Midodrine as a countermeasure for post-spaceflight orthostatic hypotension

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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 an inadequate norepinephrine release during upright posture. This two-phase study was designed 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 ingestion of 10 mg midodrine administered on the ground to examine the effectiveness of midodrine as a possible treatment for orthostatic hypotension. The second phase of this study was performed on landing day to determine the effectiveness of midodrine in preventing presyncope in two of the six astronauts who were presyncopal after oral midodrine ingestion. The effectiveness of midodrine as a countermeasure to immediate post-flight orthostatic hypotension has yet to be determined; interpretation is 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 α1-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 Time of Ignition, TIG) before reentry. Orthostatic testing occurred approximately one hour after midodrine ingestion. Midodrine given 2 hours after landing, Phase I (left) and at TIG during Phase II (right).

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 presyncope 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).

CONCLUSIONS
• Midodrine had no untoward landing day effects on crewmembers that were not susceptible to post-spaceflight orthostatic hypotension.
• Although two crewmembers developed presyncopal symptoms during landing day tilt tests, hemodynamic responses to orthostatic stress appear to be similar whether midodrine was ingested on the ground or in orbit.
• The effectiveness of midodrine as a countermeasure to immediate post-spaceflight orthostatic hypotension has yet to be determined; interpretation is difficult due to low subject number and lack of control subjects on the CTV.

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

Figure 2: Hemodynamic responses to midodrine ingestion before and after spaceflight. Orthostatic testing occurred approximately one hour after midodrine ingestion. Midodrine given 2 hours after landing, Phase I (left) and at TIG during Phase II (right).