Keynote Speaker

Past, Present and Future of Excipients: Space Research and the Quest for Better Pharma

Virginia Wotring
Science & Technology Integration Manager, National Space Biomedical Research Institute
Medications on Spaceflight Missions

V. E. Wotring
Science & Technology Integration Manager, National Space Biomedical Research Institute
Assistant Professor, Center for Space Medicine and Department of Pharmacology, Baylor College of Medicine

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6 people are living & working on the ISS right now
Many physiological systems are affected by spaceflight

- Shift of fluid toward head
- Vestibular changes
- Lack of circadian cues
- Musculoskeletal atrophy
- Elevated radiation exposure
Medical Complaints in Space

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

From Clement, Fundamentals of Space Medicine, 2003

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
First pharmaceuticals in US spaceflight

In 1963 on Mercury Atlas 9, 22 Earth orbits, 35 hours

Gordon Cooper carried pre-loaded drug injectors in space suit pocket

Demerol – pain relief
Tigan - motion sickness
Total number of medication uses shown by indication. Data from 24 crewmembers on 20 missions have been grouped together to provide a summary overview of medication use on long-duration ISS missions. Medication use was reported for acute conditions requiring treatment for 7 d or less (A) and for prolonged or recurring conditions requiring treatment longer than 7 d (B). Note that the y axis in (B) is on a different scale.

Space-related Pharmacology research

Pharmaceuticals
• Usage tracking
• Stability

Pharmacokinetics
• Absorption/Distribution
• Metabolism/Excretion

Pharmacodynamics
• all the reasons medications are required
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.
Data collection is in progress, on the ground and on ISS
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Pharmacokinetics-
Does the spaceflight environment alter PK?
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 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.
PK: Absorption in spaceflight

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Transient reduction in both volume and protein, that returns to almost normal values in a few days
Animal studies show spaceflight-associated changes that could alter pharmacokinetics

Merrill et al., 1990

Wotring, unpublished
Inflight pharmacokinetic and pharmacodynamic responses to medications commonly used in spaceflight, new research study (Wotring, Derendorf, Basner and Barger)
Rx Metabolism
will compare ground vs. space flight PK (for 2 meds) and PD for a common sleep aid

zaleplon + amoxicillin or placebo + amoxicillin

- blood draws and cognitive testing at 0, 0.5, 1, 1.5, 2, 4, 8 hours
- Cognition suite at 0, 1 and 8 hour time points
- EEG, actigraphy, sleep diary

Study expected to begin data collection in late 2016
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Venous Thromboembolism Risk
with Varsha Jain
(NIHR Academic Clinical Fellow: Ob/Gyn, King’s College, London)

Hypercoagulability
- Hereditary Deficiencies:
  - Antithrombin deficiency
  - Protein C deficiency
  - Protein S deficiency
  - Factor V Leiden
  - Prothrombin gene mutation
  - Dysfibrinogenemia
- Acquired:
  - Cancer
  - Pregnancy & postpartum period
  - Oral contraceptives
  - Hormone replacement therapy
  - Polycythemia vera
  - Smoking
  - Antiphospholipid syndrome
  - Chemotherapy

Venous Stasis
- Stasis
  - Immobility/cast/travel
  - Advanced age
  - Acute medical illness
  - Major surgery
  - Spinal cord injury
  - Obesity

Endothelial Damage
- Endothelial Damage
  - Major surgery
  - Trauma
  - Central venous catheterization

Jain & Wotring, npg Microgravity
Choices in menstruation control during spaceflight

Long-acting reversible contraceptives (LARCs) – especially intrauterine devices – may provide a safe, effective menstruation control choice for female astronauts, suggests a new study.
Many physiological systems are affected by spaceflight

- Shift of fluid toward head
- Vestibular changes
- Lack of circadian cues
- Musculoskeletal atrophy
- Elevated radiation exposure
Pharmaceutical Use on ISS

Total number of medication uses shown by indication. Data from 24 crewmembers on 20 missions have been grouped together to provide a summary overview of medication use on long-duration ISS missions. Medication use was reported for acute conditions requiring treatment for 7 d or less (A) and for prolonged or recurring conditions requiring treatment longer than 7 d (B). Note that the y axis in (B) is on a different scale.

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


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).
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 development of effective countermeasures to promote sleep.
A medication to re-set circadian rhythms could improve both crew health and crew safety.
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Space Adaptation Syndrome

- ~ 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.
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
Multisensory integration in early vestibular processing in mice: the encoding of passive vs. active motion

Ioana Medrea and Kathleen E. Cullen
Aerospace Medical Research Unit, Department of Physiology, McGill University, Montreal, Quebec, Canada
Submitted 30 November 2012; accepted in final form 26 September 2013

Pharmacological intervention sites for SAS after Nachum et al., 2006

H1
5HT
D2
NK1
5HT
3
mAch
mAch
mAch
NK1
5HT
3
mAch
H1
proprioceptive
visual
vestibular
vestibular nuclei
cerebellum
brainstem autonomic centres
vomiting centre
stomach
unfamiliar, unnatural motion stimuli
heavy, greasy meals (aggravating factor)
hormonal changes
pallor, cold sweating, changes in salivation, heart rate, respiration
nausea, vomiting
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

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

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

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 4.

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

Both PMZ and Scop permit increased rotation tolerance; antihistamines are less effective

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
Reduction in severe SAS after introduction of PMZ

Symptom severity, self reported

Self-reports of symptom severity before and after the introduction of promethazine for SMS on STS missions (n=26)

Symptoms usually manifest on the first 3 days after launch and landing – crew duties are kept light during these periods.

Davis et al., 1993
An anti-nausea medication with a better side effect profile could increase crew well-being and enable more useful duty hours.
Many physiological systems are affected by spaceflight

- Shift of fluid toward head
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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.
Medications that prevent or reduce radiation damage could improve crew health and permit longer exploration missions.
Many physiological systems are affected by spaceflight

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

- Watching selective androgen receptor modulators, in pre-clinical trials
- No clinical market (as of Fall 2015)
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
Medications that prevent or reduce muscle atrophy could improve crew health and permit longer exploration missions.
Bisphosphonates

Bisphosphonates' mechanisms of action all stem from their structural similarity to pyrophosphate, a component of bone.

Bisphosphonates, when attached to bone tissue, inhibit osteoclasts, the bone cells that break down bone tissue.
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 ($n=7$)
How can medications be used to prevent or reduce spaceflight-induced bone loss?

- Bisphosphonates proven effective in flight.
- Side effects can prevent some individuals from using.
- Watching newer osteoporosis treatments, denosumab, teriparatide, various others …
More options for protection of bone could improve crew health and safety
Space-related Pharmacology research

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Pharmacokinetics
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Pharmacodynamics
- All the reasons medications are used
Stability - how long is a medication safe and effective?

Medication Shelf Life (Frequently only 2 years total)

1. Manufacturer to distributor
2. Distributor to JSC Clinical Pharmacy
3. Clinical Pharmacy dispenses & repacks (in some cases)
4. HMS packs med kits
5. Ops delivers to launch vehicle
6. Launch
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Global Drug Shortages

Repackaging requires reducing the shelf life to no more than 1 yr

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.
Stability – how long is a medication safe and effective?

Flight-aged medications have been returned from the ISS by SpaceX Dragon and analyzed for active pharmaceutical ingredient content and degradants/impurities.
Flight aged medication samples were subjected to HPLC/MS analysis for active ingredients as well as USP-specified degradants and impurities.

Chemical Potency and Degradation Products of Medications Stored Over 550 Earth Days at the International Space Station.
Stability – How long is a medication safe and effective?

We still don’t have the answer – need well-controlled studies with additional drugs at more time points
Excipients can drive medication stability (or lack thereof!)

Ibuprofen from 11 brands in US and other countries.

Table 5. Percentage degradation of ibuprofen combined with excipients after three weeks at 70°C/75% RH.

<table>
<thead>
<tr>
<th>Excipient</th>
<th>% Total degradation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG 400</td>
<td>9</td>
</tr>
<tr>
<td>PEG 1000</td>
<td>9</td>
</tr>
<tr>
<td>PEG 3400</td>
<td>7</td>
</tr>
<tr>
<td>povidone</td>
<td>0.8</td>
</tr>
<tr>
<td>polysorbate 80</td>
<td>9</td>
</tr>
<tr>
<td>hypropomellose</td>
<td>4</td>
</tr>
<tr>
<td>sucrose</td>
<td>0.1</td>
</tr>
<tr>
<td>lactose</td>
<td>0.1</td>
</tr>
<tr>
<td>sodium benzoate</td>
<td>0.2</td>
</tr>
<tr>
<td>sodium citrate</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Ibuprofen developed in the 60’s; US approved in 1974. This study conducted in a college chemistry department, more than 30 years after approval.
Need more?

General NASA info:  
http://www.nasa.gov

Human Research at NASA:  
http://humanresearch.jsc.nasa.gov/

NASA Research Grants  
http://nspires.nasaprs.com/external/

Don Pettit’s Blog  
http://blogs.airspacemag.com/pettit/

Ginger  
virginia.wotring@bcm.edu