

Neuroscience Laboratory Pre-test Questionnaire
 This information is subject to the Privacy Act of 1974



Subject _____

Date _____

Social Security Number _____

Operator(s) _____

Test _____

General Well Being

| Yes | No | |
|--------------------------|--------------------------|--|
| <input type="checkbox"/> | <input type="checkbox"/> | Are you in your usual state of fitness today? If no, please explain. _____ |
| <input type="checkbox"/> | <input type="checkbox"/> | Have you been ill within the last week? If Yes, please explain. _____ |
| <input type="checkbox"/> | <input type="checkbox"/> | Have you taken any medications (aspirin, cold medication prescriptions, etc. within the last 48 hours? If Yes, please specify. _____ |
| <input type="checkbox"/> | <input type="checkbox"/> | Have you been exposed to any unusual motion experiences within the last week? (Amusement rides, diving, KC-135 flights, car accidents etc) If Yes, please specify. _____ |
| <input type="checkbox"/> | <input type="checkbox"/> | On a scale of 0-10 (0 = poor; 5 = normal; 10 = excellent), how do you rate your present state of well being? _____ |

Recent Activities

| Yes | No | |
|--------------------------|--------------------------|---|
| <input type="checkbox"/> | <input type="checkbox"/> | Do you use tobacco products? If Yes, please specify form and amount used daily. _____ |
| <input type="checkbox"/> | <input type="checkbox"/> | How many hours did you sleep last night? _____ |
| <input type="checkbox"/> | <input type="checkbox"/> | Was that a sufficient amount of sleep? |
| <input type="checkbox"/> | <input type="checkbox"/> | When was your last meal? _____ hour(s) ago. What did you eat/drink? _____ |
| <input type="checkbox"/> | <input type="checkbox"/> | Have you consumed beverages (soft drinks, coffee, tea) containing caffeine today? If Yes, please specify beverage and amount. _____ |
| <input type="checkbox"/> | <input type="checkbox"/> | Please specify the amount of alcohol consumed within the last 24 hours. _____ |

PMZ-PILOT Motor Performance Study

Training Sessions Log

Subject No: _____

Subject Name: _____

Four Digit Code: _____

Session No.

Date

1

2

3

4

5

6

7

8

NOTES:

Stanford Sleepiness Scale

Complete questionnaire and at every saliva sampling time

ID # ----- Subject # ----- Trial # ----- Experiment Time -----hr.

Date ----- Clock Time ----- am pm Dosing Time ----- am pm

Treatment A B (Circle one)

Check one of the seven statements below which best describes your present feelings (how you feel right now).

- Feeling active and vital; alert; wide awake.
- Functioning at a high level, but not at peak; able to concentrate.
- Relaxed; awake; responsive, but not at full alertness.
- A little foggy; let down; not at peak.
- Foggy; slowed down; beginning to lose interest in remaining awake.
- Sleepy; woozy; prefer to be lying down; fighting sleep.
- Almost in reverie; sleep onset soon; losing struggle to stay awake.

Subject ID # _____

Date: _____

Session: _____

Medicine: A or B

Time: _____

Medication Side Effects/Motion Sickness Symptoms/Pilot Checklist*Please answer according to instructions:*

| Symptoms | | None | Slight | Moderate | Severe |
|----------|-------------------------------------|------|--------|----------|--------|
| 1 | General Discomfort | | | | |
| 2 | Fatigue | | | | |
| 3 | Drowsiness | | | | |
| 4 | Headache | | | | |
| 5 | Eye Strain | | | | |
| 6 | Difficulty Focusing | | | | |
| 7 | Increased Salivation | | | | |
| 8 | Decreased Salivation | | | | |
| 9 | Sweating | | | | |
| 10 | Nausea | | | | |
| 11 | Difficulty Concentrating | | | | |
| 12 | Fullness of the Head | | | | |
| 13 | Blurred Vision | | | | |
| 14 | Dizziness With Eyes Open | | | | |
| 15 | Dizziness With Eyes Closed | | | | |
| 16 | Vertigo | | | | |
| 17 | Weakness | | | | |
| 18 | Dry Mouth | | | | |
| 19 | Ringing/Buzzing in Ears | | | | |
| 20 | Incoordination | | | | |
| 21 | Nervousness | | | | |
| 22 | Difficulty Acquiring Visual Targets | | | | |
| 23 | Euphoria | | | | |
| 24 | Tremors | | | | |
| 25 | Stuffy Nose | | | | |
| 26 | Confusion | | | | |
| 27 | Disorientation | | | | |
| 28 | Boredom | | | | |
| 29 | Warmth | | | | |
| 30 | Apathy | | | | |
| 31 | Faintness | | | | |
| 32 | Appetite Loss | | | | |
| 33 | Appetite Gain | | | | |
| 34 | Yawning | | | | |
| 35 | Distorted Smell/Taste | | | | |
| 36 | Flushing | | | | |

| | | | | | |
|----|-----------------------|----|--|-----|------------|
| 37 | Burping | No | | Yes | # of times |
| 38 | Double Vision | No | | Yes | |
| 39 | Stomach Awareness | No | | Yes | |
| 40 | Aware of Breathing | No | | Yes | |
| 41 | Desire to Move Bowels | No | | Yes | |
| 42 | Vomiting | No | | Yes | |
| 43 | Sudden Vomit | No | | Yes | |

Crew ID _____ FD _____ MET _____

**PRE-PILOT CHECKLIST
PART A**

Please answer each of the following as they apply to you right now:

| | | | | | |
|-----|--------------------------|------|--------|----------|--------------|
| 1. | General discomfort | None | Slight | Moderate | Severe |
| 2. | Fatigue | None | Slight | Moderate | Severe |
| 3. | Drowsiness | None | Slight | Moderate | Severe |
| 4. | Headache | None | Slight | Moderate | Severe |
| 5. | Eye strain | None | Slight | Moderate | Severe |
| 6. | Difficulty focusing | None | Slight | Moderate | Severe |
| 7. | Increased salivation | None | Slight | Moderate | Severe |
| 8. | Sweating | None | Slight | Moderate | Severe |
| 9. | Nausea | None | Slight | Moderate | Severe |
| 10. | Difficulty concentrating | None | Slight | Moderate | Severe |
| 11. | Fullness of the head | None | Slight | Moderate | Severe |
| 12. | Blurred vision | None | Slight | Moderate | Severe |
| | Dizziness: | | | | |
| | 13. With eyes open | None | Slight | Moderate | Severe |
| | 14. With eyes closed | None | Slight | Moderate | Severe |
| 15. | Vertigo | None | Slight | Moderate | Severe |
| 16. | Stomach awareness | | No | Yes | |
| 17. | Burping | | No | Yes | No. of times |
| 18. | Weakness | None | Slight | Moderate | Severe |
| 19. | Dry mouth | None | Slight | Moderate | Severe |
| 20. | ringing/buzzing in ears | None | Slight | Moderate | Severe |
| 21. | Incoordination | None | Slight | Moderate | Severe |
| 22. | Nervousness | None | Slight | Moderate | Severe |

PART B

How many hours have you been awake? _____

How many hours did you sleep last night? _____

List any medications taken in the last 24 hours:

| <u>Type</u> | <u>Name of Medication</u> | <u>Dose</u> | <u>How many hours ago?</u> |
|----------------|---------------------------|-------------|----------------------------|
| Sleep | | | |
| Antihistamines | | | |
| Decongestants | | | |
| Pain | | | |

Subject ID _____

Date _____

Time _____

MEDICATION SIDE EFFECTS CHECKLIST

Please answer each of the following as they apply to you right now:

| | | | | | |
|-----|--------------------------|------|--------|----------|--------|
| 1. | Drowsiness | None | Slight | Moderate | Severe |
| | Dizziness: | | | | |
| | 2. With eyes open | None | Slight | Moderate | Severe |
| | 3. With eyes closed | None | Slight | Moderate | Severe |
| 4. | Fatigue | None | Slight | Moderate | Severe |
| 5. | Weakness | None | Slight | Moderate | Severe |
| 6. | Difficulty concentrating | None | Slight | Moderate | Severe |
| 7. | Blurred vision | None | Slight | Moderate | Severe |
| 8. | Dry mouth | None | Slight | Moderate | Severe |
| 9. | Ring/buzzing in ears | None | Slight | Moderate | Severe |
| 10. | Incoordination | None | Slight | Moderate | Severe |
| 11. | Nervousness | None | Slight | Moderate | Severe |
| 12. | Euphoria | None | Slight | Moderate | Severe |
| 13. | Tremors | None | Slight | Moderate | Severe |
| 14. | Stuffy nose | None | Slight | Moderate | Severe |
| 15. | Confusion | None | Slight | Moderate | Severe |
| 16. | Disorientation | None | Slight | Moderate | Severe |
| 17. | Double vision | | No | Yes | |

Crew ID _____

FD _____

MET _____

POST-PILOT CHECKLIST

Please answer each of the following as they apply to you right now:

- | | | | | | |
|-----|-------------------------------------|------|--------|----------|--------------|
| 1. | General discomfort | None | Slight | Moderate | Severe |
| 2. | Fatigue | None | Slight | Moderate | Severe |
| 3. | Drowsiness | None | Slight | Moderate | Severe |
| 4. | Headache | None | Slight | Moderate | Severe |
| 5. | Eye strain | None | Slight | Moderate | Severe |
| 6. | Difficulty focusing | None | Slight | Moderate | Severe |
| 7. | Increased salivation | None | Slight | Moderate | Severe |
| 8. | Sweating | None | Slight | Moderate | Severe |
| 9. | Nausea | None | Slight | Moderate | Severe |
| 10. | Difficulty concentrating | None | Slight | Moderate | Severe |
| 11. | Fullness of the head | None | Slight | Moderate | Severe |
| 12. | Blurred vision | None | Slight | Moderate | Severe |
| | Dizziness: | | | | |
| | 13. With eyes open | None | Slight | Moderate | Severe |
| | 14. With eyes closed | None | Slight | Moderate | Severe |
| 15. | Vertigo | None | Slight | Moderate | Severe |
| 16. | Stomach awareness | | No | Yes | |
| 17. | Burping | | No | Yes | No. of times |
| 18. | Weakness | None | Slight | Moderate | Severe |
| 19. | Dry mouth | None | Slight | Moderate | Severe |
| 20. | Ringing/buzzing in ears | None | Slight | Moderate | Severe |
| 21. | Incoordination | None | Slight | Moderate | Severe |
| 22. | Nervousness | None | Slight | Moderate | Severe |
| 23. | Difficulty acquiring visual targets | None | Slight | Moderate | Severe |

Vertical Gaze Shifts Overshoot _____ (mm) Undershoot _____ (mm)

Horizontal Gaze Shifts Overshoot _____ (mm) Undershoot _____ (mm)

Were you strapped in the seat during the PILOT sim? No Loose Tight

Bioavailability and Performance Effects of Promethazine During Space Flight

Data Sheet

Name: _____

Date: _____

Subject #: _____

Time of Dosage: _____

PMZ: _____

| Sample | Time Sample Should be Taken | Saliva Time Sample Actually Taken | Urine Time Sample Actually Taken |
|--------|-----------------------------|-----------------------------------|----------------------------------|
| PRE | | | |
| 1 h | | | |
| 2 h | | | |
| 4 h | | | |
| 8 h | | | |
| 24 h | | | |
| 32 h | | | |
| 36 h | | | |
| 48 h | | | |

SUBJECT INFORMATION HANDOUT

Bioavailability and Performance Effects of Promethazine During Space Flight

In-Flight Protocol

The overall goal of the proposed research is to estimate, noninvasively, the bioavailability and cognitive effects of an operational dose of promethazine (PMZ) on the ground and during space flight. The specific aims designed to achieve this goal are to:

1. Estimate the bioavailability of PMZ given intramuscularly (IM) before and during flight from the concentrations of this drug in saliva.
2. Assess the psychomotor impairment effect of PMZ using the Portable In-flight Landing Operations Trainer (PILOT) device before and during flight.
3. Evaluate the pharmacodynamics of PMZ from its concentrations in saliva and the performance impairment results from the PILOT.
4. Determine the effect of space motion sickness (SMS) on PILOT test performance during flight.

Promethazine is used frequently in space to control symptoms of SMS. This research is designed to investigate the effect of microgravity on the availability and therapeutic efficiency of PMZ through the use of an in-flight landing-simulation training device, the PILOT. This information is operationally critical for the safe and effective treatment of SMS in flight.

Protocol

This study will include preflight and in-flight components (see attached table). Since crewmembers who will require PMZ during flight cannot be identified in advance, you will be assigned to the medicated group at the time you request intramuscular PMZ for SMS. If you do not experience SMS symptoms, or your symptoms are not severe enough to prompt a request for antimotion sickness medication, you will be assigned to the control group. You are asked not to take any other medications during the study, particularly SMS-relieving or sedative drugs. Brief checklists (attached) are to be completed before and after each PILOT session to record motion sickness symptoms, drug side effects, and other factors that could affect performance or that could be induced by the session. During flight, you will complete Part A of the pre-PILOT checklist with every saliva sample to document SMS symptoms and the subjective effects of IM PMZ.

Preflight Activities:

Familiarization and training sessions with the PILOT hardware are to be completed on L-180 and L-120 days. These sessions will require 4 hours and 2 hours, respectively. A data collection session will be conducted on L-80 days. At this session, you will provide a saliva and urine sample, and complete the pre-PILOT checklist, a PILOT test session (~35 min) and the post-PILOT checklist prior to administration of a 50 mg IM dose of PMZ. At 1, 2, 4, 8, 24, 36 and 48 hours thereafter, you will complete a PILOT test session including pre- and post-PILOT checklists, provide saliva and urine samples and complete a medication side effects checklist (attached). Additional 35 minute PILOT sessions (without PMZ) will be conducted on or about L-60, L-45, and L-3 days to maintain proficiency.

In-Flight Activities:

Medicated subjects will complete both pre- and post-PILOT checklists and a PILOT test before PMZ is given (as soon as possible after symptom onset). If you request IM PMZ, a saliva sample will be collected before PMZ is given, and again at 1, 2, 4, 8, 24, 36 and 48 hours after dosing. Part A of the pre-PILOT checklist will be completed every time a saliva sample is collected in order to record SMS symptoms and drug effects. You will also complete a PILOT test (with checklists) at the beginning, middle, and end of the shift on flight days (FD) 2 and 3. If possible, a PILOT session should also be conducted at the end of the shift on FD1. After adaptation has occurred (mid-mission), a PILOT session (with checklists) will be performed both at the beginning and the end of your shift. Another PILOT session with checklists will be performed at the beginning and the end of the shift 24 to 48 hours before landing.

Control [nonmedicated] subjects will be asked to complete Part A of the pre-PILOT checklist as soon as SMS symptoms are perceived. If you are assigned to this group, you will complete the PILOT test (with checklists) at the beginning and at the end of the shift on FD2 or 3. You will also complete two additional PILOT tests at the middle and the end of the mission as described above for medicated subjects.

It is required that you refrain from the consumption of alcohol or drugs that affect cognitive function for the 24 hours preceding any test outlined above. If drug administration is unavoidable, please contact the investigator as soon as possible in order to allow rescheduling of the session should the situation warrant. Prophylactic use of any antimotion sickness drug is strongly discouraged, as is the in-flight use of any sedative or antimotion sickness drug other than PMZ.

Schedule Summary

A summary of the preflight and in-flight sessions is attached.

Risks

Your participation in this project involves some risk.

1. Drug administration: Drug administration always involves some risk. Allergic reactions and side effects are always possible. An allergic reaction usually consists of a mild rash, but can be more severe and even life threatening. Fortunately, the drug used in this project has been used in medicine for a number of years and experience suggests that severe allergic reactions are extremely rare. However, if you are allergic to sulfites or have previously had an idiosyncratic or allergic reaction to promethazine (Phenergan) or other phenothiazines, PLEASE let us know. Side effects are more common. The most common side effects for promethazine are drowsiness, sedation, dizziness, impaired psychomotor performance and movement disorders. These side effects are transient; however, because of the potential sedative effects of this drug, you will not be allowed to drive yourself home after the experimental sessions. Another potential risk of taking drugs is that they can sometimes worsen certain pre-existing conditions. It is **extremely** important that you inform us if you have a history of any of the following:
 - a. Asthma or glaucoma
 - b. Difficulty in urinating
 - c. Seizure disorders
 - d. Kidney, gastrointestinal or liver disease
 - e. Heart disease, allergies or a respiratory disorder.

It is also important that you not take any other medication at the same time as the study drug. The interaction of one drug with another is potentially very dangerous and even if the medication you are taking does not interact with the study drug, it can adversely affect the quality of the data we obtain. We ask that you not take any medications (over-the-counter or prescription) within 24 hours of a scheduled test (including the training sessions); however, if this is unavoidable, please contact the lab to reschedule your test. Also, please refrain from consuming alcohol for the 24 hours preceding any session for the same reasons.

For female subjects: It is very important that you not take this medication while you are pregnant. **Please do not participate in this study if you think you might be pregnant!!**

A physician assigned by JSC will be on call and available for consultation should medical attention be necessary during pre-flight tests. A flight surgeon, who has been briefed on the experimental procedure, will be available on console during flight.

Confidentiality

As mandated by NASA Johnson Space Center Management Directive 1382.5, Maintaining the Privacy of Biomedical Research Data, your confidentiality will be ensured. Your written medical records will be stored in locked files. Information extracted from medical records (if applicable) will be treated in the same fashion as data gathered during experimentation. All data, including floppy disks, Syquest disks, optical disks and hard copies will be labeled with your designated subject code and stored in locked cabinets. Code sheets which permit the association of test results with you will be stored in the PI's locked files.

Please feel free to ask questions at any time.

Summary of
Preflight and In-Flight Activities

| Schedule | Duration | Activity |
|--|------------|--|
| Before Flight | | |
| L-180 days | 4 hours | Familiarization session |
| L-120 days | 2 hours | Training session |
| L-80 days | 8 x 40 min | Data Collection Session: <ul style="list-style-type: none"> •PILOT test with pre- & post-PILOT checklists, saliva & urine samples •PMZ dose (50 mg IM) •PILOT test, checklists, saliva & urine samples 1, 2, 4, 8, 24, 36, 48 hrs after dose |
| L-60 days | 35 min | PILOT Test Proficiency |
| L-45 days | 35 min | PILOT Test Proficiency |
| L-3 days | 35 min | PILOT Test Proficiency |
| In Flight | | |
| <i>Medicated Subjects:</i> | | |
| ASAP after symptom onset (before PMZ administration) | 40 min | PILOT test, checklists, & saliva sample |
| 1, 2, 4, 8, 24, 36 & 48 hrs after PMZ | 7 x 5 min | Saliva samples & Part A of pre-PILOT checklist |
| FD1 | 35 min | PILOT test & checklists (at end of shift, if possible) |
| FD2 and 3 | 6 x 35 min | PILOT test & checklists (at beginning, middle, & end of each shift) |
| Post-SMS Adaptation | 2 x 35 min | PILOT test & checklists (at beginning & end of shift) |
| 24-48 hrs before landing | 2 x 35 min | PILOT test & checklists (at beginning & end of shift) |
| <i>Nonmedicated Subjects:</i> | | |
| ASAP after symptom onset (if any) | 5 min | Part A of pre-PILOT checklist |
| FD2 or 3 | 2 x 35 min | PILOT test & checklists (beginning & end of shift) |
| Mid-mission | 2 x 35 min | PILOT test & checklists (beginning & end of shift) |
| 24-48 hrs before landing | 2 x 35 min | PILOT test & checklists (beginning & end of shift) |

NASA/JSC HUMAN RESEARCH INFORMED CONSENT*

1. I, the undersigned, do voluntarily give my informed consent for my participation as a test subject in the following research study, test, investigation, or other evaluation procedure:

NAME OF INVESTIGATION BIOAVAILABILITY AND PERFORMANCE EFFECTS OF PROMETHAZINE DURING SPACE FLIGHT

FLIGHT TO WHICH ASSIGNED N/A

PRINCIPAL INVESTIGATOR Deborah L. Harm, Ph.D. and Lakshmi Putcha, Ph.D.

RESPONSIBLE NASA PROJECT SCIENTIST Deborah L. Harm, Ph.D.

I understand or acknowledge that:

- (a) This procedure is part of an investigation approved by NASA.
- (b) I am performing these duties as part of my employment with _____.
- (c) This research study has been reviewed and approved by the JSC Institutional Review Board (IRB) which has also determined that the investigation involves reasonable risk to the subject.
(minimal or reasonable)

(d) Definitions:

"Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

"Reasonable risk" means that the probability and magnitude of harm or discomfort anticipated in the research are greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests, but that the risks of harm or discomfort are considered to be acceptable when weighed against the anticipated benefits and the importance of the knowledge to be gained from the research.

- (e) The research procedures were explained to me prior to the execution of this form. I was afforded an opportunity to ask questions, and all questions asked were answered to my satisfaction. A layman's description was provided to me. **
- (f) I am medically qualified to participate in the investigation.
- (g) I know that I can refuse to participate in the tests at any stage of their performance, and my refusal will be honored, except in those cases when, in the opinion of the responsible physician, termination of the tests could have detrimental consequences for my health and/or the health of the other subjects. I further understand that my withdrawal or refusal to participate in this investigation will not result in any penalty or loss of benefits to which I am otherwise entitled.
- (h) In the event of physical injury resulting from this study and calling for immediate action or attention, NASA will provide or cause to be provided, the necessary treatment. I also understand that NASA will pay for any claims of injury, loss of life or property damage to the extent required by the Federal Employees Compensation Act or the Federal Tort Claims Act. My agreement to participate shall not be construed as a release of NASA or any third party from any future liability which may arise from, or in connection with, the above procedures.

- (i) Except as provided for by Agency-approved routine uses under the Privacy Act, the confidentiality of any data obtained as a result of my participation as a research subject in this study shall be maintained so that no data may be linked with me as an individual. I understand, however, that if a "life-threatening" abnormality is detected, the investigator will notify me and the JSC Flight Medicine Clinic. Such information may be used to determine the need for care or medical follow-up, which, in certain circumstances, could affect my professional (flight) status.

Signature:

Signature:

Test Subject

Date

Witness

Date

- 2. I, the undersigned, the Principal Investigator of the investigation designated above, certify that:
 - (a) I have thoroughly and accurately described the research investigation and procedures to the test subject and have provided him/her with a layman's description of the same.
 - (b) The test setup involves reasonable risk to the test subject. All
(minimal or reasonable)
equipment to be used has been inspected and certified for safe and proper operation.
 - (c) The test subject is medically qualified to participate.
 - (d) Except as provided for by Agency-approved routine uses under the Privacy Act, the confidentiality of any data obtained as a result of the test subject's participation in this study shall be maintained so that no data may be linked to him/her as an individual.
 - (e) The test protocol has not been changed from that originally approved by the JSC IRB.

Signature:

Signature:

Deborah L. Harms
Principal Investigator

Date

Deborah L. Harms
NASA Project Scientist

Date

Notes:

- * This form is valid for the period including preflight, in-flight and postflight data collection sessions for the mission. Before the first baseline data collection, the Principal Investigator will repeat the briefing concerning risks involved in the investigation. A signed, dated copy of this form with attachments must be forwarded to Chairperson, Johnson Space Center Institutional Review Board, Attn: Dr. Charles Sawin, Mail Code SA, Lyndon B. Johnson Space Center, Houston, Texas 77058.
- ** A detailed description of the investigation will be attached to this consent form. The Principal Investigator is responsible for formulating this document, which should be in layman's terms such that the subject clearly understands what procedures will be required of him/her and the risks associated therewith.

The detailed description of the research must, at a minimum, include the following:

- (1) An explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
- (2) A description of any reasonably foreseeable risks or discomforts to the subject, including, but not limited to, possible adverse reactions of all medications to be administered and any risks/hazards resulting from exposure to ionizing radiation;
- (3) A description of any benefits to the subject or to others which may reasonably be expected from the research;
- (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
- (6) Clarification of all forms of behavior, if any, interdicted by the research protocol (e.g., exercise, diet, medications, etc.); and
- (7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

When appropriate, the following information shall also be provided in the detailed description:

- (8) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
- (9) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
- (10) Any additional costs to the subject that may result from participation in the research;
- (11) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
- (12) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and
- (13) The approximate number of subjects involved in the study.

SUBJECT INFORMATION HANDOUT

Bioavailability and Performance Effects of Promethazine During Space Flight

Ground-Based Protocol

Most crewmembers experience at least some symptoms of space motion sickness early on-orbit. For symptoms severe enough to require medications, the drug of choice is currently promethazine (PMZ). Although anecdotal reports of PMZ use during space flight suggest that the side effects of this drug are less in microgravity than on Earth, an objective assessment of performance-related effects, in combination with bioavailability, is necessary to establish safe, effective doses for PMZ in space.

We plan to use the Portable-In-flight Landing Operation Trainer (PILOT), a shuttle landing simulator device, to assess the effects of PMZ on performance both before and during flight in astronaut subjects. However, the study you are asked to participate in is being conducted to determine the effects of PMZ and motion sickness on performance parameters measured by PILOT and a set of motor coordination tests.

Protocol

This experiment consists of eight training sessions and two experimental test sessions. The experimental sessions will begin early in the morning, last most of the day, and will be separated by one week.

Training Sessions:

In order to assess performance decrements due to drug administration and motion sickness, it is necessary that you practice both the PILOT landing task, until your performance reaches a stable level, and the motor-coordination tests, until you become comfortable with the experimental procedures. Eight training sessions will be required. At each of the sessions, you will perform both the landing task and the motor-coordination tests six times. Within each motor-coordination test, there are four different tasks: 1) coordination, 2) tracking, 3) handwriting, and 4) switching. There are six trials for both the handwriting and coordination tasks for each session. There is only one trial per session for both the tracking and switching tasks. Each training session will be approximately 25 – 30 minutes in duration and can be scheduled at any time of day that is mutually convenient. Up to four training sessions can be conducted for one day. However, there must be a 10-minute rest break between sessions: and subsequent training sessions should be 24 – 48 hours after the previous training session.

Experimental Sessions:

Your first experimental session will be scheduled within 48 hours of the last training session. At each of the experimental sessions, there will be seven data collection sessions. The first will be a pre-drug administration, and the following six will be at 1-, 2-, 3-, 4-, 6-, and 8-hr post drug administration. Each data collection session will last approximately 25 - 30 minutes and will include a saliva sample, 6 landings, the motor-coordination tests, and a PILOT checklist. No other activities will be required, so please bring something to occupy yourself during the time between data collections. You will not be allowed to leave the building between arrival and completion of the 1-, 2-, 3- and 4-hr sessions. You will be allowed to leave the building after the 4- and 6-hr sessions. However, you will be restricted to walking only, and you must stay on site.

Upon arrival, you will complete a brief questionnaire. The protocol and potential side effects of PMZ will be reviewed at that time. You will then perform a "warm-up" landing and 6 additional landing simulations as well as the motor-coordination tests. You will then be asked to complete a PILOT checklist to record any symptoms which might be induced by the landing simulator, and provide a saliva sample. A 50-mg oral dose of PMZ or placebo will then be administered.

At one-hour post drug administration, you will provide a saliva sample, perform six PILOT landings, the motor-coordination tests and then fill out the PILOT checklist. The same procedures will be followed at the 2-hr post drug administration session. However, after the PILOT checklist for this session, you will then go through a motion sickness provocation test.

The motion sickness provocation test will be conducted in a rotating chair using a modified Stair Velocity Motion Test (SVMT) protocol. In this test, you will make head movements while seated in a rotating chair. Initially, the chair will be accelerated at $6^0/\text{sec}^2$ to a velocity of 2 RPM. As the chair rotates, you will execute 5 standardized head movements (front, right, back, left, front) over a 20-second period. Each head movement will be made to one of four pads positioned at each final stop location. Before the test, the pads will be adjusted such that you will attain an angle of approximately 40^0 — 45^0 to the rotating axis with each head movement. Chair velocity will be increased incrementally by 4 RPM after every 40-head movements (8 sets). You will remain in the upright seated position between sets of head movements for a 20-second period.

During the test, you will report symptoms to an experienced and trained test operator after each block of 40 head movements. The test operator will also watch for external signs of motion sickness (sweating, pallor). The reported or observed symptoms will be scored for severity using the Graybiel scale of motion sickness symptoms. The test will be terminated when you reach the Malaise III (8 points) or mild to moderate nausea endpoint of motion sickness or after 40 head movements have been performed at the maximum chair velocity of 35 RPM, whichever comes first.

Once the motion sickness provocation test has been conducted, you will begin the post-motion sickness protocol, which consists of 6 PILOT landings, the motor-coordination tests and a PILOT checklist. Depending upon the length of the motion sickness provocation test, these landing trials may serve as the 3-hr data collection trials.

The remaining data collection sessions (3- or 4-hr, 6-hr and 8-hr) will be conducted identically to previous data collection sessions (pre-drug and 1-hr). The experimental session will be repeated one week later. You will receive PMZ at one session and placebo at the other. The order of administration of PMZ or placebo will be random. Additionally, the order of PILOT landing tasks and the motor-coordination tests will be balanced to eliminate changes in performance due to experimental order.

Optional Participation:

Blood draws have been added to the study. Your participation in the blood draw portion of the study is **optional** and in no way will affect your participation in the rest of the study. Blood samples (5ml) will be collected at pre-drug administration, 1-, 2-, 3-, 4-, 6- and 8-hr post-drug administration via an intercatch placed in the antecubital vein. Urine voids will be collected once at pre-dose, and as needed for 24-hr after drug-administration. Samples will be processed and analyzed for parent drug and metabolite concentrations.

Risks

Your participation in this project involves some risk.

1. Drug administration: Drug administration always involves some risk. Allergic reactions and side effects are always possible. An allergic reaction usually consists of a mild rash, but can be more severe and even life threatening. Fortunately, the drug used in this project has been used in medicine for a number of years and experience suggests that severe allergic reactions are extremely rare. Side effects are more common. The most common side effects for promethazine are drowsiness, sedation, dizziness, impaired psychomotor performance and movement disorders. These side effects are transient. Another potential risk of taking drugs is that they can sometimes worsen certain pre-existing conditions. It is **extremely** important that you inform us if you have a history of any of the following:
 - a. Asthma or glaucoma
 - b. Difficulty in urinating
 - c. Seizure disorders
 - d. Kidney, gastrointestinal or liver disease
 - e. Heart disease, allergies or a respiratory disorder.

It is also **extremely** important that you not take any other medication at the same time as the study drug. The interaction of one drug with another is potentially very dangerous and even if the medication you are taking does not interact with the study drug, it can adversely affect the quality of the data we obtain. We ask that you not take any medications (over-the-counter or prescription) within 7 days of a scheduled test (including the practice sessions); however, if this is unavoidable, please contact the lab to reschedule your test. Also, please refrain from consuming alcohol for the 48 hours preceding any session for the same reasons.

2. Motion Sickness: Symptoms of motion sickness can include stomach awareness, nausea, sweating, headache, dizziness, and/or vomiting.

Feel free to ask any questions regarding the experimental procedure at any time. A doctor will be available for consultation.

Benefits

We cannot and do not guarantee that you will receive any benefits from this study; however, you will receive a thorough physical examination before this study and the results will be available to you.

Confidentiality

Any information obtained during this study and identified with you will remain confidential and will be disclosed only with your permission. The Food and Drug Administration of the U.S. Government may inspect the records regarding your participation in this study, but confidentiality will be maintained.

Reimbursements and Costs

You will receive \$10 per hour to compensate you for the time you spend in the laboratory, if allowed by your employer.

Nonparticipation or Withdrawal

Your decision whether or not to participate will not prejudice your future relationship with the Johnson Space Center or NASA. If you decide to participate, you are free to discontinue your participation at any time and you will receive compensation for time already invested in the project.

Read this handout carefully and if you have any questions, PLEASE ASK! If after reading this information you are willing to participate in the study, please sign the attached consent form. We will contact you soon to schedule dates for the experiments.

Date: _____

Signature of Investigator

Signature of Subject

MOTION SICKNESS SYMPTOMS

SYMPTOM SCORING

Motion sickness symptoms are scored in accordance with a diagnostic scale developed by Graybiel and his colleagues. Different levels of severity of symptoms may occur within several different symptom categories. A point value is assigned to the different severity levels. As a subject experiences symptoms during a test, the value of each symptom is recorded. When the cumulative symptom point value reaches a predetermined level, the test is terminated. It should be noted that if a symptom disappears before the test is terminated, the value of that symptom is subtracted from the cumulative total.

The Malaise III (MIII) level of motion sickness is the standard motion sickness endpoint used for most testing in the laboratory. This level of severity (accumulation of 8 points) was chosen for routine use because it requires that subjects manifest at least a few signs or symptoms that are relatively obvious changes from baseline. The MIII level, however, is not excessively severe. The symptoms are generally temporary in nature. Subjects are usually able to return to their daily activities and function normally.

SYMPTOM DEFINITION

The recognition and scoring of symptoms with this procedure is subjective. With properly trained observers and adequate instructions to the subject, it is possible to maintain reasonable accuracy and consistency of results. The following operational definitions of the signs and symptoms of motion sickness are used in an effort to maintain consistency.

Epigastric Awareness (1 point) - Epigastric awareness is the least severe symptom to occur in the nausea syndrome. It is a mild sensation that may be felt in the upper abdominal area, stomach, esophagus, or throat. To qualify as epigastric awareness, the symptom must be intermittent (i.e., it may be present when head movements are being made, but disappears when the head is held still). Epigastric awareness should not be an uncomfortable or disquieting sensation for the subject. It should be a symptom that is minimally noticeable.

Epigastric Discomfort (2 points) - Epigastric discomfort is a sensation that is slightly more intense than epigastric awareness. It may be felt in the upper abdominal area, stomach, esophagus, or throat. To qualify as epigastric discomfort, the symptom must be persistent (i.e., it is present even with the head held still although it may wax or wane slightly as a function of starting and stopping head movements). Epigastric discomfort is a symptom that the subject should regard as slightly uncomfortable, but it is not severe enough to cause any immediate concern about vomiting.

Nausea I (4 points) - Nausea I is a moderately intense and persistent unpleasant sensation that may be felt in the stomach, upper abdomen, and especially esophagus, or throat. The intensity may wax and wane and be most pronounced when head movements are made. The subject may become noticeably less talkative as he/she begins to experience Nausea I. When Nausea I is suspected, the test operator should immediately become more verbally interactive with the subject to ascertain how severe the unpleasantness has become. The subject should be asked if they feel that continuing additional head movements might get them close to the point of "throwing up". If the answer is "yes" or "maybe", Nausea I is present and the test should be stopped immediately. If the answer is "no", the test operator should verify that the subject believes he/she is in no danger of throwing up and should allow the test to continue. (At this point, the subject is probably on the border line between Epigastric Discomfort and Nausea I.) The test should be terminated as soon as the above defined conditions for Nausea occur, even if no other symptoms are present. Even though

Nausea I is 4 points and the desired MIII endpoint is 8 points, the risk of the subject going rapidly from Nausea I through Nausea II to vomiting is normally too great to warrant continuing the test.

NOTE: If the test operator believes the conditions for Nausea I have not been met, but in response to the question, "Do you feel nauseated?" the subject answers "yes", then the test should be terminated.

Nausea II/III (8 points) - This is a very severe symptom and is to be avoided if at all possible in the laboratory. Nausea II/III is present when the subject is forcefully swallowing, indicates that one more head movement will probably cause him/her to throw up, or is in such distress that he/she cannot even open his/her mouth to verbalize the stress. The test operator should be acutely alert to this situation and in a clear, distinct manner ask the subject to give a hand signal if he/she wants to stop. An emesis bag should be handed to the subject, the subject should be told to hold his/her head still, and the chair should be stopped at a nominal rate. The chair should not be allowed to continue rotating if the subject is vomiting or retching.

Vomiting (16 points) - Vomiting is to be avoided in the laboratory if at all possible. Vomiting is the overt act of expelling the contents of the stomach through the mouth. Loud gagging or coughing sounds usually accompany the expulsion of the vomitus substance. Vomit is unpleasant to the sight, smell, and touch of both the subject and test operator, hence, the above warning.

Flushing/Subjective warmth (1 point) - This is a symptom reported by the subject that is experienced as a gradual or sudden sensation of increased warmth of the surface of the body. It usually starts as a flushed sensation of the face and neck. It may be seen by the test operator as a blushing of the face. The warmth may also be localized to the chest, back, underarms, or thighs.

Pallor I (2 points) - Pallor is detected by the test operator. Pallor I is the first noticeable blanching or whitening (palling) of the skin color on the face. It may not involve the entire face, but be limited to small areas such as around the mouth or the ear lobes. A faint pale splotchy appearance of the face would be Pallor I. The detection of Pallor I is difficult, but may sometimes be aided by using the subject's clothing (if light colored) or the walls of the room as a color reference. (Prior to the start of the test, the test operator should also spend 30-60 seconds carefully reviewing the subject's face to establish a "visual fix" of the subject's normal facial color.)

Pallor II (4 points) - Pallor II is more easily detected than Pallor I. Pallor II is present when the subject's entire face, and possibly ears, neck, and upper chest (if visible) have lost their normal color. Pallor II should normally be the most severe form of pallor induced under laboratory test conditions.

Pallor III (8 points) - Pallor III is a rare condition and should be reserved for situations where the subject's face and upper torso appear totally devoid of any color. The skin has an ashen white appearance and the phrase "white as a ghost" would accurately describe the subject. This severe form of pallor would normally occur only on the KC-135 during parabolic flight or in some other situation where the stress is extreme and prolonged.

Sweat I (2 points) - Sweat I is the first noticeable onset of mild cold sweating that is sensed by the subject. Sweat I is normally not visually apparent to the test operator. Instead, the subject is aware of a light amount of sweat on the forehead, upper torso, or underarms. Sweat I may be experienced as a mild clammy or sticky feeling before the actual appearance

of sweat. In certain tests at higher RPM's, the subject's skin may feel cooler due to sweat evaporation. It is advisable for the test operator to occasionally ask the subject to touch his/her forehead to check for any light sweating.

Sweat II (4 points) - Sweat II is a moderate level of more generalized body sweat that is distinctly felt by the subject and noticeable to the test observer. Sweat II may be seen as small beads of perspiration on the forehead or face. If the subject is wearing tight fitting clothing, it may be seen as a slight dampening of the clothing. Again, at higher RPM's, the sweat may evaporate causing the subject to feel cool.

Sweat III (8 points) - Sweat III is a very profuse whole-body sweat that can be easily seen as large beads or rivulets of sweat on exposed parts of the subject's body, especially face and neck. With Sweat III, the subject's clothing will be noticeably damp, particularly on the chest, underarms, and back. Sweat III is rare and typically will not be seen in the laboratory.

Increased Salivation I (2 points) - This is the first noticeable onset of a slight increase in the amount of saliva accumulating in the mouth. The subject may experience a slight increase in the need to swallow. Salivation I is a difficult symptom to detect and can be easily faked by the subject. It is helpful for the test operator to ask the subject at the beginning of the test if his mouth feels normal or dry and to stay aware of any changes.

Increased Salivation II (4 points) - Salivation II is a pronounced increase in the amount of excess saliva accumulating in the subject's mouth. With Salivation II, the subject has a noticeable need to swallow more frequently. This increased swallowing should not be confused with Nausea II/III. However, if such swallowing is present, the test operator should clearly determine if it is Salivation II, or due to Nausea II/III.

Increased Salivation III (8 points) - This is a symptom which is essentially non-existent as far as our symptom scoring is concerned. Salivation III would be seen as copious amounts of saliva bordering on drooling of the mouth. In actual practice, we do not see Salivation III and should not use it in our symptom scoring vocabulary.

Drowsiness I (2 points) - This symptom is a slight decrease in the mental alertness of the subject where the subject reports being a little bit sleepy or experiences a slight mental confusion. With Drowsiness I, the subject may be less verbally responsive to the test operator's questions. If the subject reports he feels relaxed, he/she may have Drowsiness I.

Drowsiness II (4 points) - This symptom is an extension of Drowsiness I where all of the signs and symptoms described above are very obvious to both subject and test conductor. With Drowsiness II, the subject may be excessively sluggish in his verbal interaction and head movements, and may indicate he feels like he could fall asleep. Drowsiness II should not be confused with Nausea II/III. If the subject shows obvious signs of slowing down all of his actions, the test operator must take immediate steps to determine if Nausea II/III is present.

Drowsiness III (8 points) - This symptom is scored when the subject is observed to be literally falling asleep during the test and appears unable to perform required tasks (e.g., head movements) even when prompted by the test operator. This is a rare symptom not generally seen in laboratory tests where the stimulus exposure is relatively short.

Headache (1 point) - This symptom is defined as a mild to moderate headache that the subject believes has been caused by the motion sickness test. The headache may be

localized to one region of the head or it may involve the entire head. It may be of a persistent nature or it may wax and wane. A sensation of head fullness would qualify as Headache. During testing in the laboratory, Headache is usually a rare symptom and is mild when it occurs. If, however, a fairly intense and uncomfortable headache develops, a score of 2 points should be given.

Dizziness (1 point) - This symptom includes subject reports of dizziness, vertigo, spatial disorientation, wobbliness, or unsteadiness. If any of these sensations are present and persistent, Dizziness is scored. If these sensations are present only when the subject's head is undergoing motion but disappears within seconds after head motion stops, then by definition, Dizziness is not scored. In rare cases, Dizziness may become a dominant and distressful sensation for the subject. In these cases, 2 symptom points should be scored.

Possible Side Effects of PMZ

Common Side Effects:

Drowsiness
Sedation
Dizziness
Impaired Psychomotor Performance
Movement Disorders
Blurred Vision
Dryness of Mouth
Confusion (rare)
Disorientation (rare)

Contact Medical Monitor Immediately if:

Torticollis (an abnormal twisting of the neck, associated with muscle contracture) (rare)
Dystonia (twitching of the muscles in the trunk and/or limbs that can sometimes be severe) (rare)
Oculogyric Crisis (fixation of the eyeballs at one point in space, usually upward) (rare)
Protrusion of the Tongue (tongue hanging out, not on purpose) (rare)

Allergic reactions:

Mild Rash
Photosensitivity (rare)
Swelling (rare)
Increased Blood Pressure/ Heart Rate/ Respiration

PMZ can also worsen a pre-existing condition, such as:

Asthma or Glaucoma
Difficulty in Urinating
Seizure Disorders
Kidney, Gastrointestinal, or Liver Disease
Heart Disease or Respiratory Disorder

Be alert of these warning signs and contact the medical monitor if any symptoms are reported, besides the common side effects, or the common side effects become excessive. Also, *make sure to contact the medical monitor if the subjects' vital signs fall outside of 50-100 heartbeats per minute or 90/50-140/90 for blood pressure (S/D)*. If you're not sure, or you feel the symptom is borderline, contacting the medical monitor can't hurt. Better to be safe than sorry.