Midodrine as a countermeasure for post-spaceflight orthostatic hypote n

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ABSTRACT

One possible mechanism for post-spaceflight orthostatic hypotension, which affects approximately 30% of astronauts after short duration shuttle missions, is inadequate norepinephrine release during upright posture. We performed a two phased study to determine the effectiveness of an α1-adrenergic agonist, midodrine, as a countermeasure to post-spaceflight orthostatic hypotension. The first phase of the study examined the landing day orthostatic responses of six veteran astronauts after oral midodrine (10 mg) administered on the ground within approximately two hours of wheel stop. One female crewmember exhibited orthostatic hypotension in a previous flight but not after midodrine. Five male crewmembers, who did not exhibit orthostatic hypotension during previous flights, also did not show signs of orthostatic hypotension after midodrine. Additionally, phase one showed that midodrine did not cause *hypertension* in these crewmembers. In the second phase of this study, midodrine is ingested inflight (near time of ignition, TIG) and orthostatic responses are determined immediately upon landing via an 80° head-up tilt test performed on the crew transport vehicle (CTV). Four of ten crewmembers have completed phase two of this study. Two crewmembers completed the landing day tilt tests, while two tests were ended early due to presyncopal symptoms. All subjects had decreased landing day stroke volumes and increased heart rates compared to preflight. Midodrine appears to have increased total peripheral resistance in one crewmember who was able to complete the landing day tilt test. The effectiveness of midodrine as a countermeasure to immediate post-spaceflight orthostatic hypotension has yet to be determined; interpretation is made more difficult due to low subject number and the lack of control subjects on the CTV.

INTRODUCTION

- Many astronauts experience orthostatic hypotension and presyncope upon return to Earth.
- A number of physical and pharmacological countermeasures have been tried to counteract these problems, unfortunately none have been entirely successful.
- We recently identified a contributory mechanism for post-spaceflight orthostatic hypotension: Presyncopal astronauts had smaller pressor responses to phenylephrine, and did not release sufficient norepinephrine during postflight tilt tests to maintain standing blood pressure.
- Enhancement of adrenergic response with an alpha-1 adrenergic agonist (midodrine) might prevent orthostatic intolerance.

HYPOTHESIS

Midodrine will reduce the incidence of orthostatic hypotension on landing day without significant side effects.

Midodrine was chosen as an investigational countermeasure because:

- It acts in place of norepinephrine on the blood vessels.
- It does not stimulate the central nervous system.
- It does not stimulate the heart directly.
- Its peak effect is at one hour, so it can be taken at Time of Ignition (TIG).

METHODS

Midodrine Tolerance Test
Three months prior to flight, a single 10 mg dose of midodrine was administered orally and the subject was monitored every 15 minutes for brachial artery pressure and heart rate as they went about their normal activities for 4 hours.

Preflight tilt test
Orthostatic responses were determined ten days before flight (L-10). Blood pressure, EKG and stroke volume were acquired during five minutes of supine posture followed by up to ten minutes of 80° head-up tilt. Cardiac output, heart rate and total peripheral resistance were calculated offline.

Phase I
Six veteran astronauts ingested 10 mg midodrine approximately two hours after landing. One hour after this, orthostatic responses were determined using the exact same protocol as L-10.

Phase II
Ten healthy astronauts (7 short duration and 3 long duration) were recruited to take 10 mg of midodrine inflight (near TIG) before reentry. Orthostatic responses, similar to those on L-10, were measured immediately upon landing in the CTV.

Figure 1: Crew Transport Vehicle (CTV) at Kennedy Space Center (above) and Tilt Test on CTV (left).

RESULTS

PHASE I

- A single, 10 mg oral dose of midodrine did not cause any untoward hemodynamic effects on landing day in five male, non-presyncopal subjects, and prevented presyncope in one female subject.

PHASE II

- Four of ten subjects completed to date. One subject withdrew due to unpleasant side effects during tolerance test.
- Two subjects developed presyncopal symptoms on landing day.
- Although two subjects were presyncopal, hemodynamic responses onboard the CTV after midodrine was ingested inflight were similar to those from Phase I.
- Results are confounded by poorly controlled environmental variables on the CTV (temperature, motion, sound, etc).

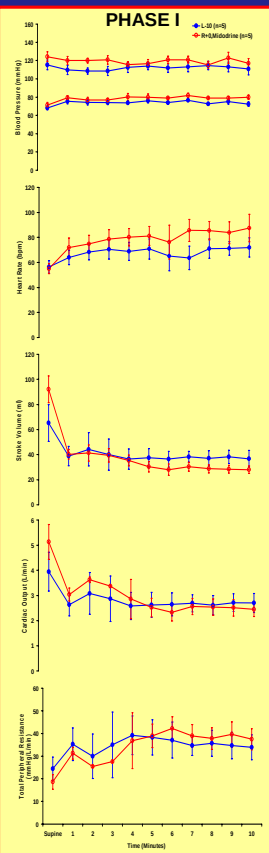
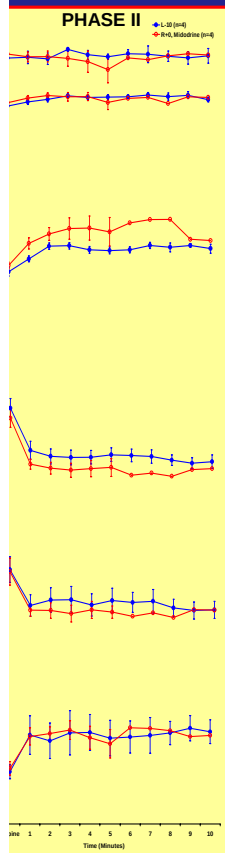


Figure 2: Hemodynamic responses to midodrine testing occurred approximately one hour after m landing, Phase I (left) and at TIG during Phase



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CONC S

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