Pharm Res (2019) 36: 148
https://doi.org/10.1007/s11095-019-2679-3

EXPERT REVIEW

Medications in Space: In Search of a Pharmacologist's Guide to the Galaxy

Sara Eyal[1] • Hartmut Derendorf[2]

Received: 17 May 2019 / Accepted: 30 July 2019 / Published online: 14 August 2019

ABSTRACT Medications have been used during space missions for more than half a century, yet our understanding of the effects of spaceflight on drug pharmacokinetics and pharmacodynamics is poor. The space environment induces time-dependent alterations in human physiology that include fluid shifts, cardiovascular deconditioning, bone and muscle density loss, and impaired immunity. This review presents the current knowledge on the physiological effects of spaceflight that can translate into altered drug disposition and activity and eventually to inadequate treatment. It describes findings from studies in astronauts along with mechanistic studies in animal models and *in vitro* systems. Future missions into deeper space and the emergence of commercial spaceflight will require a more detailed understanding of space pharmacology to optimize treatment in astronauts and space travelers.

KEYWORDS international space station · microgravity · pharmacokinetics · pharmacodynamics · spaceflight

ABBREVIATIONS

ABC	Adenosine triphosphate binding cassette
Cmax	Peak concentration
CSF	Cerebrospinal fluid
CYP	Cytochrome P450
GFR	Glomerular filtration rate
GST	Glutathione sulfur transferase
ISS	International Space Station
MRP	Multidrug resistance-associated protein
NASA	National Aeronautics and Space Administration
PBPK	Physiologically based pharmacokinetic
P-gp	P-glycoprotein
Tmax	Time to peak concentration
USP	United States Pharmacopeia

✉ Sara Eyal
sarae@ekmd.huji.ac.il

[1] Institute for Drug Research, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Ein Kerem, 91120 Jerusalem, Israel

[2] Department of Pharmaceutics, University of Florida, Gainesville, Florida 32610-0494, USA

INTRODUCTION

Medications have been carried aboard space vehicles since the beginning of human spaceflight. For instance, the list of medications in the Gemini-7 inflight medical and accessory kits counted 10 pharmacologically active compounds and that of Apollo 11 counted 13 (1). In 2014, medical kits on the International Space Station (ISS) included 78 medications (2) and the number keeps increasing, counting 107 item according to an 2017 evidence report by the National Aeronautics and Space Administration (NASA) (3). Drugs have been used during spaceflight mostly to manage non-life threatening problems, with the most common reasons for taking medications being sleep problems, motion sickness, pain, congestion, or allergy (4–6). Particularly, falling asleep is difficult in a zero-gravity environment without the normal response to lying down to sleep. Additional medications reported to be used by NASA astronauts include anti-infectives (1,6), wakefulness-promoting countermeasures (1,4), vitamins (1,7), medications for digestive disorders (1), alendronate (8) and oral contraceptives (9). During a 166-day Mir mission, cosmonauts used medications for cardiovascular, neurologic and digestive disturbances (1).

The majority of spaceflights remained in the Low Earth Orbit and were limited in time (10). To date, only four people have participated in missions lasting one year or more (7). The planned next phase of human space exploration to the Moon and Mars (11) gives rise to many challenges including

substantial radiation exposure, limited communication with the ground, and inability to evacuate severely ill crewmembers to Earth (3,12). In addition, commercial enterprises are expected to afford less heathy individuals the opportunity to travel to space (12,13). Medical conditions reported so far in space travelers include bullous emphysema and ventricular and atrial ectopy (14–16). Providing medical care within these limitations requires understanding of spaceflight's impact on human physiology, developing appropriate countermeasures, and adjusting terrestrial treatments to the unique space environment.

This review will focus mostly on data obtained throughout spaceflight. The majority of findings presented here were obtained during Low Earth Orbit missions (vehicles in orbit around Earth at an altitude of 200–400 km, e.g., the ISS) (14). We included relevant information from the recently published NASA Twins Study that compared molecular and physiological traits between monozygotic twin astronauts, one of whom spent 340 days on the ISS while the other remained on Earth (7). Several studies were conducted during exploration class missions (the Apollo missions to the Moon) or during parabolic flights (repeated parabolas during which the vertical load factor goes from 1.8 g to near-zero gravity for about 22 s) (17). However, the latter is not a straightforward model of spaceflight because of alternating microgravity and high gravity conditions. Studies in models of weightlessness such as bed rest and the tail-suspended rats have been reviewed elsewhere (18–20) and will not be discussed here.

MEDICAL CHALLENGES OF THE SPACE ENVIRONMENT

Physiological changes that occur during spaceflight are defined by the duration and the type of the mission and involve almost every organ system in the human body. Factors contributing to altered human physiology in space are acceleration forces during launch, microgravity, radiation exposure and sleeplessness. Astronauts additionally encounter noise, less-then-ideal sanitation, dietary changes, dehydration, and the psychological challenges of isolation (3,12,14,18,21). Each of the phases of spaceflight is associated with another set of physiological challenges to the body that might translate to changes in pharmacokinetics and pharmacodynamics. Altered bacterial virulence (22–24) and chemical degradation of medications (25–27) add to the complexity of drug treatment in space.

Fluid Shifts and Changes in Local Blood Flow

Gravity plays a key role in fluid distribution. Even the supine prelaunch position of astronauts with the legs elevated above the thoracoabdominal plane leads to fluid shifts (20). The fluid shift continues during orbit and by the second day of spaceflight the plasma volume decreases by 16–17% (Fig. 1). During the next days of flight, cardiac output increases and arteries and veins in the upper body are distended (7,28,29). However, the plasma volume remains approximately 90% of preflight values (30,31). Fluid shifts from intravascular to extravascular compartments (31,32) have been attributed to increased permeability of capillary membranes (31). This assumption is supported by the increased permeability observed *in vitro* in human umbilical vein endothelial cells in a flight simulator (33) and aboard the ISS (34,35). Over a period of a few days, diuresis reduces extracellular fluid and plasma volume (12), although urine volume decreases over time due to reduced water intake and low relative humidity of the ISS environment (7,36). The absence of hydrostatic pressure gradients gradually leads to attenuated baroreceptor responses that can result in initial orthostatic hypotension upon return to Earth (12). In the days after landing astronauts additionally experience fluid retention (7).

The initial changes in plasma volume translate to altered hematocrit values. A study in the six first sent astronauts into space during Project Mercury (1961 to 1963) demonstrated increased hematocrit after several hours of spaceflight (37) (Fig. 1). During longer flights, the mass of red blood cells has been generally reported to decrease in association with reduced erythropoietin levels (30,38). However, in two cosmonauts who spent a year in space red blood cell-related parameters were within normal limits and decreased immediately after return. The hematological parameters returned to baseline levels within 1.5–2 months after return (38).

Increased volume of the cerebrospinal fluid (CSF) during spaceflight, especially long-term missions (longer than 5 months), is an emerging concern (39–42). In one study, these changes were partially reversible within one month (39). In another study, long-term follow-up (average, 209 days postflight) demonstrated that ventricular CSF volume had returned toward preflight values, whereas the CSF volume in the entire subarachnoid space had increased (42). Recently, a study in seven astronauts who completed shorter (≤30 days) and eight who competed longer-term (≤200 days) ISS missions demonstrated redistribution of cerebral free water (43). The increase in intracranial and periorbital CSF volume contributes to the spaceflight-associated neuro-ocular syndrome (reduced near visual acuity, optic disk edema, cotton wool spots, and structural ocular changes) (7,12). Spaceflight has been additionally associated with altered cerebral blood flow (44–46).

Pulmonary perfusion is more homogeneous in space compared to preflight and diffusion capacity increases (47,48). Combined with the higher deposition of aerosol inhaled in microgravity (19,49), this change can affect the absorption of drugs given by inhalation and their systemic toxicities (19). According to a list of medications that was released in 2016

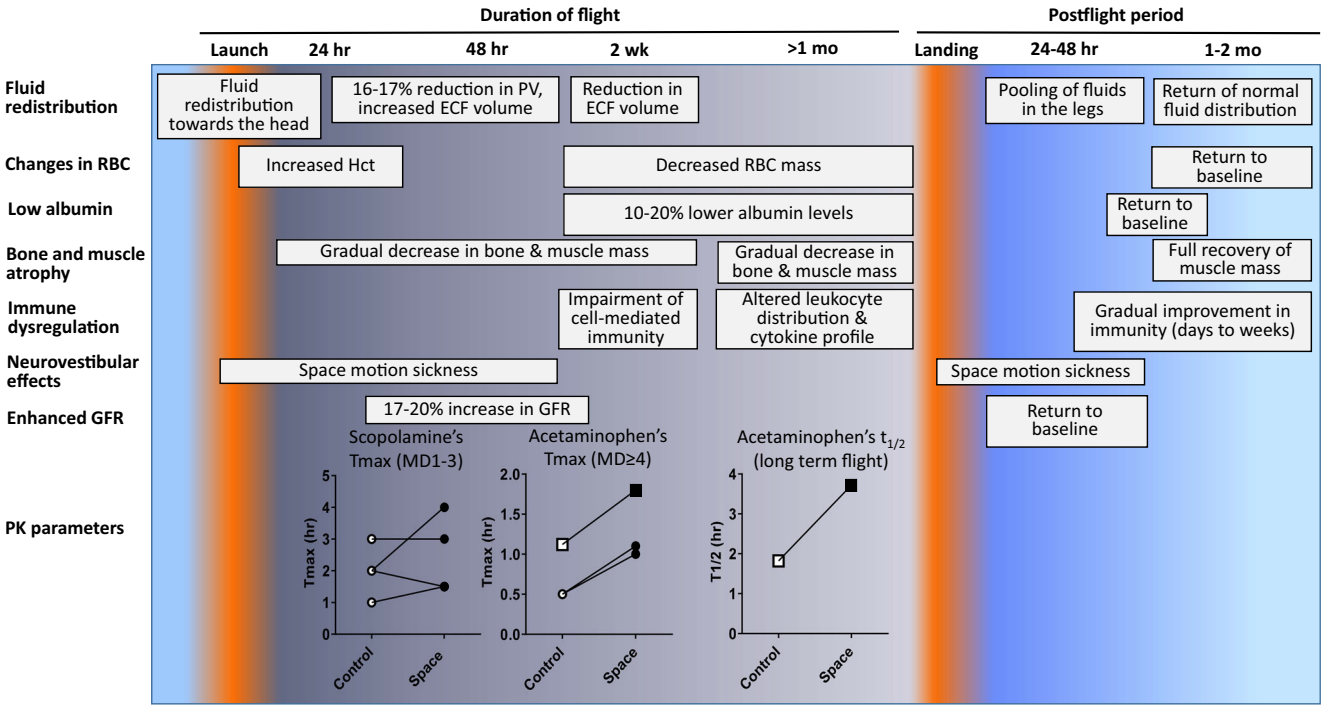

Fig. 1 Timeline of some physiologic changes that occur in astronauts during and after spaceflights and related changes in drug pharmacokinetics. Based on Williams *et al.*, 2009 (67). CSF, cerebrospinal fluid; GFR, glomerular filtration rate; Hct, hematocrit; MD, mission day; RBC, red blood cells; PV, plasma volume; $T_{1/2}$, the time required for the drug's concentration to reduce to half its initial value; Tmax, time to maximal concentration. Scopolamine data are from Cintron *et al.*, 1987a (108). Acetaminophen data are from Cintron *et al.* 1987b (107) and Kovachevich *et al.*, 2009 (111). Circles represent individual values. Squares represent means of five individuals

upon request via the Freedom of Information Act, at least two types of inhalers (salmeterol and fluticasone) are available at the ISS (50).

The above mentioned changes in local blood flow and in plasma and extravascular volumes can potentially affect the rate and extent of drug absorption, distribution (e.g., cerebral distribution) and elimination (21,51,52).

Increased Risk of Arrhythmia

Although no fatal arrhythmias have been reported so far, astronauts experienced arrhythmias during spaceflight and even during extravehicular activity. Reported cases include atrial and ventricular premature contractions, short-duration atrial fibrillation and an episode of ventricular tachycardia (1,12,53,54). Cardiac dysrhythmias and other fluctuations in the cardiovascular system were the second most frequent medical problem during the Mir program era (55). A study in 59 cosmonauts during MIR missions that lasted over 6 months found prolonged repolarization and T-depression with no pathology in the myocardial bioelectrical activity (56). However, others reported that corrected QT intervals (QTc) were prolonged during long-duration spaceflights (57). Hence, the heart might be more sensitive to drug-induced QT prolongation during spaceflight.

Changes in Drug-Binding Plasma Proteins

Analysis of serum from crewmen of three Skylab flights demonstrated decreases of 10%–20% in albumin levels during the first two weeks of flight and low levels as compared to baseline values for up to 84 days in space (58) (Fig. 1). However, in a later report of the same group serum albumin levels tended to return to baseline by mission day 12 (31). In a study in cosmonauts who participated in long missions on the Salyut and Mir stations, albumin levels were slightly increased compared to normal values on the day of landing and decreased on the third day and 14th day after landing (59). In a later proteomic analysis of plasma from 18 cosmonauts who conducted long-duration missions onboard the ISS, albumin levels decreased to 91% and 92% of preflight levels on the first and the seventh day after landing, respectively, but the decreases were not statistically significant. The respective values of α1-acid glycoprotein 1 were 65% and 62% (60). The fate of albumin and other plasma proteins is not clear. In the study conducted on the Salyut and Mir stations urinary albumin excretion was higher in space (61). However, subsequent works in astronauts and cosmonauts demonstrated reduced albuminuria during spaceflights to very low values, below the low-normal range of healthy individuals (62,63). Extracellular albumin was not elevated in space (31).

On the ground, even if plasma protein levels change, the clinical exposure to most drugs whose protein binding is high

(e.g., phenytoin, diazepam and ceftriaxone) will usually not be affected (64). However, given the other changes that may occur in space, e.g., increased capillary permeability, this assumption cannot necessarily be applied to spaceflight.

Bone Loss and Muscle Atrophy

Prolonged microgravity exposure leads to alterations in all components of the musculoskeletal system, resulting in loss of bone mineralization and muscle mass and increased risk of injury (14,65). For example, after an eleven day flight muscle fibers were 16–36% smaller than before flight (66). Thirty percent muscle loss has been noted on longer missions, lasting 3–6 months (67). Muscle loss not only contributes to potential hampering of astronauts' performance and to postflight orthostatic symptoms, but can affect the tissue binding of drugs (20). Onboard excursive countermeasures attenuates but does not prevent loss of muscle mass and strength (65).

Impaired Immunity

Spaceflight has deleterious effects on the immune system, with some aspects of immune hypersensitization (68). Changes include altered leukocyte distribution and T cell function, increased levels of immunoglobulins, and altered cytokine profiles (20,38). For example, a study in 23 astronauts participating in 6-month ISS expeditions demonstrated reductions in mitogen-stimulated production of interferon γ, interleukins 5,6, and 10, and tumor necrosis factor α, that persisted during spaceflight (69). In the NASA Twins Study, some functions of the immune system, including the response to the first test of vaccination in space, were not significantly altered onboard the ISS (7). However, the levels of the majority of assayed cytokines differed between prelight, inflight and postflight in the brother who spent 340 days in space, with some changes lasting six month after return to Earth (7).

The immune system is linked with homeostasis of almost every organ (20) and can affect various aspects of pharmacokinetics. As an example, alterations in immune function have been shown to translate to changes in the pharmacokinetics of low molecular weight drugs (70,71). Moreover, altered immune activity may be associated with hypersensitivity symptoms in astronauts (6,68) and can potentially put them at increased risk of adverse hypersensitivity reactions to medications.

Altered Function of the Gastrointestinal System

Absorption during spaceflight depends on the formulation and can be affected by several physiological factors, including reduced water intake, gastric emptying, intestinal transit rate, and intestinal microbiota (21). About 60% to 80% of astronauts experience within the first three days of flight space adaptation syndrome (space motion sickness), which includes headache, nausea and occasionally vomiting. Space motion sickness may require the use of antiemetic medications but subsides or disappears in 2 to 7 days (12,14,19,67) (Fig. 1). A similar period of motion sickness occurs upon return to ground. However, no symptoms of motion sickness have been reported by the Apollo crew members during acclimatization to lunar gravity (67). Ground-based studies demonstrated that motion sickness is associated with gastric stasis, and that the anti-motion sickness drugs scopolamine, dextroamphetamine and promethazine add slightly to the inhibition of gastric emptying already present (21,72,73). The slower gastric emptying in space, combined with potentially related increase in intestinal transit time, may lead to variability in drug absorption (19).

In a study conducted during the Mir 18 mission in 1995, breath methane and hydrogen levels were several fold higher during flight than on the ground, indicative of gut stasis, change in gut wall bacterial flora, or a combination of both. However, no anomalies in the bacterial flora were noticed after return from flight (74). More recently, the NASA Twins study demonstrated more changes in the composition of the gut microbiome during the flight period in space than in the equivalent period on Earth, without a decrease in the microbiome diversity (7). The alterations in microbiome were reversible upon return to Earth and were classified into a low-risk level. Changes were additionally detected in small molecule markers of microbial metabolism, including secondary bile acid metabolites.

Taken together, these data suggest that drug absorption in astronauts may be affected by both space conditions and interactions with other medications, and that the changes might not be limited to specific periods of flight.

Changes in Hepatic Function

Currently available data suggest that hepatic configuration and dimensions in humans change after prolonged spaceflight. However, the activity of hepatic drug-metabolizing enzymes in humans has overall not been phenotyped (38). In a study in two crewmembers antipyrine was used as a marker of hepatic metabolic activity during space flight (74). Only one preflight data collection session was completed, and data from one set of the 24 to 48 h collection period were not available. Yet, that study demonstrated variable hepatic metabolism during flight, with a decrease of more than 50% in antipyrine clearance in one crewmember and an increase of 30% in another. The clearance of antipyrine postflight decreased approximately 20% in both astronauts. Antipyrine is metabolized by several cytochrome P450 (CYP) isoenzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C18, and CYP3A4) (75), and the observed changes are a composite measure of spaceflight effect on these isozymes.

Initial studies in rats flown on Cosmos biosatellites during the 1970s suggested that their hepatic function is altered during spaceflight (76). In 1985, inclusion of six rats aboard Spacelab 3 for seven days allowed analyzing the activity of hepatic enzymes involved in the metabolism of endogenous compounds and xenobiotics (77). In that study, liver weight of the spaceflight animals remained unchanged compared to controls but hepatic cytochrome P450 content decreased by 50% (Table I). This finding was supported by subsequent analyses of liver samples from rats flown aboard Cosmos 1887 for 12.5 days (78). The activities of aniline hydroxylase and ethylmorphine N-demethylase (later shown to represent the CYP isozymes 2E1 (79) and 3A4 (80,81), respectively) and glutathione-S-transferase (GST) were also lower in the flight group. The latter observation was confirmed in a later study in rats flown on a 8.3-day mission (82).

In the Cosmos 2044 mission the liver weights of rats which were flown for almost 14 days were comparable between the flight and the control groups (76). Morphological analysis demonstrated larger hepatocytes than those of controls, likely due to increased glycogen storage (83). In contrast to previous reports, CypP450 content did not differ between the groups.

The hepatic content of some Cyp450 isoforms was evaluated again in 2013 in mice flown aboard the Bion-M1 biosatellite for 30 days (84). The livers of the flight and re-adaptation mice were examined in 13–25 h and 7 days after landing, respectively (85,86). The Cyp content was measured by targeted proteomics using mass spectrometry. This analysis demonstrated significant increases in the content of Cyps 1a2 (1.9-fold), 2e1 (1.8-fold) and 2c29 (1.5-fold) in the flight group compared to ground controls as well as significant inter-individual variability. The changes in Cyps 1a1, 2c39, 2c50,54, 2d9, 2d10, 2d26, and 3a11 were not statistically significant. In livers form the re-adaptation group, Cyp2e1 levels remained elevated, Cyp2c29 levels returned to control values, and Cyp2d9 decreased in comparison with control levels (84). A follow-up study extended the analysis of hepatic protein content to 1046 proteins but focused mostly on the effects of readaptation. Upregulated proteins in the readaptation group compared to the flight group included Cyp2d subfamily members, Cyp1a2, Cyp2f2, epoxide hydrolase and several UDP-glucuronosyl transferases. Members of the Cyp3a subfamily were down-regulated (85).

Another analysis of Cyp and stress-related gene expression in the liver of rats after a 9-day spaceflight demonstrated increased Cyp4a1 expression (Table 1), whereas expression of CYPs 2c11, 2a2 and 3a2 did not change (87). The effect of spaceflight on hepatic Cyp4a1 expression was confirmed in a later study in rats flown for 12 days. In that study, the expression of 20 other Cyp genes did not change (88) (Table I).

The inconsistencies across the above mentioned studies can be attributed to multiple factors, including small animal numbers, species differences, radiation exposure, length of flight, and duration from flight to tissue preparation. For example, during the seven day Spacelab 3 flight, the rats had ad libitum access to food and water, but fasted during the 12–15 h delay from landing to tissue collection (76,77). In the Cosmos 1887 mission rats were flown for 12.5 days and were sacrificed 53–56 h after landing (due to unexpected landing location) (76,89). Hence, some of the findings could additionally represent changes during the post flight recovery period (78). Housing conditions could contribute to variability across studies. Animals were either kept in a 12 h light and 12 h dark cycle (77) or on a cycle of 16 h of light and 8 h of dark (76,83). The number of animals kept in each cage could also affect their behavior, particularly because these studies were conducted in males.

Some of the studied isozymes well represent the human orthologues. For example, the rat Cyp2e1 seems to be the best model for the human CYP2E1, which metabolizes many endogenous small molecules, ethanol and drugs such as acetaminophen (90,91). The murine Cyp1a2 also exhibits many similarities to its human orthologue (92). In humans, CYP1A2 metabolizes caffeine, melatonin and lidocaine, which are included in the ISS repository (93,94). In contrast, CYP3A isoforms expressed in different species differ in their substrate specificities and in their transcriptional regulation, complicating the extrapolation from rodents to humans (91). Genetic variation in some of these enzymes (e.g., CYPs 2C9 and 2C19) may further compromise prediction of drug disposition in space (2).

The mechanisms contributing to altered hepatic enzyme expression in space are largely unknown. A study in mice flown on the space shuttle Atlantis for approximately 13.5 days demonstrated a spaceflight-induced increase in the activity of peroxisome proliferator-activated receptor (PPAR)α-driven pathways (95), which can regulate the expression of several drug-metabolizing enzymes (92). Other potentially contributing factors include altered hormonal and cytokine profile and changes in DNA methylation (7).

The findings summarized here demonstrate that the many years of research on hepatic metabolism in space have not yet yielded a dataset that can contribute to clinical recommendations or significantly help prioritizing hepatic enzymes whose activity should be further investigated.

Altered Renal Excretion

Adaptation of the kidneys to space conditions has been studied since the early 70s, but until the 1990s reliable measurements were obtained from only few astronauts and cosmonauts, with creatinine as the reporter of glomerular filtration rate (GFR) (96). In 1996, Leach *et al.* (31) reported on a transient increase of 17%–20% in GFR on the first two days and on day 8 of spaceflight using an inulin analog as the GFR marker. Effective renal plasma flow, estimated using para-

Table I Changes in Hepatic Parameters during Spaceflight

Parameter	Units	Species	Duration of flight (days)	Fold change vs. controls	Reference
Liver weight					
	g	Rat	7	0.89	(77)
	g	Rat	12.5	1.12	(78)
	g	Rat	14	0.98	(76)
	g	Rat	8.3	1.02	(82)
Microsomal protein content					
	mg/g liver	Rat	7	0.75	(77)
	mg/g liver	Rat	12.5	0.73*	(78)
	mg/100 g BW	Rat	12.5	0.93*	(78)
Cytochrome P450 content					
	nmol/mg protein	Rat	7	0.51*	(77)
	nmol/mg protein	Rat	12.5	0.86*	(78)
	nmol/mg protein	Rat	14	0.98	(76)
	nmol/g liver	Rat	7	0.45*	(77)
	nmol/g liver	Rat	12.5	0.62*	(78)
	nmol/g liver	Rat	14	1.27	(76)
Phase I enzymes					
Cyp1a1	fmol/μg total protein	Mouse	30	1.15	(86)
Cyp1a1	mRNA expression	Mouse	12	Not changed	(88)
Cyp1a2	fmol/μg total protein	Mouse	30	1.87*	(86)
Cyp1a2	mRNA expression	Mouse	12	Not changed	(88)
Cyp2c29	fmol/μg total protein	Mouse	30	1.45*	(86)
Cyp2c29	mRNA expression	Mouse	12	Not changed	(88)
Cyp2c39	fmol/μg total protein	Mouse	30	1.36	(86)
Cyp2c50,54	fmol/μg total protein	Mouse	30	1.47	(86)
Cyp2d9	fmol/μg total protein	Mouse	30	1.39	(86)
Cyp2d9	mRNA expression	Mouse	12	Not changed	(88)
Cyp2d10	fmol/μg total protein	Mouse	30	0.86	(86)
Cyp2d10	mRNA expression	Mouse	12	Not changed	(88)
Cyp2d26	fmol/μg total protein	Mouse	30	0.85	(86)
Cyp2d26	fmol/μg total protein	Mouse	30	1.5*	(85)
Cyp2d26	mRNA expression	Mouse	12	Not changed	(88)
Aniline hydroxylase activity	U/mg	Rat	12.5	0.82*	(78)
Aniline hydroxylase activity	U/g liver	Rat	12.5	0.59*	(78)
Cyp2e1	fmol/μg total protein	Mouse	30	1.81*	(86)
Cyp2e1	mRNA expression	Mouse	12	Not changed	(88)
Ethylmorphine N-demethylase activity	nmol/(min*mg)	Rat	12.5	1.16*	(78)
Ethylmorphine N-demethylase activity	nmol/(min*g liver)	Rat	12.5	0.84*	(78)
Cyp3a11,16	fmol/μg total protein	Mouse	30	0.98	(86)
Cyp3a16	mRNA expression	Mouse	12	Not changed	(88)
Cyp3a16	mRNA expression	Mouse	12	Not changed	(88)
Cyp3a11,41	fmol/μg total protein	Mouse	30	0.75	(86)
Cyp4a1	mRNA expression	Mouse	12	Not changed	(88)
Cyp4a1	mRNA expression	Rat	9	>3*	(87)
Phase II enzymes					
GST activity	nmol/(min*mg protein)	Rat	12.5	0.85*	(78)
GST activity	μmol/(min*g liver)	Rat	12.5	0.9	(78)
GST activity	μmol/(min*g)	Rat	8.3	0.83*	(82)

*Statistically significant difference

BW, body weight; *CYP*, cytochrome P-450; *GST*, glutathione S-transferase

aminohippurate (which is also a prototypical organic anion substrate (97)), did not differ significantly from preflight values. GFR returned to baseline values on the landing day (31). In another study GFR increased after landing, probably due to the saline-loading countermeasure (98). A series of organ on chip studies launched to the ISS in May 2019 by a team from the University of Washington (PIs Edward Kelly, Jonathan Himmelfarb and Cathy Yeung) evaluates the effects of spaceflight on several parameters of renal function.

Increased Membrane Fluidity

Studies in plain lipid membranes and in a human neuroblastoma cell line demonstrated that membrane fluidity increases in microgravity (99). The same group later assessed alterations in membrane fluidity at the presence of lidocaine, a local anesthetic agent included in the ISS medical kit (2,50). The study was conducted in the microgravity phase during a sounding rocket flight (up to 6 min). Fluidization of asolectin vesicles was measured by fluorescence polarization (100). Lidocaine increased the membrane fluidity under both study conditions, but the increase was significantly lower in microgravity. The authors speculated that the anesthetic effect of lidocaine may be reduced in space, and that altered membrane fluidity might affect both drug pharmacodynamics and pharmacokinetics.

Altered Transporter Activity

Adenosine triphosphate binding cassette (ABC) transporters are a large family of efflux pumps widely expressed in many organisms. The expression of ABC transporter genes has been shown to be upregulated in space in fungi (101) and in bacteria (102) and is high in microbial communities in ISS environmental locations (94). The effect of spaceflight on mammalian ABC transporters has not yet been systemically studied, but several observations were made in the course of transcriptomic or proteomic analyses. For example, Zhang *et al.* (103) studied changes in global gene and miRNA expression in confluent human fibroblast cells in an experiment conducted aboard the ISS. After a 3-day incubation, both the flown cells and ground control cells were still proliferating slowly. Among the genes that were differently expressed in space was *ABCB1* (encoding P-glycoprotein; P-gp), whose expression was upregulated 2.3-fold. However, when the same comparison was made in cells that have been in space for two weeks, no significant changes in gene expression was found. It was concluded that the microgravity of space affects human fibroblasts more in the proliferating stage, but the authors commented that the results may not be valid for living organisms. Changes in P-gp expression in humans can have clinical implications, because this transporter plays an important role in the pharmacokinetics of many drugs (51).

A vesicular transport assay was adapted to evaluate the ATP-activated transport activity of estradiol-17-β-glucuronide by ABCC2 (multidrug resistance-associated protein 2; MRP2) (104), an efflux transporter whose typical substrates include glucuronide–, sulphate– and gluthatione-conjugated drugs (105,106). Experiments were performed during parabolic flights. MRP2 net transport activity was significantly reduced in microgravity when compared to ground 1 *g* controls. The microscopic structure of the vesicles remained stable during simulated hypergravity, but conformational changes of lipid structures could not be ruled out (104), in line with the above mentioned changes in membrane fluidity and membranal incorporation of small molecules.

The limited data available so far suggest that efflux transporter activity might be altered in space, although the exact mechanisms of such changes have yet to be clarified. Whether the activity of uptake transporters is altered in microgravity conditions is currently unknown.

CASE STUDIES

Pharmacokinetics in Space

Until today, the only three drugs whose pharmacokinetics have been assessed in space are acetaminophen, scopolamine, and antipyrine (the latter used as a marker of hepatic clearance, as described above). Acetaminophen and scopolamine concentrations were measured noninvasively in saliva based on the consistent saliva/plasma concentration ratio over the entire measurement period of both drugs (107,108). These limited studies are now over 30 years old, no new pharmacokinetic studies have been published in recent years. It is difficult to understand why the issue of dosing astronauts when far away from the next hospital in an unknown environment has not risen to the level of conducting a pharmacokinetic study. Since pharmaceutical companies are probably not interested in sponsoring such a study, it would be NASA or other international space agencies that should perform these studies to make sure that the doses used in astronauts in space have the same or similar risk-benefit-assessment as on Earth. This is particularly important in the field of anti-infective agents since even very healthy astronauts can get infected in the closed environment of a space station. A potential therapeutic failure of an anti-infective agent due to changes in pharmacokinetics and /or pharmacodynamics could be potentially disastrous.

Acetaminophen

Acetaminophen has been a standard for inflight absorption measurements because it is readily and quickly absorbed by passive diffusion in the small intestine, and it has been given therapeutically many times during flight (21). Hence, it was

used as a marker of absorption processes in two inflight studies during the 1980s.

The first study investigated the pharmacokinetics of acetaminophen after oral administration of two 325 mg tablets in five crewmembers on three different missions (107). On mission day 2 peak acetaminophen concentrations (Cmax) that were measured in two individuals were elevated and the time to peak concentrations (Tmax) was shorter than before flight. However, on day 4 of the mission absorption rate was slower than during preflight in two other individuals. In the crewmember who underwent the inflight study on mission day 3, Cmax was higher but the peak was delayed as compared to control values. The elimination of the drug appeared unaffected, but oral clearance or AUC values were not reported. The variability in absorption was attributed to differences among crewmembers in response to spaceflight, including severity of space motion sickness and degree of hydration, and to differences in mission days (107,109). It is not clear if the subjects used additional drugs. Extension of the analysis to 12 subjects on seven different flights confirmed the reduced absorption rate during spaceflight (110). Cmax tended to decrease on flight day 0 compared to preflight values and increased on flight days 2 and 3. Tmax tended to increase along the four first days of flight.

In the second study, five crewmembers took a tablet and five took a capsule of 500 mg acetaminophen during a long term mission on the ISS (111). The mission day of the study was not specified. The change in AUC in space was modest (approximately 20%) and Cmax was only marginally affected, but absorption was significantly delayed, with a Tmax of 1.80 h *versus* 1.12 h under usual living conditions. The delayed absorption during spaceflight was associated with two peaks in salivary acetaminophen concentrations, at 0.5 h and 2 h after administration of the drug.

When acetaminophen was administered as capsules, the Tmax decreased by 30% as compared to ground condition (0.6 h *versus* 0.9 h, respectively), and it was one third of the tablet value (111). The drugs' half life as determined by measurements in saliva was 2-fold longer than under usual living conditions. The AUC did not differ significantly between the space and the ground measurements. The changes in the rate of absorption from the capsule could result from altered position of the formulations in the stomach: the tablet may not sink toward the pylorus and the capsule that contains a small amount of trapped air may not float on top of the liquid contents of the stomach (21).

The results of these studies suggest that spaceflight mostly affects the rate of acetaminophen exposure, whereas the changes in its extent are smaller. Based on the current data, and given that there have been no reports on symptoms of acetaminophen overdose or of reduced efficacy during flight, it appears that alterations in prescribing are probably not warranted (21). However, the changes in drug pharmacokinetics and effects are dynamic and can depend on the mission length. Therefore, these findings cannot be extrapolated to longer missions.

Scopolamine

The pharmacokinetics of a 0.4 mg dose of oral scopolamine combined with 5 mg dextroamphetamine as a capsule were studied in three astronauts. The saliva sampling frequency was less than optimal due to dryness of the mouth caused by both dehydration and scopolamine itself (108). Scopolamine has an erratic oral absorption even on the ground but its combination with dextroamphetamine was among the most commonly used drugs during the first 33 space shuttle missions (109). The inflight kinetics of scopolamine were also erratic and highly varied across subjects and between two study days in the same subject. Besides the above mentioned sources of variation in the acetaminophen studies, scopolamine absorption could be affected by simultaneous ingestion of other medications (and vice versa) (108,109).

Pharmacodynamics in Space

Very little is known if the assumption that therapeutic drug concentrations on Earth and in space do not differ significantly is correct. There is some evidence that bacterial growth rates and antibiotic potency change in zero-gravity which may require dose adjustments in infected astronauts (22–24). Also, since sleep medication use is very frequent in astronauts, studies should be performed in zero-gravity to explore if the pharmacodynamic response to drugs like zaleplon or zolpidem is the same as on Earth or if space-specific dosing is warranted to avoid overdoses or impair the performance of astronauts. The use of biomarkers (electroencephalography) could be an appropriate tool to perform these studies in space. Furthermore, drugs that increase alertness and overcome tiredness such as armodafinil should be studied to assess their appropriateness during spaceflight.

STABILITY OF MEDICATIONS IN SPACE

An additional factor that can affect medication efficacy and safety, especially in long missions (two years or more) in space is drug stability. Although the temperature and humidity conditions on the ISS are within the ideal ranges for medication storage (26), radiation may accelerate degradation of medicines in space. In a study by Du *et al.*, four out of 14 solid dosage forms of medications stored for 28 months on the ISS did not meet the United States Pharmacopeia (USP) requirements, as compared to two of the ground controls (26). The physical characteristics of six medications were altered in space, whereas those of two medications were altered on the

ground. The number of medications failing stability requirements was associated with time in space, and degradation was faster especially in light-sensitive medications. However, loss of Active Pharmaceutical Ingredient (API) content was generally less than 20% of label claim. In a later opportunistic study, in which each medication was available for one time point, eight of nine medications met stability requirements (27). An exception was a melatonin preparation that failed to meet USP requirements at 11 months after expiration. No unusual degradation products were identified. Notably, stability might be affected by repacking of medications on the ISS into bags to reduce the volume of the medication kit (27).

Several approaches have been suggested to prevent radiation-induced degradation of drugs, including the use of radiation-attenuating containers and packaging materials with appropriate designs, cryogenic temperatures and space-hardy formulations, e.g. micro- and nanoformulations (112). In the future, pharmaceuticals may be produced in space, for example by radiation-resistant fungi (113).

OUTLOOK

The limitations of the studies presented in this review stem to a large extent from the unique conditions that restrict research in space. However, lessons learned through these earlier studies, together with technological advances, can significantly enhance our understanding of space pharmacology, with some projects already underway. It would be desirable to prioritize studies related to drugs which are commonly used by astronauts, such as antibiotics, sleep inducing agents and antiemetics. Mechanistic studies focusing on processes common to multiple drugs such as major elimination mechanisms are urgently required as well. The latter may not require studies in humans as they can imply experimental models such as organ on chip systems.

For *in vivo* studies in humans, an important consideration is minimal invasiveness. For instance, liquid biopsies (plasmasomes), supported by omics- approaches, can be used to probe changes in the expression and activity of enzymes, transporters and receptors. In addition, sensors can be used to continuously monitor biomarkers. One example is the above mentioned electroencephalography. Near infrared and other types of imaging can detect changes in various processes with or without the use of exogenous compounds (e.g., indocyanine green as a marker of hepatic blood flow and hepatic transporter activity (114,115)). Computer-based simulated tasks might be used for monitoring drug effects on astronaut performance in space.

Future studies to be conducted on the ISS should be designed to be as automated as possible due to the very busy schedule of astronauts. An emerging alternative approach is conducting automated studies onboard unmanned space vehicles that can transmit signal to ground stations, return the specimens to Earth, or both. Organ on chip systems are ideal for such studies.

The use of physiologically based pharmacokinetic (PBPK) models can be used for simulating system changes in space. A preliminary PBPK model for estimating the plasma concentration-time profile of acetaminophen under different experimental conditions has been suggested 25 years ago (116), but in the absence of data this approach has not been applied to other medications. With the expanding information obtained from various experimental systems, PBPK could prove very useful for predicting drug effects in space.

CONCLUSIONS

Current anecdotal evidence suggests that physiological changes that occur during spaceflight are likely to alter drug potency, efficacy and safety. The changes depend on the drug and even the formulation, as well as on the duration of flight and on environmental factors. Hence, the available data may not apply to longer missions, e.g., to Mars, which are expected to involve substantial radiation exposure and overall increased likelihood of significant changes in human physiology and in drug stability. Given the huge gap of knowledge, future studies aimed at understanding drug effects in space should be prioritized, e.g. based on medication utility. Such studies are likely to increasingly rely on newer, less-invasive technologies, automatization that reduce the workload of astronauts, and unmanned space vehicles. Importantly, conventional assumptions cannot be applied to pharmacokinetics and pharmacodynamics, and studies should be controlled for factors such as changes in membrane fluidity. Better understanding of space pharmacology can help select drugs whose effects in longer missions are more likely to be predicted, e.g., based on expected changes their receptor binding or predominant route of elimination, adjust dosage, and eventually improve treatment outcomes.

ACKNOWLEDGMENTS AND DISCLOSURES

No financial support was received for this study.

Sara Eyal is affiliated with the David R. Bloom Centre for Pharmacy and Dr. Adolf and Klara Brettler Centre for Research in Molecular Pharmacology and Therapeutics at The Hebrew University of Jerusalem, Israel.

COMPLIANCE WITH ETHICAL STANDARDS

CONFLICT OF INTEREST

Sara Eyal is on sabbatical leave at SpacePharma, Israel, from July 1st 2019.

REFERENCES

1. Pavy-Le Traon A, Saivin S, Soulez-LaRiviere C, Pujos M, Guell A, Houin G. Pharmacology in space: pharmacotherapy. Adv Space Biol Med. 1997;6:93–105.
2. Stingl JC, Welker S, Hartmann G, Damann V, Gerzer R. Where failure is not an option -personalized medicine in astronauts. PLoS One. 2015;10:e0140764.
3. Antonsen, E., Bayuse, T., Blue, R., Daniels, V., Hailey, M., Hussey, S., *et al.* Evidence report: risk of adverse health outcomes and decrements in performance due to in-flight medical conditions. National Aeronautics and Space Administration, Houston, Tx, USA. Approved for public release: May 8, 2017. Available at: https://humanresearchroadmap.nasa.gov/risks/risk.aspx?i=95. Accessed: March 30, 2019.
4. Barger LK, Flynn-Evans EE, Kubey A, Walsh L, Ronda JM, Wang W, et al. Prevalence of sleep deficiency and use of hypnotic drugs in astronauts before, during, and after spaceflight: an observational study. Lancet Neurol. 2014;13:904–12.
5. Putcha L, Berens KL, Marshburn TH, Ortega HJ, Billica RD. Pharmaceutical use by U.S. astronauts on space shuttle missions. Aviat Space Environ Med. 1999;70:705–8.
6. Wotring VE. Medication use by U.S. crewmembers on the international space station. FASEB J. 2015;29:4417–23.
7. Garrett-Bakelman FE, Darshi M, Green SJ, Gur RC, Lin L, Macias BR, et al. The NASA Twins Study: A multidimensional analysis of a year-long human spaceflight. Science. 2019;(364): eaau8650.
8. Leblanc A, Matsumoto T, Jones J, Shapiro J, Lang T, Shackelford L, et al. Bisphosphonates as a supplement to exercise to protect bone during long-duration spaceflight. Osteoporos Int. 2013;24: 2105–14.
9. Murad A. Contraception in the cosmos: the combined oral contraceptive pill in space. J Fam Plann Reprod Health Care. 2008;34:55–9.
10. Aubert AE, Larina I, Momken I, Blanc S, White O, Kim Prisk G, et al. Towards human exploration of space: the THESEUS review series on cardiovascular, respiratory, and renal research priorities. NPJ Microgravity. 2016;2:16031.
11. NASA 2018 Strategic Plan. Overview for NASA Advisory Council. March 29, 2018. Availble at: https://www.nasa.gov/sites/default/files/atoms/files/6-nasa_2018_strategic_plan_mar2018_tagged.pdf. Last accessed: March 30, 2019.
12. Stepanek J, Blue RS, Parazynski S. Space medicine in the era of civilian spaceflight. N Engl J Med. 2019;380:1053–60.
13. Grenon SM, Saary J, Gray G, Vanderploeg JM, Hughes-Fulford M. Can I take a space flight? Considerations for doctors. BMJ. 2012;345:e8124.
14. Hodkinson PD, Anderton RA, Posselt BN, Fong KJ. An overview of space medicine. Br J Anaesth. 2017;119(suppl 1):i143–i53.
15. Jennings RT, Garriott OK, Bogomolov VV, Pochuev VI, Morgun VV, Garriott RA. Giant hepatic hemangioma and cross-fused ectopic kidney in a spaceflight participant. Aviat Space Environ Med. 2010;81:136–40.
16. Jennings RT, Murphy DM, Ware DL, Aunon SM, Moon RE, Bogomolov VV, et al. Medical qualification of a commercial spaceflight participant: not your average astronaut. Aviat Space Environ Med. 2006;77:475–84.
17. National Aeronautics and Space Administration. Parabolic flights. Available at: https://www.nasa.gov/analogs/parabolic-flight. Last updated: Jun 11 2018. Last accessed: Feb 17 2019.
18. Braddock M. Ergonomic challenges for astronauts during space travel and the need for space medicine. J Ergonomics. 2017;7: 221.
19. Graebe A, Schuck EL, Lensing P, Putcha L, Derendorf H. Physiological, pharmacokinetic, and pharmacodynamic changes in space. J Clin Pharmacol. 2004;44:837–53.
20. Kast J, Yu Y, Seubert CN, Wotring VE, Derendorf H. Drugs in space: Pharmacokinetics and pharmacodynamics in astronauts. Eur J Pharm Sci. 2017;109s:S2–s8.
21. Wotring VE. Evidence report: risk of therapeutic failure due to ineffectiveness of medication. National Aeronautics and Space Administration, Lyndon B. Johnson Space Center, Houston, Texas. Available at: https://humanresearchroadmap.nasa.gov/evidence/reports/pharm.pdf. Approved for Public Release: August 02, 2011. Last accessed: Feb 9 2019.
22. Aunins TR, Erickson KE, Prasad N, Levy SE, Jones A, Shrestha S, et al. Spaceflight modifies Escherichia coli gene expression in response to antibiotic exposure and reveals role of oxidative stress response. Front Microbiol. 2018;9:310.
23. Tixador R, Richoilley G, Gasset G, Templier J, Bes JC, Moatti N, et al. Study of minimal inhibitory concentration of antibiotics on bacteria cultivated in vitro in space (Cytos 2 experiment). Aviat Space Environ Med. 1985;56:748–51.
24. Wilson JW, Ott CM, Honer zu Bentrup K, Ramamurthy R, Quick L, Porwollik S, *et al.* Space flight alters bacterial gene expression and virulence and reveals a role for global regulator Hfq. Proc Natl Acad Sci U S A 2007;104:16299–16304.
25. Bogomolov VV, Kondratenko SN, Kovachevich IV. [Testing stability of tableted acetaminophen and furosemide after 6-month storage in space flight]. Aviakosm Ekolog Med 2015;49:12–15.
26. Du B, Daniels VR, Vaksman Z, Boyd JL, Crady C, Putcha L. Evaluation of physical and chemical changes in pharmaceuticals flown on space missions. AAPS J. 2011;13:299–308.
27. Wotring VE. Chemical potency and degradation products of medications stored over 550 earth days at the international Space Station. AAPS J. 2016;18:210–6.
28. Norsk P, Asmar A, Damgaard M, Christensen NJ. Fluid shifts, vasodilatation and ambulatory blood pressure reduction during long duration spaceflight. J Physiol. 2015;593:573–84.
29. Norsk P, Damgaard M, Petersen L, Gybel M, Pump B, Gabrielsen A, et al. Vasorelaxation in space. Hypertension. 2006;47:69–73.
30. Alfrey CP, Udden MM, Leach-Huntoon C, Driscoll T, Pickett MH. Control of red blood cell mass in spaceflight. J Appl Physiol (1985). 1996;81:98–104.
31. Leach CS, Alfrey CP, Suki WN, Leonard JI, Rambaut PC, Inners LD, *et al.* Regulation of body fluid compartments during short-term spaceflight. J Appl Physiol (1985). 1996;81:105–16.
32. Leach CS, Inners LD, Charles JB. Changes in total body water during spaceflight. J Clin Pharmacol. 1991;31:1001–6.
33. Sumanasekera WK, Sumanasekera GU, Mattingly KA, Dougherty SM, Keynton RS, Klinge CM. Estradiol and dihydrotestosterone regulate endothelial cell barrier function after hypergravity-induced alterations in MAPK activity. Am J Physiol Cell Physiol. 2007;293:C566–73.
34. Kapitonova MY, Muid S, Froemming GR, Yusoff WN, Othman S, Ali AM, et al. Real space flight travel is associated with ultrastructural changes, cytoskeletal disruption and premature senescence of HUVEC. Malays J Pathol. 2012;34:103–13.
35. Muid S, Froemming GRA, Manaf A, Muszaphar S, Yusoff K, Nawawi H. Changes in protein and gene expression of adhesion molecules and cytokines of endothelial cells immediately following short-term spceflight travel. Gravit Space Biol. 2010;23:S1–11.
36. Diedrich A, Paranjape SY, Robertson D. Plasma and blood volume in space. The Am J Med Sci. 2007;334:80–6.
37. Carpentier WR, Charles JB, Shelhamer M, Hackler AS, Johnson TL, Domingo CMM, et al. Biomedical findings from NASA's project mercury: a case series. NPJ Microgravity. 2018;4:6.

38. Grigoriev AI, Bugrov SA, . , Bogomolov VV, Egorov AD, Kozlovskaya IB, Pestov ID. Preliminary medical results of the Mir year-long mission. Acta Astronaut 1991;23:1–8.
39. Alperin N, Bagci AM, Lee SH. Spaceflight-induced changes in white matter hyperintensity burden in astronauts. Neurology. 2017;89:2187–91.
40. Koppelmans V, Bloomberg JJ, Mulavara AP, Seidler RD. Brain structural plasticity with spaceflight. NPJ Microgravity. 2016;2:2.
41. Roberts DR, Albrecht MH, Collins HR, Asemani D, Chatterjee AR, Spampinato MV, et al. Effects of spaceflight on astronaut brain structure as indicated on MRI. New Engl J Med. 2017;377:1746–53.
42. Van Ombergen A, Jillings S, Jeurissen B, Tomilovskaya E, Rühl RM, Rumshiskaya A, et al. Brain tissue–volume changes in cosmonauts. New Engl J Med. 2018;379:1678–80.
43. Lee JK, Koppelmans V, Riascos RF, Hasan KM, Pasternak O, Mulavara AP, *et al.* Spaceflight-associated brain white matter microstructural changes and intracranial fluid redistributionspaceflight-associated brain white matter microstructural changes and intracranial fluid redistributionSpaceflight-associated brain white matter microstructural changes and intracranial fluid redistribution. JAMA Neurol. 2019. Epub Jan 23. doi: https://doi.org/10.1001/jamaneurol.2018.4882.
44. Blaber AP, Goswami N, Bondar RL, Kassam MS. Impairment of cerebral blood flow regulation in astronauts with orthostatic intolerance after flight. Stroke. 2011;42:1844–50.
45. Iwasaki K, Levine BD, Zhang R, Zuckerman JH, Pawelczyk JA, Diedrich A, et al. Human cerebral autoregulation before, during and after spaceflight. J Physiol. 2007;579:799–810.
46. Zuj KA, Arbeille P, Shoemaker JK, Blaber AP, Greaves DK, Xu D, et al. Impaired cerebrovascular autoregulation and reduced CO(2) reactivity after long duration spaceflight. Am J Physiol Heart Circ Physiol. 2012;302:H2592–8.
47. Prisk GK, Guy HJ, Elliott AR, West JB. Inhomogeneity of pulmonary perfusion during sustained microgravity on SLS-1. J Appl Physiol (1985). 1994;76:1730–8.
48. Verbandt Y, Wantier M, Prisk GK, Paiva M. Ventilation-perfusion matching in long-term microgravity. J Appl Physiol (1985). 2000;89:2407–12.
49. Prisk GK. Microgravity and the respiratory system. Eur Respir J. 2014;43:1459–71.
50. Governmentattic.org. "Rummaging in the government's attic". National Aeronatutics and Space Administration (NASA) Emergency Medical Procedures Manual for the International Space Station (ISS) [partial], 2016. Requested date: Dec 24 2015. Released date: Mar 14 2016. Posted date: Mar 21 2016. Available at: https://www.governmentattic.org/19docs/NASA-ISSmedicalEmergManual_2016.pdf. Accessed: Mar 7 2019.
51. Eyal S, Hsiao P, Unadkat JD. Drug interactions at the blood-brain barrier: fact or fantasy? Pharmacol Ther. 2009;123:80–104.
52. Rowland M, Tozer TN. Clinical pharmacokinetics - concepts and applications. 3rd ed. Media, PA: Williams & Wilkins; 1995.
53. Anzai T, Frey MA, Nogami A. Cardiac arrhythmias during long-duration spaceflights. J Arrhythm. 2014;30:139–49.
54. Fritsch-Yelle JM, Leuenberger UA, D'Aunno DS, Rossum AC, Brown TE, Wood ML, et al. An episode of ventricular tachycardia during long-duration spaceflight. Am J Cardiol. 1998;81:1391–2.
55. Gontcharov IB, Kovachevich IV, Pool SL, Navinkov OL, Barratt MR, Bogomolov VV, et al. In-flight medical incidents in the NASA-Mir program. Aviat Space Environ Med. 2005;76:692–6.
56. Golubchikova ZA, Alferova IV, Liamin VR, Turchaninova VF. Dynamics of some electrocardiographic parameters in cosmonauts during long-term Mir mission. Aviakosm Ekolog Med. 2003;37:41–5.
57. D'Aunno DS, Dougherty AH, DeBlock HF, Meck JV. Effect of short- and long-duration spaceflight on QTc intervals in healthy astronauts. Am J Cardiol. 2003;91:494–7.
58. Leach CS, Altchuler SI, Cintron-Trevino NM. The endocrine and metabolic responses to space flight. Med Sci Sports Exerc. 1983;15:432–40.
59. Ushakov AS, Popova IA. Metabolism. In: Nicogossian AE, Mohler SR, Gazenko OG, Grigoriev AI, editors. Space biology and medicine. III. American Institute of Aeronautics and Astronautics: Reston, VA, USA; 1996.
60. Larina MI, Percy AJ, Yang J, Borchers CH, M. Nosovsky A, I. Grigoriev A, *et al.* Protein expression changes caused by spaceflight as measured for 18 Russian cosmonauts. Sci Rep. 2017;7:8142.
61. Grigoriev AI, Morukov BV, Vorobiev DV. Water and electrolyte studies during long-term missions onboard the space stations SALYUT and MIR. Clin Investig. 1994;72:169–89.
62. Cirillo M, De Santo NG, Heer M, Norsk P, Elmann-Larsen B, Bellini L, et al. Urinary albumin in space missions. J Gravit Physiol. 2002;9:P193–4.
63. Cirillo M, De Santo NG, Heer M, Norsk P, Elmann-Larsen B, Bellini L, et al. Low urinary albumin excretion in astronauts during space missions. Nephron Physiol. 2003;93:p102–5.
64. Benet LZ, Hoener BA. Changes in plasma protein binding have little clinical relevance. Clin Pharmacol Ther. 2002;71:115–21.
65. Lang T, Van Loon J, Bloomfield S, Vico L, Chopard A, Rittweger J, et al. Towards human exploration of space: the THESEUS review series on muscle and bone research priorities. NPJ Microgravity. 2017;3:8.
66. Edgerton VR, Zhou MY, Ohira Y, Klitgaard H, Jiang B, Bell G, *et al.* Human fiber size and enzymatic properties after 5 and 11 days of spaceflight. J Appl Physiol (1985). 1995;78:1733–9.
67. Williams D, Kuipers A, Mukai C, Thirsk R. Acclimation during space flight: effects on human physiology. Can Med Assoc J. 2009;180:1317–23.
68. Frippiat JP, Crucian BE, de Quervain DJ, Grimm D, Montano N, Praun S, et al. Towards human exploration of space: the THESEUS review series on immunology research priorities. NPJ Microgravity. 2016;2:16040.
69. Crucian B, Stowe RP, Mehta S, Quiriarte H, Pierson D, Sams C. Alterations in adaptive immunity persist during long-duration spaceflight. NPJ microgravity. 2015;1:15013-.
70. Ferri N, Bellosta S, Baldessin L, Boccia D, Racagni G, Corsini A. Pharmacokinetics interactions of monoclonal antibodies. Pharmacol Res. 2016;111:592–9.
71. Yamamoto Y, Takahashi Y, Horino A, Usui N, Nishida T, Imai K, et al. Influence of inflammation on the pharmacokinetics of Perampanel. Ther Drug Monit. 2018;40:725–9.
72. Stewart JJ, Wood MJ, Wood CD, Mims ME. Effects of motion sickness and antimotion sickness drugs on gastric function. J Clin Pharmacol. 1994;34:635–43.
73. Wood MJ, Wood CD, Manno JE, Manno BR, Redetzki HM. Nuclear medicine evaluation of motion sickness and medications on gastric emptying time. Aviat Space Environ Med. 1987;58:1112–4.
74. Putcha L, Kovachevich I. Physiologic Alterations and Pharmacokinetic Changes During Space Flight (2.3.1). Available at: https://lsda.jsc.nasa.gov/Experiment/exper/359. Last accessed: Mar 9 2019.
75. Engel G, Hofmann U, Heidemann H, Cosme J, Eichelbaum M. Antipyrine as a probe for human oxidative drug metabolism: identification of the cytochrome P450 enzymes catalyzing 4-hydroxyantipyrine, 3-hydroxymethylantipyrine, and norantipyrine formation. Clin Pharmacol Ther. 1996;59:613–23.

76. Merrill AH, Popova IA, Wang E, Mullins RE, LaRoque R, Hargrove JL, *et al.* Part I: Analysis of selected parameters of carbohydrate, amino acid, lipid, and xenobiotic metabolism in liver and serum, from rats flown on Cosmos 2044. Ames Research Center, Moffett Field, CA, USA.: 1994 NASA Technical Memorandum 108802.
77. Merrill AH Jr, Wang E, Jones DP, Hargrove JL. Hepatic function in rats after spaceflight: effects on lipids, glycogen, and enzymes. Am J Phys. 1987;252:R222–6.
78. Merrill AH Jr, Hoel M, Wang E, Mullins RE, Hargrove JL, Jones DP, et al. Altered carbohydrate, lipid, and xenobiotic metabolism by liver from rats flown on Cosmos 1887. FASEB J. 1990;4:95–100.
79. Amato G, Longo V, Mazzaccaro A, Gervasi PG. Chlorzoxazone 6-hydroxylase and p-nitrophenol hydroxylase as the most suitable activities for assaying cytochrome P450 2E1 in cynomolgus monkey liver. Drug Metab Dispos. 1998;26:483–9.
80. Amacher DE, Schomaker SJ. Ethylmorphine N-demethylase activity as a marker for cytochrome P450 CYP3A activity in rat hepatic microsomes. Toxicol Lett. 1998;94:115–25.
81. Liu Z, Mortimer O, Smith CA, Wolf CR, Rane A. Evidence for a role of cytochrome P450 2D6 and 3A4 in ethylmorphine metabolism. Br J Clin Pharmacol. 1995;39:77–80.
82. Hollander J, Gore M, Fiebig R, Mazzeo R, Ohishi S, Ohno H, et al. Spaceflight downregulates antioxidant defense systems in rat liver. Free Radic Biol Med. 1998;24:385–90.
83. Racine RN, Cormier SM. Effect of spaceflight on rat hepatocytes: a morphometric study. J Appl Physiol (1985). 1992;73(2 Suppl):136s–41s.
84. Andreev-Andrievskiy A, Popova A, Boyle R, Alberts J, Shenkman B, Vinogradova O, et al. Mice in Bion-M 1 space mission: training and selection. PLoS One. 2014;9:e104830.
85. Anselm V, Novikova S, Zgoda V. Re-adaption on earth after spaceflights affects the mouse liver proteome. Int J Mol Sci. 2017;18.
86. Moskaleva N, Moysa A, Novikova S, Tikhonova O, Zgoda V, Archakov A. Spaceflight effects on cytochrome P450 content in mouse liver. PLoS One. 2015;10:e0142374.
87. Baba T, Nishimura M, Kuwahara Y, Ueda N, Naitoh S, Kume M, et al. Analysis of gene and protein expression of cytochrome P450 and stress-associated molecules in rat liver after spaceflight. Pathol Int. 2008;58:589–95.
88. Hammond TG, Allen PL, Birdsall HH. Effects of space flight on mouseliver versus kidney: gene pathway analyses. Int J Mol Sci. 2018;19:4106.
89. Grindeland RE, Popova IA, Vasques M, Arnaud SB. Cosmos 1887 mission overview: effects of microgravity on rat body and adrenal weights and plasma constituents. FASEB J. 1990;4:105–9.
90. Guengerich FP. Comparisons of catalytic selectivity of cytochrome P450 subfamily enzymes from different species. Chem Biol Interact. 1997;106:161–82.
91. Martignoni M, Groothuis GM, de Kanter R. Species differences between mouse, rat, dog, monkey and human CYP-mediated drug metabolism, inhibition and induction. Expert Opin Drug Metab Toxicol. 2006;2:875–94.
92. Nelson DR, Zeldin DC, Hoffman SM, Maltais LJ, Wain HM, Nebert DW. Comparison of cytochrome P450 (CYP) genes from the mouse and human genomes, including nomenclature recommendations for genes, pseudogenes and alternative-splice variants. Pharmacogenetics. 2004;14:1–18.
93. Hammond TG, Benes E, O'Reilly KC, Wolf DA, Linnehan RM, Taher A, et al. Mechanical culture conditions effect gene expression: gravity-induced changes on the space shuttle. Physiol Genomics. 2000;3:163–73.
94. Singh NK, Wood JM, Karouia F, Venkateswaran K. Succession and persistence of microbial communities and antimicrobial resistance genes associated with International Space Station environmental surfaces. Microbiome. 2018;6:204.
95. Jonscher KR, Alfonso-Garcia A, Suhalim JL, Orlicky DJ, Potma EO, Ferguson VL, et al. Spaceflight activates lipotoxic pathways in mouse liver. PLoS One. 2016;11:e0152877.
96. Liakopoulos V, Leivaditis K, Eleftheriadis T, Dombros N. The kidney in space. Int Urol Nephrol. 2012;44:1893–901.
97. Nigam SK, Bush KT, Martovetsky G, Ahn SY, Liu HC, Richard E, et al. The organic anion transporter (OAT) family: a systems biology perspective. Physiol Rev. 2015;95:83–123.
98. Grigoriev AI, Huntoon CL, Morukov BV, Lane HW, Larina IM, Smith SM. Endocrine, renal, and circulatory influences on fluid and electrolyte homeostasis during weightlessness: a joint Russian-U.S. project. J Gravit Physiol. 1996;3:83–6.
99. Sieber M, Hanke W, Kohn FPM. Modification of membrane fluidity by gravity. Open J Biophys. 2014;4:105–11.
100. Kohn FPM, Hauslage J. The gravity dependence of pharmacodynamics: the integration of lidocaine into membranes in microgravity. NPJ Microgravity. 2019;5:5.
101. Crabbé A, Nielsen-Preiss SM, Woolley CM, Barrila J, Buchanan K, McCracken J, et al. Spaceflight enhances cell aggregation and random budding in Candida albicans. PLoS One. 2013;8:e80677.
102. Morrison MD, Fajardo-Cavazos P, Nicholson WL. Comparison of Bacillus subtilis transcriptome profiles from two separate missions to the International Space Station. NPJ Microgravity. 2019;5:1.
103. Zhang Y, Lu T, Wong M, Wang X, Stodieck L, Karouia F, et al. Transient gene and microRNA expression profile changes of confluent human fibroblast cells in spaceflight. FASEB J. 2016;30:2211–24.
104. Vaquer S, Cuyàs E, Rabadán A, González A, Fenollosa F, de la Torre R. Active transmembrane drug transport in microgravity: a validation study using an ABC transporter model [version 1; referees: 2 approved]. F1000Research. 2014;3:1–15.
105. Keppler D. Multidrug resistance proteins (MRPs, ABCCs): importance for pathophysiology and drug therapy. Handb Exp Pharmacol. 2011;201:299–323.
106. Nicolazzo JA, Katneni K. Drug transport across the blood-brain barrier and the impact of breast cancer resistance protein (ABCG2). Curr Top Med Chem. 2009;9:130–47.
107. Cintron NM, Putcha L, Vanderploeg JM. Inflight pharmacokinetics of acetaminophen in saliva. In: Bungo MW, Bagian TM, Bowman MA, Levitan BM, editors. NASA Technical Memorandum 58280 Results of the Life Sciences DSOs Conducted Aboard the Space Shuttle 1981–1986. Huston, TX, USA: National Aeronautics and Space Administration; 1987. p. 19–23.
108. Cintron NM, Putcha L, Chen Y-M, Vanderploeg JM. Inflight salivary pharmacokinetics of scopolamine and dextroamphetamine. In: Bungo MW, Bagian TM, Bowman MA, Levitan BM, editors. NASA Technical Memorandum 58280 Results of the Life Sciences DSOs Conducted Aboard the Space Shuttle 1981–1986. Huston, TX, USA: National Aeronautics and Space Administration; 1987. p. 25–29.
109. Tietze KJ, Putcha L. Factors affecting drug bioavailability in space. J Clin Pharmacol. 1994;34:671–6.
110. Putcha L, Cintron NM. Pharmacokinetic consequences of spaceflight. Ann N Y Acad Sci. 1991;618:615–8.

111. Kovachevich IV, Kondratenko SN, Starodubtsev AK, Repenkova LG. Pharmacokinetics of acetaminophen administered in tablets and capsules under long-term space flight conditions. Pharm Chem J. 2009;43:130–3.
112. Mehta P, Bhayani D. Impact of space environment on stability of medicines: challenges and prospects. J Pharm Biomed Anal. 2017;136:111–9.
113. Countryman S. Influence of microgravity on the production of Aspergillus secondary metabolites (IMPAS) – a novel drug discovery approach with potential benefits to astronauts' health. https://www.nasa.gov/mission_pages/station/research/experiments/explorer/Investigation.html?#id=1164. Accessed May 13 2019.
114. Mann A, Semenenko I, Meir M, Eyal S. Molecular imaging of membrane transporters' activity in cancer: a picture is worth a thousand tubes. AAPS J. 2015;17:788–801.
115. Mann A, Han H, Eyal S. Imaging transporters: transforming diagnostic and therapeutic development. Clin Pharmacol Ther. 2016;100:479–88.
116. Srinivasan RS, Bourne DW, Putcha L. Application of physiologically based pharmacokinetic models for assessing drug disposition in space. J Clin Pharmacol. 1994;34:692–8.