Recent Pharmacology Studies on the International Space Station

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11 December 2014
Many physiological systems are affected by spaceflight.
Medical Complaints in Space

Based on ISS Missions:
- Anorexia
- Space motion sickness
- Fatigue
- Insomnia
- Dehydration
- Dermatitis
- Back pain
- Upper respiratory infection
- Conjunctival irritation
- Subungual hemorrhage
- Urinary tract infection
- Cardiac arrhythmia
- Headache
- Muscle strain
- Diarrhea
- Constipation

Based on Space Shuttle,

1988-1995
- Facial Fullness
- Headache
- Sinus congestion
- Dry skin, irritation, rash
- Eye irritation, dryness, redness
- Foreign body in eye
- Sneezing/coughing
- Sensory changes
- Upper respiratory infection
- Back muscle pain
- Leg/foot muscle pain
- Cuts
- Shoulder/trunk muscle pain
- Hand/arm muscle pain
- Anxiety/annoyance
- Contusions
- Ear problems (usu. Pain)
- Neck muscle pain
- Stress/tension
- Muscle cramp
- Abrasions
- Fever, chills
- Nosebleed
- Psoriasis, folliculitis, seborrhea
- Low heart rate
- Myoclonic jerks

From Clement, Fundamentals of Space Medicine, 2003
Pharmaceutical Use on Shuttle

Our Mission at the JSC Pharmacology Lab...

...is to ensure that flight surgeons have good information about how administered pharmaceuticals will work in the extreme conditions of spaceflight

...which means that we have to understand the physiological changes caused by living in the spaceflight environment

...as well as the effect of the spaceflight environment on the stored drugs themselves

...as well as the pharmaceuticals’ mechanism of action
Research in JSC Pharmacology

Pharmaceuticals
- Usage tracking
- Stability

Pharmacokinetics
- Absorption/Distribution
- Metabolism/Excretion

Pharmacodynamics
- all the reasons medications are used
Medication Usage

How are medications used on spaceflight missions?

Retrospective Analysis of Medication Usage During Long Duration Spaceflight — a research study (PI: Wotring) that analyzes medication uses on past missions, conducted in partnership with occupational health efforts in JSC Pharmacy, directed by Dr. Tina Bayuse
**Medication Usage**

*Dose Tracker Application for Monitoring Crew Medication Usage, Symptoms and Adverse Effects During Missions* – a research study (PI: Wotring) that uses a specially designed iPad app for crew to record their medication uses.
Medication Usage

Dose Tracker
User: 7992

Time: 11:20 PM

Efficacy: No entries

Cancel Type

Time: 12:00 PM

Type: Headache

Cancel Side Effects

Quantity: Post nasal drip/cough

Medication: Congestion/stuffy head

Other: Enter ailment type

Efficacy: Vision problems

Type: Itching

Quantity: None

Add another side effect: [ ]

Wotring  JSC NASA Pharmacology  11 December 2014
Human Exploration Research Analog (HERA)

The Human Exploration Research Analog is a two-story, four-port habitat unit. It is cylindrical with a vertical axis, and connects to a simulated airlock and hygiene module.

Duration: 4-60 days
Room Temperature: 72° F. (+/- 5 degrees)
Light/Dark Cycle: Lights on 0600, lights out 2130, 7 days per week, no napping is permitted
Monitoring of study operations 24 hours a day
Stability –
How long is a medication safe and effective?

Flight-aged medications that have been returned from the ISS by SpaceX Dragon are being analyzed for active pharmaceutical ingredient content and degradants/impurities (in-house and in collaboration with FDA & academic experts; working with JSC Pharmacy)
Stability –
How long is a medication safe and effective?

1. Evaluating packaging materials & methods to increase useful lifespan (working with JSC Pharmacy)
2. Low Gravity Drug Stability Analyzer (PI: Farquharson, Real Time Analyzers)
Stability-
How long is a medication safe and effective?
With non profit, academic and pharma partners, evaluating packaging materials & methods to increase useful lifespan, possibly even reformulation.

Health and Environmental Sciences Institute
Mission: Engage scientists from academia, government, industry, research institutes, and NGOs to identify and resolve global health and environmental issues.
Pharmacokinetics

Does the spaceflight environment alter PK?

*Inflight pharmacokinetic and pharmacodynamic responses to medications commonly used in spaceflight,* new research study (Wotring, Derendorf and Barger)
Pharmacokinetics -
Does the spaceflight environment alter PK?
PK Evidence: Flight studies

Cintron & Putcha acetaminophen case studies, 1987

Salivary acetaminophen measured over time after oral administration of tablets (acetaminophen is the gold standard for examination of oral absorption, but substitution of saliva concentrations for plasma not established)

3 individuals - each panel shows data from a single individual. Use of other medications is unspecified.

Two individuals show reduced peak concentration for FD1-2 (middle and lower)
One person shows slower absorption preflight, but this value is much slower than average ground values from the literature (0.8 h).

Paucity of data and variability in data preclude definitive conclusion.
Effect of Simulated Microgravity on the Disposition and Tissue Penetration of Ciprofloxacin in Healthy Volunteers

Edgar L. Schuck, PhD, Maria Grant, MD, and Hartmut Derendorf, PhD, FCP

This study evaluated the effects of simulated microgravity (μG) on the pharmacokinetics of ciprofloxacin. Six healthy volunteers participated in a crossover study to compare the pharmacokinetics of ciprofloxacin after a single 250-mg oral dose in normal gravity (1G) and μG. Plasma and urine samples were collected, and in vivo microdialysis was employed to obtain the free interstitial concentrations in the thigh muscle. Tissue penetration (T) was determined as the ratio of the free tissue area under the concentration versus time curve (AUC_{free.too})/AUC_{plasma.too}. Plasma and free interstitial ciprofloxacin concentrations were simultaneously fit to a 1-compartment body model after correction for protein binding and tissue penetration. Total and free plasma concentrations were very similar in μG and 1G. Tissue penetration in μG (T = 0.61 ± 0.36) was slightly lower than in 1G (T = 0.92 ± 0.63); however, the difference was not significant. The authors conclude that the disposition of ciprofloxacin was not affected by simulated microgravity.

Keywords: Pharmacokinetics; microgravity; ciprofloxacin; tissue penetration; microdialysis


Figure 3. Fitted total plasma (■) and free interstitial (○) concentrations in 1G (top) and μG (bottom). Experimental points represent the means of 6 subjects. Vertical bars represent the standard deviation of the mean.
Transient reduction in both volume and protein, that returns to almost normal values in a few days.

Leach, et al., 96
**PK Evidence: Bedrest**

![Graph showing clearance over time during head-down tilt (HDT).](image)

**Lidocaine clearance increased by ~ 30% during 7 days of HDT.**  
This suggests that hepatic metabolism is increased.

Lidocaine undergoes significant protein binding. An apparent change in clearance could be due to a change in protein binding.

Data are mean ± SEM, n= 8 males. Mean data with large errors doesn’t distinguish between individuals with systematic (but varying degrees of changes) and high variability within subjects.

Subjects were vertical for a short period on the morning of day 6. Lidocaine is a commonly used PK probe for hepatic metabolism. Bedrest has not been established as a good model for clearance.

Saivin *et al.*, 1995
PK Evidence: bedrest

Bedrest has no effect on tubular secretion by kidney

Penicillin given IV before (closed symbols) and after (open symbols) 7 d supine bedrest, n=12, mean ± SEM. Supine, not HDT, but neither bedrest position has been shown to be a good model for spaceflight.

Kates et al., 1980
Pharmacokinetics -

Does the spaceflight environment alter PK?

Inflight pharmacokinetic and pharmacodynamic responses to medications commonly used in spaceflight, new research study (Wotring, Derendorf and Barger)
Sleep

Most medications used inflight are for sleep problems.
Insufficient sleep leads to poor performance, both physically and mentally, and has negative health effects.
Sleep aids like zolpidem and zaleplon increase sleep time.
But sleep aids with a long half-life can impair next-day performance due to residual drug in the system.
And in the event of an emergency that requires early awakening, any sleep aid could impair performance.
The cause of inflight sleep disturbances is not understood.
Melatonin and its analogs can be used to help set circadian rhythms even in the absence of normal cues.
Lack of normal circadian cues probably contributes to sleep problems. Typical indoor ambient lighting is dimmer than most terrestrial indoor lighting (between 10-100 lux on the middeck and in Spacelab) while the flight deck, with its large windows to the outside, experiences continual 90 minute cycles with highs of 1000 lux (sometimes almost 100,000) and lows of ~1 lux (Dijk et al.,2001).

This variability is not unlike the 15 min at 10,000 lux followed by 60 min at <3 lux cyclical paradigm found to have similar phase resetting properties as the same total time period of 10,000 lux (Rimmer et al.,2000).
Prevalence of sleep deficiency and use of hypnotic drugs in astronauts before, during, and after spaceflight: an observational study

Methods
...crew members assigned to Space Transportation System shuttle flights with in-flight experiments between July 12, 2001, and July 21, 2011, or assigned to International Space Station (ISS) expeditions between Sept 18, 2006, and March 16, 2011...wrist actigraphy, and subjective sleep characteristics and hypnotic drug use via daily logs, in-flight and during Earth-based data-collection intervals...

Findings
We collected data from 64 astronauts on 80 space shuttle missions (26 flights, 1063 in-flight days) and 21 astronauts on 13 ISS missions (3248 in-flight days), with ground-based data from all astronauts (4014 days). Crew members attempted and obtained significantly less sleep per night as estimated by actigraphy during space shuttle missions (7·35 h [SD 0·47] attempted, 5·96 h [0·56] obtained), in the 11 days before spaceflight (7·35 h [0·51], 6·04 h [0·72]), and about 3 months before spaceflight (7·40 h [0·59], 6·29 h [0·67]) compared with the first week post-mission (8·01 h [0·78], 6·74 h [0·91]; p<0·0001 for both measures). Crew members on ISS missions obtained significantly less sleep during spaceflight (6·09 h [0·67]), in the 11 days before spaceflight (5·86 h [0·94]), and during the 2-week interval scheduled about 3 months before spaceflight (6·41 h [SD 0·65]) compared with in the first week post-mission (6·95 h [1·04]; p<0·0001). 61 (78%) of 78 shuttle-mission crew members reported taking a dose of sleep-promoting drug on 500 (52%) of 963 nights; 12 (75%) of 16 ISS crew members reported using sleep-promoting drugs.

Interpretation
Sleep deficiency in astronauts was prevalent not only during space shuttle and ISS missions, but also throughout a 3 month preflight training interval. Despite chronic sleep curtailment, use of sleep-promoting drugs was pervasive during spaceflight. Because chronic sleep loss leads to performance decrements, our findings emphasise the need for...
Figure 1: Mean sleep duration before, during, and after shuttle missions
Horizontal lines within box plots show the median value for each interval based on means for each participant; the 25th and 75th percentiles are represented by the bottom and top of the box, respectively, and the 10th and 90th percentiles as error bars. The dots represent individual participants with means lower than the 10th or higher than the 90th percentile. *Mean sleep duration was less during the two preflight periods and in-flight than in the 7-day post-flight interval (adjusted p<0.0001 for all three comparisons).
Sleep deprivation has cognitive effects

The two images above show areas of the brain where blood flow decreases when a person is deprived of sleep for 24 hours, compared with when they are rested. Researchers suspect that reduced blood flow in such areas as the prefrontal cortex, located toward the front of the head (the top of each image), may be linked to deficits in concentration and other kinds of cognitive performance that are noted in people who have lost a lot of sleep. SfN, Brain Briefings, Summer 2008
Inflight pharmacokinetic and pharmacodynamic responses to medications commonly used in spaceflight

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Study will include measures of sleep and ultrasounds, in addition to standard pharmacokinetic measures (circulating drug concentrations over time).
Samples must be returned to Earth for analysis currently, but in the future, lab-on-a-chip methods could enable inflight analysis.

The eight holes on this chip are ports that can be filled with fluids or chemicals. Tiny valves control the chemical processes by mixing fluids that move in the tiny channels that look like lines, connecting the ports.
How can medications be used to prevent or reduce spaceflight-induced bone loss?

Bisphosphonates proven effective in flight.

Watching new osteoporosis treatments, denosumab, teriparatide, various others ...
Bisphosphonates' mechanisms of action all stem from their structures' similarity to pyrophosphate, a component of bone. Bisphosphonates, when attached to bone tissue, inhibit osteoclasts, the bone cells that break down bone tissue.
Bisphosphonates as a supplement to exercise to protect bone during long-duration spaceflight

A. LeBlanc · T. Matsumoto · J. Jones · J. Shapiro · T. Lang · L. Shackelford · S. M. Smith · H. Evans · E. Spector · R. Ploutz-Snyder · J. Sibonga · J. Keyak · T. Nakamura · K. Kohri · H. Ohshima

Fig. 1 Change in DXA BMD after long-duration space flight. 1 \( p < 0.05 \), pre vs. post; 2 \( p < 0.05 \) (bisphosphonate group significantly different from pre-ARED); 3 \( p < 0.05 \) (bisphosphonate group significantly different from ARED). Pre-ARED (n=18); ARED (n=11); bisphosphonate (n=7)
Muscle Atrophy

How can medications be used to prevent or reduce spaceflight-induced muscle atrophy?

• Watching selective androgen receptor modulators, mostly in pre-clinical trials
Testosterone is an anabolic steroid

Testosterone binds androgen receptors, nuclear receptors that initiate gene expression. Androgen receptors are found in many tissues: muscle, prostate, brain, skin, etc. Testosterone treatment resulted in increased muscle mass and strength.

Because testosterone has effects on many tissues, its therapeutic use (to improve muscle mass) is linked to effects on reproductive organs, mood, behavior, blood lipids, other organs.

Changes from Base Line in Mean (SE) 10 Weeks of Treatment. The P values shown are for the comparison between the change indicated and a change of zero. The asterisks indicate P < 0.05 for the comparison between the change indicated and that in either no-exercise group; the daggers, P < 0.05 for the comparison between the change indicated and that in the group assigned to placebo with no exercise; and the double daggers, P < 0.05 for the comparison between the change indicated and the changes in all three other groups.

Bhasin et al., 1996
Selective androgen receptor modulators (SARMs)

3β,19-NA increases muscle without affecting reproductive tissues

A new steroid analog 19-Nor-4-Androstenediol-3β,17β-Diol (3β,19-NA) increases muscle (and bone mineral density, not shown) without affecting reproductive tissues

24 weeks of treatment (implanted pump), n=28 male rats per group

Page et al., 2008
~ 70% of crew experience SAS
In the top 4 reasons for inflight medication use
Includes nausea, pallor, cold sweating, and sometimes vomiting
Generally occurs during periods of environmental transition, in either the first few days of flight, or the first few days back on Earth, or both
SAS symptoms and/or Rx side effects limit crew activities flight day 1-3 and again at landing.
Space Adaptation Syndrome

How can medications be used to treat or prevent space adaptation syndrome?

- Can a training protocol permit reduced dependence on medication? (PI: Young)
Motion sickness is used to model space motion sickness

The rotating chair has a maximum velocity up to 360 degrees/second.

www.graybiel.brandeis.edu/.../facilities.html
Pharmacological intervention sites for SAS

after Nachum et al., 2006
Not all antiemetics are effective against rotation-induced illness

Self-ratings of illness with ondansetron are no different than with placebo. Ondansetron is the 5HT3 antagonist antiemetic that revolutionized cancer chemotherapy, N=12, double-blind, repeated measures, 1 week intervals, rotating drum stimulus.

Levine et al., 2000
Not all antiemetics are effective against wave-induced illness

N=16 sailors prone to seasickness in double-blind, cross-over design, on two voyages with similar sea conditions

Self-ratings of illness with ondansetron are no different than with placebo

Data from Hershkovitz et al., 2009
Neurokinin antagonists are ineffective against motion-induced illness

N=16, double-blind, randomised, crossover design; stimulus was a rotating chair, subjects performed head movements during rotation; trials were stopped at subject report of Malaise

data from Reid et al., 2000
Promethazine and Scopolamine are the best currently available motion sickness treatments.

Both PMZ and Scop permit increased rotation tolerance; antihistamines are ineffective.

N=15 per group, each participant was randomly given placebo or one of the study drugs, sessions separated by 2 weeks.

Dornhoffer et al., 2004
PMZ reduced severe SAS on STS flights
Self-reports of symptom severity before and after the introduction of promethazine for SMS on STS missions. N=26 (after).

Davis et al., 1993
Vision and Intracranial Pressure Changes

New issue – hasn’t been well defined yet

• Are medications involved in vision and intracranial pressure changes seen in spaceflight? (Data mining study in progress, PI Wotring)

• Investigating treatment options
Radioprotectants

How can medications be used to prevent or reduce physiological effects of radiation exposure?

— Watching antioxidants, as well as other more selective compounds, in pre-clinical trials.
Need more?

General NASA info: [http://www.nasa.gov](http://www.nasa.gov)


Bedrest Study Info: [http://www.bedreststudy.com](http://www.bedreststudy.com)

Postdoctoral Opportunities [http://nasa.orau.org/postdoc/](http://nasa.orau.org/postdoc/)


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