TEMAZEPAM, BUT NOT ZOLPIDEM, CAUSES ORTHOSTATIC HYPOTENSION IN ASTRONAUTS AFTER SPACEFLIGHT

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ABSTRACT

Background Many astronauts do not sleep well due to the difficult environment in space. Hypnotics such as temazepam or zolpidem are often taken while in space and/or the night prior to returning to Earth. Until now, no data have illustrated the effect of these sleeping medications on postflight hemodynamic responses. The purpose of this study was to determine if the use of different hypnotics during flight has any effect on cardiovascular responses to standing in astronauts upon returning to Earth's gravity.

Methods Astronauts were separated into three groups: control group (n = 40), temazepam group (15 or 30 mg; n = 9), and zolpidem group (5 or 10 mg; n = 8). In this study, temazepam and zolpidem were only taken the night before landing. The systolic and diastolic blood pressures and heart rates of the astronauts were measured during stand test before spaceflight and on landing day.

Results Systolic blood pressure decreased and heart rate increased significantly in the temazepam group when compared with the control group on landing day. However, systolic blood pressure and heart rate were not different between zolpidem and control groups.

Conclusions Temazepam may aggravate orthostatic hypotension after spaceflight.

Zolpidem may be a better choice as a sleep aid while in space.

Key words: astronaut, spaceflight, orthostatic hypotension, temazepam, zolpidem,

INTRODUCTION

Many astronauts experience difficulty sleeping during spaceflight.[1-3] Because sleep deprivation affects performance and can cause other medical and operational problems, the in-flight use of sedative-hypnotics as sleeping aids is common.[4] Two hypnotics, temazepam (Restoril, a benzodiazepine) and zolpidem (Ambien, an imidazopyridine), are used by astronauts during their missions, including the night prior to shuttle landings. Some sedative-hypnotics have side effects that affect the cardiovascular system by decreasing arterial blood pressure and increasing heart rate.[5] After spaceflight, astronauts experience orthostatic hypotension[6-8] due to, among other things, reduction of plasma volume and autonomic dysfunction. It is possible that the use of these hypnotics is an additional contributor. Temazepam belongs to the benzodiazepine family that causes sedation, hypnosis, decreased anxiety, muscle relaxation, anterograde amnesia, and anticonvulsant activity.[9] Zolpidem is an imidazopyridine that differs structurally from the benzodiazepines.[10] It has sedative-hypnotic properties, but has only minor anxiolytic and anticonvulsant properties, and no myorelaxant activity.[11,12] Although the National Aeronautics and Space Administration (NASA) began using temazepam and zolpidem as

inflight sleeping aids in 1990 and 1994, respectively, the effects of these medications on cardiovascular responses to upright posture have not been documented. Therefore, the purpose of this study was to assess whether hypnotics exacerbate orthostatic intolerance in astronauts on landing day.

METHODS

This study was conducted in two parts. The first part was a prospective study in laboratory volunteers on the effects of temazepam on cardiovascular responses to standing. Based on those results, a retrospective analysis was performed on astronauts' preflight stand test, and postflight stand tests with and without the influence of temazepam or zolpidem.

Subjects. The NASA Johnson Space Center Committee for the Protection at Human Subjects approved these protocols. There were two sets of subjects: astronauts and non-astronauts.

Ground-based Study. All subjects (non-astronauts) had passed an Air Force Class III physical exam before their participation and signed written informed consent. Ten

subjects were studied before and ten hours after a single, 30 mg oral dose of temazepam.

Subjects abstained from caffeine, alcohol, and any medications for 12 hours prior to each

study and ate a light breakfast before reporting to the laboratory. Testing on the first day

began at 8 AM. After the test session, subjects were given 30 mg of temazepam which

they ingested orally at 10 PM that night. They were studied again at 8 AM the following

morning, ten hours after taking the drug. For each test, subjects were placed on a bed in a

quiet, air-conditioned room where the temperature was 23-25 °C. After 20 minutes of

supine rest, baseline arterial blood pressure and heart rate were recorded. Then a tightly

sealing Silastic chamber, connected to a computer-controlled bellows, was strapped to the

anterior neck.[13] During held expiration, and triggered by successive R-waves, the

pressure in the neck chamber was increased to +40 mmHg for four heart beats and then

reduced to, +25, +10, -5, -20, -35, -50, and -65 mmHg, and then returned to ambient

pressure. This sequence was repeated seven times. R-R intervals were plotted against

carotid distending pressures (systolic blood pressure minus chamber pressure). After the

neck suction protocol was completed, a stand test was performed. Subjects were assisted

to a standing position by three investigators who lifted them behind both shoulders and

swept their feet off the bed. This helped to minimize artifactual arterial blood pressure changes with the effort of standing. Subjects remained standing without support for ten minutes unless presyncopal symptoms necessitated the termination of the test. Their heart rates were recorded with electrocardiogram (SpaceLabs, Redmond, WA), and systolic and diastolic blood pressures were measured manually with sphygmomanometer every minute. Finger arterial blood pressure was measured by a beat-to-beat pressure detector (Finapres, Ohmeda, Tewksburi, MA).

Flight-based Study. Informed consent was obtained according to the guidelines set forth by the Committee for the Protection at Human Subjects at the NASA Johnson Space Center. The astronaut subjects were separated into three different groups: those who took no medication the night before landing (n = 40), those who took oral temazepam (15 or 30 mg) the night before landing (n = 9), and those who took oral zolpidem (5 or 10 mg) the night before landing (n = 8). No astronaut took either medication before flight and no additional medications other than the hypnotics were taken before landing. This retrospective analysis encompasses a 7-year period from January 1990 until December 1996. Stand tests were performed according to the same protocol described above, ten

days before launch and two to four hours after landing. All preflight stand tests were

conducted at Johnson Space Center in Houston, Texas, and landing day stand tests were

conducted either at Kennedy Space Center, Florida, or Dryden Flight Research Center at

Edwards Air Force Base, California.

Data Analysis - Carotid Baroreceptor-Cardiac Reflex Response. All

electrocardiograms and neck pressures were recorded on digital tape for subsequent

analysis. R-R intervals were measured from the electrocardiogram. Carotid-cardiac

baroreflex responses were determined off-line using standard data acquisition and

analysis packages. Responses to baroreflex were reduced to the following set of

parameters for analysis: range of R-R response, maximum slope, and operational point.

Maximum slopes were identified with linear regression analyses applied to each set of

three consecutive data pairs on the stimulus-response relation. Operational points were

defined as [(R-R interval at 0 mmHg neck pressure - minimum R-R interval) / (R-R

interval range)] × 100%. The operational point is a measure of the amount of buffering

capacity above and below baseline systolic blood pressure due to increases or decreases

in cardiac-vagal outflow, respectively.

Data Analysis - Stand Tests. The stand portion of the test assessed the systolic and diastolic blood pressures and heart rates pre- and post-temazepam and zolpidem. Both systolic and diastolic blood pressures and heart rates were measured every minute for six minutes supine and ten minutes standing. Systolic and diastolic blood pressures and heart rates were stable in the supine position, so only the last supine measurement was reported.

Statistics. All data are presented as mean ± SE. A Kruskal-Wallis one-way analysis of variance (ANOVA) on Ranks was used for between groups comparison (i.e. control group vs. temazepam or zolpidem group). A paired t-test was used for within-group comparisons (i.e. pre- vs. post-temazepam). For all tests, significance was set at $P < 0.05$.

RESULTS

The anthropometric data for all subjects are presented in Table 1. Age, body weight, and height did not differ significantly among any of the groups. Between January 1990 and December 1996, 13.7% of astronauts took temazepam and 4.6% took zolpidem

during flight. Therefore, astronauts took temazepam three times more than zolpidem during this period.

Ground-based Results. In non-astronauts, one subject who had not become presyncopal before taking temazepam became presyncopal during standing after taking it. Two additional subjects reported feeling lightheaded and dizzy the morning after taking temazepam but before reporting to the laboratory. These two subjects did not become presyncopal during their stand tests. Fig. 1 shows that finger arterial blood pressures and heart rates decreased in the subject who became presyncopal after taking temazepam. Before temazepam (upper panel), arterial systolic blood pressure was maintained the entire time of standing. After temazepam, systolic blood pressure dropped to 70 mmHg (bottom panel) and the subject became presyncopal. Standing heart rate post-temazepam was 15 bpm higher than pre-temazepam until presyncope occurred.

Fig. 2 represents supine and standing arterial blood pressures and heart rates before and after 30 mg of temazepam in the ground-based subjects. As a group, there was no effect of temazepam on supine or standing arterial blood pressures. Supine heart rates

were not different after temazepam, but standing heart rates were significantly higher (P < 0.05).

Carotid Baroreceptor Reflex Test. Carotid baroreceptor-cardiac reflex responses before and after temazepam are shown in Fig. 3 and Table 2. Temazepam resulted in no change in slope, range, or operational point, but caused a significant shift on the R-R interval axis which paralleled the increase in heart rate.

Flight-based Results. Fig. 4 depicts supine and standing systolic and diastolic blood pressures and heart rates for the subjects who took temazepam the night before landing and those who did not. No astronaut took any drug preflight. Before flight (Fig. 4 left), supine and standing blood pressures and heart rates were not different between groups, although blood pressures were somewhat lower in the temazepam group. On landing day (Fig. 4 right), supine blood pressures were higher than preflight in both groups, but those who had taken temazepam had very dramatic falls in systolic blood pressure with standing that were significantly greater than in those who had not taken the drug (P < 0.05). There were no intergroup differences in supine or standing heart rates before

flight, however on landing day, the temazepam group had significantly higher standing heart rates than those who did not take the drug.

Fig. 5 depicts supine and standing systolic and diastolic blood pressures and heart rates preflight and postflight in the control group of astronauts versus those who took zolpidem the night before landing. Unlike the temazepam data, there were no intergroup differences in supine or standing values either preflight or postflight.

DISCUSSION

This study was initially undertaken because 14% of astronauts were taking in-flight sleeping medications[4], and it was unknown what effects this practice had on arterial pressure control. The most important finding from this study is that astronauts who took temazepam as a sleeping aid the night before landing had significantly lower standing systolic blood pressures after landing than those who did not. This finding was not reproduced in astronauts who took zolpidem the night before landing. It also was not reproduced in subjects who did not fly in space. These results suggest that the use of

temazepam as an in-flight sleeping aid has contributed significantly to the high incidence of post-spaceflight orthostatic hypotension in returning astronauts.

The most apparent difference between the two drugs studied is the half-life. The half-life of temazepam is 11 - 20 hours and the half-life of zolpidem is 1.5 - 4 hours.[14] Therefore, zolpidem is probably eliminated by the time of landing. In addition, there also are differences in the mechanisms of actions between the two drugs.

In the initial study, the ground-based subjects did not, as a group, experience low blood pressure during standing after temazepam, but they did have significantly higher standing heart rates. These findings were not unexpected. Several studies have shown that temazepam does not affect arterial blood pressure, yet can cause significant increases in heart rate during sitting,[5] standing[5] and lower body negative pressure[15]. However, one subject did become presyncopal after taking temazepam, and two additional subjects reported incidents of dizziness and hypotension after taking the drug.

In the retrospective analysis of the astronaut stand tests, temazepam was associated with significant falls in standing systolic blood pressure after spaceflight (Fig. 4). In fact, their hemodynamic responses to upright posture fell within the range of clinical

orthostatic hypotension: systolic blood pressure falls greater than 20 mmHg and/or heart rate increases greater than 27 beats per minute[16]. Thus, it is clear that temazepam has hemodynamic effects which are significantly exaggerated when combined with the effects of spaceflight itself.

Temazepam, a benzodiazepine, binds non-selectively to all three subtypes of the benzodiazepine receptor (BZ1, BZ2, and BZ3). Thus, in addition to BZ1 sedative effects, benzodiazepine also has BZ2, and BZ3's anticonvulsant, myorelaxant, and anxiolytic effects.[14] The muscle relaxant properties probably enhance venous pooling during upright posture. This normally does not result in systolic blood pressure falls because baroreflex-mediated increases in heart rate maintain cardiac output. This idea is supported by the present finding that carotid baroreceptor-cardiac reflex is intact after temazepam. However, in individuals who are hemodynamically compromised, such as the elderly[17-19] temazepam can cause significant falls in systolic blood pressure.[20] We suggest that returning astronauts are affected by temazepam because they are already compromised by reduced plasma volume,[8] autonomic dysfunction,[21] increased leg compliance,[22] and skeletal muscle atrophy.[23,24]

Unlike temazepam, zolpidem had no effect on arterial blood pressure and heart rate responses to standing after spaceflight. Zolpidem is not a benzodiazepine, but an imidazopyridine, which only selectively binds the BZ1 benzodiazepine receptor subtype. Thus it does not have BZ2 and BZ3 myorelaxant properties[25-27] and is not likely to aggravate venous pooling.[10,28,29] Zolpidem rarely causes cardiovascular effects such as hypotension or tachycardia[30] even in elderly patients.[11]

In summary, we compared hemodynamic side effects of two kinds of sleeping medications that are routinely taken by astronauts the night before landing. On landing day, temazepam clearly caused orthostatic hypotension. Zolpidem had no such effect. Thus, temazepam should not be the initial choice as a sleeping aid for astronauts the night before landing. Instead, zolpidem may be a first choice when choosing sedative-hypnotics for use in space.

ACKNOWLEDGMENTS

REFERENCES

1. Stampi C. Sleep and circadian rhythms in space. J Clin Pharmacol 1994;34:518-34.

2. Gundel A, Polyakov VV, Zulley J. The alteration of human sleep and circadian rhythms during spaceflight. J Sleep Res 1997;6:1-8.

3. Dijk DJ, Neri DF, Wyatt JK, et al. Sleep, performance, circadian rhythms, and light-dark cycles during two space shuttle flights. Am J Physiol Regul Integr Comp Physiol 2001;281:R1647-64.

4. Putcha L, Pool SL, Cintron NM. Pharmacology. In: Nicogossian AE, Huntoon CL, Pool SL, eds. Space physiology and medicine (3rd edition). Philadelphia, PA: Lea & Febiger, 1994:435-446.

5. Matejcek M, Neff G, Abt K, Wehrli W. Pharmaco-EEG and Psychometric study of the effect of single doses of temazepam and nitrazepam. Neuropsychobiology 1983;9:52-65.

6. Buckey JC Jr, Lane LD, Levine BD, et al. Orthostatic intolerance after spaceflight. J Appl Physiol 1996;81:7-18.

7. Fritsch-Yelle JM, Whitson PA, Bondar RL, Brown TE. Subnormal norepinephrine release relates to presyncope in astronauts after spaceflight. J Appl Physiol 1996;81:2134-41.

8. Waters WW, Ziegler MG, Meck JV. Postspaceflight orthostatic hypotension occurs mostly in women and is predicted by low vascular resistance. J Appl Physiol 2002;92:586-94.

9. Charney DS, Mihic SJ, Harris RA. Hypnotics and sedatives. In: Hardman JG, Limbird LE, Gilman AG, eds. Goodman & Gilman's the pharmacological basis of therapeutics (10th ed.). New York, NY: McGraw-Hill Co., 2001:399-427.

10. Depoortere H, Zivkovic B, Lloyd KG, Sanger DJ, Perrault G, Langer SZ, Bartholini G. Zolpidem, a novel nonbenzodiazepine hypnotic. I. Neuropharmacological and behavioral effects. J Pharmacol Exp Ther 1986;237:649-58.

11. Ganzoni E, Santoni JP, Chevillard V, Sebille M, Mathy B. Zolpidem in insomnia: a 3-year post-marketing surveillance study in Switzerland. J Int Med Res 1995;23:61-73.

12. Langtry HD, Benfield P. Zolpidem. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential. Drugs 1990; 40:291-313.

13. Sprenkle JM, Eckberg DL, Goble RL, Schelhorn JJ, Halliday HC. Device for rapid quantification of human carotid baroreceptor-cardiac reflex responses. J Appl Physiol 1986;60:727-32.

14. Mitler MM. Nonselective and selective benzodiazepine receptor agonists-where are we today? Sleep 2000;23(Suppl 1):S39-47.

15. Patrick JM, Dikshit MB, Macdonald IA, Fentem PH. Human orthostatic reflexes after taking temazepam at night. Br J Clin Pharmacol 1987;24:799-807.

16. Streeten DHP, Orthostatic disorders of the circulation. New York, NY: Plenum Medical Book Co., 1987:111-126.

17. Cunha UV. Management of orthostatic hypotension in the elderly. Geriatrics 1987;42:61-8.

18. Masaki KH, Schatz IJ, Burchfiel CM, Sharp DS, Chiu D, Foley D, Curb JD. Orthostatic hypotension predicts mortality in elderly men: the Honolulu Heart Program. Circulation 1998;98:2290-5.

19. Viramo P, Luukinen H, Koski K, Laippala P, Sulkava R, Kivela SL. Orthostatic hypotension and cognitive decline in older people. J Am Geriatr Soc 1999;47:600-4.

20. Ford GA, Hoffman BB, Blaschke TF. Effect of temazepam on blood pressure regulation in healthy elderly subjects. Br J Clin Pharmacol 1990;29:61-7.

21. Fritsch-Yelle JM, Charles JB, Jones MM, Beightol LA, Eckberg DL. Spaceflight alters autonomic regulation of arterial pressure in humans. J Appl Physiol 1994;77:1776-83.

22. Convertino VA. Exercise and adaptation to microgravity environments. In: Fregly MJ, Blatteis CM, eds. Handbook of Physiology: Environmental Physiology. New York: Oxford University Press, 1996:889-939.

23. Akima H, Kawakami Y, Kubo K, Sekiguchi C, Ohshima H, Miyamoto A, Fukunaga T. Effect of short-duration spaceflight on thigh and leg muscle volume. Med Sci Sports Exerc 2000;32:1743-7.

24. Murthy G, Watenpaugh DE, Ballard RE, Hargens AR. Exercise against lower body negative pressure as a countermeasure for cardiovascular and musculoskeletal deconditioning. Acta Astronaut 1994;33:89-96.

25. Benavides J, Peny B, Ruano D, Vitorica J, Scatton B. Comparative autoradiographic distribution of central omega (benzodiazepine) modulatory site subtypes with high, intermediate and low affinity for zolpidem and alpidem. Brain Res 1993;604:240-50.

26. Langer SZ, Arbilla S. Imidazopyridines as a tool for the characterization of benzodiazepine receptors: a proposal for a pharmacological classification as omega receptor subtypes. Pharmacol Biochem Behav 1988;29:763-6.

27. Arbilla S, Depoortere H, George P, Langer SZ. Pharmacological profile of the imidazopyridine zolpidem at benzodiazepine receptors and electrocorticogram in rats. Naunyn Schmiedebergs Arch Pharmacol 1985;330:248-51.

28. Garnier R, Guerault E, Muzard D, Azoyan P, Chaumet-Riffaud AE, Efthymiou ML. Acute zolpidem poisoning-analysis of 344 cases. J Toxicol Clin Toxicol 1994;32:391-404.

29. McCann CC, Quera-Salva MA, Boudet J, Frisk M, Barthouil P, Borderies P, Meyer P. Effect of zolpidem during sleep on ventilation and cardiovascular variables in normal subjects. Fundam Clin Pharmacol 1993;7:305-10.

30. Monti JM. Effect of zolpidem on sleep in insomniac patients. Eur J Clin Pharmacol

1989;36:461-6.

FIGURE LEGENDS

Fig. 1. Finger arterial blood pressure and heart rate (black line) in one subject during stand tests before (top panel) and ten hours after (bottom panel) temazepam. Note the presyncopal episode in the bottom panel.

Fig. 2. Systolic (SBP, top panel) and diastolic blood pressures (DBP, center panel) and heart rates (HR, beats per minute = bpm, bottom panel) pre- (open triangle) and post-temazepam (closed triangle) during stand tests in ground-based subjects (non-astronauts). Each value shows mean ± SE. * $P < 0.05$ vs. pre-temazepam.

Fig. 3. Average R-R interval responses to ramped neck pressure-suction in pre- (open circle) and post-temazepam (closed circle) administration in groud-based subjects (non-astronauts). The open and closed triangle symbols represent the R-R intervals of pre- and post-temazepam group at 0 mmHg neck pressure, respectively. Each value shows mean ± SE.

Fig. 4. Systolic (SBP, top panel) and diastolic blood pressures (DBP, center panel) and heart rates (HR, beats per minute = bpm, bottom panel) of astronauts preflight (left panel) and on landing day (right panel). Preflight, astronauts in both control (open circle)

and temazepam (open triangle) groups did not take any medication. On landing day, astronauts in the control group (closed circle) did not take any drug, but in the temazepam group (closed triangle) took 15 or 30 mg of temazepam. Each value shows mean ± SE. *$P < 0.05$ vs. control group, **$P < 0.01$ vs. control group.

Fig. 5. Systolic (SBP, top panel) and diastolic blood pressures (DBP, center panel) and heart rates (HR, beats per minute = bpm, bottom panel) of astronauts preflight (left panel) and on landing day (right panel). In preflight, astronauts in both control (open circle) and zolpidem (open triangle) groups did not take any medication. On landing day, astronauts in the control group (closed circle) did not take any drug, but in the zolpidem group (closed triangle) took 5 or 10 mg of zolpidem. Each value shows mean ± SE. There were no differences between zolpidem and control groups.
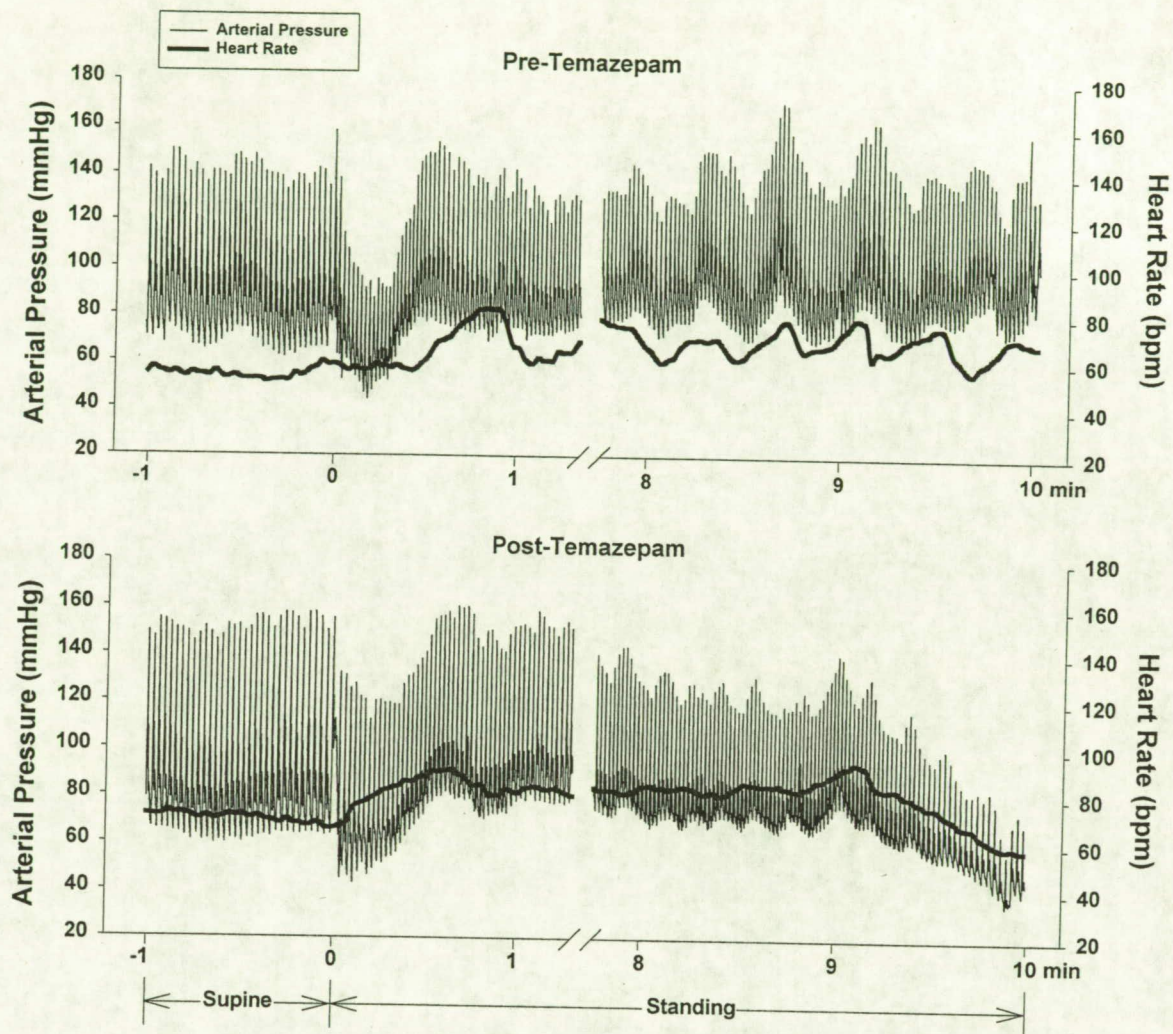
Fig. 1. Finger arterial blood pressure and heart rate (black line) in one subject during stand tests before (top panel) and ten hours after (bottom panel) temazepam. Note the presyncopal episode in the bottom panel.

Table 1. *Age, body weight and height in different groups of non-astronauts and astronauts*

Type	Number	Age (yr)	Weight (kg)	Height (cm)
Non-Astronauts (Pre- & Post-Temazepam)	10 (M=6, F=4)	39.2 ± 1.8 (30 - 50)	75.0 ± 1.6 (64 - 81)	176.0 ± 3.2 (152 - 188)
Astronauts (Control Group)	40 (M=37, F=3)	42.0 ± 0.7 (33 - 50)	76.8 ± 1.8 (46 - 99)	178.7 ± 1.8 (160 - 193)
Astronauts (Temazepam Group)	9 (M=8, F=1)	44.7 ± 2.0 (35 - 51)	76.8 ± 2.0 (68 - 84)	176.8 ± 2.6 (173 - 185)
Astronauts (Zolpidem Group)	8 (M=8, F=0)	42.4 ± 2.4 (33 - 53)	80.5 ± 3.9 (66 - 95)	182.0 ± 2.8 (170 - 188)

Values are expressed as means ± SE for all groups. M: male; F: female. Numbers in parentheses are ranges of age, body weight, and height.
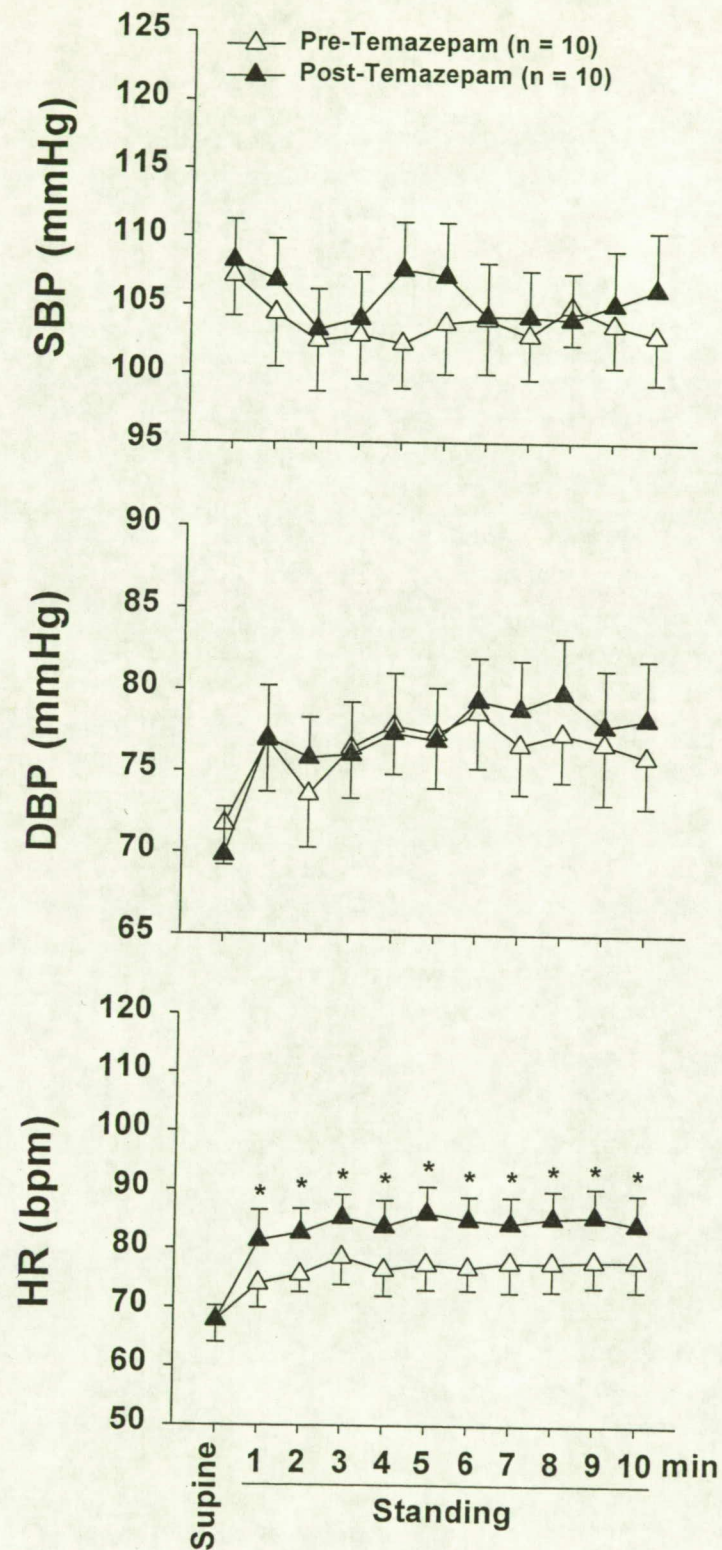
Non-astronauts

Fig. 2

Table 2. *Descriptors of carotid baroreflex function*

Measurement	Pre-Temazepam	Post-Temazepam
Minimum R-R interval (msec)	980 ± 70	923 ± 65
Maximum R-R interval (msec)	1189 ± 93	1110 ± 65
Pressure at maximum R-R interval (mmHg)	159 ± 3	172 ± 3
Operational point (%)	41 ± 9	36 ± 5
Maximum slope (msec/mmHg)	5.3 ± 0.7	4.7 ± 0.7
Response range (msec)	236 ± 44	223 ± 29

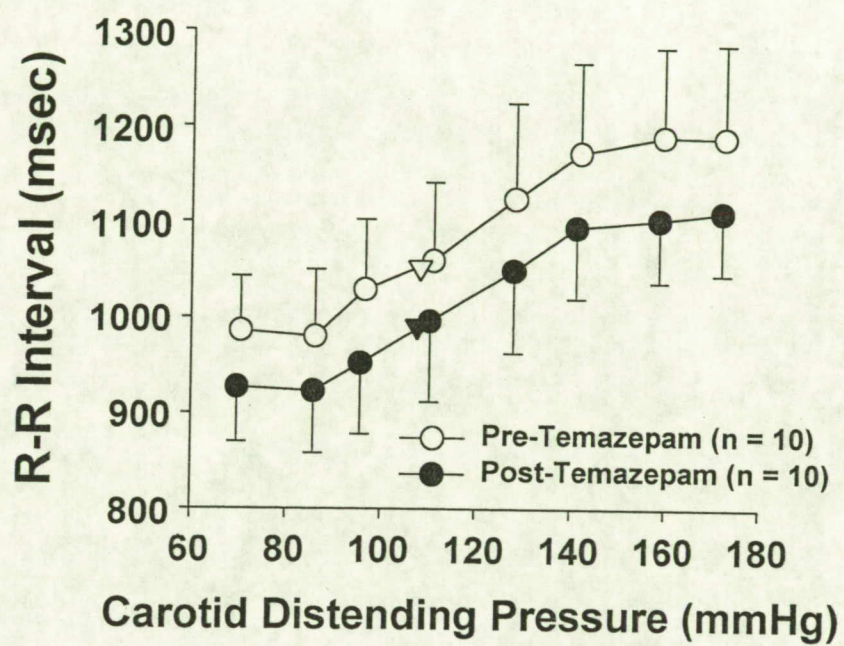The values are from two curves of R-R interval with carotid distending pressure in Fig.2
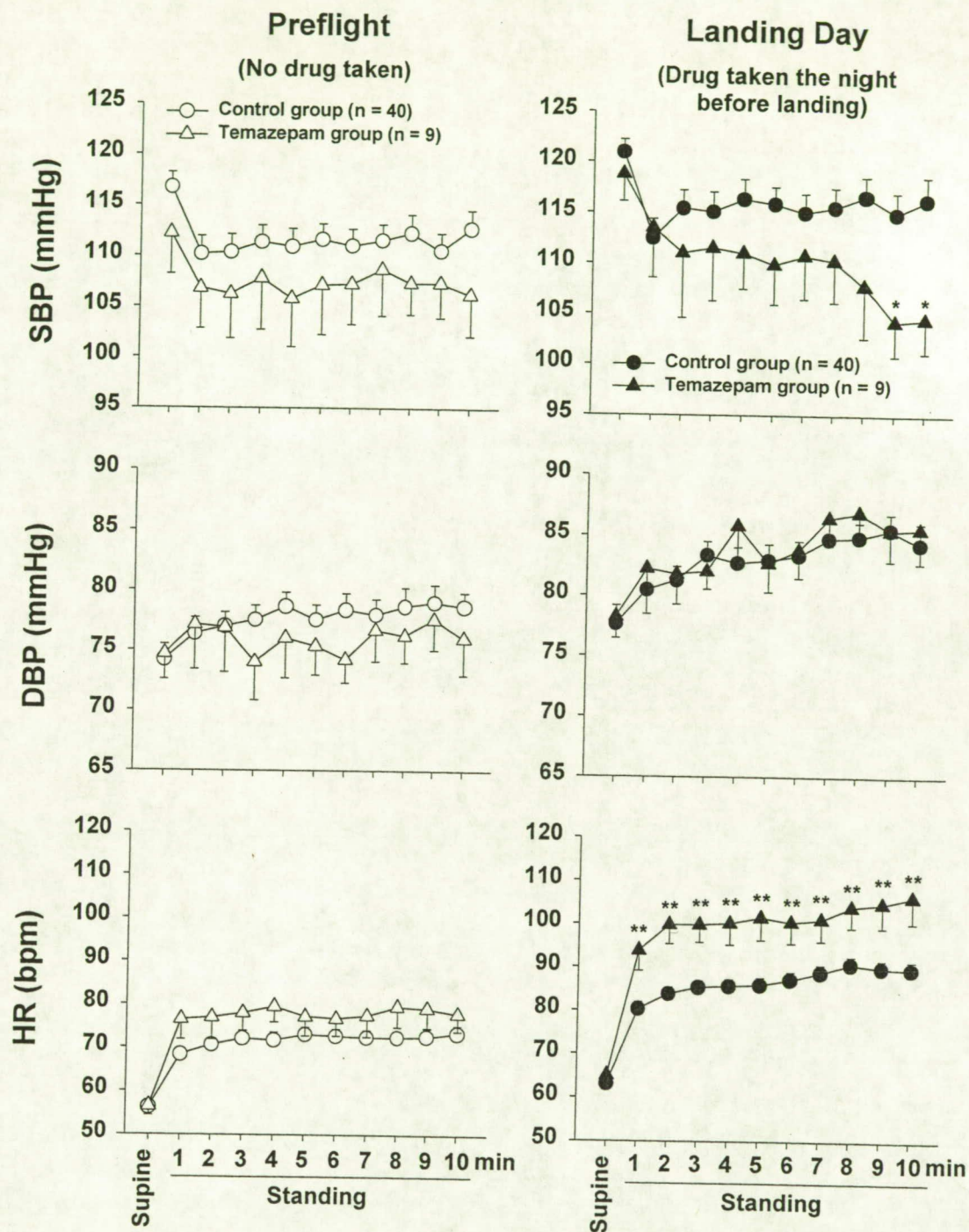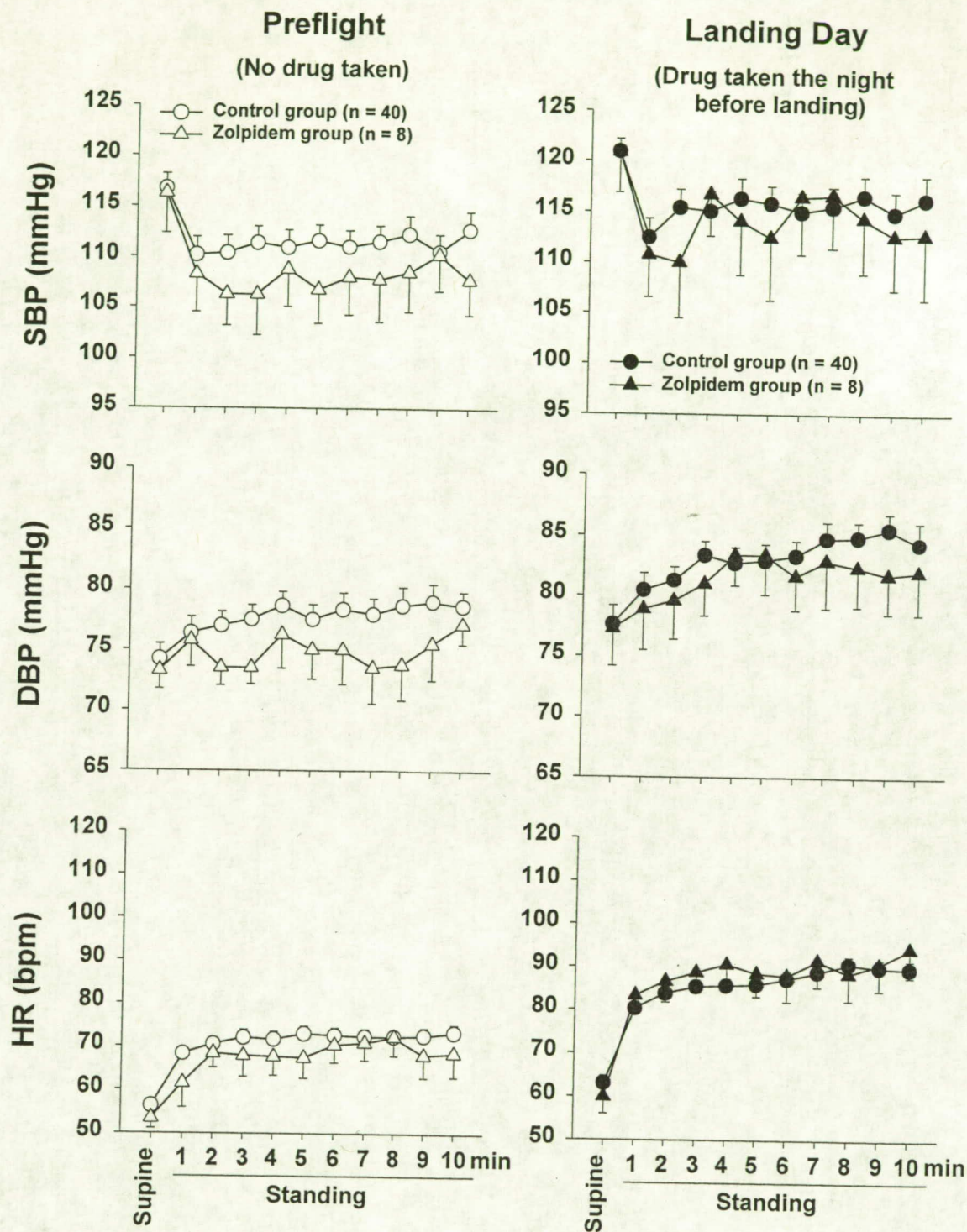
(means ± SE).

Fig. 3

Fig. 4

Preflight
(No drug taken)

Landing Day
(Drug taken the night before landing)

Fig.5