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PHARMACOKINETIC CHANGES AND PHARMACOTHERAPEUTIC APPROACHES IN SPACE ASTRONAUT

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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. Space medicine is fundamental to the human exploration of space. It supports survival, function and performance in this challenging and potentially lethal environment. It is international, intercultural and interdisciplinary, operating at the boundaries of exploration, science, technology and medicine. This review introduces the field of space pharmacology and describes the different types of environmental challenges, associated medical and physiological effects, and medical considerations. It will describe the varied roles of the space pharmacist. 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 regimens 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 lights, Space Pharmacology, Space Physiology.

INTRODUCTION

The action of drugs changes in space compared to that on earth. Use of drugs without sufficient data may result in inadequate treatment or therapeutic failure. This has been evidenced during and immediately after space flights. The spaceflight pharmaceutical knowledge helps in improving treatment in crewmembers.[1] Pharmacology has a role in the treatment of diseases. It includes pharmacokinetic and pharmacodynamics studies. Pharmacology is the scientific study of drugs mechanism of action, metabolism and interactions.[2] The pharmacology in association with space or astronomy ia known as space pharmacology or astropharmacy. It plays an important role in health care of astronauts. Cosmonaut Yuri Gagarin was the first person to fly in space. Alan B. Shepard launched from Cape Canaveral on a Mercury Redstone 3 rocket was the first NASA astronaut to fly in space. The astronauts may fly for short duration or long duration, medical support is needed in short term and long term flights. The medicine and health care for astronauts is included under space medicine. It deals with the health and problems experienced by crew members during short term and long term space flights. The main and only goal is to adapt to space environment and also to earth. The crewmembers suffer severe loss of normal physiology; they experience loss of vision and bone mineral density. Hence very careful treatment should be given. Space flight affects various bodies' systems. Radiation injuries experienced during flights may even impact the crew members post flight.[3,4,5] Loss of consciousness on entering earth's atmosphere is the serious risk in many astronauts.[6]

Space Environment

2.1. Microgravity

The Earth creates a gravitational field around itself that attract objects with a force inversely proportional to the square of the distance between the centre of the object and the centre of Earth. The measure of acceleration of an object upon which only by Earth's gravity act at Earth's surface, is referred as 1 g or one Earth's gravity. Whichare approximately 9.8 m/s2.[7] Microgravity is also known as free-fall or weightlessness or zero-G. It alters the pharmacokinetics and pharmacodynamics of the drug. Astronauts experience lower gravity than on earth in space flights after reaching earth's orbit, which is known as microgravity .Many people mistakenly think that gravity does not exist in space.. Gravity is the attraction between any two masses, when one mass is very large. Gravitational field of earth at about 250 miles above the surface is 88.8 percent of its strength at the surface.[6] Effects of microgravity: Microgravity causes bone loss, immunosuppression, muscle loss and movement of body fluids towards head, spaceflight osteopenia, decrease in the function of cardiovascular system functions, anaemia, balance disorders,loss of body mass nasal congestion sleep disturbance. Most of the symptoms are reversible and subsides on returning to gravity zone.[8]

2.2 Other factors

Other than microgravity, living organisms are also affected by ionizing radiation, isolation, confinement, and changes in circadian rhythm during space flights. Seasonalaffective disorder syndrome is a disease related to excessive secretion of the pineal hormone, melatonin, and is experienced by crew members. Prolonged exposure to inadequate lighting may adversely affect mood of astronauts and their performance. They may even experience various noises and vibrations.[7]

Types of Space Flights

Spaceflight are those journeys that take place more than 100 km above sea level. This internationally recognised altitude boundary is known as the Karman line. In broad terms the Karman line is the altitude above which the atmosphere is insufficiently dense for the aerodynamic control surfaces of conventional aircraft to be effective; beyond that lays space. There are three categories of human spaceflight: i) suborbital, ii) low Earth orbit (LEO; e.g. the International Space Station), and iii)exploration class missions (e.g. missions to the Moon and Mars). Suborbital spaceflights are short, generally lasting no more than a few hrs. of which only a few min are spent experiencing the weightlessness of microgravity. The flights involve exposure to increased acceleration in the vertical (Gz) and horizontal (front-to-back; Gx) planes, which can affect the cardiorespiratory systems. The degree of acceleration experienced is typically referenced to the acceleration as a result of gravity near the Earth's surface (g; 9.8 m s2), for example, þ6 Gz is head-to-toe acceleration equal to six times g. Cabin pressures are likely to be equivalent to commercial aircraft cabins (6–8000 ft pressure altitude). Low Earth orbit implies vehicles in orbit around Earth at an altitude of 200–400 km. This is where almost all of human space exploration has occurred; from Russia's Vostok 1 through to the US Space Shuttle program and today's International Space Station (ISS). Exploration class space flight refers to missions beyond low Earth orbit. These encompass expeditions to the Moon, Mars and other celestial objects and locations including Lagrange points and near Earth objects such as asteroids. Lagrange points are locations where gravitational forces between two large bodies (e.g. the Sun and Earth or the Moon and Earth), are balanced such that a smaller body, such as a space station, can effectively be 'parked' in space and is maintained in a stationary position relative to the two larger bodies. The remoteness of these missions from Earth and their comparatively long duration distinguishes them from the vast majority of our experience in human space flight to date.[13]

4. Effect of Spaceflights on Astronauts

Breathable air and drinkable water and a group of devices are crucible in space that allows human beings to survive in outer space. The life support system supplies air, water and food. It also maintainstemperature and pressure and manages waste. Shielding against harmful external influences such as radiation and micro-meteorites is also necessary.Microgravity leads to loss of proprioception, changes in fluid distribution, and deterioration of the musculoskeletal system. Temperature changes and radiation are also major problems to be faced in space. Physiological effects of spaceflight includes space motion sickness, fluid redistribution, cardiac rhythms, decompression sickness, decompression illness in spaceflight, decreased immunity , loss of balance, loss of bone density, wasting of muscles, loss of eyesight, disruption of taste, decrease mental health, orthostatic intolerance, sleep disorders, impaired renal function, impaired protein metabolism, lowering of plasma protein, weight loss, changes in skin physiology and blood pressure changes.Increased oxidative damage post flight in humans is observed which is due to impaired protein metabolism and musculoskeletal system damage.[7,9,10]

5. Physiology In Space

5.1 Early effects

The sensory disturbance is the early sign seen. Space adaptation syndrome i.e. nausea, pallor, vomiting, is observed in 60 to 80 per cent of astronauts in first 3 days of flight.[11] This symptoms may be disturbing hence for future short duration commercial flights, astronaut are supposed to take prophylactic treatment to minimise the risk of being affected like I.M. promethazine.[12] Movement of body fluid from lower to upper body is the early visible sign, which is the result of elimination of gravity. This manifests as the so-called 'puffy face' associated with facial oedema and reduced leg volume giving the characteristic 'chicken legs' appearance. Accompanying the fluid shift, plasma volume is also reduced by 10–15% as intravascular fluids shift into the extracellular space because of increased capillary permeability. This relative hypovolemia, along with reduced sensitivity of the baroreflexes results in post flight orthostatic intolerance.[13]

5.2 Musculoskeletal system in space

Increased bone demineralization is seen which may result in increased calcium excretion and calcified stones in renal tract.[13] Mean losses of bone are in the order of

1%–1.6% per month in the spine, femur neck, trochanter and pelvis. Medical countermeasures to limit bone loss have been considered such as bisphosphonates and diet but the main countermeasure has been exercise. Resistive exercise, in particular, is thought to stimulate osteogenesis.[13] In absence of exercise muscle atrophy is seen, but in space even after focused exercise, muscle mass loss is seen that is due to absence of gravitational loading force. ISS crew have various exercise programmes and access to a number of aerobic and resistive exercise devices, which operate to mimic those in the terrestrial 1 G environment in order to prevent muscle loss.[15]

5.3 Neurological system in space

It involves Space Adaptation Syndrome and impairments of visuomotor tracking tasks and the vestibulo-ocular reflex. The impairments of the neurovestibular system increases with increase in stay. A relatively recent and concerning finding is the degradation in visual acuity; on short and long-duration missions respectively post flight but is not seen in all astronauts.[16] This collection of findings including optic disc oedema, globe flattening, choroidal folds and cotton wool spots is termed Spaceflight Associated Neuroocular Syndrome (SANS), previously known as visual impairment and intracranial pressure syndrome (VIIP).The aetiology is unknown but postulated causes include cephalad fluid shifts, radiation and inspired CO2 levels.[17]

5.4 Cardiovascular system in space

One of the major concerns for both short- and long-duration spaceflight is the phenomenon of cardio-vascular deconditioning. Exercise deconditioning during spaceflight may significantly affect a crewmember's ability to perform strenuous or prolonged task during and after a spaceflight mission, respond to an emergency situation, or assist a crewmate who might be incapacitated. Electrolyte imbalance and fluid shift results in orthostatic imbalance. Heart may even enlarge. Decreased blood pressure is seen. Research on the effects of spaceflight on the cardio-vascular system currently includes three types of approach:

(a) Mechanistic studies to develop a generic model;
(b) Descriptive studies of cardiovascular anomalies; and
(c) Validations studies of countermeasures for cardio-vascular deconditioning.[7]

The below table show's list of equipment's available in ISS.[7]

Bloodpressure: non-invasive monitoring and collection of BP data, the data can be collected manually or automated methods during periods of rest or exercise.
Electricalstimulation of **muscles**: high current stimulator used for local non- invasive muscle stimulation that provides pulses up to 0.8 amps.
ECG/EEG/EMG: multichannel data can be collected by means of portable, crew-worn devices or via rack mounted devices for time period of 24hrs.
Blood oxygen: a pulse oximeter is used.
Lung volume: continuous monitoring of lung volume using respiratory impedance plethysmography.
Metabolic activity/pulmonary physiology • Two gas analysers, one based on mass spectrometry and other on infrared gas analysis technique. • Combined with ancillary equipment, including gas supplies for supplying special respiratory gas mixture. • Measure: breath by breath VO2, VCO2, diffusion capacity for CO2, expiratory reserved volume, volume of pulmonary capillary blood, dead space ventilation, cardiac output.

5.5 Respiratory system in space

For the respiratory system despite of uniform ventilation and perfusion there are alterations in both static and dynamic lung volumes, decrease In efficient gas exchange as that on Earth.[19]

5.6 Renal system in space

Renal stone cases have been reported in space. In addition to hypercalcuria as a result of bone demineralization, other factors contributing to renal stones include decreased urinary output and changes in the concentration of urine, with increased urinary phosphate and sodium. Decreased urine output may be due to upward fluid shift.[20]

5.7 Other systems

Spaceflight affects the immune system, causes elevated granulocytes, decreased lymphocytes, elevated B cells and decreased natural killer (NK) cells.[13] Decrease in haemopoiesis also seen which effects red cell mass leading to a so-called "space anaemia'.[18]

Spaceflight also leads to significant sleep disruption as a result of gross alterations in light and dark cycles, illumination and crew workload.[13]

6. Extravehicular Walk

'Extra-Vehicular Activity' refers to human activities occurring outside the spacecraft and ishazardous activities. It is also known as spacewalk. It is performed to install new equipment, or to carry out repairs, maintenance investigation in space. It requires much physical efforts and generate significant amount of metabolic heat. Special space suits that protect against environmental threats including thermal stress, micrometeoroids, radiation hazards and hard vacuum, are designed while maintaining a breathable, habitable atmosphere for astronauts. These space suits are pressurised lower than the normal atmospheric pressures in order to maintain mobility and reduce suit rigidity. The ISS is pressurised to sea level, whereas NASA space suits provide only 29.5 kPa (4.3 psi). This pressure difference, however, creates the possibility of decompression sickness (DCS: release of nitrogen gas from tissues and body fluids in low pressure conditions, it is characterized by bends disease, confusion, motor incoordination, loss of consciousness).[21,22]

7. Routes of Administration

Routes of administration which have been used during spaceflight including intravenous, intramuscular, subcutaneous, intranasal, inhaled, oral, topical, and rectal. Crew medical officers are trained on all these routes, oral and intramuscular are the most commonly preferred routes. Before flight, drugs are tested by crewmembers I order to prevent any reactions during space flight.[6]

8. Pharmacokinetic Changes in Space

Decreased absorption of drug due to delayed gastric emptying time. First pass metabolism is altered. Altered drug excretion.

8.1 Changes in absorption

Change in gastric transit time, that is gastric emptying time is seen. Microgravity causes change in particle size and there by gastric emptying. The particles are not restricted to pyloric region of stomach instead they are distributed throughout the stomach resulting in increased gastric time. As gastric motility is decreased there is change in intestinal transit time. Intestinal transit time is dependent on gastric transit time. Therefore zero gravity not only decrease absorption but also effects the plasma drug concentration.[6]If absorption increased, particularly in the case of a drug with a narrow therapeutic index, peak plasma concentration may raise up to toxic range, resulting in overdose. Alternatively, low GI blood flow or vomiting results in no drug absorption, and symptoms remain essentially untreated. These scenarios are unlikely, but could be life-threatening or mission-compromising. Acetaminophen is the gold standard drug used for absorption measurements, and it has been given therapeutically many times during flight. There have been no reports of sub therapeutic or over dose of it. A systematic record of crew symptoms, therapy used, perceived effectiveness, and description of side effects could be extremely useful for deciding if further absorption studies are required for particular drugs.[7]

8.2 Change in distribution

Volume of distribution is altered in space because of decrease in total body water and plasma volume and also muscle loss. The dosing may become sub therapeutic or toxic. Hence proper dose calculation should be done. Protein binding id altered because of muscle atrophy and decreased lean body mass.[6] Anyways no proper data for distribution from flight studies is available; therefore, no ground model for distribution can be validated. Therapeutic use of drugs during flight has been reported to be largely effective, suggesting that most drugs must be distributed in a near-normal fashion. However, because of concerns about fluid shifting and the potential for dehydration, it is essential to determine if drug distribution is altered during flight. Flight experiments with classical distribution probes (erythromycin, propranolol) would likely provide the data needed to study distribution. A systematic record of crew symptoms, therapy used, perceived effectiveness, and description of side effects could be extremely useful for deciding if additional distribution studies are required for particular drugs.[7]

8.3 Change in metabolism and excretion

Due to zero gravity decrease in cytochrome P 450 enzymes and other microsomal enzymes is observed. As a result metabolism of drug is affected.Decreased body water, dehydration may affect urinary excretion of drug. The decreased excretion, higher doses may cause toxicity.[23,24] If metabolism of drug increases it leaves the compliance untreated. Alternatively, if metabolism slowed, plasma concentration of the drug would be higher, leading to increased chances of severity of side effects, and possibly toxicity. This is may be because of the possibility that not all enzyme systems are equally affected by spaceflight. Data are available for only a few enzymes and range over a wide variety of flight analogues and other varied conditions. Knowledge of how and by which enzymes a drug is metabolized allows prediction of whether the compound may cause drug–drug interactions or be susceptible to marked individual variation in metabolism due to genetic polymorphisms. Detailed experiments on these identified genes and enzymes have to be performed, especially those that metabolize the drugs used in spaceflight.[7]

9. Other Considerations

9.1 Bioavailability

Hepatic first pass metabolism is altered in space. Drug dissolution, gastric emptying and intestinal absorption affect the bioavailability. Other factors like space motion sickness, change in micro flora, gut enzyme release and distribution also effects bioavailability.[6]

9.2 Volume of distribution

The fluid is redistributed in central compartment, fluid shifts to cephalic region, and also due to restricted fluid consumption before launch results in decreased total body water and plasma volume. Muscle atrophy and protein loss results in decreased drug binding and effects distribution. As a result therapeutic efficacy is affected and toxic effects can be seen.[6]

10. Pharmacodynamics Changes in Space

Ion channels are influenced by gravity. Gravity directly causes the integral open state probability of native ion channels. Pharmacodynamics changes will be effected that is caused by a given drug concentration. In zero gravity there may be change in drug receptor or change in disease characteristics. In a study it was observed that promethazine produces less sedation on flight than on earth, this is because of altered drug action.[6] Another issue is change in growth of microorganisms in microgravity, as a result of change in physiology of body that may influence drug response.[25] Due to altered pharmacodymanic there may be ineffective or less effective response of sedatives and hypnotics.[6]

11. Use of Medicine in Space

Medications are used for various indications during space flight. Astronauts take drugs in flight to prevent symptoms of space motion sickness, headache, sleeplessness, backache, nasal congestion. Although the discomfort associated with acute responses to microgravity (e.g.,space motion sickness) is expected to diminish with length of time in flight. The delayed onset responses (e.g., maintaining nutritional status, bone and muscle strength, and perhaps immune response) may affect health and quality of life during longer missions.[26] Therefore, as the duration of space flights increases, the need for treatment with medications is expected to increase. Higher antibiotic resistance were reported in the bacterial samples collected on the crew Apollo-Soyouz 425.[27] route of administration also matters, studies have shown that intramuscular administration have better response than oral . These findings support the need for the development of novel drug delivery systems for acute and chronic treatment in space.[6]

Table below shows the conditions that occurs in space.[30]

Common	Occasional	Space exploration medical condition	Not addressed
space motion sickness	renal stone	radiation sickness	cardiogenic shock
nasal congestion	acute urinary retention	severe decompression illness	malignancy
headache, back pain	cardiac dysrhythmias	osteoporosis	glaucoma
constipation	urinary tract infection	seizure	compartment syndrome
insomnia	otitis media	anxiety, depression	hypovolemic shock
upper respiratory tract infection	gastroenteritis	sepsis, anaphylaxis	lumbar spine fracture
musculao-skeletal trauma	near drowning after space suit failure	dental problems eye penetration appendicitis airway obstruction	shoulder/elbow dislocation

Medication stability in space

A drug is considered stable when, its physical and chemical properties are maintained overtime. Alteration of physical properties includes changes in appearance or consistency; alteration of chemical properties includes loss of potency, alterations of dissolution and solubility of the medication, alteration of excipients (inert contents of a given formulation), excipient-active ingredient interactions, or toxic degradation.[31,32] In order to determine that a pharmaceutical is unchanged by prolonged storage or environment, a drug must be demonstrated following exposure to have no significant alteration of its active pharmaceutical ingredients (APIs). At the same time, the drug must not develop significant degradation products that are either toxic themselves or in some way alter the pharmaceutical properties of the original medication.[33] The United States Pharmacopeia (USP) provides guidelines for acceptable API content in medications approved by the U.S. Food and Drug Administration (FDA), commonly within 10% of label-specified content (though this can vary considerably by drug type or API).[37] A medication would be considered degraded or unstable if API concentration fails to meet USP requirements following storage, environmental exposure, or time. Alterations of API or development of degradation products can affect drug potency and efficacy, rendering the drug ineffective or potentially dangerous.One important consideration regarding stability in space flight is the shelf life of a drug; shelf life varies from manufacturer to manufacturer and formulation to formulation of a single drug. In a 2006 study, Lyon et al. demonstrated that many medications, when maintained in original and unbroken packaging, may last significantly longer than labelled expiration dates, though stability was unpredictable and varied even between samples of the same drug, manufacturer, and drug lot.[34] On board the shelf lives for drugs are labelled for less than 24 months.[35] Radiation adjustments to drug packaging may alter drug stability during spaceflight. Many of the medications examined in spaceflight studies have previously been in operational use, meaning that packaging was opened at some time during flight; this may increase degradation secondary to factors, such as temperature, humidity, and radiation. Some of the pharmaceuticals currently flown on board the ISS are repackaged by NASA pharmacists to manage mass and volume constraints and to limit packaging waste in the closed environment of a space vehicle. Repackaging itself may affect shelf life or stability of stored medications.[30,33,36]

13. Role of pharmacist in space

Pharmacist in space medicine mainly focuses on preparing medical kits for astronauts. They are two types of kits

1. Convenience kit: contains medication usually taken during trip.
2. Contingency kit: these are stocked medicines used for emergencies, and include antibiotics and cardiac life support.[28]

As the medication works in different way in space pharmacist have to choose them based on volume, mass, but this may be problematic with formulations like powders and liquids.[28]Using injection while wearing a spacesuit is a big question. Pharmacist role comes in picture in, in selecting alternate route, maintaining all this and solving the mystery of how drugs may react to space environment and radiation outside. In future pharmacist will be needed to accompany manned mission. The pharmacist should know about disease and disorder that may arise in space and even later in life post flight and should know the management for them. Additionally pharmacist should consider how space travel affects a person's disease or side effect to medication as well.[29]

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. The role of pharmacist comes in picture in selection of right dose and right drug for astronauts during space flights and even for post flight complications.

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