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ORIGINAL ARTICLE

Hemodynamic Effects of L-Threo-3,4-Dihydroxyphenylserine (Droxidopa) in Hypotensive Individuals With Spinal Cord Injury

Jill M. Wecht, EdD,[a,b,c,d] Dwindally Rosado-Rivera, EdD,[a] Joseph P. Weir, PhD,[e] Adrian Ivan, MS,[a] Christina Yen, BS,[a] William A. Bauman, MD[a,b,c,d]

From the [a]Center of Excellence and [b]Medical Service, James J. Peters Veterans Affairs Medical Center, Bronx, NY; Departments of [c]Medicine and [d]Rehabilitation Medicine, The Mount Sinai School of Medicine, New York, NY; and [e]Department of Health sport and Exercise Sciences, The University of Kansas, Lawrence, KS.

Abstract

Objectives: To determine the effect of an escalating dose of droxidopa (100, 200, and 400mg) compared with placebo on seated blood pressure (BP) in hypotensive individuals with spinal cord injury (SCI). Secondarily, we aimed to determine the effect of droxidopa on (1) supine BP and heart rate, (2) the change in BP and heart rate when these individuals were transferred from the supine to the seated position, and (3) adverse event (AE) reporting.

Design: Open-label dose titration trial.

Setting: A Veterans Administration Medical Center.

Participants: Participants with SCI (C3-T12) (N = 10) were studied during 4 laboratory visits. Subjects visited the laboratory for about 5 hours on each visit, which incorporated a 30-minute seated baseline, a 30- to 60-minute supine, and a 4-hour seated postdrug observation.

Interventions: Placebo on visit 1, droxidopa 100mg on visit 2, droxidopa 200mg on visit 3, and droxidopa 400mg on visit 4.

Main Outcome Measures: BP and heart rate changes from baseline to the postdrug period, orthostatic heart rate and BP responses, and subjective AE reporting.

Results: Seated BP was significantly elevated with 400mg droxidopa compared with placebo and 100mg droxidopa for 3 hours and was elevated for 2 hours compared with 200mg droxidopa. Increase in supine BP was not worsened following droxidopa, and the expected fall in BP when transferred to the seated position was prevented with droxidopa 200 and 400mg. There were no significant differences in the heart rate response or AE reporting among the study visits.

Conclusions: Our preliminary findings suggest that droxidopa, at the doses tested, does not cause excessive increases in supine BP and the 400-mg dose appears to be effective at increasing seated BP for up to 3 hours in persons with SCI.

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In addition to motor and sensory deficits, partial or complete interruption of autonomic cardiovascular innervation is reported in persons with spinal cord injury (SCI).[1,2] The prevailing thought is that blood pressure (BP) disorders result from decentralized sympathetic neural cardiovascular control and significantly reduced plasma norepinephrine (NE) levels are reported at rest and during orthostasis.[3-6] As a consequence of impaired sympathetic cardiovascular control, individuals with tetraplegia are prone to chronic hypotension and orthostatic hypotension (OH).[1,7-10] The prevalence of hypotension in veterans with SCI was reported as 16%[11]; however, we recently documented an incidence of 35% in individuals with tetraplegia and 27% in those with high thoracic lesions (T1-T6).[12] Although many individuals with SCI remain clinically asymptomatic, chronic hypotension and OH hinder the rehabilitation process during the acute and subacute phases of SCI,[7,13-15] and may hamper resumption of independence and functional activities in persons with chronic SCI.[1,14] Furthermore, analogous to findings in the general population,[16-20] we reported significantly reduced memory and marginally reduced attention/processing speed and executive function in asymptomatic hypotensive individuals with chronic SCI compared to their normotensive counterparts.[21] Thus, chronic

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hypotension and OH might be expected to significantly limit the quality of life in individuals with SCI, and safe and effective treatment options should be considered.

L-Threo-3, 4-dihydroxyphenylserine (droxidopa) is a synthetic amino acid that undergoes conversion to the potent vasoconstrictor NE in the presence of aromatic-amino-acid decarboxylase and pyridoxal phosphate. In models of autonomic failure, droxidopa has been shown to increase and normalize plasma concentrations of NE and systemic BP.[22,23] The pressor effect of droxidopa has been documented in models of autonomic nervous system dysfunction, including those characterized by loss of peripheral sympathetic nerve terminals (pure autonomic failure [PAF]) and those characterized by more central autonomic deficits with preserved peripheral autonomic neurons (multiple system atrophy [MSA], parkinsonism, and cerebella dysfunction).[22-25] Because droxidopa appears to be effective at increasing BP in models of both peripheral and central dysfunction, it is theorized that conversion of droxidopa to NE occurs predominantly in nonneuronal tissues.[26,27] Moreover, although the magnitude of the relation between plasma levels of droxidopa and plasma levels of NE was 5-fold greater in those with MSA compared to those with PAF, the slope of this relation was comparable, confirming the likelihood of nonneuronal conversion to and storage of NE.[26] The concept of a nonneuronal release of NE holds substantial intrigue for use of droxidopa to treat hypotension and OH in the SCI population because decentralized autonomic cardiovascular control results in markedly reduced plasma levels of NE and the absence of coordinated release with orthostatic provocation.[6] Supportive evidence on the utility of droxidopa to treat hypotension in the SCI population was documented in a case report in which plasma NE was increased and the fall in BP reduced during sitting in an individual with T4 paraplegia.[28]

The primary objective of this investigation was to determine the effect of an escalating dose of droxidopa (100, 200, and 400mg) compared with placebo on seated BP in hypotensive individuals with SCI. We hypothesized that seated BP would be increased in a dose-dependent manner following droxidopa administration in individuals with SCI. Secondarily, we aimed to determine the effect of droxidopa on (1) supine BP and heart rate, (2) the change in BP and heart rate when these individuals were transferred from the supine to the seated position, and (3) adverse event reporting. Our secondary hypotheses were, compared with placebo, that droxidopa would, in a dose-dependent manner, (1) increase supine BP and reduce supine heart rate, (2) reduce the orthostatic fall in BP and the orthostatic elevation in heart rate, and (3) that the adverse event reporting would not differ among study visits.

List of abbreviations:

BL	**baseline**
BP	**blood pressure**
DBP	**diastolic blood pressure**
MSA	**multiple system atrophy**
NE	**norepinephrine**
OH	**orthostatic hypotension**
PAF	**pure autonomic failure**
SBP	**systolic blood pressure**
SCI	**spinal cord injury**
WHO	**World Health Organization**

Methods

Subjects

Eleven subjects with chronic SCI volunteered to participate; 1 subject did not complete all testing days because of prolonged infection; therefore, data are reported in 10 subjects. No study subject had a history of cardiovascular disease, none were prescribed medications with known cardiovascular or autonomic effects, and none were current smokers. All study participants were neurologically stable. There were 2 female participants; 8 had tetraplegia (C3-7), 1 had high thoracic paraplegia (T4), and 1 had low thoracic (T10) paraplegia. Half of the study population was motor and sensory complete according to their American Spinal Injury Association Impairment Scale classification. The study protocol was approved by the local Institutional Review Board with strict adherence to the standards established in the Helsinki Declaration. Subjects were recruited through word of mouth from the National Center of Excellence for the Medical Consequences of Spinal Cord Injury database, which is located at the James J. Peters Veterans Affairs Medical Center, Bronx, NY. Written informed consent was obtained by a trained research coordinator designated by the investigators prior to performing the study procedures.

Study procedures

All subjects underwent 4 separate but identical days of testing: visit 1, placebo; visit 2, 100mg droxidopa; visit 3, 200mg droxidopa; and visit 4, 400mg droxidopa. These doses were selected for use in the study on the basis of prior reports in which the optimal dose was reported as 200 to 2000mg/d 3 times a day in models of autonomic impairment.[22] On arrival at the laboratory, subjects remained in their wheelchair for instrumentation and a 30-minute baseline (BL) data collection period. Three electrocardiogram electrodes were applied to the chest for continuous heart rate monitoring (IVY 101NR[a]); electrodes were placed at the distal right and left clavicle, and the recording electrode was placed in the left lateral fifth intercostal space (V-5) using standard skin-abrading and hair-shaving methods, as needed. Brachial BP was measured using a standard adult BP cuff placed around the left upper arm.[b] BL data were collected for heart rate and BP at 10-minute intervals (0, 10, and 20min). After completion of the seated BL observation, subjects were transferred to the supine position for 30 to 60 minutes; differences in the length of time allotted for the supine observations were due to a protocol change made after data collection was complete in 4 subjects, which allowed us to determine the effects of droxidopa on supine hemodynamics for an additional 40 minutes postdrug. During the supine observation, heart rate and BP data were collected at 10- to 20-minute intervals and placebo/droxidopa was administered 20 minutes into the supine observation period. Because of the protocol change, transfer back to the seated position occurred 20 minutes postdrug in 4 subjects and 60 minutes postdrug in 6 subjects. Subjects remained in their wheelchair in the laboratory for an additional 4-hour observation period, during which heart rate and BP data were collected at 30-minute intervals. During the 4-hour observation period, subjects were able to watch a movie or read a book. Droxidopa was supplied for this investigation by Chelsea Therapeutics, Inc. Pharmacokinetic data suggest that plasma droxidopa levels peak approximately 3 hours after