Chapter 12
Clinical Pharmacology & Therapeutics
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Chapter Outline
1. Abstract
2. Learning Objectives
3. Introduction
4. History of Therapeutics In Space
5. Medications in Space Medical Kits
6. Patterns of Medication Use During Flight
7. Stability of Drug Preparations in Space Missions [Space Shuttle and ISS]
8. Pharmaceutics and Drug Development for Space Missions
9. Test Beds for the Study of Space Pharmacokinetics
   a. Gastrointestinal (GI) Absorption
   b. Hepatic and Renal Clearance
   c. Therapeutic Response Monitoring
   d. Microgravity Analogs
10. In-Flight Pharmacokinetics
11. Future Directions
   a. Radioprotection, Infection and Immunity
   b. Shelf Life and Packaging of Drugs for Space Missions
   c. Factors Unique to the Space Environment that May Influence Stability of On-board Medications
12. Case Studies from the Aeromedical Practice
13. Self-study Questions
14. Key Points to Remember
15. References
ABSTRACT

Pharmaco-therapeutics is an important element of space medicine practice. Assessing health risks, developing countermeasures, selecting relevant supplies for medical kits and appropriate crew member training on the use of medical kits prior to the mission start is a major contributor to the space flight success. In this chapter, the standards applicable to clinical pharmacy practice are discussed, and best practices recommended. A review of existing evidence on the incidence and management of clinical conditions that have occurred during space flight is presented along with results of research conducted of drugs under the influence of microgravity. Ground-based models, such as bed-rest and animal surrogate studies supplement and validate clinical observations from space missions. Space flight is associated with morphological and profound physiological changes, including alterations in fluid, electrolytes and gastrointestinal absorption changes capable of affecting the pharmacodynamics - primarily oral administration of medications. Exposure to the space environment, particularly radiation, can also shorten the shelf life of many chemical preparations, hence potentially affecting their efficacy and alter their bioavailability. Special packaging, radiation hardening of the medical storage area, and periodic return of samples to determine individual medication’s biological activity is possible in Low Earth Orbit where the International Space Station offers a unique environment. The evidence on the absorption, distribution, metabolism, and excretion of major drug categories, in the space environment is incomplete, the experimental evidence is sparse, and practitioners rely primarily on observational evidence and individual crew opinions gathered from prior missions.

Keywords: Pharmaco-therapeutics, Clinical Pharmacology, Pharmacokinetics, Pharmacodynamics, Space Pharmacy, Pharmaceutical Stability, Acetaminophens, Scopolamine, Antibiotics (Lak, please add additional key works)
Learning Objective

1. Review the principles of space pharmacology, and
2. Address the use and efficacy of medications in the unique environment of space.

Introduction

A wide variety of medications are provided for each human space mission. Astronauts are prescribed medications to ameliorate or prevent symptoms of space motion sickness (SMS), headache, sleeplessness, backache, nasal congestion, and constipation during space flight.

Russian cosmonauts reportedly use medications to prevent metabolic cardiac disturbances, maintain “normal” intestinal flora and optimize individual’s work capacity. While early and limited discomfort associated with acute responses to microgravity (e.g., SMS) typically diminishes over the first few days in flight, the onset of other responses (decrements in muscle strength, bone integrity, and perhaps immune function) continues, and might require therapeutic interventions in longer missions [see Chapter 3]. It is anticipated that as the duration of space flight increases, the need for treatment with medications is expected to rise accordingly.

Pharmacology in space medicine is an important and still evolving discipline. Medical kits flown on space crafts are limited to the predicted health hazards and risks encountered by astronauts. Size and weight are major space craft design imposed limitations. The primary reliance of the space medicine practice is on prevention and surveillance of diseases prior to flight. Space pharmacology is governed by the same principles as on Earth; and is divided into the following:

1. *Pharmaco-dynamics* defines the interactions of drugs with biological receptors;
2. *Pharmaco-kinetics* addresses the absorption, distribution, metabolism, and excretion (ADME) of drugs in individuals; and
3. *Pharmaco-therapeutics* knowledge of the clinical use [indications] and effects of medications

The onset, intensity, and duration of the response produced by any drug depends upon its rate of absorption, distribution, metabolism, and elimination; space flight-induced changes in blood flow and the function of the gastrointestinal (GI) tract, liver, or kidneys can affect these processes.
Some drugs, when used in space, have been reported to be less efficacious than expected. For example, low efficacy of oral anti-motion sickness preparations. The current U.S. Space Program evolved from relatively short duration Space Shuttle flights, to longer missions on the International Space Station (ISS), and in anticipation of future planetary explorations, understanding space pharmacology and avoidance of iatrogenic effects becomes a priority. This chapter begins with a review of pharmacologic issues in space medicine, discusses results from research conducted in space, and identifies challenges that need to be addressed for effective pharmaco-therapeutics practice.

**History of Therapeutics in Space**

Astronauts use medications for treatment of a variety of illnesses during space travel. The list of medications in the space flight formulary has increased from a few drugs for SMS, sleep and anti-pain, to an expanded formulary to treat a variety of illness and minor injuries during space flight. Medications for the treatment of common colds, aches, pains, insomnia, and other minor illnesses are standard in the current space flight formulary. Also included are neuro-cognitive, antibiotics, and emergency preparations for cardiovascular events. In addition to the standard “ambulatory type “ care ISS medications, astronauts are allowed to carry prescriptions waived conditions during space flight. Results of an extensive data mining effort to assess clinical conditions occurring during space shuttle flights STS-1 through STS-94 are shown in [Figure 12-1](#).

**Incidence of Clinical Conditions**

Sensorimotor disturbances, manifesting mostly as space adaptation syndrome or SMS, are the most common ailment, occurring in close to 40% of shuttle crew members, followed by digestive system disturbances (9%) and infectious diseases, which most commonly involve the respiratory and urinary tracts.
Medications in the Space Medical Kits

Four types of medications were provided on the first 4 Mercury flights: (1) cyclizine (45 mg in a 0.9-mL injector, for SMS), (2) meperidine hydrochloride (90 mg in a 0.9-mL injector, for pain), (3) epinephrine (1:1000), and (4) dextroamphetamine. An injector system was devised to allow the astronaut to deliver medication through the space suit into the thigh muscle; however, none of the injectors were actually used during flight [1-GRAEBE]. On the fifth Mercury flight, only injectable cyclizine and meperidine were flown; on the sixth and last Mercury mission, these drugs were supplemented with dextroamphetamine sulfate tablets, provided both in the suit and in the survival kit. On this flight, pilot Gordon Cooper became the first astronaut to use oral medication during space flight, taking dextroamphetamine before starting the retro sequence, prescribed by the mission surgeon [2-IDVAIDEK,3-PAULE].

The space medication kit was expanded considerably for the Gemini program. Crew members were asked to test each of the medications in the kit before flight to determine individual reactions to them. The recommendation of the crew surgeon [flight surgeon], at the time was to take dextroamphetamine sulfate with a decongestant before the reentry sequence to maintain alertness and prevent possible ear barotrauma secondary to “head-fullness.” Antimotion-sickness medication was also taken in one instance before atmospheric reentry to reduce the possibility of SMS after the spacecraft splashed down in the Atlantic Ocean. Lomotil® (diphenoxylate), an inhibitor of gastro-intestinal [GI] motility, was prescribed to induce constipation, during flight, due to the lack of convenient hygiene systems, and smell in close quarters, [only special kits

At the post-Gemini summary conference in 1967, the consensus reached was that “no difficulty had been experienced in the use of oral medications, which in the opinion of the flight physicians had produced the desired effects.”
consisting of a fecal bag, gloves and tissue were available]. This approach was acceptable on most of the Gemini flights which were fairly brief, [4-CHECK THIS].

For Apollo, medications were provided in two separate kits, one located in the command module and one in the lunar module (Tables 12-1 and 12-2). Two cardiovascular drugs, quinidine sulfate and dipyridamole, were added to the basic Apollo kit for the Apollo-Soyuz Test Project [5-NICOGOSSIAN]. According to Hawkins and Ziegleschmid [5-HAWKINS, ET AL], the medications taken most frequently during the 10 Apollo flights were aspirin, acetaminophen, triprolidine (Actifed secobarbital, Lomotil, Afrin (oxymetazoline), and Marezine (cyclizine). (The latter was included only on the first 4 flights.) All of these agents, except for the nasal spray Afrin, were in tablet form and taken orally.

The Shuttle Orbiter Medical System (SOMS) and its component kits for the Space Shuttle Program were developed in the late 1970s. Medications for the Gemini/Apollo medical kits were selected and the list was expanded on by flight surgeons who chose medications for the treatment of minor ambulatory care symptoms, first aid, and basic life support [7]. The early version of the SOMS medical kit consisted of two primary groupings, one containing injectable, dental, and intravenous medications; and the other containing oral and topical medications. The SOMS kit design was modified in 2000, (Figure 12-a and b) and flown for the first time in 2001 on STS-98.

One of the most noticeable changes in the redesign was the use of Ziploc® re-sealable plastic bags instead of pill bottles. Injectable medications were supplied as prefilled syringes

The redesigned Space Shuttle kit consisted of 6 subpacks: (1) Drug; (2) Trauma; (3) Eyes, Ears, Nose, and Throat; (4) Airway; (5) Intravenous, and (6) a saline supply bag. Each subpack was limited to 6.8 kg (15 lb).

Transport and stowage of supplies into space, including medications, must fulfill certain engineering and safety requirements to prevent off-gassing and damage to equipment while allowing easy access for use by crew members.
instead of vials, as had been the case in earlier medical kits. The SOMS kit contents remained the same over the ensuing six years except for minor additions and deletions based on commercial product availability and crew surgeon preference. Most medications are repackaged into Ziploc® bags and plastic amber vials stored in fabric containers that are closed with VELCRO® (Figure 12-3). Medications are inventoried with “part numbers” in engineering documents. This system of packing, stowage, and tracking was used on the space shuttle and continues to be used on the ISS.

Because of the off-nominal dispensing operations of space missions, shelf-life considerations are an important aspect of pharmacovigilance in space. Stability is an essential quality attribute for medications with regard to their safety, efficacy, and quality [8]. Potential adverse effects of an unstable medication can include loss of content uniformity, formation of toxic degradation products, and changes in bioavailability [9]. Changes in the integrity of packaging (ie, the SOMS kits) and the storage conditions resulting from the harsh environmental conditions, including exposure to ionizing radiation during space flight, are suspected of compromising pharmaceutical stability in space.

**Patterns of Medication Use During Flight**

For Gemini missions, the medication kit was expanded and crew members were asked to test each of the medications in the kit before flight to assess their individual reactions to the medications. The recommendation was to take dextroamphetamine sulfate with a decongestant before the reentry sequence. Anti-motion-sickness medication was also taken in one instance.
before atmospheric reentry to reduce the possibility of SMS after the spacecraft splashed down. Because most of the Gemini flights were fairly brief, diphenoxylate, an inhibitor of gastrointestinal motility, was prescribed to assist in avoiding defecation during flight [10]. At the time of the Gemini summary conference in 1967, the general consensus of the flight surgeons was that no difficulty had been experienced in the use of oral medications and the medications had produced the desired effects.

During Apollo missions, medications were provided in two separate kits, the first located in the Command Module and the second in the Lunar Module. Two cardiovascular drugs, quinidine sulfate and dipyridamole, were added to the basic Apollo kit for the Apollo-Soyuz Test Project [11].

Medications carried on Space Shuttle missions varied somewhat from flight to flight, depending on the needs of the individual crew members, availability, and consensus from the Formulary Committee or flight surgeons. Use of medications during the Space Shuttle Program appeared more prevalent due to easy accessibility as well as availability of increased formulary inventory, or the incidence of ailments during space flight increased, possibly related to the longer flight duration.

Most of the medications taken to date have been ingested orally in tablet form, although intramuscular injections, rectal suppositories, ocular preparations, and topical agents are also available in the on-board formulary. The relatively extensive formulary manifested on Space

According to Johnson [12], the medications taken most often during the ten Apollo flights were aspirin, acetaminophen, triprolidine, secobarbital, diphenoxylate, oxymetazoline, and cyclizine, all of which - except for oxymetazoline, which was available in a nasal spray - were administered as tablets.

In general, the standard formulary for space shuttle missions included the following classes of drugs: analgesics (nonsteroidal anti-inflammatory agents and narcotics), antibiotics, antihistamines, antifungals, antipyretics, antivirals, cardiovascular, central nervous system stimulants, decongestants, emergency care (anticonvulsants, antipsychotics, epinephrine, lidocaine, narcotic reversal agents), gastrointestinal (dyspeptics, laxatives, stool softeners), urinary agents (alkalinizing agents, analgesics, antiseptics, antispasmodics), sedatives (narcotic and nonnarcotic), steroids, and topical medications for the skin and eyes.
Shuttle flights and also on current ISS flights, although enhancing treatment capabilities in space increases the risk of treatment failure or drug interactions. This condition is further compromised by the lack of systematically collected data for the pharmacokinetic and pharmacodynamic behavior of the candidate drugs under space flight conditions and the resultant clinical outcomes, as described below.

Analysis of the use and effectiveness of medications as documented from post-flight medical debriefings of crew members over 25 years of Space Shuttle flights STS-1 through STS-80 [13, 43, 48] showed that, of the 219 logs (person-flights), 94% report some medication was taken during the mission. Most (88%) of the doses were taken orally, 5% intranasally, 4% intramuscularly, and 2% rectally. Less than 1% of the doses were by topical application or intravenous injections. Of those crew members who reported taking medications during flight, 47% took SMS formulations, 45% used sleep aids, and a lesser percentage took analgesics or anti-inflammatory drugs. Profiles of medication use during Space Shuttle flights lasting 18 days or less indicate that the number of doses of sleep medications used did not decrease significantly as a function of flight duration, in contrast to the number of medications used for motion sickness, pain, and congestion on later flight days. Recent findings indicate that sleep disturbances, and use of somnifers, prevail throughout the missions [67] (Figure 12-4). A more recent analysis of data from STS-1 through STS-94 showed slightly different trends with respect to medication use with pain medications accounting for approximately 37% of all prescriptions recorded, followed by sleep (22%), space motion sickness (18%), decongestion (14%), and all others (14%).
Analysis of the same debriefings on the use of drugs to ameliorate SMS revealed that about 150 of 317 crew members experienced symptoms of SMS. Nearly 90% of those 150 crew members took medication for SMS symptoms, for a total of 387 dosing episodes. The medications taken most often for space motion sickness are shown in Table 12-3. Promethazine (Phenergan™; formerly manufactured by Wyeth Industries, Madison, NJ) was taken most often (201 total doses), and in most cases this resulted in symptom improvement (130 crew members [65%] reported feeling much or somewhat better). Although fewer total doses of the combination of promethazine and dextroamphetamine were taken (45 doses), slightly more than half of those doses resulted in improvement (Figure 12-5). The combination of scopolamine and dextroamphetamine (“Scop/Dex”), on the other hand, was reported to be effective in only 37% of cases, with 36 of 97 total doses resulting in improvement (much or somewhat better). A somewhat higher percentage (24%) of Scop/Dex doses was reported to be ineffective compared with promethazine alone or in combination with dextroamphetamine (10% and 7%, respectively). Comparisons of the effectiveness of the different dosage forms of promethazine revealed that intramuscular injection was most effective in alleviating symptoms, with 55% feeling much better, 16% feeling somewhat better, and only 7% feeling no effect or worse (Figure 12-6).
Regarding medication use during flight, the reader should keep in mind that, in addition to the operational medical kit as a source of medications in flight, crew members can also request specific medications for inclusion in their personal carry-on supply packs. Such requests are made at the flight physical ten days before launch.

Review of crew medical debriefings also suggests that oral promethazine is less likely to produce sedation during flight than when used on the ground [12], which could be due to reduced drug potency during flight or lower bioavailability as a result of the physiological changes associated with space flight. For example, promethazine at doses several times higher than normal during space flight was reportedly required to achieve the desired effect, but no increase in side effects was reported [13]. Another observation from analysis of these subjective data on the effectiveness of medications used by crew members during space flight indicates that about 8% of all treatments administered in the Space Shuttle Program were reported as being ineffective. Unfortunately, such observations must remain anecdotal due to the shortcomings of the documentation process.

Reports on medications contained in astronaut’s personal packs are not included in the post flight debriefings, and as such medications used from the carry-on kits are most likely not recorded or captured consistently in the medical logs.

Both physicians and astronauts reported using more and higher doses of medications to aid sleep and ameliorate SMS during several Space Shuttle flights than would be expected on the ground.

Any additional information about ISS activities? – Lak - Do we need to add short paragraph on observations from the space missions?
Stability of Drug Preparations in Space Missions

To investigate factors that may adversely affect treatment efficacy during space flight, a total of 15 medications from space shuttle and ISS medical kits, identified as potentially vulnerable to the harsh environmental conditions of spacecraft (including radiation), were examined for changes in physical and chemical properties after space flight. A ground-control set of those medications was procured from identical brand and lot numbers where possible. Another seven formulations were included in response to crew and physician concerns about therapeutic efficacy in space, resulting in a total of 22 medications retrieved for analysis from 18 space shuttle and ISS flights. Several medications from the flight kits showed changes in physical characteristics and reductions in the amount of active pharmaceutical ingredient (API). These changes compromise USP-recommended standards regarding the physical stability of pharmaceuticals. Amoxicillin/clavulanate, sulfamethoxazole/trimethoprim, ciprofloxacin, and promethazine tablets, as well as ciprofloxacin ointment, promethazine injections and suppositories, exhibited physical changes that included discoloration of tablets and solution and changes in texture of ointment and suppositories.

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commercial packaging, suggesting that repackaging in flight-specific containers compromises the expected shelf life.

Subsequently, a follow on ISS payload investigation was conducted for a more systematic evaluation of a total of 32 formulations stored on board the ISS in specially configured stability payload kits. Results from this study indicated that there may be differences with respect to potency and rate of degradation of formulations stored in space compared to those on the ground.

As we prepare for more distant exploration missions to Mars and beyond, methods to identify and mitigate the risks of untoward therapeutic consequences of unstable pharmaceuticals on board must be examined and established. A contributing factor to compromised shelf life in space may well be packaging; thus, it is prudent to examine and identify special packaging needs, such as shielding capabilities for vibration, light- and radiation-sensitive formulations, and select a robust formulary that can withstand the space exploration environment.

The difficulties involved in conducting definitive studies of drug efficacy during U.S. space flights have been compounded by the absence of a systematic approach to determining which drugs were taken by whom and under what circumstances. Attempts made to address this problem include holding confidential medical conferences between individual crew members and the mission flight surgeon during and after Space Shuttle flights. Astronaut debriefings after 79 U.S. Space Shuttle missions were recently reviewed for information on medication use during flight; from the 219
records obtained, each representing one person-flight, 94% involved some medication having been taken during flight [14]. Of that number, 47% were for SMS, 45% for sleep disturbances, and smaller percentages for headache, backache, and sinus congestion. Drugs were most often taken orally, followed in decreasing order of frequency by intranasal, intramuscular, and rectal routes. Drugs for space motion sickness were taken mostly during the first 2 days of flight, drugs for pain during the first 4 days, and drugs for sleeplessness and sinus congestion were taken consistently over 9 flight days. About 85% of all doses had no reported side effects, and 80% were considered effective. Most reports of side effects and ineffectiveness occurred during the first mission day.

Profiles of medication use during space shuttle flights lasting 18 days or fewer indicate that the number of doses of sleep medications used did not decrease significantly as a function of flight duration, unlike the number of medications used for motion sickness, pain, and congestion on later flight days. Although this indicates that sleep disturbances may prevail throughout the missions, these reports included data from only a few long-duration flights (Figure 12-6). A more recent analysis of data from STS-1 through STS-94 showed slightly different trends with respect to medication use[17], with pain medications accounting for approximately 37% of all prescriptions recorded, followed by sleep (22%), space motion sickness (18%), decongestion (14%), and all others (14%).

Many problems are encountered with using debriefing reports for therapeutic assessment. First, these reports rely on crew member memory to report the medications taken during flight and the reasons for taking them. Clearly, information SMS and other symptoms associated with adaptation to microgravity generally occur within the first 3 days of flight, when most medications would be taken; thus, crew members must recall medications taken almost 3 weeks before the debriefing.
could be missed with this type of record keeping. Second, some of the questions on the debriefing pertaining to space motion sickness are subjective and could be interpreted differently among crew members—or among flight surgeons. A third issue with using the medical debriefings as evidence of medication effectiveness is that the database must be created from handwritten debriefing forms, typed transcriptions, and, if available, medication cards. The transcriptions were not subjected to rigorous quality assurance or quality control or data authentication. While such procedures might minimize the risk of transcription errors, they would also delay the availability of information on medication usage in a discernable format. Collectively these shortcomings limit the application of these data for rigorous evaluation of the safety and efficacy of therapeutic interventions in space.

Another confounding factor is the fact that the operational medical kit is not the only source of medications. Crew members can request that specific medications be included in their personal carry-on supply packs. Such requests are made at the flight physical 10 days before launch. No questions are asked during the debriefings to distinguish use of a medication from the SOMS kit from use of a medication from a crew member’s personal supplies, and thus medications used from the carry-on kits are most likely not recorded or captured consistently between flight surgeons or across the decades.

Review of crew medical debriefings also suggests that promethazine was less likely to produce sedation during flight than when used on the ground, which could result from the drug being less potent during flight or less bioavailable owing to the physiological changes associated with space flight. Both physicians and astronauts reported using more and higher doses of medications to aid sleep and ameliorate space motion sickness during several space shuttle flights than what would be expected on the ground. As an example, promethazine at doses several times higher
than normal during space flight was reportedly required to achieve the desired effect, but no increase in side effects was reported [13]. Another observation from analysis of these subjective data on the effectiveness of medications used by crew members during space flight indicates that about 8% of all treatments administered in the Space Shuttle Program were reported as being ineffective. Unfortunately, such observations must remain anecdotal owing to the shortcomings of the documentation process.

Information such as this on the frequency of drug-dose events and efficacy, although useful, should be expanded to include objective measures so that more accurate qualitative analyses of therapeutic efficacy can be performed. The multiple physiological changes associated with space flight present a formidable challenge to this effort. The following sections describe current understanding of pharmacokinetic changes and physiological factors that contribute to these changes in space.

**Pharmacotherapeutics and Drug Development for Space Missions**

Pharmacotherapeutics includes two distinct but interdependent, processes: pharmacokinetics and pharmacodynamics. Pharmacokinetics deals with the rate and extent of absorption, distribution, metabolism, and elimination of administered medications. Pharmacodynamics describes the processes associated with the rate, duration, and extent of the pharmacologic and toxicologic effects of the drug.
As discussed in Chapter 3, space flight induces a wide range of physiological and biochemical changes, including disruption of GI function and physiology, alterations in liver function, fluid and electrolyte imbalances, and changes in circulatory dynamics and organ blood flow [15,16,17,18]. Each of these changes can influence the pharmacokinetic behavior and pharmacodynamic consequences of medications administered to crew members during space flight.

Although results concerning the effect of microgravity on the physiological systems governing pharmacokinetics are equivocal, a substantial body of research information is available to suggest that changes in GI and hepatic function affect drug disposition. Some recent findings on this topic are reviewed in the remainder of this chapter.

Test Beds for the Study of Space Pharmacokinetics

Gastrointestinal (GI) Absorption

Because most orally ingested substances are absorbed through the GI tract, changes in GI physiology such as blood flow, pH, and motility influence the bioavailability of drugs and other compounds [8,19]. Two important variables that govern GI function are gastric emptying and intestinal motility. The rate of gastric emptying depends on body position, slowing while subjects are supine [20]. GI motility, which determines the rate at which particles move through the GI tract, is influenced by particle size, density, and volume as well as posture, caloric intake, exercise, and overall physiological condition [6,7,20,21]. The absence of a gravity vector and the attendant changes in body posture, fluid loss, and fluid distribution during space flight have been
hypothesized to decrease the rate of GI motility. Changes in blood flow patterns resulting from exposure to microgravity are expected to decrease the rate of gastric emptying \[9\], which in turn depresses the hunger sensation \[22\]. A consequence of all of these changes in GI physiology in general, and of decreased gut motility and emptying in particular, is malabsorption of nutrients, fluids, and electrolytes. This effect, in addition to tipping energy balance to the negative \[15,16,17,18,24,25\], also affects the bioavailability of oral medications \[26\].

The healthy adult human GI tract contains 10 microorganisms \[16,27\], mostly bacteria \[28\]; many of these resident bacterial species cannot be cultured but metagenomic analysis of the GI microbial flora by sequence determination of small-subunit ribosomal RNA has revealed complex communities in the human gut comprising from a few hundred up to nearly one thousand bacterial species. The intestinal microbiota of astronauts undergoes significant change during spaceflight. After two weeks there was a significant reduction in the number of gastrointestinal bacterial species and concomitant interchange of gut bacteria between crew members \[32,33\]. A reduction in the number of bacterial species recovered from the GI tracts of Apollo and Skylab crews concomitant with the emergence of robust Gram-negative aerobic species such as *Klebsiella* and *Pseudomonas* has also been described \[34\]. Studies of changes to human microbiota as a result of space travel have to date been undertaken with traditional culture methods, which will not produce a holistic portrait of GI tract diversity.

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Russian studies of rats and humans suggest that gastric hypersecretion takes place during simulated and actual weightlessness. Simultaneous increases in human gastric and pancreatic secretions were reported after 140- and 175-day flights on Salyut-6; however, after an 185-day flight that included the use of countermeasures, these increases were described as less distinct \[23\], (Smirnov, 1986).

It is evident that the resident microbiota exerts a conditioning effect on intestinal homeostasis and plays a key role in the orchestration of the mucosal immune response; perturbation of the microbiota may result in manifestation of disease \[29,30,31\].
Previous studies of the physiological aspects of GI function during flight have been limited by the lack of sufficiently sensitive noninvasive techniques suitable for use in flight. A lactulose–breath-hydrogen test [27,36] was modified for use during space flight to assess changes in GI motility. The test is based on the principle that lactulose, a nonabsorbable disaccharide, is broken down by the microbial flora of the cecum, resulting in the release of hydrogen gas that appears in the breath; the time at which hydrogen appears in the breath after lactulose ingestion (mouth-to-cecum transit time), is an indirect measure of GI transit time. A ground-based study conducted to validate the use of this test for flight indicated that GI transit time decreased considerably (63%) in normal subjects undergoing 10 days of head-down bed rest (Figure 12-7). This test was given to members of the Mir-18 crew to assess GI function during flight. Results indicated a sustained increase in GI transit time throughout the mission; this increase had not returned to preflight baseline by 7 days after return to Earth (Figure 12-7). These in-flight results are similar to those from the ground-based study.

Results from 2 studies with acetaminophen during space missions, one with tablets and the other with a liquid formulation, may indicate that oral absorption of acetaminophen is highly influenced by dosage form (liquid vs. tablet) but less affected by food intake since maximum acetaminophen concentrations were higher and less variable after a liquid dose in the fed state than after a solid dosage form (tablet) in the fasted state.
The increase in GI transit time during flight observed in this study may adversely affect the absorption and bioavailability of oral dosage forms from the GI tract in general, suggesting that the bioavailability of other orally administered medications may be affected as well. To this end, the reduction in maximum concentration alongside an increase in time to reach maximum concentration of acetaminophen during flight would correlate well with the observed reduction in GI motility.

Between one third and one half of the general population has methanogenic bacteria in the distal colon that convert hydrogen to methane. In the Mir-18 study, both of the crew members tested excreted low levels of methane (less than 40 ppm) before and after flight, but both exhaled high levels of hydrogen and methane during all 3 in-flight sessions (Table 12-5). High breath concentrations of methane and hydrogen have been associated with bacterial overgrowth in the GI tract and possibly proliferation of the pathogenic bacteria Helicobacter pylori [37]. However, no anomalies in bacterial flora were found in fecal samples from the Mir-18 crew after return from flight (personal communication from Dr. Lizko, Institute for Biomedical Problems, Moscow). Further studies concerning gut flora and physiology are warranted to evaluate the potential health risk to crew members from Helicobacter pylori.

The aforementioned discussion, points to the fact that reductions in GI motility along with changes in the microbial environment of the GI tract during space flight that persisted during the first week after return to Earth. During the first few days of space flight, many if not most astronauts experience SMS, and in some cases the associated symptoms persist for a few days. Some of these symptoms may be correlated with the observed reductions in GI motility; however, the severity of
SMS symptoms may not be associated with changes in GI transit time. The reductions in the absorption and bioavailability of acetaminophen tablets reported previously [31], may reflect the observed increases in GI transit time in this study, which would suggest that the absorption and bioavailability of orally ingested medications for SMS and other indications may compromise the efficacy of oral dosage forms during space flight. Administering a prokinetic agent, an agent that speeds up GI motility may alleviate symptoms such as lack of appetite and dyspepsia experienced during the early days of space flight. One crew member showed evidence of bacterial overgrowth and positive test results for *H. pylori* proliferation after flight. These observations, however, are insufficient to draw definitive conclusions regarding how changes in the GI microbial environment may affect the bioavailability of orally ingested medications in space. It has been reported that cosmonauts commonly take lactobacillus preparations, probably in an attempt to promote GI microbial health during long-duration space travel [6].

Although the clinical relevance of changes in GI function discussed in this chapter may be less significant during the longer-duration ISS missions than were in the Space Shuttle Program, understanding the effects of such changes is important for ensuring good overall health and the effectiveness of therapeutics in space, particularly drugs for sustained health and wellness on the ISS and future exploration missions.

*Hepatic and Renal Clearance*
The elimination of medications and toxicants from the body is governed by hepatic metabolism and blood flow. Scientists from the U.S. and Russia have studied indices of liver metabolism in rats and humans exposed to microgravity [38,39].

In the tail-suspension model, a cast-like apparatus is fashioned on the tail and rats are suspended from swivels attached to the cage top to create an angle of about 30° angle between the rat’s body and the cage floor. Using this model, Brunner et al. reported an increase in the total body clearance of antipyrine, suggesting that pharmacokinetic parameters are altered by simulated microgravity [12]. In antiorthostatic bed rest models, clearance of marker compounds like antipyrine and indocyanine green have been used to assess hepatic metabolism and perfusion, respectively [40,41]. In one study, undergoing 24 hours of bed rest did not affect the clearance of indocyanine green [42]. Longer bed-rest studies may be required to characterize the hepatic clearance of this and other marker compounds.

Space flight studies of hepatic metabolism and function are few. In one experiment, rats had higher liver glycogen, lower liver cholesterol, higher serum cholesterol, and a 50% decrease in cytochrome P450 activity after flight relative to ground-based controls [39]. Oxidative hepatic metabolism in two members of the Mir-18 crew, assessed by measuring antipyrine clearance from saliva samples, varied during flight (Figure 12-9), with a decrease of more than 50% in antipyrine clearance for one crew member and a 30% increase for the other.
The limited in-flight data collected to date, although suggestive of diminished GI and hepatic function during flight, are inadequate to characterize the magnitude of the changes. Further, underlying mechanisms are difficult to identify because of the large number of variables that can influence disposition profiles and kinetic parameters during flight. Additional investigations are required to generate information that will be useful for developing pharmaceutical and nutritional countermeasures for microgravity-induced deconditioning. Elucidating the flight-induced changes in the pharmacology of medications administered in space is critical for ensuring effective treatment of crew members so that optimum health and performance can be maintained during flight and re-adaptation is prompt upon their return to a gravitational environment.

*Therapeutic Response Monitoring*

In classic ground-based pharmacokinetic studies, the rates of absorption, distribution, metabolism, and excretion of compounds are estimated from measurements of the amount of the drug and its metabolites in plasma as a function of time. Investigators at the Johnson Space Center have identified and validated methods for measuring drug levels in saliva as a way of monitoring the kinetics and dynamics of acetaminophen and scopolamine.

Both drugs are used commonly in flight, acetaminophen for headache [43] and a scopolamine-dextroamphetamine combination for motion sickness [44]. The suitability of measuring saliva to evaluate the pharmacokinetics and bioavailability of acetaminophen has been verified in ground-based testing. Therapeutic concentrations of acetaminophen can be detected in human saliva after oral administration [10]; moreover, the saliva-to-plasma ratio of acetaminophen consistently remains close to 1 over a range of plasma concentrations [45] (Figure 12-10) and
pharmacokinetic parameters calculated from saliva match those from plasma. In other studies, scopolamine also appeared readily in saliva after intravenous or oral administration; its saliva-to-plasma ratios were consistent over the disposition profile, but varied among subjects, with the correlation coefficient ranging from 0.87 to 0.99. The pharmacokinetics of acetaminophen after oral administration has been tested in space using this method (see below); studies of scopolamine were postponed after the discovery of irregularities in the drug dosage form.

Microgravity Analogs

Microgravity simulations such as bed rest are used frequently to develop and validate methods for use during space flight, to establish reference ranges under well-controlled experimental conditions, and to accumulate data for identifying changes in drug dynamics and mechanisms of action. (See Chapter 18) As noted earlier in this chapter, reports on the effects of posture and bed rest on hepatic function and pharmacokinetics are inconclusive and conflicting [11,13,46]. In a study conducted at the NASA Lyndon B. Johnson Space Center, the pharmacokinetics of orally and intravenously administered scopolamine were evaluated after 24 hours of antiorthostatic bed rest. Plasma concentration profiles indicated significant decreases in the absorption and bioavailability of oral scopolamine (Table 12-6) [47]; distribution and elimination of intravenous scopolamine were no different during bed rest than during the control periods. These early results suggest that the absorption of scopolamine, but not its distribution or elimination, may be affected by space flight.

Insert Figure 12-10 about here

Insert Table 12-6 about here
Another ground-based study involved testing the effect of a single intramuscular dose of promethazine on the performance of commercial airline pilots. Promethazine administration was associated with an elevation in the Stanford Sleep Scale Score, which paralleled concentrations of the drug in saliva.

**In-Flight Pharmacokinetics**

Measurements of drug concentrations in saliva were used to assess the pharmacokinetics of acetaminophen in twelve crew members before and during seven brief Space Shuttle flights [48]. Acetaminophen concentration profiles were different during flight than during the preflight control period (Figure 12-11); the most pronounced changes were apparent in the absorption phase. The absorption rate seemed to decline during flight, and the time to reach maximum drug concentration in the saliva (Tmax) during flight increased, indicating that absorption time was prolonged. In all subjects, the maximum concentrations of drug in the saliva (Cmax) on the first day of flight were less than those measured before flight; however, these concentrations varied widely, even in the same subject on different flight days. Mean Cmax and Tmax values indicated that Cmax was decreased on flight-day 0 and increased on flight days 2 and 3, whereas Tmax was increased on these days. Despite the wide variability and the limited number of subjects, it seems likely that the variability in absorption during flight, which was much greater than the variability during the preflight control period, arose from differences in crew members’ adjustments to microgravity. The incidence of motion-sickness symptoms, GI motility, exercise, and rest-activity cycles undoubtedly affect drug disposition as well. Future studies will characterize the pharmacokinetics of acetaminophen and other drugs during longer flights.

**Iatrogenic effects of SMS drugs**

Promethazine is associated with drowsiness that lasts for up to eight hours after the administration. Trends toward increased fatigue and decreased ability to concentrate were also reported. These results, demonstrate that intramuscular promethazine has marked and persistent effects.
Pharmaceutics and Drug Development for Space Missions

Because early results have suggested that space flight interferes with drug absorption by slowing GI motility, alternatives to enteral dosage forms may be advisable. In one study, the bioavailability of the motion-sickness medication scopolamine was evaluated after intranasal, intravenous, and oral administration [49]. The onset and duration of effect, as measured by reduction in salivary flow rate and salivary pH, were comparable after intravenous and intranasal administration; oral doses produced no change in either measure. Intranasal scopolamine was slower to reduce the salivary flow rate to its minimum than was intravenous scopolamine (1.05 hours vs. 0.27 hours, respectively (Figure 12-12). The maximum reduction in pH occurred 1.5 hours after dosing, when the pH dropped from control levels (mean 6.7) to 4.8 after intravenous and 5.0 after intranasal doses. Finally, scopolamine concentrations in plasma over time followed the effect-time curves closely (Figure 12-13). These results suggest that intranasal administration of this drug may improve its bioavailability and clinical effect. Similar dosage forms for other operationally important medications are under development.
The bioavailability of these 2 dosage forms were compared with that of the conventional intramuscular route in dogs [50]. The intranasal microsphere formulation of promethazine offers great promise as an effective, noninvasive alternative for treating SMS because of its rapid absorption and bioavailability.

**Future Directions**

As a final note, challenges for optimizing therapeutics in space in the future must include the development of pharmaceuticals with extended stability, optimal efficacy and bioavailability with minimal toxicity and side effects. Innovative technology development goals may include sustained/chronic delivery preventive health care products and vaccines, low-cost high-efficiency noninvasive, non oral dosage forms with radio-protective formulation matrices and dispensing technologies coupled with self-reliant tracking technologies for quality assurance and quality control assessment. These revolutionary advances in pharmaceutical technology will assure human presence in space and healthy living on Earth. Rationale and objectives to meet some of these challenges are described here.

**Radioprotection, Infection and Immunity**

The colonization of the lunar surface, three year missions to Mars and potential missions to Phobos and near-Earth objects such as asteroid 1999 AO10 will expose crew to risks that differ both quantitatively and qualitatively from those encountered during LEO missions and will impose an unknown risk of safety and crew health [16]. Few drug options are available for radiation protection. Amifostine is currently approved for use as supportive treatment in
radiation therapy, improving side effects and prognosis of radiotherapy. It scavenges free radicals and may inhibit apoptosis and is considered a broad spectrum radioprotective (15 is this a reference?). Two developmental drugs are currently in clinical trials as radioprotectants, Ex-Rad, 4-carboxystyryl-4-chlorobenzylsulfone sodium, developed in part by the US Armed Forces Radiobiology Research Institute [6] and the compound, CBLB502, a flagellin derived from Salmonella enterica [3].

Alternative paradigms for the treatment of infections that do not rely on the killing of the pathogen, with its attendant risk of emergence of drug-resistant variants, but modify them to produce a “less fit” phenotype with reduced capacity to survive at the site of infection could also be advantageously applied. There are conceptual reasons to suppose that this approach will result in less selective pressure on the bacteria and delay the emergence of resistant genotypes [25]. Drug candidates that reverse resistance mechanisms or reduce bacterial virulence are being actively investigated and these include a number of naturally occurring plant secondary metabolites that could be cultured and purified for treatment of infections [7,39]. Similarly, host-directed therapies, whereby natural mechanisms in the host are exploited to enhance therapeutic benefit, could be used alongside conventional or unconventional anti-infective therapies, to initiate or enhance protective antimicrobial immunity whilst limiting inflammation-induced tissue injury. Such therapies would rely on the multimodal innate and adaptive immune systems and are unlikely to engender resistance themselves. Therapeutically, these strategies would support existing antimicrobial agents to aid resolution of local and systemic inflammatory processes. Again, natural products with immune-enhancing potential could be produced and

| Treatment of on-board bacterial infections could be compromised by reversible or irreversible increases in antibiotic resistance and the emergence of multi-drug-resistant opportunistic pathogens, a currently unquantifiable risk, suggesting that a wide range of anti-infectives should be made available on board for treatment on exploration missions. |
exploited for treatment of infections in space and such supplements should not engender
insuperable drug formulation challenges [37].

\textit{Shelf Life and Packaging of Drugs for Space Missions}

At present, medication lots contained in the ISS operational formulary that are within six months
of labeled expiration date are replaced as needed in compliance with FDA guidelines. However,
this will not be possible for exploration missions planned for the future which warrants the need
for research and development of space-hardy formulations as well as packaging and dispensing
technologies.

Packaging plays an important role in the shelf life of drugs. Drugs marketed in the U.S. are
generally required to maintain 90-115\% of the label claim (of dose), while in unopened
containers, until the expiration date printed on the container. Solid formulations like tablets and
capsules are typically removed from manufacturer’s packaging and dispensed to patients in
secure closure containers, thus invalidating the expiration date by exposure to environmental
factors such as heat, light, humidity that can accelerate degradation. For space missions such as
to Mars, travel times and repacked mediation storage times will likely be longer than
manufacturers’ expiration dates and radiation exposure in missions beyond the LEO will most
likely be higher; therefore, radiation attenuating properties of packaging and stowage materials
becomes important. Daughter ions are formed when radiation passes through metals actually
increasing radiodosimetry [1]); thus, radiation shielding of drugs may require use of nonmetals
and new polymer technologies. On large scales, inert gases have been considered for the
protection of spacecraft, but on the small scale their use in custom manufacturing directly by
pharmaceutical industry may potentially enhance shelf life of drugs, if not through shielding then
by reducing oxidation. Concepts of radiation attenuation by applying portable shielding using lightweight materials such as high-density varieties of polyethylene (water, tungsten, and boron impregnated) may be applicable in the design of medical kits and drug dispensers for long duration missions [22]. New materials with multiple interfacial layers providing both deflection and attenuation characteristics, such as hydrated organic capillary-porous matrices may also be of interest as shielding materials.

Innovative drug delivery technologies: Alternatives to standard oral formulations that include sustained and targeted delivery technologies for preventive healthcare in space will be a welcome addition to the space formulary and may include controlled release topical, subcutaneous, intranasal and inhalation dosage forms. There is less demand for the development of innovative sustained drug delivery technologies because of their limited use in Earth-based healthcare other than for chronic conditions like asthma and diabetes. Leveraging operational needs of NASA for space exploration by collaboration with the commercial space industry, the Department of Defense and pharmaceutical vendors can facilitate cost effective development of novel pharmaceuticals that will enhance chronic clinical care capabilities. An example of such a technology development endeavor can be nanotechnology-based multi-stage drug cocktail and vaccine delivery systems. Nanostructures also have the ability to protect drugs encapsulated within them from physiologic degradation, target their delivery with sustained release and are suitable for per oral routes of administration [4]. The use of nanostructures such as polymeric nanoparticles offers a non-invasive approach for penetrating the blood brain barrier for management of neurodegenerative disorders, cerebrovascular and inflammatory diseases [20]. Finally, nanotechnology offers great potential for the development of safe and efficacious drug delivery systems for preventive health care in space and on Earth.
Factors Unique to the Space Environment that May Influence Stability of On-board Medications

The shelf life of pharmaceutical products is determined by the stability of the product, defined as the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical microbiological, therapeutic, toxicological, protective and informational specifications [51]. Manufacturers are legally bound to undertake stability testing of products as required by regulatory agencies and the dedicated amongst them will perform tests over and above the minimum demands to ensure that user safety is paramount. However, many manufacturers of generic versions of off-patent medications do not have the resources available to major pharmaceutical companies and often focus on tests designed to detect loss of the active component, resulting in sometimes inferior products [53]. At the outset, procurers for space agencies should source medications only from the most reliable manufacturers.

Environmental factors such as heat, light and moisture and chemical factors such as pH, oxidation, reduction, hydrolysis, or racemization, can play a vital role in the degradation process. Their impact on drug stability has been well documented [52,54] and formulations are invariably designed to compensate for these effects. However, the unique conditions encountered in space...
presents challenges for assuring drug stability that may have not been anticipated during formulation development for terrestrial use. Fluctuations in temperature are usually of short duration and low magnitude inside orbiting platforms. For example, the Orbiter environment experienced varying fluctuations in temperature during the course of a mission with observed temperatures as high as 86°F recorded during STS-41. The environment on board the ISS is more likely to present a humidity-related problem for stability of pharmaceuticals. Experience from orbiting platforms such as Skylab and Mir reveals that ambient humidity fluctuations may be of significant magnitude and duration to impact on drug stability. Specifications for the internal operational environment for Skylab allowed for a relative humidity of 25-85%; relative humidity on Mir ranged between 30 to 70% and long-term exposure to elevations in humidity could have significant adverse effects on some formulations.

Importantly, cyclic variations in humidity, particularly when combined with elevations in ambient temperature, may impart physical stress on compacted tablets, weakening their structure.

Many drugs are particularly susceptible to degradation when in solution. In addition to chemical stability, physical properties such as sedimentation, discoloration, precipitation, crystal growth, and creaming of many liquid and semi-solid pharmaceuticals need to be taken into account. Onboard medical kits contain many drugs in solution, and these may undergo subtle degradation during flight. For example, Promethazine is dispensed in three different dosage forms: tablet, solution for injection and suppository; the hydrochloride undergoes thermal and photolytic degradation that is oxidative in character, yielding a wide variety of degradation products, including some that are colored [29]. The superior stability of some formulations for a given

Alterations in the hardness or compaction of solid dosage forms may significantly affect dissolution and disintegration following oral administration, and deleteriously influence bioavailability.
drug over others could, therefore, be a major factor in the determination of onboard therapeutic regimens for everything other than minor ailments.

It is of concern that some formulations flown on the shuttle and ISS and examined by Du et al. [55] did not meet USP/FDA requirements after periods of less than twenty days in space; degradation of such formulations are likely to occur even more rapidly and to a greater extent in deep space. Factors contributing to this factors instability have not been defined, but candidates include heat, light, vibration and, particularly, various forms of radiation. Intuitively, it could be assumed that microgravity and noise would be unlikely to contribute significantly but in the absence of firm data to the contrary, should not be excluded.

Conventional final product packaged medications should undergo stress tests to simulate vibration encountered during transportation [56]. Vibration above 3 Hz may cause pack problems such as loosening of screw caps and breakage; lower frequencies may increase the electrostatic charge on polymers in drug formulations, resulting in powder separation [52] but this parameter has been systematically investigated. The ISS has a high density of resonant vibration modes and it was predicted during its design that the structure would have more than 200 dynamic modes below 15 Hz and 5,000 below 50 Hz, with the lowest frequencies of 0.06 Hz [57]. Items stowed on the middeck of the shuttle were routinely tested for hardiness, including vibrational hardiness, but medications stored mid-deck were not tested for vibrational hardiness.

Release of drug from its dosage form is highly dependent on the physical properties of the dosage form, properties which are altered by vibrational and concussive forces. Altering the release profile of many drugs can reduce the potency or

During launch and ascent, medications are exposed to short periods of vibration over a frequency range of 20-2,000 Hz of less than 10 sec and it is not clear whether this exposure will affect the performance of on-board medications.
efficacy and side effect profile of a drug, so there is a need for more systematic research into this issue.

Photolytic degradation of medications due to low energy electromagnetic radiation, particularly the ultraviolet and visible portions of the spectrum, is well-documented and of clear importance to the manufacture, storage and use of pharmaceutical products. Regulatory guidelines advocate testing of dosage forms for stability to light and the packaging used for pharmaceutical products reflects the potential for light to interact unfavorably with the product in warehouses, controlled pharmacy conditions and during short periods of transit [52]. Some commonly-used antibiotics are susceptible to ultraviolet [58] and fluorescent light [59]; light is destructive to many classes of drug and amber bottles are standard for the dispensing of most dosage forms. Coating of tablets, using opaque rather than transparent capsules and using capsules that incorporate a dye that screens out all or part of the photoreactive spectrum should also prevent photolytic degradation [52].

High energy forms of electromagnetic or particulate radiation are likely to be the primary causes of drug formulation instability in space. Spacecraft in LEO such as the ISS, which has a stable orbit within the thermosphere between 320 and 380 km above the Earth, are exposed to greater amounts of particulate ionizing radiation than the planet surface. In addition to galactic cosmic rays and SEP events, spacecraft will be exposed to energetic electrons and protons originating from particles captured from the solar wind and solar cosmic rays and trapped within the Earth’s geomagnetic field. The ISS will encounter trapped electrons in the inner Van Allen belt, most with energies of less than 5 MeV that will not penetrate the spacecraft skin [60]. More highly energetic (~150–250 MeV) trapped protons normally occupy a belt above that traversed by the...
ISS but, due to an 11° offset of the Earth’s magnetic dipole axis from its axis of rotation, the geomagnetic field is displaced to produce the “South Atlantic Anomaly” (SAA) over the coast of Brazil where the belt reaches less than 200 km above the Earth’s surface. The ISS is forced to pass through the inner fringes of the proton belt at the SAA and receives significant exposure to protons. In total, the ISS receives over one half of its primary ionizing radiation dose from these trapped protons and much of the remainder from galactic cosmic rays [61,62]. If particles from these sources collide with the spacecraft structure they will undergo nuclear reactions to produce neutrons and high linear energy transfer (LET) target and projectile fragments that contribute to ionizing radiation exposure. Reports from the NASA-4/Mir-23 mission indicated a high-LET flux behind heavily shielded space station locations, as compared to less shielded areas, indicating that fragmentation ions generated from the collision of high energy ions creates higher and more complex radiation doses than those present in interplanetary space [60,62]. Ionizing radiation is associated with extremely high energies per nucleon [63], which may be very destructive to certain classes of drugs, but this is an under-researched and under-reported area.

Some clues as to the effect of radiation on drug stability have come from a few studies of sterilization of drug formulations by γ-radiation, which has the capacity to degrade both drug and excipients [64]. The current knowledge of space pharmacology is summarized in Table 12–4

**Case Study from the Aeromedical Practice**

**Objective:** Treating an indwelling catheter infection in space flight.

A thirty six year old male ISS astronaut agreed to participate as a research subject in an experiment requiring, preflight insertion of an indwelling venous catheter and injection of a dye to study renal function in space. The purpose is to determine the early diuresis in microgravity. The study was approved by the NASA Space Flight Institutional Review Board [IRB] and
briefed to the Multilateral IRB, composed of the ISS partner’s medical experts. The intravenous indwelling catheter was inserted nine hours prior to the launch, and a sterile dressing impregnated with triple topical antibiotic ointment [bacitracin] applied.

No untoward reaction either from the catheter or the injected dye reported on the second day of the mission. The crewmember was directed to remove the catheter, following the procedure developed by the flight surgeon and the principle investigator. Removal was successful, and a two-way video conference showed no inflammation around the puncture wound. A sterile dressing was applied. Three days into space flight the crewmember complained of pain at the puncture site. The dressing was removed and a video image sent to the mission control flight surgeon. Mild swelling and 4 cm redness around the puncture site [left arm decubitus area], tender to palpation and no evidence of sticking, or enlarged lymph nodes were noted. Heart rate 80 bpm, blood pressure 120/68 mmHg, respiration 12/minute, temperature 99.0° F (37.3° C). Prior sensitivity to penicillin is present [skin rash]. Symptoms do not interfere with the performance of duty.

A diagnosis of localized cellulitis due to the infected catheter is made. The on-orbit designated crew medical officer advised to clean with an antiseptic soap preparation [no alcohol to be used since it remains in a closed environment of ISS and can contaminate the life support system], apply a new sterile dressing [use proper caution while discarding the contaminated dressing and dispose in a sealable bag to be returned to Earth for further analysis], and administer oral Erythromycin 500 mg. every 6 hours.

Twenty four hours later, the crewmember woke up complaining of a headache, fewer, chills, nausea, myalgia, and generalized malaise. Respiration 20/minute, heart rate 100, blood pressure
110/60 mmHg and temperature 104.0° F (40.0° C). There is no increase in streaking or swelling of the area, possible small left axillary node present.

Following consultation with ground infectious diseases experts, using private medical conferencing and telemedical support, a diagnosis of secondary bacteremia due to ISS non sterile conditions is made. Possibility of early mission termination was discussed with the flight director and the mission managers. The crewmember is started on intramuscular Aminoglycoside 15mg/kg daily divided in 3 doses [every 8 hours] and Cephalosporin 1st generation, intramuscular injections every six hours. Crew member was relocated to a well-ventilated area [to promote a more efficient body heat dissipation in the absence of convection in microgravity, the use of the liquid cooled garment was placed on standby if the temperature rises above 42° C].

The crewmember health starts to improve and 12 hours later he was symptoms free and the temperature was down to 38° C. Forty eight hours following the initiation of the therapy, the CMO starts the tapering of antibiotics. The crewmember is fully recovered on the 7th day mission and completes successfully the 148 days tour of duty on the ISS.

**Self-study Questions**

1. How microgravity expanded the scope of pharmacology and therapeutics over the past five decades?

2. How has the space mission’s complexity and biomedical research changed the medical kits formulary available to crew members?

3. Discuss the adequacy of crew debriefings on the therapeutic efficacy and side effects, on future space clinical practice and safety.

**Key Points to Remember**
1. Evidence on pharmacokinetics and pharmacodynamics in space is limited to a few preparations.

2. Efficacy of in-flight medications is based on clinical assessments and crew member reports.

3. Exposure of medications to space flight conditions results in faster degradation of bioavailability.

4. It is advisable to allocate storage spaces for medical kits, under appropriately monitored environmental and radiation shielding, during the design of space crafts for long duration missions, to ensure shelf life and bioavailability.

5. In the low Earth Orbit [US missions only], all medical conditions responded to therapy and did not require unscheduled mission termination or emergency crew evacuation.

6. It appears that oral medications are not as well absorbed and excreted, as compared to their disposition on Earth.

7. Intramuscularly administered medications produce the desired response in space-flight.

8. Extended duration missions should include in addition to emergency equipment, appropriate resuscitation medications.

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Pharmacological agents for the prevention and treatment of toxic radiation exposure in spaceflight.

Langell J1, Jennings R, Clark J, Ward JB Jr.

Author information

Abstract

BACKGROUND:

Astronauts are exposed to toxic ionizing radiation sources, including galactic cosmic radiation and solar particle events (SPE). Exposure to these radiation sources can lead to cataracts, heritable genetic mutations, cancer, acute life-threatening physiological compromise, and death. Current countermeasures focus on spacecraft shielding and creation of heavily shielded safe havens. At issue is the extraordinarily high cost of launching these heavy structures into space and their inability to provide adequate shielding from heavy ions.
at a feasible shield thickness. Pharmacological enhancement of cellular radiation resistance, an alternative method to limiting radiation toxicity, has received less attention.

METHODS:

We have conducted an extensive literature review and critical evaluation of the scientific data pertaining to this field of study. Publications for review were identified through a Medline search using relevant terms, including radiotherapeutics, galactic cosmic radiation, radiopharmacology, radioprotectants, radiation countermeasures, solar particles, solar flares, radiation toxicity, and radiotoxicity.

RESULTS:

We identified 15 agents with significant radiation dose reduction factors, ranging from 1.1 to 2.4, in experimental models. Of these, only amifostine is FDA approved for use in treating radiation toxicity.

CONCLUSIONS:

Current data do not support the use of radiopreventive agents in the treatment of low-level ionizing radiation exposures. However, pharmacological countermeasures should be instituted for life-threatening, high-level radiation exposures, as occur with SPE. Given the catastrophic effects of SPE, the risk of toxicity from radioprotective agents is warranted. The current data supports treatment with high-dose amifostine (at 910 mg m(-2)) 30 min prior to radiation exposure.
Plasma Scopolamine Concentrations After Oral Administration to Subjects

Concentration (pg/ml)

Control
Bedrest

Time (h)
Figure 12-1 Frequency in percentage of medications used during shortduration missions by US crews [adapted from Putcha]

Legend: CNS refers to central nervous system; CV is cardiovascular and TBD means undetermined
Figure 12-3a. Pharmaco-kinetics stability kit [courtesy NASA]

Figure 12-3b Redesigned Space Shuttle and ISS Pharmacology kit
Figure 12-1 Space Shuttle Emergency and ISS pharmacology kits [Courtesy NASA]
Figure 12-5XX Advanced life support kit
Figure 12 -5 Schematic representation of oral and intravenous drug metabolism curves
### Table 12-4: Subjective Evaluation of the Strength of Evidence in Space Pharmacology

<table>
<thead>
<tr>
<th>Subject</th>
<th>Knowledge</th>
<th>Reference (s)</th>
<th>Strength</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Release</td>
<td>Not Available</td>
<td>None</td>
<td>Insufficient</td>
<td>Additional inflight studies required</td>
</tr>
<tr>
<td>Absorption</td>
<td>Limited</td>
<td>[Gandia 2005]</td>
<td>Fair</td>
<td>Limited to few compounds</td>
</tr>
<tr>
<td>Distribution</td>
<td>Not available</td>
<td>None</td>
<td>Insufficient</td>
<td>Additional inflight studies required</td>
</tr>
<tr>
<td>Metabolization</td>
<td>Limited</td>
<td>Cintron 1987</td>
<td>Fair</td>
<td>Additional inflight studies required</td>
</tr>
<tr>
<td>Excretion</td>
<td>Not Available</td>
<td>None</td>
<td>Insufficient</td>
<td>Additional inflight studies required</td>
</tr>
<tr>
<td>Adverse reactions</td>
<td>Not Available</td>
<td>None</td>
<td>Insufficient</td>
<td>Additional inflight studies required</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Not Available</td>
<td>None</td>
<td>Insufficient</td>
<td>Additional inflight studies required</td>
</tr>
<tr>
<td>Shelf life</td>
<td>Documented</td>
<td>Du 2002</td>
<td>Good</td>
<td>Extending shelf life of medications is required for missions beyond LEO</td>
</tr>
<tr>
<td>Empiric Information</td>
<td>Clinical Observations based on crew reporting</td>
<td>Not Available</td>
<td>Fair</td>
<td>Post mission crew debriefing, mission medical</td>
</tr>
<tr>
<td></td>
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<td>communication</td>
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</tr>
</tbody>
</table>
Tables 12-X. Medications classes and type [generic name] provided in medical kits and usage

<table>
<thead>
<tr>
<th>Space craft</th>
<th>Mercury</th>
<th>Gemini</th>
<th>Apollo</th>
<th>Skylab Orbital Station</th>
<th>Apollo/Soyuz Test Project</th>
<th>Space Shuttle</th>
<th>ISS</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications</td>
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<tr>
<td>Analgesics</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Meperidine [injector]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Most commonly used in space for back pain, and headaches</td>
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<tr>
<td>Antibiotics</td>
<td></td>
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<tr>
<td>Antimotion sickness</td>
<td>Cyclizine [injector]</td>
<td></td>
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<tr>
<td>Stimulants</td>
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<tr>
<td></td>
<td>Dextroamphetamine [oral]</td>
<td></td>
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<tr>
<td>Antihistaminics</td>
<td>Epinephrine [injector]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oral preparations used for congestion</td>
</tr>
</tbody>
</table>

Explanation: [1] used in space flight;
Tables to be considered – They are about 10 years old

Table 12-X. Bioavailability of Oral Scopolamine During Bed Rest

<table>
<thead>
<tr>
<th>Subject</th>
<th>Bioavailability</th>
<th>Control period</th>
<th>Bed rest period</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.6</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>23.5</td>
<td>31.2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>11.6</td>
<td>19.0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>21.4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>73.6</td>
<td>39.6</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>19.3</td>
<td>14.4</td>
<td></td>
</tr>
</tbody>
</table>

Mean (SE) 26.0 (9.0)     17.3 (6.0)

(Adapted from Putcha et al., 1989)
Table 12-X. Inflight Medications for Prolonged Space Flight

- Analgesics
- Antibiotics and antiinfective agents
- Antiemetics (e.g., scopolamine)
- Antihistamines, including histamine H2-receptor antagonists
- Cardiovascular agents (antihypertensives, antiarrhythmics, plasma-volume expanders)
- CNS stimulants
- Nonsteroidal anti-inflammatory agents
- Sedative-hypnotics
- Agent(s) to prevent bone and muscle atrophy; radiation protectants; chronomodulators – WHAT KIND OF DRUG IS THIS?
Table 12-x. Example of Medications Taken During U.S. Space Flights – NEED TO FINISH THE TABLE

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Generic name</th>
<th>Dose (mg)*</th>
<th>No. of Times Used</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analgesics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>acetylsalicylic acid</td>
<td>298</td>
<td></td>
</tr>
<tr>
<td>Tylenol</td>
<td>acetaminophen</td>
<td>222</td>
<td></td>
</tr>
<tr>
<td>Advil, Motrin</td>
<td>ibuprofen</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Ascriptin</td>
<td>acetylsalicylic acid (buffered)</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Lomotil</td>
<td>diphenoxylate HCl with atropine sulfate</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>APC</td>
<td>aspirin with phenacetin and codeine</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Excedrin</td>
<td>acetaminophen with aspirin+caffeine</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Naprosyn</td>
<td>naproxen</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Naloxone</td>
<td>naloxone HCl</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Parafon forte</td>
<td>chlorzoxazone</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>AntiEmetics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scope-Dex</td>
<td>Scopolamine with dextroamphetamine</td>
<td>0.4/5.0</td>
<td>123</td>
</tr>
<tr>
<td>Scope-Dex</td>
<td>Scopolamine with dextroamphetamine</td>
<td>0.4/2.5</td>
<td>39</td>
</tr>
<tr>
<td>Phenergan</td>
<td>Promethazine HCl (patch)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Phenergan</td>
<td>Promethazine HCl 50 (IM)</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Phenergan</td>
<td>Promethazine HCl (supp)</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Phenergan</td>
<td>Promethazine HCl 25(IM)</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Phenergan</td>
<td>Promethazine HCl (PO)</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Phenergan</td>
<td>Promethazine HCl 15(IV)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Phenergan</td>
<td>Promethazine HCl with ephedrine</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Reglan</td>
<td>Metoclopramide HCl 10(PO)</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Reglan</td>
<td>Metoclopramide HCl 10(IV)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Compazine</td>
<td>Prochlorperazine (supp)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>Codeine</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Sedative-Hypnotics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restoril</td>
<td>temazepam</td>
<td>15</td>
<td>96</td>
</tr>
<tr>
<td>Dalmane</td>
<td>flurazepam HCl</td>
<td>15</td>
<td>85</td>
</tr>
<tr>
<td>Halcion</td>
<td>triazolam</td>
<td>0.5</td>
<td>20</td>
</tr>
<tr>
<td>Halcion</td>
<td>triazolam</td>
<td>0.25</td>
<td>10</td>
</tr>
<tr>
<td>Drug</td>
<td>Description</td>
<td>Quantity</td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
<td>--------------------------------------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td>Valium</td>
<td>diazepam</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Seconal</td>
<td>secobarbital sodium</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Chloral hydrate</td>
<td>chloral hydrate</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Decongestants &amp; H1-Blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afrin</td>
<td>oxymetazoline HCl</td>
<td>(IN) 61</td>
<td></td>
</tr>
<tr>
<td>Sudafed</td>
<td>pseudoephedrine sulfate</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Actifed</td>
<td>triprolidine HCl with pseudoephedrine HCl</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Seldane</td>
<td>terfenadine</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Benedryl</td>
<td>diphenhydramine HCl</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Marezine</td>
<td>cyclizine HCl</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Dimetapp</td>
<td>brompheniramine maleate with phenylpropanolamine HCl</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ornade</td>
<td>phenylpropanolamine HCl with chlorpheniramine maleate</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>GI-Related</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dulcolax</td>
<td>bisacodyl</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Surfak</td>
<td>docusate calcium</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Pepto-Bismol</td>
<td>bismuth subsalicylate</td>
<td>9</td>
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<tr>
<td>Mylanta</td>
<td>aluminum hydroxide with magnesium hydroxide and simethicone</td>
<td>6</td>
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</tr>
<tr>
<td>Tagamet</td>
<td>cimetidine</td>
<td>400</td>
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</tr>
<tr>
<td>Imodium</td>
<td>loperamide HCl</td>
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<td></td>
</tr>
<tr>
<td>Kaopectate</td>
<td>kaolin with pectin</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Lovastatin</td>
<td>lovastatin</td>
<td>15</td>
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</tr>
<tr>
<td>Dexedrine</td>
<td>dextroamphetamine sulfate</td>
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<td></td>
</tr>
<tr>
<td>NoDoz</td>
<td>caffeine</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Septra DS</td>
<td>trimethoprim-sulfamethoxazole</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Amoxil</td>
<td>amoxicillin</td>
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</tr>
<tr>
<td>Polysporin</td>
<td>polymyxin B sulfate with bacitracin zinc</td>
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<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Ingredient</td>
<td>Quantity</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>---------------------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td>UroCit-K</td>
<td>potassium citrate</td>
<td>2</td>
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</tr>
<tr>
<td>Flexeril</td>
<td>cyclobenzaprine</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lo/ovral</td>
<td></td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Legend: HCl = hydrochloride; IM = intramuscular; IN = intranasal; IV = intravenous; PO = oral

*Dosage form is oral (PO) unless otherwise noted