

HUMAN RESEARCH MASTER PROTOCOL INFORMATION

Spacelab or Shuttle Flight Designation STS 51-D
Experiment Designation DSO 455

1. Title

Clinical Characterization of Space Motion Sickness

2. Organization Conducting the Research

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3. Hypothesis

The overall objective of this project is to better define the clinical characteristics of space motion sickness. The time and nature of SMS onset, progression and resolution of SMS symptoms, and the relationship of treatment modalities to speed of recovery will be examined. In obtaining this clinical characterization, the validity of several theories will be tested.

These theories are:

- A. SMS is due to otolith-otolith imbalance.
- B. A decrease in the gain of the horizontal VOR is a causative factor for SMS symptomatology.
- C. Upward-downward asymmetries of the vertical optokinetic responses are otolith-dependent and would be maximized in zero gravity.
- D. Alteration of gastrointestinal motility is a marker of SMS and is detectable prior to the onset of overt G.I. symptoms.
- E. G.I. motility signs can be a useful indication of efficacy of treatment either of G.I. directed drugs or other treatment modalities.
- F. SMS produces autonomic signs different from classical acute motion sickness signs.

We hypothesize that a careful examination, directed toward the specific ocular motor abnormalities that the above mentioned theories predict, together with an assessment of gastric motility and a survey of autonomic reactions as SMS indicators constitutes the most practical method for characterizing SMS and for future development of SMS countermeasures.

5. Purpose of Research

A. Historical Background

Space motion sickness has emerged as a significant factor in the space shuttle program. Symptoms with some similarity to those of other types of motion sickness have been reported by various astronauts since 1961. During the Mercury and Gemini programs, complaints of SMS were rare. However, since the beginning of the Apollo missions when astronauts have been free to move around in space crafts, the incidence of SMS has approached 50%. On first exposure to weightlessness, 45-50% of crewmembers experience this transient syndrome which may include motion sensitivity, malaise, anorexia, vomiting, lethargy, somnolence, headache and nausea. Since this symptom complex is related to movement, particularly pitching and rolling motions, it seems appropriate to label it motion sickness. However, since it does not typically include the hallmarks of terrestrial motion sickness such as sweating or pallor, the qualifying term "space" has been added. Further, there is frequently no correlation between terrestrial motion sensitivity and space motion sickness in a given individual. Despite the interest in and many studies of SMS since the Apollo program, this

malady remains poorly understood and treatment is unsatisfactory.

B. New Information Expected

The primary objective of this proposal is to more completely define the clinical characteristics and temporal profile of space motion sickness, pre-requisites for the effective management of SMS. Information concerning the reaction of previously flown subjects will be of particular importance since knowledge of the temporal aspects of the process are incomplete without such information. The approach to be used is to obtain clinical history and examination information by a trained astronaut on crewmembers affected by SMS.

The history portion should concentrate on accurate description of symptoms, their evolution and precipitants. Accurate characterization of central and autonomic nervous system symptoms of SMS will be possible only if affected individuals are examined and asked specific questions at the time they are sick.

Such a clinical approach offers several advantages: (1) Since the evaluations will be brief, they can be tailored to fit in with other schedules or performed more frequently in individuals who must curtail their activities because of SMS. The ability to perform a rapid examination is also important because plastic-adaptive changes in the vestibulo-ocular reflex (VOR) are rapid so that some abnormalities might only be observable for a relatively short period after the onset of weightlessness. (2) Clinical tests require no specialized or bulky equipment -- an ophthalmoscope, Frenzel lenses, a Maddox Rod and a recording stethoscope are the main items. (3) Although clinical tests do not provide permanent records, they are very sensitive--more sensitive than most quantitative methods for recording eye movements. For example, electro-oculography can provide only semiquantitative measurement of vertical eye movements. By contrast, the clinical observer can detect eye movements as small as 20 minutes of arc.

While observation is frequently the most sensitive and informative method of characterization, it has limitations. Many processes cannot be observed (electrical activity) or only approximated (temperature), nor can they be recorded for objective measurement. For this reason, the senses must be augmented by simple and convenient recordings. Some fundamental measures of autonomic reactivity, EKG intervals, electro-oculography, color and temperature are included in the simplest possible manner. In addition to examinations directed toward the evaluation of ocular motor changes, evaluation of alterations in the gastrointestinal system is an integral part of the clinical

characterization of SMS. Past research has shown that decreased gastric contraction and tone are associated with some types of motion sickness. Since the gastro-intestinal system frequently demonstrates the most obvious response to motion sickness with symptoms culminating in vomiting, the historical progression of abdominal symptoms, together with examination of gastrointestinal motility will help to complete the characterization of SMS.

Our goals are therefore threefold:

1. To continue the specific characterization of the clinical symptomatology of SMS.
2. To test the efficacy of proposed SMS countermeasures
3. To evaluate the efficacy of selected pharmacologic agents on the gastrointestinal symptoms of SMS.

6. Justification For Use of Human Subjects

Human testing is required to document the clinical characteristics of SMS in crewmembers on-orbit.

7. Study Plan and Schedule

A. Dates/Duration

Training in examination and history techniques will require 3 sessions with each session lasting one hour. These sessions will include familiarization with unique hardware, experimental protocols and methods of reporting. The first of these should be conducted by at least F-3 months and all should be complete no later than F-1 month. Baseline data collection can be easily conducted in conjunction with sims. A total of 3 baseline sessions is required within the F-90 day to F-30 day time frame.

B. Place of Training/Test

All training/testing activities will be conducted at JSC for STS 51-D.

C. Subjects

Mission Specialist Maj. S. Nagel will participate as the clinical observer during the STS 51-D study, and Dr. Shannon Lucid and Gregory Jarvis (Hughes PS) will serve as subjects.

D. Overview of Schedule

PREFLIGHT

ACTIVITY	TIME (MINUTES)	CONSTRAINTS
1. Examination Technique Training	180	JSC
2. Baseline Data Collection	180	With Sims F-90 days F-60 days F-45 days

INFLIGHT CREW ACTIVITIES

ACTIVITIES	TIME (MINUTES)	CONSTRAINTS
1. Clinical Exam	30	Early & late--MD1 Daily--MD 2, 3, 5
2. Bowel Sounds	30	Sick crewman with first use of medication (can be performed simultaneously with clinical exam)
3. Head Movements and Reporting	15	MD 1, 2, 5

POSTFLIGHT REQUIREMENTS

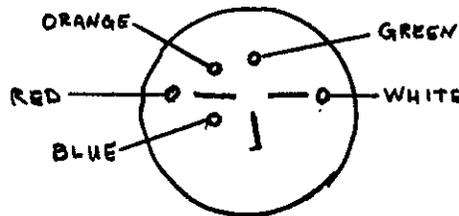
ACTIVITY	TIME (MINUTES)	CONSTRAINTS
Examination	15	L+0 days L+7 days

8. Experimental Protocols and Equipment

A. Protocol: EOG Procedures

1. Unstow EOG amplifier, electrode harness, electrode supplies, and recorder with the subcarrier oscillator (SCO).

2. Apply color-coded electrodes at the outer canthus of each eye for measuring horizontal eye movements and above and below the orbital ridge of the right eye for vertical eye movements. A ground electrode should also be applied at the center of the forehead. (See sketch below.)



3. Attach electrode harness to the electrodes (color coded to position).

4. Plug electrode harness into the EOG amplifier. *small plug*
(large plug)

5. Connect amplifier cable *into* recorder/SCO assembly *(small plug)*

6. Insert tape and record subject ID and MET.

7. Check recorder controls:

REC LEVEL - Max clockwise

LINE IN/MIC - LINE IN

COUNTER - 000

Simultaneously depress - PLAY, RECORD

SCO - ON

8. Perform calibration eye movements using the extended wand.

9. Perform procedures specified under Clinical Exam with EOG recording throughout.

B. Protocol: Clinical Exam

1. Have subject look straight ahead without fixation look for nystagmus, vertical skew deviation, or other abnormal eye motion. Describe estimated amplitude, direction, and duration.

2. Have subject focus on light source while looking through Maddox Rod lens and report whether the observed horizontal red line falls above, below or on the light point.

3. Have subject look 30 degrees right and left; then 20 degrees up and down. At each end-eye position, observe for nystagmus or abnormal eye motion. Describe amplitude, direction of fast component, and duration.
4. Repeat #1 and #3 observing subject through Fresnel lenses.
5. Repeat #1 and #3 observing subject through ophthalmoscope.
6. Have subject track your finger through 8 directions.
7. Have subject look between two targets held 30 - 45 apart first in the horizontal and then in the vertical plane. Fix eyes on each target briefly. Observe for overshoot or undershoot and describe direction estimated amplitude, and duration.
8. Have subject oscillate head 15 - 20 degrees first horizontally, then vertically while focusing on wrist watch. Record any blurring or oscillopsia (apparent movement of watch) compared to preflight. Oscillate head at increasing frequencies.

NOTE: Discontinue with any complaint by subject.
Record complaint and corresponding activity.

9. Using ophthalmoscope, observe retina while subject oscillates head at 1-2 Hz, first horizontally then vertically. Record retinal movement--stationary, right, left, up, or down.
10. Have subject track head-fixed target at frequencies of 1 Hz, first horizontally then vertically. Observe and record nystagmus or corrective saccades with head movements (direction, preponderance, and duration).

C. Protocol: Bowel Sounds

1. Unstow Sony Walkman, cassettes, and microphone belt.
2. Remove shirt.
3. Strap microphone belt around abdomen with battery pack midline.
4. Plug connector into Sony (red jack-LINE IN/MIC)
5. Insert tape, record subject ID and time on tape.

6. Set recorder controls:

REC LEVEL - Max clockwise
LINE IN/MIC - LINE IN
COUNTER - 000
Simultaneously depress - PLAY, RECORD
Microphone battery pack - on

7. Don earphones and ensure sound (ambient noise, tap microphones, etc) is present. If not, check controls, etc.

8. If symptomatic, take two 10 mg Reglan tablets. Record time.

9. Continue recording until cassette complete (45min).

10. If time allows, reverse tape and continue recording for another 45 min. (Record time and ID on second side of tape.)

11. Microphone Battery - OFF

12. Disconnect and stow.

D. Protocol: Temperature and Color

1. Obtain paper thermometer.

2. Place under tongue at back of mouth.

3. After 5 minutes remove, wait 1 min, record.

4. Obtain pallor (skin color) card.

5. Move to source of good illumination (daylight if possible).

6. Place card beside cheek and record # of color that most closely matches.

E. Protocol: EKG Recording

1. Obtain Holter recorder.

2. Record clock time in recorder window:
Flashing colon - PM
Steady colon - AM

3. Grasp silver electrode handles (pb in left hand).

4. Depress pb for 1 minute.

5. Stow recorder.

F. Protocol: Estimation of Movement

1. Have subject close his/her eyes.
2. In random sequence, slowly move the subject sequentially through 30, 45, 60, and 120 degrees of rotation in roll, pitch, and yaw.
3. After each movement record the subject's estimate and the actual degree of movement.
4. Note and record the axis in which the subject is most sensitive to movement.

G. Equipment List

Clinical Characterization Kit containing:

1. Ophthalmoscope
2. Frenzel Lens
3. Head Fixed Pointer
4. Bowel Sound Recorder Assembly:
 - WMD6 Tape Recorders
 - Abdominal Stethoscope
 - Battery Pack
 - Pallor Card
 - Cassette Tapes
 - Headset (WMD6)
5. Maddox Rod
6. Paper Thermometers
7. Holter Recorder Assembly:
 - Holter Recorder
 - Hand Grip Electrode Set
 - Tape and Take-up Reel
8. EOG Recording Assembly:
 - Subcarrier Oscillator
 - DC Amplifier
 - Electrode Harness
 - Amplifier Connecting Harness
 - Calibration Wand
 - Electrodes in Ziplock Bag
 - Spare Batteries
 - Cassette Tapes

9. HAZARDS ANALYSES AND SAFETY PRECAUTIONS

A. Potential Hazards:

Minimal risk is associated with the administration of Metoclopramide. Persons at risk would generally possess specific medical conditions that would be detected in the course of a flight physical examination. (For more details on contraindications and side effects, refer to Appendix A.)

B. Safety Precaution to be Applied:

Those crewmen potentially taking Metoclopramide to eliminate GI symptoms will undergo the usual NASA clinical sensitivity trials preflight.

10. POSSIBLE INCONVENIENCES OR DISCOMFORTS TO SUBJECTS

Some parts of the clinical examination may aggravate existing SMS symptoms. If this occurs, the clinical exam will be abbreviated to omit those portions aggravating SMS symptoms.

11. EXTENT OF PHYSICAL EXAMINATIONS

The currently required physical is sufficient for this study.

12. AVAILABILITY OF A PHYSICIAN AND MEDICAL FACILITIES

A physician is available as needed during pre- and post-flight activities. The flight surgeon will be available through the MOCR during flight.

13. REQUIRED STATEMENTS FOR FLIGHT PERSONNEL SUBJECTS

A. The subject will be free to withdraw from the research at any time.

B. The identity of human subjects will not be released to the general public without his or her a consent unless specifically required by law.

C. There will be no additional wage, salary or other payment of any form paid, given, or in any manner delivered to the crewperson subjects of this investigation in that the subjects are NASA employees or under contract to NSDS and the terms of their contracts with NASA include their participation as subjects in approved experiments.

D. The crewperson subjects are NASA employees or under contract to NASA and the training/testing is part of their employment circumstances. Therefore, NASA is responsible for compensation for injury, death, or property damage to the extent required by the Federal Employees Compensation Act or the Federal Tort Claims Act.

14. REQUIRED ATTACHMENTS

1. Appendix A: Side Effects of Metoclopramide

2. Curricula Vitaes are on file.

APPENDIX A

SIDE EFFECTS

Some adverse effects may occur if Metoclopramide is given in the usual therapeutic doses. Side effects have been reported in up to 20% of patients, but these are usually mild, transient and reversible after withdrawal of the drug.

Drowsiness and lassitude are the commonest side effects, being reported in up to 10% of patients. Also, feelings of anxiety, agitation, or motor restlessness may occur. These feelings are dose-related and occur more frequently after intravenous administration. In addition, urticaria or maculopapular rash may occur on rare occasions. Extrapyramidal side effects are uncommon. True dystonic reactions occur in only about 1% of patients and include trismus, torticollis, facial spasms, opisthotonos and oculogyric crises. These reactions disappear within 24 hours after withdrawal of Metoclopramide. Parkinson symptoms of tremor, rigidity and akinesia are rarely seen except after excessively high doses or in patients with decreased renal function. Children are particularly susceptible to developing symptoms resembling parkinsonism that respond rapidly to anti-parkinson drugs such as intramuscular diazepam or benztropin.

Metoclopramide is a potent stimulant of prolactin release. Long-term administration may lead to breast enlargement or nipple tenderness, galactorrhea, and menstrual disorders in some patients.

DOSAGE

The usual oral dosage of metoclopramide in adults is 10mg., 20 to 30 minutes before meals and at bedtime. Dosage up to 80mg/day can be tolerated but the incidence of side effects increases above 40mg/day. For diagnostic procedures in adults, 20mg of Metoclopramide can be given orally 30 minutes before the procedure or 10 to 20mg can be given parenterally 5 minutes before examination.

HIGH DOSES OF METOCLOPRAMIDE

Doses of Metoclopramide ranging from 70 to 210 mg. i.v. have been administered to patients to control emesis associated with chemo-therapy. Usually this dose is given five times within a 24 hour period. Thus, the chemotherapy patient can receive between 350 and 1050 mg of the drug in one 24 hour period. The use of these levels of the drug is approved by the Food and Drug Administration (FDA). According to recent reports by a number of investigators at the Annual Meeting of the American Society of Clinical Pharmacology and Therapeutics (March, 1983), these higher doses of metoclopramide do not result in the appearance of any new side effects,

although the frequency of their incidence increases slightly. In addition, according to these investigators, the doses of 10 and 20 mg described in the Physicians Desk Reference are low, therapeutic doses that were initially tested to obtain FDA approval for introduction of the drug for other uses and indication. It was the experience and opinion of the researchers that those individuals displaying the more troublesome side effects (e.g. extrapyramidal side effects) would probably experience these symptoms at higher doses. In all cases, these side effects were readily reversible with diphenhydramine, an antihistamine that is currently sold over-the-counter to treat motion sickness (Brand Name: Benadryl).