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Review article

Physiological, Pharmacokinetic, Pharmacodynamic and Microbial Virulence Changes during Space Flight

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Abstract

The space environment provides several challenges: variable gravity; constant radiation; extreme temperature and pressure; and on other planets, a new physical and chemical environment - perhaps even an entire ecosystem. These challenges in human induce physiological changes that may lead to pharmacokinetic and pharmacodynamic changes of drug administered to crew in space shuttle. In addition, space environment exerted on micro organisms, which are inevitably present by way of contaminants and crew member microflora, thus making the occurrence of adaptive response probable. Various factors associated with the space flight environment have been to potentially compromise the immune system of crew member, increase microbial proliferation and microflora exchange, alter virulence and decrease antibiotic effectiveness.

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INTRODUCTION

The landmark success of India's moon launch in October 2008 has all eyes set on the Indian space program. On October 22, 2008 Chandrayaan-I, India's first unmanned spacecraft, was launched on a two year mission to the moon from the Satish Dhawan space centre at Sriharikota spaceport near Chennai. Anticipating the success of its first Moon mission, Indian Space Research Organization (ISRO) has already signed an agreement in 2007 with Russian space agency Roskosmos to make

Chandrayaan-II a joint mission. Indian Space Research Organisation's also plans to send astronauts to space within six to seven years. Human space flight is a complex undertaking that entails numerous technological and biomedical challenges. Since the beginning of the 1960s, humans have embarked on the conquest of space: a new world, but hostile for a number of different reasons. The primary hostile factor is the lack of gravity, which can induce space motion sickness and induces several physiological changes in the human body. It is likely that the physiological modifications induced by weightlessness also act on the pharmacokinetics[1] of the drugs present in the first-aid kit of the shuttle and administered during the spaceflight. Various physiological, pharmacokinetic and pharmacological observed in space flight and analogs, can also affect *in vivo* drug efficacy.

PHYSIOLOGICAL CHANGES IN MICROGRAVITY

Skeletal system

Space flight results in loss of bone mass, especially in weight-bearing bones, a condition that is suggested to be similar to disuse osteoporosis. The skeletal unloading experienced by astronauts in microgravity causes a site-specific loss of as much as 1% to 2% per month of bone mineral density. Os calcis density decreased after short space flights and after long space flights [2]. During short space flights (1-14 days), an increasing negative calcium balance was found. During long space flights (> 2 weeks), excretion of calcium into urine increased in the first month. After 10 days of flight, the fecal calcium excretion increased continually throughout the flight. On the *Mir* year long mission, bone measurements showed a 10% reduction of lumbar vertebrae as compared to pre-flight [3].

Muscular system

Muscle strength, tone, and endurance decreased significantly during space flight, both in humans and animals. In rats, a 37% decline in muscle mass was reported after one week of microgravity[4]. Muscle atrophy and loss in lean body mass, associated with a decline in peak force and power are reported[5]. The maximal voluntary contractions of the plantar flexor decreased 20% to 48% in humans after 6 months in space[2]. An increase in sodium current density may reduce the resistance to fatigue of antigravity muscle fibers, an effect that may contribute to muscle impairment during long-term space flight[6]. The main losses were found in antigravity muscle groups[7-9].

Immune system

The immune system is a complex network of highly specialized cells and organs that work together to defend the body against foreign invaders. Space flight has been shown to induce varied immune responses, many of them potentially detrimental. Some of these changes occur immediately after arriving in space while others develop throughout the span of the mission [10]. The causal factors include microgravity, the stress due to high-demand astronaut activities and the social interactions of confinement[11], diet[12], lack of load bearing[13, 14] and radiation[15, 16]. To date, the only consistent effects on the immune

system observed have been a reduction in T-cell counts and a decrease in natural killer (NK) cell concentration and functionality[17,18], a reduction in cell-mediated immunity, altered cytokine production[18,19] and constant levels of immunoglobulins[18]. More recent research shows that there is an increased susceptibility to infection under space flight conditions[20, 21]. The main concern of a weakening immune system in the closed environment of a spacecraft is the possibility of having altered ability to heal from bacterial and certain fungal, viral, and parasitic invasions.

Excretory system

The urinary sodium, potassium, and chloride generally increased in microgravity, while serum osmolality and sodium are decreased throughout flight[22]. Data from *Spacelab-2* showed that after an increase early in flight, the atrial natriuretic factor (ANF), one of the hormones that regulates sodium and water excretion, was decreased by 59% and blood sodium decreased by 1% late in flight, whereas potassium had been increased by[22] 9% . On the other hand, the excretion of sodium, potassium, and water was decreased the day after landing compared to the preflight period[24]. A slight increase in serum sodium immediately after landing compared to pre-flight was also observed, while potassium and calcium were unchanged[24].

Endocrine system

Alterations in hormone levels during space flight are strongly related to stress and the cardiovascular adaptive response to the microgravity environment. During long space flights (> 2 weeks), cortisol levels are increased, and adrenocortotropic hormone (ACTH) and insulin are decreased. Postflight, angiotensin, aldosterone, thyroid-stimulating hormone (TSH), and growth hormone (GH) levels are also increased[25]. Microgravity also stimulates functional activity of the parathyroid and suppresses the thyroid C cells, which affects the production of parathyroid hormone and calcitonin, respectively[26]. This may play a significant role in the pathogenesis of disorders in calcium turnover in microgravity.

Enzymes

Several studies have demonstrated that the activities of a variety of enzymes, including certain drug metabolizing enzymes, are altered in animals that are subjected to space flights. The activities of some intestinal digestive enzymes, including leucine aminopeptidase, acid phosphatase, adenosine triphosphatase, and glucose-6-phosphatase, showed a transient increase during space flights[27-29]. The activity of Hydroxymethylglutaryl-CoA (HMG-CoA) reductase, the rate-limiting step in the biosynthesis of cholesterol, was also shown to increase in microgravity[30]. In rats flown on *Cosmos*, the amount of microsomal P-450 and the activity of aniline hydroxylase and ethylmorphine- N-demethylase, cytochrome P-450-dependent enzymes, were decreased[30].

Cardiovascular system

Cardiovascular adaptation to microgravity is probably, together with bone physiology, the well-studied response of the body to weightlessness. Orthostatic intolerance is observed in most astronauts after returning to Earth and is a consequence of cardiovascular adaptation to weightlessness[31]. Postflight stroke volume, left ventricular end diastolic volume, and estimated left ventricular mass decreased compared to preflight, while heart rate and mean blood pressure (both systolic and diastolic) were elevated and remained higher than preflight levels during the mission[32].

Oxidative stress

Our body generates about 5 g of reactive oxygen species (ROS) per day, mostly by leakage from the electron transport chain during oxidative phosphorylation[33] (Halliwell, 1997). The major products of this "leakage" are the two ROS: the superoxide radical (O_2-) and H_2O_2 [33]. Other ROS include free radicals such as nitric oxide and compounds such as ozone and HOCl. ROS can attack and damage cellular constituents such as DNA, proteins, and membrane lipids. Oxidative damage from free radicals to DNA and lipids has been implicated in the etiology of a wide variety of chronic diseases and acute pathologic states. The chronic diseases range from cancer to cardiovascular disease and neurodegenerative disease including Alzheimer and Parkinson diseases[34-38].

Russian investigators found evidence for increased lipid peroxidation in human erythrocyte membranes and reductions in some blood antioxidants after long-duration space flight[39-41]. The potential for radiation damage during long-duration flights (particularly for flights out of low Earth orbit, where the exposure to radiation flux is greater) is currently believed to be the most serious impediment to interplanetary travel. Isoprostane excretion was decreased and 8-OH dG was essentially unchanged during a flight on *Mir*[42].

A subsequent post flight Studies shows both 8-oxo-7, 8 dihydro-2 deoxyguanosine (8-OH dG) and 8-iso-prostaglandin $F_{2\alpha}$ were increased by more than two-fold after more than 3 months on *Mir*. The implication is that oxidative damage after an extended period in orbit is increased after landing. There is other evidence for increased oxidative damage after space flight. Spot blood analyses by Russian investigators on cosmonauts after long-duration flights showed a non-statistically significant trend for an increase in the accumulation of lipid oxidation products in the serum and erythrocyte membranes[40].

The simplest explanation for the increased oxidative damage postflight in humans is that the increase is due to a combination of 1) 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) the in-flight protein depletion from inadequate dietary intake, and 3) the increased anabolism associated with protein repletion. With increased generation

of adenosine triphosphate, leakage of ROS from the mitochondrial electron transport chain will be increased [33].

PHARMACOKINETIC CHANGES IN MICROGRAVITY

Absorption

Preflight and in-flight salivary levels of acetaminophen where shown to differ, probably due to changes in gastrointestinal transit time[42]. 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 interindividual variability compared to those of preflight data[44]. 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[31].

Distribution

Physiological changes, such as the decrease in total body water (TBW) and plasma volume (PV), and the muscle loss described in the previous section 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[31]. Altered tissue binding is observed as result of protein loss, muscle atrophy, and decrease in lean body mass[25].

Metabolism and Excretion

The amounts of cytochrome P-450 isoforms and other enzymes decreased during space flight and simulated microgravity[30, 45, 46], which suggests that xenobiotic metabolism, may also be altered by space flight. Altered nutritional or energy requirements may have effects on urine excretion of drugs, and dehydration may result in changes in urine excretion of drugs[31].

PHARMACODYNAMIC CHANGES IN MICROGRAVITY

Many drugs act by altering the function of specific ion channels either directly or indirectly. It was recently shown that ion channels are gravity sensitive[47]. Gravity directly influences the integral open-state probability of native ion channels (porins) incorporated into planar lipid bilayers. In microgravity, the open-state probability is decreased, while in hypergravity, it was increased[47]. The

immune system is altered in microgravity. The activity of white blood cells, such as lymphocytes, macrophages, and natural killers, was affected during space flights. Consequently, drugs that have these cells as their pharmacological targets, such as interferons, colony-stimulating factor (CSF), and other cytokines, can have their effects altered. In one study, observed a depression in the capacity of femoral bone marrow cells to respond to CSF[48], which supports this theory, although more studies are necessary before any conclusions are made. The cardiovascular system is largely affected by the exposure to microgravity, and this may lead to modifications on the pharmacological effect of drugs such as antihypertensives and diuretics.

MICROBIAL VIRULENCE CHANGES IN MICROGRAVITY

Studies on *in vitro* bacterial growth in space typically indicate outcomes beneficial for the microbes, such as reduced lag-phase duration and increased final cell population density relative to normal-gravity controls[49,51]. Because flight opportunities are infrequent, various ground-based devices designed to simulate certain aspects of microgravity are frequently used as analogs[50,51]. Many of the early studies indicated that antibiotics were typically less effective against suspension cultures in the space environment but these traits appeared to be transient and not retained in post-flight testing[52-58].

Although the experiments have spanned several decades, the underlying causes of reduced drug efficacy in space have not yet been identified and remain of current interest. To further complicate matters, recent reports of decreased in-flight drug potency and shelf-life are now being investigated[59]. Various physiological, pharmacological and pharmacodynamic changes, observed in space flight and analogs, can also affect *in vivo* drug efficacy[31]. Factors related to isolated, confined environments have been shown to contribute to increased resistance: ground-based isolation in an airtight environment for 96 to 175 days was found to increase the resistance spectrum and number of antibiotic-resistant organisms isolated from humans[60]. Changes in the intestinal flora composition are thought to be responsible for antibiotic resistance. A study of the microflora of cosmonauts from five space flights indicated that the crew exchanged intestinal flora in the closed spacecraft environment intestinal flora accumulates antibiotic resistance determinants from the indigenous microflora of individuals in the sealed environment during the exchange. The rate of antibiotic resistance determinant accumulation is proportional to the influx rate of immigrant strains containing new resistance determinants, and resistant strains can become dominant. It was concluded that the use of antibiotics without evaluating the sensitivity of the microflora could become a risk factor for infection[61]. Coliform bacteria isolated from cosmonauts also became resistant to tetracycline, owing to microbial and plasmid exchange between the visiting and prime crews of the Salyut 7 spacecraft: no tetracycline resistant coliform bacteria were present in the prime crew before

flight. Similar reports from Apollo and shuttle missions provide further evidence of in-flight microflora exchange leading to an increased presence of pathogens for crewmembers compared with preflight baselines[62,64].

CONCLUSION

Several pharmaceutical products are being employed in space to treat a variety of disorders. Hence, knowledge of the physiological, pharmacokinetic, and pharmacodynamic aspects under microgravity would be useful in making appropriate dosing recommendations. Similarly advances in traditional laboratory research techniques can be applied to better understand how microbes adapt to the space environment, the reciprocity of studying responses to space flight to gain novel insight into the fundamental processes of drug resistance acquisition and virulence factor development might not be so intuitive. Innovations in treating clinically relevant infections will have far reaching implications across all walks of society, including those of future spacefarers.

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