated two cases of orthostatic hypotension that had been refractory to classic treatment interventions.
Conclusion: Midodrine hydrochloride should be included in the armamentarium of the physician treating orthostatic hypotension in spinal cord injury.
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Keywords: midodrine hydrochloride; orthostatic hypotension; spinal cord injury

Introduction

Three related pathophysiologic phenomena occur in patients who suffer spinal cord injury (SCI) resulting in tetraplegia: reduced sympathetic nervous system outflow, peripheral α-adrenergic receptor hyperresponsiveness, and loss of supraspinal control of sympathetic nervous system activity, especially in complete injuries.[1] Orthostatic hypotension (OH), a consequence of reduced sympathetic nervous system outflow and loss of supraspinal control, is a common phenomenon experienced by patients with early tetraplegia. Guttman[2] in tilt stable studies, noted that patients with new spinal cord injuries with lesions above T5 experienced a rapid and steep fall in blood pressure, a rise in pulse rate, and syncope in a few seconds or minutes after a postural change from the horizontal to the vertical. Guttman attributed these constellation of symptoms to a vascular maladaption to the postural change due to an interruption of sympathetic splanchnic control. As a result of reduced sympathetic nervous system outflow to the splanchnic vascular bed as well as lower extremity blood vessels, peripheral α-adrenergic receptors in the sympathetically 'denervated' blood vessels are believed to become hyperresponsive.[1]

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Guttman's recommendations for the treatment of OH, including progressive mobilization from supine to vertical, the use of abdominal binders, and ephedrine, continue to be advocated today as first-line therapies. However, in some patients orthostatic symptoms persist despite these interventions. In an attempt to take advantage of the hyperresponsiveness of the 'denervated' α-adrenergic receptors in the vasculature below the level of injury, we have prescribed midodrine hydrochloride, a relatively new α_1-adrenergic agonist, to treat OH in early tetraplegia.

Case reports

Case 1
The patient, a 44-year-old white male with benign past medical history, was admitted for comprehensive inpatient rehabilitation 22 days after a motor vehicle accident, out of spinal shock, and functioning neurologically as a C6 ASIA B anterior cord syndrome. Despite the use of antiembolic hose, an abdominal binder, and progressive mobilization from supine to sitting with both tilt table and reclining wheelchair with elevating legrests, the patient experienced symptomatic OH with blood pressures that were repeatedly noted to be approximately 90–100/80 while

supine and 75–80/50 at 45°. The orthostasis significantly limited the amount of time that the patient was spending in therapy. A trial of fludrocortisone acetate 0.1 mg by mouth (po) daily (qd) was initiated. The fludrocortisone acetate was discontinued after 7 days when the patient began experiencing pitting edema of his hands and lower extremities that was temporally related to the initiation of the medication. The patient was subsequently begun on a trial of midodrine hydrochloride 10 mg po thrice daily (tid). By the third day of midodrine usage, the patient's orthostatic symptoms had resolved. Blood pressures taken 1 h after drug consistently ran approximately 145–150/90–95 while supine and 100–115/70–75 while sitting at 90°. The patient was able to complete his inpatient rehabilitation program and was discharged to home with continued outpatient therapy. At 4 months after injury, the patient continues to require midodrine to support his blood pressure.

Case 2

The patient, a 55-year-old white male with past medical history of anxiety disorder, was admitted for comprehensive inpatient rehabilitation 21 days after a motor vehicle accident, no longer in spinal shock, and functioning neurologically as a C5 ASIA A anterior cord syndrome. Again, despite the use of antiembolic hose, an abdominal binder, and progressive mobilization with a reclining wheelchair with elevating legrests, the patient experienced symptomatic OH with blood pressures that were consistently noted to be 100/70–80 while supine and 70–80/50 when at 75°. The patient was prescribed fludrocortisone acetate 0.1 mg po qd. The dosage was increased to 0.1 mg po twice daily (bid) at which time he developed pitting edema in his lower extremities and increasing episodes of autonomic dysreflexia associated with increased urine volumes. The fludrocortisone acetate was discontinued with a resolution of his fluid retention related symptoms. Midodrine hydrochloride was prescribed at a dosage of 10 mg po tid. The patient's orthostatic symptoms resolved. Blood pressures 1 h after drug were noted to consistently range from 140–150/90 when supine and 100–110/80 while sitting at 90°. At 4 months after injury, the patient has discontinued the antiembolic hose and abdominal binder but continues to require midodrine hydrochloride without significant orthostatic symptoms.

Discussion

The exact incidence and prevalence of OH in early tetraplegia is not known. The pathophysiology of OH after SCI results from the interruption of efferent sympathetic pathways arising from brainstem vasomotor centers (medulla and pons).[3] With injuries between T1 and T4, the supraspinal sympathetic splanchnic influence is lost. However, sympathetic efferents to the heart remain, allowing for an increase in heart rate and contractility in response to decreasing blood pressure. With cervical injuries, however, all sympathetic control is lost. The inability to vasoconstrict the vascular beds in the viscera and extremities leads to the pooling of blood with resultant impaired venous return and low cardiac output. The combination of decreased peripheral vascular resistance and low cardiac output results in OH.

Typically, orthostatic symptoms resolve as autonomic spinal reflexes return and spasticity develops. Until that time, however, OH may be distressing to the patient and limit the acute rehabilitative process. Classically, nonpharmacologic interventions are undertaken first. These usually include the use of a tilt table and/or tilt/reclining wheelchair with elevating legrests for progressive mobilization from supine to vertical, and the use of compressive garments such as elastic stockings and abdominal binders. If these interventions fail, pharmacologic therapy is warranted. Salt loading with concomitant hydration may be undertaken but care should be taken to minimize the risk of bladder distention and autonomic dysreflexia. Ephedrine and pseudoephedrine, sympathomimetic amines, display both α- and β-receptor activity resulting in vasoconstriction of the vascular bed as well as an increase in heart rate and myocardial contractility.[4] Caution must be maintained when prescribing these in patients with a history of hypertension, coronary artery disease, congestive heart failure, and diabetes. Naso[5] recommends ephedrine be trialed at dosages of 20–30 mg po qd to four times daily (qid). Blackmer[6] has found pseudoephedrine to be efficacious at dosages of 30 mg po bid to 60 mg po tid. We, however, have not found the sympathomimetic amines to be particularly efficacious in treating OH in our clinical practice. Thus, as in the two cases presented, we do not routinely prescribe them. For those patients that do not respond favorably to sympathomimetic amines, adrenal mineralocorticoid steroids such as fludrocortisone acetate are typically the next line of pharmacologic therapy. The mineralocorticoid effect of fludrocortisone acetate at the renal distal tubule results in reabsorption of sodium with a concomitant increase in intravascular volume and, theoretically, an increase in venous return and cardiac output.[7] As a result of its fluid retaining mechanism of action, fludrocortisone acetate may predispose the patient with tetraplegia to autonomic dysreflexia. As with sympathomimetic agents, care should be taken when prescribing mineralocorticoids in persons with a history of hypertension, congestive heart failure, and coronary artery disease. As well, because potassium and hydrogen are wasted in the process of retaining sodium, signs and symptoms of hypokalemia and metabolic alkalosis should be monitored. The dosage of fludrocortisone acetate should not exceed 0.4 mg po qd when attempting to treat OH.

Midodrine hydrochloride has only rarely been described in the treatment of OH in SCI.[6,8] Midodrine hydrochloride is a prodrug whose thera-

peutic effect is due to its major metabolite desglymidodrine, an α_1-agonist.[9,10] Desglymidodrine exerts its sympathomimetic effect via activation of α-adrenergic receptors in the vasculature resulting in an increase in venous return and blood pressure. Desglymidodrine diffuses poorly across the blood-brain barrier, and, therefore, has negligible effects on the central nervous system. Midodrine hydrochloride is rapidly absorbed after oral administration with peak serum levels occurring in approximately 30 min. Desglymidodrine reaches peak blood concentrations at approximately 1–2 h after a dose of midodrine hydrochloride. Midodrine hydrochloride results in a rise of standing, sitting, and supine systolic and diastolic pressures in patients with OH of various etiologies. Systolic blood pressure may be elevated by 15–30 mmHg or more 1 h after a 10 mg dose, with some effect persisting for at least 2–3 h. The most serious side effect that can be seen with midodrine hydrochloride is marked elevation in supine blood pressure (>200 mgHg of systolic pressure). For that reason and given its onset of action, it is recommended that midodrine hydrochloride be given during daytime hours, approximately 1 h before the patient is to arise, and not closer than 4 h before bedtime. Patients should be advised of symptoms of supine hypertension (eg, cardiac awareness, pounding in the ears, headache, blurred vision). If supine hypertension occurs, the dosage of midodrine hydrochloride may be reduced; sleeping with the head of the bed elevated may relieve supine hypertension in some patients. As with other sympathomimetic agents, care should be taken when prescribing midodrine hydrochloride in persons with hypertension, congestive heart failure, and coronary artery disease. Close monitoring should occur when prescribing midodrine hydrochloride with vasoactive agents and agents that cause bradycardia because midodrine may result in an exaggerated response. The manufacturer's recommended dose for midodrine hydrochloride is 10 po tid with doses taken at least 3 h apart. However, some clinicians recommend an initial dose of 2.5 mg po bid-tid, increasing the dosage by 2.5 mg po bid-tid at approximately weekly intervals until the orthostatic symptoms have abated. Naso recommends that a gradual attempt to withdraw medications used to treat OH be attempted at 2–3 months after SCI, when spinal reflexes have returned and spasticity has developed.

We believe that the use of midodrine hydrochloride should be entertained in those patients whose orthostatic symptoms are refractory to first-line therapies and experience side effects with other pharmacologic interventions.

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