Midodrine prevents orthostatic intolerance associated with simulated spaceflight

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Midodrine prevents orthostatic intolerance associated with simulated spaceflight. J Appl Physiol 90: 2245–2248, 2001.—Many astronauts after being weightless in space become hypotensive and presyncope when they assume an upright position. This phenomenon, known as orthostatic intolerance, may interfere with astronaut function during reentry and after spaceflight and may limit the ability of an astronaut to exit a landed spacecraft unaided during an emergency. Orthostatic intolerance is more pronounced after long-term spaceflight and is a major concern with respect to the extended flights expected aboard the International Space Station and for interplanetary exploration class missions, such as a human mission to Mars. Fully effective countermeasures to this problem have not yet been developed. To test the hypothesis that α-adrenergic stimulation might provide an effective countermeasure, we conducted a 16-day head-down-tilt bed-rest study (an analog of weightlessness) using normal human volunteers and administered the α1-agonist drug midodrine at the end of the bed-rest period. Midodrine was found to significantly ameliorate excessive decreases in blood pressure and presyncope during a provocative tilt test. We conclude that midodrine may be an effective countermeasure for the prevention of orthostatic intolerance following spaceflight.

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The Cardiovascular System undergoes significant alterations during spaceflight, which appear to serve well during flight. These changes include in-flight reductions in heart rate (HR) and arterial blood pressure (BP) (5) as well as changes in autonomic control of arterial BP (4). However, these in-flight adaptations do not serve well on return to Earth’s gravity, when a significant number of astronauts suffer from orthostatic hypotension. About 20% of astronauts after short missions and 83% of astronauts after long missions are not able to support standing arterial pressure for 10 min (12). In one study, the incidence was as high as 67% (2). Current countermeasures involve oral loading with salt and water and inflation of an anti-gravity suit before reentry. However, these measures have not prevented the occurrence of orthostatic hypotension.

Postflight orthostatic intolerance is thought to have several contributing factors, including reduced intravascular volume (1, 7) and dysfunction of autonomic regulation of arterial BP (3, 4, 6), which can prevent compensatory responses to venous pooling during upright posture. A recent study showed that astronauts who suffer most severely from postflight orthostatic hypotension lack appropriate responses of the sympathetic nervous system, as evidenced by standing plasma norepinephrine levels and standing total peripheral resistance that are lower than those in astronauts who are less severely affected (6).

The test of midodrine reported here is a subset of a series of head-down-tilt bed-rest studies in normal human volunteers to simulate the effects of weightlessness on the cardiovascular system. The first subject underwent 9 days of head-down bed rest, and the next three subjects underwent a longer 14-day period of head-down bed rest. Our observations of these initial subjects during orthostatic stress after bed rest lead to the hypothesis that low venous return and instability
in peripheral vascular resistance are largely responsible for post-bed-rest orthostatic intolerance. We therefore elected to begin a randomized, double-blind trial of the α-agonist vasoconstrictor drug midodrine as a countermeasure against orthostatic intolerance in 11 additional bed-rest subjects exposed to 16 days of head-down-tilt bed rest. The study was designed to test the hypothesis that the α-sympathetic agent midodrine would significantly reduce orthostatic intolerance after bed rest. We hypothesized that midodrine as a venoconstrictor would decrease venous pooling and increase venous return and, as an arteriolar constrictor, would increase arterial resistance, thus increasing arterial BP. Midodrine was approved in 1997 by the United States Food and Drug Administration for treatment of orthostatic intolerance, primarily in patients with autonomic neuropathies due to diabetes mellitus or Parkinson’s disease.

METHODS

Fifteen male subjects in excellent health [age = 33.5 ± 11.3 (SD) yr, height = 70 ± 2.4 (SD) in., weight = 76.8 ± 7.6 (SD) kg] were selected after being screened via physical and psychological examinations. Screening tests included a 12-lead electrocardiogram, complete blood count with differential, chemistry profile, thyroid function tests, and urinalysis. The exclusion criteria included history or evidence for psychiatric disorders, hypertension, diabetes, coronary artery disease, renal insufficiency, thyroid disease, alcohol or drug abuse, viral hepatitis, and anemia. The Brigham and Women’s Hospital (Boston, MA) Research Committee approved the protocol, and informed consent was obtained from the individuals.

After completion of the screening procedures, subjects were admitted to the Brigham and Women’s Hospital General Clinical Research Center. They spent 3 (subjects 1–4) or 5 (subjects 5–15) days undergoing baseline testing and equilibrating to an isocaloric diet consisting of 200 meq sodium, 100 meq potassium, and 2,500 ml of fluid.

Subjects were then instrumented for continuous noninvasive monitoring of arterial BP using Portapres, TNO, or Finapres, Ohmeda) and HR via a surface electrocardiogram. A tilt-stand test was then conducted in which the subjects were tilted upright on a tilt table to 30 degrees for 10 min and then to 60 degrees for 10 min. Finally, the subjects stood upright quietly for an additional 140 min. The test was immediately terminated if a subject experienced a sudden precipitous drop in BP and/or had difficulty appropriately responding to questions, i.e., manifested mental status changes consistent with presyncope symptoms.

Subjects then underwent a 5-degree head-down-tilt bed rest for 9 (subject 1), 14 (subjects 2–4), or 16 days (subjects 5–15). Subjects were strictly confined to bed for the entire bed-rest period. They ate all meals lying on their side, propped up with one elbow. They used a bedpan to urinate or defecate. The tilt-stand test described above was repeated at the end of the bed-rest period and again after 2 (subjects 1–4) or 3 (subjects 5–15) days of normal ambulatory activity.

After the first four subjects had completed the bed-rest study with no countermeasure, the use of midodrine was evaluated. Ten subjects were randomized to receive midodrine (5 mg po) or placebo on a double-blind basis on the final day of bed rest, 1 h before the tilt-stand test. The ratio of midodrine to placebo was adjusted such that 6 of these 10

Fig. 1. Hemodynamic data from a normal human volunteer (subject 4) during a tilt test before bed rest (left), after 14 days of untreated head-down tilt bed rest (middle), and after 16 days of head-down tilt bed rest treated with midodrine 1 h before upright tilt (right). These data are from the same subject studied on 2 separate occasions several months apart. Dashed lines indicate the periods of tilt to 30 and 60 degrees of head-up tilt. Dashed lines at the end of the 60-degree head-up-tilt period (center) indicate the presyncope episode, at which time the subject was returned to a horizontal position. After bed rest during the tilt test, this subject experienced a decrease in peripheral resistance and then a decrease in heart rate (HR), which resulted in a dramatic decrease in blood pressure (BP) and presyncope (middle). When midodrine was administered 1 h before the tilt-stand test, this subject did not experience decreases in HR or BP and did not become presyncopal (right).
subjects received midodrine. In addition, one of the original four subjects that completed the bed-rest study without any countermeasure was restudied several months later and administered 5 mg of midodrine in an open-label design 1 h before the post-bed-rest tilt-stand test. Thus eight untreated bed-rest subjects were compared with seven subjects who received midodrine (six of whom receive midodrine on a randomized basis and one of whom received midodrine in an open-label design). All subjects who received midodrine underwent the longer 16-day period of head-down-tilt bed rest, whereas four of eight control subjects underwent a somewhat shorter period of bed rest (9 days for the first subject and 14 days for the second, third, and fourth subjects). The study protocol was the same in all subjects except for the shorter period of bed rest in the first four subjects.

RESULTS

The cardiovascular responses of one subject during three different tilt-stand tests are illustrated in Fig. 1. These data are from the only subject who was studied before and after two separate bed-rest studies, once with midodrine and once without midodrine. Figure 1, left, illustrates the pre-bed-rest tilt test. Figure 1, middle, illustrates the immediate post-bed-rest tilt test without midodrine. Figure 1, right, illustrates the immediate post-bed-rest tilt test when this subject was treated with 5 mg of midodrine 1 h before upright tilt. The dashed lines separate the horizontal, 30-degree upright, and 60-degree upright tilt periods. In the middle column, the dashed lines at the end of the 60-degree tilt period correspond to the presyncopal event and the return of the subject back to the horizontal position. Note that, in the post-bed rest without midodrine group (middle), arterial BP began to trend down sharply just before 20 min, whereas HR continued to increase. Just after the 20-min time point, HR decreased precipitously as well, terminating with the presyncopal event. This is a typical vasovagal pattern of presyncope. In Fig. 1, right, note that treatment of this subject with midodrine 1 h before the tilt-stand test resulted in no decrease in BP or HR.

Most of the patients had a presyncopal pattern similar to that seen in Fig. 1. Figure 2 illustrates a presyncopal event in one patient involving a different pattern of a gradual reduction in arterial BP. This is more similar to that seen with dysautonomia (8, 18) and that seen in a large number of subjects after spaceflight (6).

Kaplan-Meier analysis of presyncope-free survival data is shown in Fig. 3. After head-down-tilt bed rest, subjects who were treated with midodrine 1 h before the tilt-stand test had a 71.4% rate of presyncope-free survival compared to 80% for the control group. Subject survival exceeded 50% for 150 min in the midodrine group and for only 90 min in the control group (Fig. 3). The Kaplan-Meier survival curves also show a lower percentage of presyncope-free survival in the control group compared to the midodrine group, with a significant difference between the two groups (P < 0.0036).
survival, whereas untreated control subjects had only a 25% rate of syncope-free survival ($P = 0.036$).

**DISCUSSION**

We tested the $\alpha$-adrenergic agonist midodrine as a countermeasure to orthostatic hypotension following head-down bed rest, an analog of bed rest. The success of these trials after bed rest suggests that midodrine may also be an effective treatment for orthostatic hypotension following spaceflight.

There is evidence that both venous return and peripheral vascular resistance are reduced after spaceflight. Although they are not the only contributors, both of these factors most certainly increase the incidence of postspaceflight orthostatic hypotension and presyncope. Several studies have demonstrated a reduction in cardiac stroke volume on return from space (2, 6, 10), and others have shown reduced resistance responses to standing, particularly in those astronauts who have the most difficulty maintaining arterial BP while standing (2, 6). Midodrine is an agonist at $\alpha$-adrenergic receptors located on smooth muscle in both veins and arterioles, thus reducing venous pooling and increasing peripheral vascular resistance (9, 16, 17).

After completion of head-down-tilt bed rest, most subjects exhibited the hemodynamic pattern exhibited in Fig. 1, middle, that is, a decrease in BP, followed shortly by a decrease in HR, accompanied by a further reduction in BP. This may be mediated through the Bezold-Jarisch reflex, which is thought to play a major role in vasovagal syncope (13, 15) and has been suggested as a possible mechanism for postflight orthostatic intolerance (11, 14). At least one subject (see Fig. 2) demonstrated a pattern more commonly associated with dysautonomia.

Both patterns of presyncope seen in this study have been documented after spaceflight (2, 6). The occurrence of vasovagal presyncope postflight may be provoked by hypovolemia and decreased venous return, which leads to ventricular contraction around a relatively empty ventricular chamber, stimulating inhibitory mechanoreceptors in the inferoposterior ventricular wall (i.e., the Bezold-Jarisch reflex). The other pattern of postflight presyncope is associated with inadequate norepinephrine release and resistance responses (6). We suggest that the use of midodrine would alleviate both types of hypotension and presyncope after spaceflight in a manner similar to that shown after bed rest. However, we note that this study establishes neither vasovagal syncope nor dysautonomia as the mechanism for the development of bed-rest presyncope. We also note that the dose of midodrine used in this study, 5 mg, was small; future studies might want to examine the use of a larger dose.

In summary, orthostatic intolerance is an operational problem that has plagued the human space program for over 30 years. This study demonstrates an effective pharmacological countermeasure against orthostatic intolerance resulting from simulated microgravity exposure. However, these results need to be confirmed under actual postflight conditions.

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