Hemodynamic effects of midodrine after space flight in astronauts without orthostatic hypotension

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Abstract

Introduction

Orthostatic hypotension and presyncope are common and potentially serious risks for astronauts returning from space. Susceptible subjects fail to generate an adequate adrenergic response to upright posture. The α-1 adrenergic agonist, midodrine, may be an effective countermeasure. We tested the hypothesis that midodrine would have no negative hemodynamic effect on healthy astronauts returning from space.

Methods

Five male astronauts participated in preflight and postflight tilt testing on a control flight as well as on the test flights, where midodrine (10 mg, orally) was administered after landing, ~1 hour before testing.

Results

None of these astronauts exhibited orthostatic hypotension or presyncope before or after either flight. Midodrine did not cause any untoward reactions in these subjects before or after flight, in fact a modest beneficial effect was seen on postflight tachycardia (p =0.036).

Discussion

These data show that midodrine protected against post-spaceflight increases in heart rate, without having any adverse hemodynamic effects on non-presyncopal, male astronauts. Among these subjects, midodrine was a safe cardiovascular countermeasure.

Introduction

Orthostatic intolerance affects virtually every astronaut upon their return to earth. In roughly 80 % of crew members, this manifests as a standing heart rate that is significantly elevated over preflight levels. In about 20% of Shuttle astronauts symptoms of orthostatic intolerance result in orthostatic hypotension (absolute standing systolic pressure < 70 mmHg)) and presyncope (light headedness, dizziness or nausea sufficient to terminate test) during postflight tilt tests (14). Presyncopal subjects also experience lower resistance, lower systolic and diastolic pressure and higher heart rates on landing day than their non-presyncopal counterparts (14,15,22). All astronauts who do not experience presyncope generate a hyperadrenergic response (increased plasma norepinephrine) to tilt testing on landing day, while the astronauts who become presyncopal do not (7,15). These findings led us to hypothesize that post-spaceflight orthostatic hypotension could be ameliorated with an α-1 adrenergic agonist to act in place of the norepinephrine, close to or after landing.

Midodrine is an α-1 adrenergic agonist that is used clinically to treat orthostatic hypotension. There are a number of reports showing its usefulness in treating hypotensive disorders including; exercise-induced hypotension (20), dialysis-induced hypotension (11,18), autonomic failure (9,16), and neurally mediated syncope (2,10). We proposed that midodrine would also be effective in treating, or preventing, post-spaceflight orthostatic hypotension. According to the package insert, the most common side effects of midodrine include parathesia (18.3%), piloerection (13.4%), dysuria (13.4%), pruritis (12.2 %) and supine hypertension (7.3%). Countermeasures in our unique situation will be given in a remote setting, the final hour of spaceflight, without

the possibility of direct intervention if some adverse side effect or interaction occurs. Thus spaceflight-based countermeasures must correct a symptom in the target group, without creating new symptoms in the target or non-target group. If midodrine is to become a prophylactic countermeasure it has to be safe for use in all crewmembers, including rookies, thus it must prevent postflight orthostatic hypotension in susceptible astronauts without causing hypertension (increased systolic BP > 30 mmHg) in non-susceptible astronauts. Accordingly, it must be tested in both of those groups. Here we hypothesize that oral administration of midodrine (10 mg) will not cause a significant increase in arterial pressure.

We have previously reported that midodrine, taken 1 hour before the tilt test on landing day, prevented orthostatic hypotension in an astronaut who had been susceptible on a prior flight (17). We now report results from five astronauts who volunteered for this study but had not been susceptible to orthostatic hypotension or presyncope following their previous space flights. Comparisons were made between the hemodynamic responses during tilt/stand testing following flights with and without midodrine.

Methods

This study included both retrospective and prospective aspects. Retrospectively, we used data from tilt or stand tests that had been performed on astronauts as a part of an earlier research protocol or as part of a test performed for medical operations. From those results, astronauts were identified who had completed landing day tilt tests without symptoms of hypotension or presyncope. Then, as those crew members were assigned to upcoming flights, we asked them to take midodrine on landing day as the prospective part

of the study. Thus tilt/stand test data from the prior flights (control flight) were compared with tilt test data from the new flights (midodrine flight).

Subjects

We identified astronauts who had previously flown in space and for whom we had tilt test data, and thus knew if they were susceptible to postflight orthostatic hypotension and presyncope. From this group, five veteran, male astronauts volunteered to participate in our study. This approach was appropriate because postflight tilt test outcomes are highly reproducible from flight to flight (12). All subjects gave written, informed consent to participate in this protocol, which was approved by the Johnson Space Center Committee for the Protection of Human Subjects.

Subjects returned to earth in the seated position following short duration space flights averaging 11.86 ± 0.81 days. Upon arrival, astronauts were assisted off the orbiter and onto the crew transport vehicle where they were de-suited. Crew members were then transported back to the data collection facility. During transport crew members were ambulatory and were allowed to consume water *ad libitum*. Midodrine was given as soon as the crew members arrived at the data collection facility (about 2 hours after landing). Post-flight activities were similar for all flights.

There were no changes in either arterial pressure or heart rate during the midodrine tolerance tests. The time between the 1st flight (control flight) and the 2nd flight (midodrine flight) was 53.8 ± 10.7 months. Median flight duration for the midodrine flights was 10.3 days while the median for the control flights was 12.8 days. While height and weight did not vary between flights, BMI's were significantly higher following the midodrine flight (24.22 ± 1.52 vs 26.42 ± 1.7, $p \leq 0.05$) as was age ($45.62 \pm$

1.3 vs 50.2 ± 1.42 years p ≤0.05) . Other than mild piloerection, no side effects associated with midodrine were observed in the course of this study.

Midodrine tolerance

When midodrine is administered orally, the peak plasma concentration of the active metabolite (deglymidodrine) occurs between 60 and 90 minutes with a half life of between 2-4 hours (8,23). There is minimal effect of a single dose of midodrine on normal, healthy individuals, although a slight increase in systolic blood pressure is sometimes seen (8,23). About three months before flight the astronauts came to the laboratory for a midodrine tolerance test. **Although midodrine has not been directly linked to cardiac dysrhythmias, midodrine, along with other adrenergic agonists, is listed by the Arizona Center for Education and Research on Therapeutics as potentially causing a risk of ventricular dysrrhythmias (e.g. Torsades de Pointes) in subjects with a prolonged Q-T$_c$ interval (>0.46 seconds)(1,21).** Thus, **as a precaution**, a 12-lead ECG was taken and the Q-T$_c$ interval was measured. If it was < 0.46 seconds, a single 10 mg dose of midodrine was administered orally and the subjects were monitored every 15 minutes for brachial artery blood pressure and heart rate, while they went about their normal activities for 4 hours. Subjects were also monitored for side effects due to midodrine. No subjects were excluded from this study due to Q-Tc interval or any adverse reaction to midodrine.

Protocol

Tilt/stand tests were performed ten days before flight and about 3 hours after landing. During a 5 minute supine rest period, ECG, finger blood pressure (beat-to-beat), brachial artery blood pressure (every minute) and stroke volume (Doppler ultrasound of

ascending aorta) were measured. Then the subjects were moved to the upright posture by one of two methods: following the control flight, three subjects had their shoulders lifted off the bed, while their feet were swept off the bed by investigators (stand test), The remaining two subjects had tilt tests done after the control flight where an automatic tilt table was used to tilt the subjects passively to 80º for 10 minutes, during which all measurements continued. All subjects underwent tilt testing before and after the midodrine flight. Previous published work from this laboratory has shown that the stand tests and tilt tests elicit orthostatic hypotension and presyncope at statistically indistinguishable rates (14).

Every attempt was made to match protocols between the control and midodrine flights. For all flights, the astronauts performed the standard oral fluid load (equivalent to isotonic saline at 15 ml/kg within 2 hours) prior to landing, and had their anti-gravity suits fully inflated (1.5 psi). The subjects abstained from caffeine, alcohol, and medications for 12 hours before the test session; were at least 2 hours postprandial; and had not exercised maximally 24 hours before testing. The main differences in protocols between the control and midodrine flights were as follows. After the control flights, no pharmacological countermeasures were used; after the midodrine flights a single 10 mg dose of midodrine was given following landing, and ~1 hour before the tilt test was performed. Because there is some evidence that space flight can effect Q-Tc interval (5), a conservative approach was taken and after the midodrine flights, an additional 12-lead ECG was performed before midodrine administration to verify that the Q-T$_c$ interval was < 0.46 seconds. A catheter was inserted into an antecubital vein for blood collection. Blood was collected for a baseline measure and then every 15 minutes to measure the

concentration of midodrine and de-glymidodrine, the active metabolite (Bioassay Laboratory, Inc. Houston, TX). The subjects were placed supine on the table and the tilt/stand test was performed so that they were tilted as close to 1 hour after midodrine ingestion as possible .

Analysis and statistics

Stroke volumes were obtained by measuring the aortic blood flow with Doppler ultrasound after the method of Childs et.al. (4). All measurements were made by highly trained sonographers that are registered by the American Registry of Diagnostic Medical Sonographers, each having greater than 15 years of echo Doppler experience. In order to reduce operator bias during doppler analysis, all of the data was analyzed by two independent sonographers who were blinded to the test parameters. These data were averaged to produce the final stroke volumes.

Heart rate was calculated from the electrocardiogram. Cardiac output was calculated as (stroke volume x heart rate) and total peripheral resistance (TPR) was calculated as (mean arterial pressure/cardiac output). All results are presented as means ± SE unless otherwise indicated. Statistical analyses were performed using a commercially available software package (SigmaStat v. 3.0). All data were tested for normalcy and equal variance using the Kolmogorov-Smirnov test and the Levene Median test, respectively. Differences were determined using either a one-tailed, paired t-test (vital statistics as well as supine and 10 minute value if the ANOVA showed significance) or a 1-way repeated measures analysis of variance (**control vs midodrine** or pre-flight vs landing day time curves). Comparisons were considered significant if $P \leq 0.05$.

Results

Tilt test responses

Systolic pressure **(108 ± 2.87 vs 119 ± 3.99 mmHg)** , diastolic pressure **(74.8 ± 4.55 vs 80.4 ± 1.63 mmHg)** and cardiac output **(2.82 ± 0.40 vs 2.45 ± 0.26 l/min)** during tilt/stand tests were similar between control and midodrine flights **respectively** (10 minute post flight data shown).

[Figure 1 here]

Figure 1 shows preflight and postflight mean data for heart rate stroke volume and total peripheral resistance during tilt/stand tests before and after both the control and midodrine flights. There were no statistically significant differences between blood pressure or cardiac output. No subject experienced hypotension or presyncope during any test. Hemodynamic responses were very similar between flights. Of note, however, is that mean postflight upright heart rate was significantly higher than the preflight baseline for the control flight (p = 0.001), but was not after the midodrine flight (p = 0.185), compared to their respective preflight upright heart rates. Importantly, midodrine did not result in significantly increased supine or upright blood pressure. Additionally, supine stroke volume (P = 0.056) tended to be higher after midodrine, compared to preflight. Figure 2 shows the individual preflight and postflight heart rate, stroke volume, and total peripheral resistances, at time 0 (supine) and after 10 minutes of standing, for the control and midodrine flights.

[Figure 2 here]

Drug clearance

Plasma concentrations of midodrine and the active metabolite de-glymidodrine both peaked at times that were reported previously (8,13). Midodrine peaked at

30 minutes and de-glymidodrine peaked at 90 minutes (data not shown).

Discussion

This study is an essential step towards the implementation of midodrine as a countermeasure for post-spaceflight orthostatic hypotension. The astronauts who participated represent the 80% who do not experience orthostatic hypotension because they have very high sympathetic responses to upright posture. Thus the possibility that midodrine might raise pressure was real. If midodrine becomes one of the drugs included in the flight formulary, it will be available to all crew members, with flight surgeon approval, even those who may not be susceptible to orthostatic hypotension. For that reason, it was necessary to study this group.

Midodrine did not significantly increase blood pressure in this group of subjects. Most studies in which midodrine was reported to increase blood pressure included patients with autonomic failure (9), neurally mediated syncope (2,10), hemodialysis-induced hypotension (11,18), or diabetes (24).Those subjects tended to have supine hypertension (3,13); and increased sensitivity to adrenergic agonists due to chronic autonomic denervation. Studies in healthy subjects have shown no (8,10,13) or very modest (<10 mmHg) (6,13) changes in arterial pressure.

There were no striking hemodynamic differences between the control and midodrine tilt responses, but the data suggest that midodrine had a modest beneficial effect. Although no astronauts were hypotensive following their control flights, increases in heart rates during tilt on landing day (Fig 1) indicate that they were less tolerant of the procedure than before flight. They had a less pronounced increase in heart rate following midodrine and standing systolic pressure tended to be higher after midodrine (Fig. 1).

Thus, there was a trend for midodrine to preserve normal upright hemodynamics.

Limitations

The main limitation of this study is the small number of subjects, a fact that is exacerbated by the current lack of shuttle flights. We addressed this difficulty by using each astronaut as his own control. A second limitation is that an average of ~1604 days elapsed between the control flight and the midodrine flight. We have previously shown that there is a high degree of reproducibility between post-flight tilt tests (12), for flight that were separated by an average of 708 days. It may be possible that the extended amount of time between flights in the current study influenced our results.

Summary

A single, 10 mg oral dose of midodrine did not significantly increase blood pressure in male, non-presyncopal astronauts and tended to improve tolerance to the postflight tilt test. These results, **combined with bed rest studies, a case report describing post-spaceflight results in a presyncopal astronaut, as well as many clinical reports showing the efficacy of midodrine for orthostatic hypotension (16,17,19),** suggest that midodrine may help prevent postflight syncope. It appeared to be safe in these five astronauts. Midodrine could potentially be available to all astronauts between time of ignition and landing (possibly at entry interface), thus allowing for the maximal benefit at landing. Individual use would be determined by the flight surgeon, depending on specific conditions.

ACKNOWLEDGEMENT

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FIGURE LEGENDS

FIGURE 1. Mean preflight (●) and landing day (○) heart rate, stroke volume and total peripheral resistance measurements during supine rest and 10 minutes of tilt/stand for control flight (left panels) and midodrine flight (right panels). Bars represent SEM. * = p = 0.001; $ = p = 0.056.

FIGURE 2. Individual preflight (●) and landing day (○) heart rate, stroke volume and total peripheral resistance measurements at supine rest and 10 minutes of tilt/stand for measurements during supine rest and tilt for control flight (left panels) and midodrine flight (right panels).