Space Pharmacology: An Overview

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Abstract

Space Pharmacology is the study of use of pharmaceutical drugs during spaceflights. Space flight can alter administered drug act on the body. Pharmacology scientists are conducting research to improve crew health and well-being. Astronauts are not the only ones who benefit from space medicine research. Space pharmacology research will benefit health care on Earth. Several medical products have been developed that are space spinoffs, that is practical applications for the field of medicine arising out of the space program. It is difficult to conclude the optimal drug regimen in microgravity to ensure safe, effective, and definitive treatment of space travellers. This study is mainly focused on the health issues in space, space medicine for astronauts, pharmacokinetic, pharmacodynamics and pharmacotherapeutics in space and medicine spinoffs.

Keywords: Microgravity, space suits, spinoffs

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Introduction

Pharmacology plays a crucial role in the treatment of many diseases on earth. Space Pharmacology uses pharmaceuticals during spaceflights. Space Pharmacology plays a major role in the health care system of astronauts. Cosmonaut Yuri Gagarin became the first human to fly in space. Alan B. Shepard launched from Cape Canaveral on a Mercury Redstone 3 rocket to become the first NASA astronaut to fly in space. Medical support needed for prolonged space flights missions. Space medicine mainly focussed on the practice of medicine on astronauts. Space Medicine deals with the medical problems experienced by humans during space flight. The ultimate aim is to adopt for the microgravity environment and also can adapt to the Earth's
environment after returning from their voyage. Manned mission leads to blindness and bone loss. Extreme care with drug treatment will be given to humans during their frequent interplanetary exploration and also who experience severe injury and illness. Long term space flight medical consequences are countered by pharmacologic treatment. This provides an overview of the influence of microgravity on pharmacotherapeutics.

Space flight affects biological systems. Exposure to microgravity can alter the musculoskeletal, neurosensory and cardiovascular systems. Radiation exposure injuries continue for the duration of the mission and may have implications in the post-flight period. A serious group of risks which includes the loss of consciousness occurs during re-entry to the Earth's atmosphere.

2. Microgravity

Microgravity is also termed as weightlessness or free-fall and zero-G. Microgravity alters the pharmacokinetics and pharmacodynamics of drug in the body. After reaching orbit in the space flight, astronauts experience much lower gravity than on Earth. This is known as microgravity. Many people mistakenly think that gravity does not exist in space. Earth's gravitational field at about 250 miles above the surface is 88.8 percent of its strength at the surface. Sir Isaac Newton described the nature of gravity more than 300 years ago. Gravity is the attraction between any two masses, most apparent when one mass is very large (like Earth).

2.1 Effect of microgravity

Microgravity condition affects human body causing bone loss, immunosuppression, enlargement of bones, muscle loss and movement of body fluids towards head, spaceflight osteopenia, decrease in the function of cardiovascular system functions, decreased production of red blood cells, balance disorders, and also weaken the human immune system. Effects of sex and gender on adaptation to space were also studied. Lesser symptoms include fluid redistribution ("moon-face"), loss of body mass, nasal congestion, sleep disturbance, and excess flatulence. Most of these effects begin to reverse quickly upon return to Earth.

2.2 Fluid distribution in microgravity

An astronaut’s circulatory system receives a different set of signals and stimuli in microgravity and adapts to the new environment. The heart does not need to work as hard to send blood to the upper body as it does when it working against gravity. This causes blood volume to increase in the upper body.
2.3 Absence of gravity
A "stationary" micro-g environment would require travelling far enough into deep space so as to reduce the effect of gravity by attenuation almost zero but it is impractical. To reduce the gravity to one thousandth of that on Earth's surface, one needs to be at a distance of 200,000 km.

Fig 1: Comparison of the gravitational potential (Credits: Wikipedia).

2.4 Commercial application of microgravity
2.4.1 High quality crystals
Space scientists are helping find out how to grow the best quality crystals with protein crystals, like insulin (used to help people with diabetes). Protein crystals made in space are a great opportunity to design new medicines in the future.

2.5 Effects of spaceflight on astronauts
Life support system plays a crucial role in the manned mission. Breathable air and drinkable water and a group of devices that allow human beings to survive in outer space. The life support system supplies air, water and food. It must also maintain temperature and pressure within acceptable limits and relates with waste products of body. Shielding against harmful external influences such as radiation and micro-meteorites is also necessary. Microgravity environment impacts the body such as loss of proprioception, changes in fluid distribution, and deterioration of the musculoskeletal system. Direct exposure to the extreme environment of space includes extreme variations in temperature and increased radiation levels. Physiological effects of
spaceflight includes space motion sickness, fluid redistribution, cardiac rhythms, decompression
sickness, decompression illness in spaceflight, barotraumas, decreased immune system
functioning, loss of balance, loss of bone density, wasting of muscles, loss of eyesight, disruption
of taste, decrease metal health, orthostatic intolerance, sleep disorders, renal function
impairment, impaired protein metabolism, lowering of plasma protein synthesis, body weight
loss, changes in skin physiology and blood pressure variation. Dysregulation of immune system
of astronauts were reported in the space flight mission. Increased oxidative damage post flight
in humans is that the increase is due to a combination of the consequences of the loss of protein
secondary to the in-flight reductive remodelling of skeletal muscle from the decreased work load
on the antigravity muscles.

2.6 Space medicine for astronauts
Space medicine is the practice of medicine on astronauts and it deals with the prevention or
control of exposure to the hazards that may cause astronaut ill health.

2.6.1 History of medication carried by astronauts
Medications have been carried aboard US spacecraft since the inception of the Mercury program
in the early 1960s. On the first 4 Mercury flights (May 1961 to May 1962), injector systems were
developed to allow an astronaut to deliver medication through his spacesuit and directly into the
thigh muscle. Three medications were carried via an injector such as Epinephrine (1:1000),
Cyclizine for motion sickness (45 mg/0.9 mL), and Meperidine for pain (90 mg/0.9 mL). On the
fifth Mercury flight (October 1962), only Cyclizine and Meperidine was carried. For the sixth
flight (May 1963), Cyclizine and Meperidine injections and Dextroamphetamine tablets were
supplied. For Project Gemini (April 1964 to November 1966) astronauts were instructed to take
Dextroamphetamine with a decongestant before reentry, and Diphenoxylate was prescribed to
prevent defecation during flight. Anti-motion sickness medication was prescribed in 1 instance
before atmospheric re-entry to reduce the possibility of motion sickness after splashdown.
During Project Apollo, medical kits consists of Oral doses of aspirin or Acetaminophen,
Triprolidine, Cyclizine, Secobarbital, and Diphenoxylate, Oxymetazoline nasal spray. During the
Apollo-Soyuz Test Project in 1975, Quinidine, and Dipyridamole were added to the medical kit.
Pharmaceutical use in the shuttle program found that at least 75% of astronauts had taken
medication for similar nonemergency indications during their missions. Medications are routinely
available to astronauts primarily in oral dosage forms (tablets and capsules), but intramuscular
injections, rectal suppositories, ocular preparations, and topical agents are also available in the on-board medical kit.

2.6.2 Pharmaceuticals for astronauts
Modafinil helps ISS crew members optimize their performances. Zoledronate showed promise by slowing the bone-mass loss. Astronauts sometimes turn to ScopeDex, Scopolamine and Dexedrine to prevent and treat nausea. Fifty percent of space shuttle astronauts take sleeping pills and still get two hours or less of sleep.

2.7 Space blanket
A space blanket reduces the heat loss in a person's body which would otherwise occur due to thermal radiation, water evaporation, or convection. They may be included in first aid kits and also in camping equipment. The space blankets are waterproof and windproof. In first aid the blankets are used to prevent/counter hypothermia. The airtight foil reduces convection, heat loss caused by evaporation of perspiration, moisture or blood is minimized by the same mechanism, limited extent the reflective surface inhibits losses caused by radiation.

2.8 NASA medical kits
Since the dawn of human space exploration medicine has had to evolve quickly to support the presence of human beings in space. Life support, safety, and health were addressed on an a priori basis and were mainly founded on aviation medicine.

2.9 Project Mercury
Auto injectors carried on the Mercury-Atlas 9 flight. The injectors provide the astronaut with injection tubes of Tigan, for preventing motion sickness and Demerol, for relieving pain.

3.0 Route of administration
Different routes of administration have been used during spaceflight including intravenous, intramuscular, subcutaneous, intranasal, inhaled, oral, topical, and rectal. Crew medical officers are trained on drug administration through all of these routes, though oral and intramuscular are the routes most commonly used. Additional research into the efficacy and bioavailability of each of these routes is needed. Prior to flight, many drugs are tested by crewmembers. This is done in an attempt to prevent atypical reactions during the mission.

3.1 Pharmacokinetics changes in space
The pharmacokinetic of drugs may alter in the environment of space. Pharmacokinetic changes will affect the drug concentrations produced by a certain dosage regimen. Physiological
changes due to free fall may induce changes in pharmacokinetic behaviour of drugs and influence their dosage regimen. Pharmacokinetics studies in humans, one has generally only access to drug concentrations in plasma and urine which are the results of several concurrent mechanisms. During free fall, different changes may occur in each step of the drug disposition process.

3.1.1 Change in absorption
Pre-flight and in-flight salivary levels of acetaminophen where shown to differ, probably due to changes in gastrointestinal transit time. In-flight salivary concentration-time curves of scopolamine/ dextroamphetamine, given as conventional oral tablets, also were shown to be erratic and exhibited higher intra and inter-individual variability compared to those of pre-flight data. Gastric emptying in microgravity can also be altered due to changes in particle size discrimination by the stomach, which is strongly dependent on the force of gravity. Also, particles are not restricted by gravity to the lower pyloric region of the stomach anymore but move throughout all regions of the stomach. This array of factors can lead to variability in drug plasma levels. Intestinal transit rate in a gravity environment is highly dependent on the motility state of the gastrointestinal (GI) tract either fasted or fed, partly due to the higher viscosity of chyme in the fed state. In space, the absence of gravity may tend to increase the transit rate along the small intestine by decreasing the dimensionless ratio of gravitational forces to viscous forces. In zero gravity, therefore, these alterations in GI emptying and intestinal transit rate could lead to inefficient absorption and erratic plasma levels.

3.1.2 Change in distribution
Physiological changes, such as the decrease in Total Body Water (TBW) and Plasma Volume (PV), and the muscle loss may alter the volume of distribution of drugs. This will have an impact on the plasma and tissue concentrations achieved after the administration of a drug in space and, depending on the magnitude of the change, will require that a completely new dosing scheme be designed to avoid sub-therapeutic or toxic concentrations. Altered tissue binding is observed as result of protein loss, muscle atrophy, and decrease in lean body mass.

3.1.3 Change in metabolism and excretion
The amounts of cytochrome P-450 and other enzymes decreased during space flight and simulated microgravity. Altered nutritional or energy requirements may have effects on urine excretion of drugs, and dehydration may result in changes in urine excretion of drugs.14,15
3.2 Pharmacokinetic parameters in space

3.2.1 Efficacy of medications used during space missions

Some orally administered medications taken during flight were reported to be less effective than expected. A typical dose of a medication used to treat headache, for example, did not relieve the headache completely (or at all) when taken during human spaceflight mission.

3.2.2 Bioavailability

Oral bioavailability of medications during spaceflight, several factors, including alterations in drug dissolution rate in gastric juices, gastric emptying, gastric or intestinal absorption, hepatic first-pass metabolism, and intestinal blood flow, could all be influenced by microgravity. Other conditions related to early microgravity exposure could also influence bioavailability, including space motion sickness or changes in gut micro flora and gut enzymatic release and distribution.

3.2.3 Volume of distribution

Cephalad fluid shifts, redistribution of fluid out of the central compartment, and fluid decreases due to prelaunch intake restrictions, along with losses due to space motion sickness and diuresis, produce total body water and plasma volume losses upon entry into space. Tissue binding of medications can be altered because of protein loss secondary to muscle and tissue atrophy, redistribution of plasma proteins out of the central compartment, alterations in blood lipid levels, or reduced erythrocyte production. Thus, volume losses coupled with reduced tissue binding could alter the distribution of a medication throughout the body, which could influence therapeutic and toxic effects.

3.2.4 Absorption rate

In a small study involving 5 astronauts from 3 shuttle missions, acetaminophen was administered (650 mg as two 325-mg tablets orally). Salivary samples rather than blood sample were analyzed to determine the pharmacokinetics of the drug during ground-based testing and during flight. A decrement in absorption of acetaminophen was observed in space compared with ground based testing, as noted by a consistently lower maximum salivary concentration ($C_{\text{max}}$) and greater time to reach peak concentration ($T_{\text{max}}$) in the test group. Moreover, salivary concentrations of acetaminophen varied greatly among individual astronauts when measured over several flight days; the reasons for this are unclear, but factors may include changes in gut motility, gut absorption, and space motion sickness.
3.2.5 Clearance
Microgravity could affect drug elimination via the kidneys. As suggested by anti-orthostatic bed rest studies, it could also affect liver metabolism of drugs owing to changes in perfusion secondary to the cephalad redistribution of blood.

3.3 Pharmaceutical stability
Altered physiochemical properties cause reduced release/absorption, reduced therapeutic activity. Proposed radiation-induced effects such as Gamma and nucleon, Radiolabile (space), reduction in therapeutic content, exposure may generate potentially toxic species

3.3.1 Drug formulation (dosage form) stability
Humidity, temperature, pH, and radiation exposure can affect the stability of a medication. When medications are exposed to any or all of these factors, they are prone to degradation.

3.4 Pharmacodynamic changes in space
Many drugs act by altering the function of specific ion channels either directly or indirectly. Ion channels are gravity sensitive. Gravity directly influences the integral open-state probability of native ion channels (porins) Pharmacodynamic changes will affect the response that is produced by a given drug concentration. They can be caused by changes in drug-receptor interaction or changes in disease characteristics. During crew medical debriefings, astronauts observed that promethazine was less likely to produce sedation in flight than when used on the ground, suggesting that altered bioavailability, pharmacodynamics was at play during spaceflight. Another pharmacodynamic issue in space may relate to microgravity induced changes in microorganism growth, as opposed to physiologic changes to the body that influence drug response. Clinical assessment includes altered pharmacodynamics (PD), frequent use of hypnotics/sedatives, oral drug treatment may be ineffective or less effective (anecdotal reports).

3.5 Pharmacotherapeutics changes in space
Pharmacotherapeutics in space is the study of the therapeutic uses and effects of drugs in space. The goal of pharmacotherapeutics research at the Johnson Space Center is to enable successful space medical operation to deliver Safe and effective diagnostic and products, procedures, and strategies to support successful space medical operations. Highlights of the pharmacotherapeutic research reviewed include development and validation of methods for pharmacologic research, in-flight pharmacokinetics and alternative drug delivery methods in space. Pharmacotherapeutics for Space Exploration includes Pharmaceutical stability of dosages
forms, Evidence Based Medical practice, PK/PD changes, Therapeutic monitoring Systematic evaluation, enabling technologies for drug treatment, monitoring and management.

3.6 Use of medicines in space
Medications are used for a wide variety of indications during space flight. Astronauts have taken drugs in flight to ameliorate or prevent symptoms of space motion sickness, headache, sleeplessness, backache, nasal congestion. Although the discomfort associated with some acute responses to microgravity (e.g., space motion sickness) is expected to diminish with length of time in flight, other responses that have delayed onset (e.g., maintaining nutritional status, bone and muscle strength, and perhaps immune response) may affect health and quality of life during longer missions. Therefore, as the duration of space flights increases, the need for treatment with medications is expected to increase accordingly. Higher antibiotic resistance were reported in the bacterial samples collected on the crew Apollo-Soyuz 425. Test Project Mission. Oral route may not be ideal for those suffering motion-sickness symptoms, intramuscular and intranasal preparations are being tested. Intramuscular administration of promethazine hydrochloride has been reported to be more effective in alleviating motion-sickness symptoms.

Data currently available suggest that space flight affects absorption of orally administered medications and stability of drug formulations. These findings support the need for the development of novel drug delivery systems for acute and chronic treatment in space.

3.7 NASA pharmacotherapeutic laboratory
The goal of the Pharmacotherapeutics Laboratory is to mitigate pharmacotherapeutic risk by identifying and providing safe and effective diagnostics tools, pharmaceutical preparations, therapeutic procedures and intervention strategies. The Pharmacology Laboratory in close collaboration with the Space and Clinical Operations Division, supports medical requirements for the International Space Station, and space exploration programs. Activities include clinical pharmacy services, pharmacokinetics and pharmacodynamics research, therapeutic drug monitoring, specialized therapeutic monitoring for spaceflight-related pathophysiology, novel dosage form development, and pharmaceutical stability assessment.

3.8 Space flight challenges and risk factor
Environmental extremes, Time and distance in which clinical care and monitoring of medicinals will be impacted. Space flight challenges includes physiological responses to microgravity such as Bone, muscle, and cardiovascular changes, neurovestibular alterations,
decreased immune function, variations in endocrine system. Risk Factors includes GI, hepatic and renal function changes, pharmacokinetic/ pharmacodynamic alterations and therapeutic implications, adverse drug reactions, stability and shelf-life of pharmaceuticals.

3.9 Medicine spinoffs
Spinoffs that improve fitness, treat disease, and save lives. NASA medicine spinoffs such as Thermometer pill helps athletes beat the heat, non-invasive test detects cardiovascular disease, circulation-enhancing device improves CPR, rocket enginetechology keeps heart’s pumping, polymer coating aids heart failure treatment, LEDs (Tiny light-emitting diode), alleviate pain, speed rehabilitation, robotics offer new surgical capabilities, CCDs (Charge coupled devices) enable clearer, more efficient biopsies, corrosive space gas scrubs surgical implants, inline filter purifies dental water plays a crucial role in health care system in earth.

Conclusion
This research plays a major role in understanding the importance of space pharmacology in astronauts during the space mission. In conclusion, optimization of therapeutics for space exploration requires research and development of enabling technologies and methods for the diagnosis and treatment of acute and chronic ailments encountered by astronauts while in space and upon return to Earth. Space spinoffs will benefit health care on Earth.

Conflicts of interest
We declare that we have no conflicts of interest.

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