Title: Physiological adaptations affecting drug pharmacokinetics in space: what do we really know? A critical review of the literature.

Running title: Drug PK in space medicine

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Abstract

As human spaceflight continues with extended mission durations, the demand of effective and safe drugs is going to increase. To date, the medications used during missions (for space motion sickness, sleep disturbances, allergies, pain and sinus congestion) are administered under the assumption that they act similarly as on Earth. During spaceflights however fluid shifts, muscle and bone loss, immune system dysregulation and changes in the gastrointestinal tract and metabolism are documented. These alterations may change the pharmacokinetics (PK) and

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pharmacodynamics. The information gained from bed rest studies and from in-flight observations is partial and demonstrates variability in drug PK. The objectives of this review are to report: i) the impact of the space environmental stressors on human physiology in relation to PK; ii) the state-of-the-art on experimental data in space and/or in ground-based models; *iii*) the validation of ground-based models for PK studies; and *iv*) the identification of possible research gaps.

Keywords: pharmacokinetics, space stressor, drugs, formulations, animal studies, bed rest studies, real evidence in space, pharmacotherapy in space.

1. Introduction

When exposed to the space environment, all systems and organs undergo adaptations that can affect drug pharmacokinetics (PK) and thus their efficacy (Putcha & Cintrón, 1991; Derendorf, 1994; Czarnik & Vernikos, 1999; Graebe, Schuck et al., 2004; Kast, Yu et al., 2017; Strollo, Gentile et al., 2018). Beside weightlessness, other space environmental factors and stressors can influence the response to drugs. The highly demanding and stressful work, isolation and confinement, forced interpersonal relationships, circadian misalignment and exposure to artificial light and noises heavily affect astronaut's mood and central nervous system well-being, with consequences on all the organs and physiological systems. Reduced sanitation and exposure to radiation alter human microbial balance, increase the risk of DNA damage, thus compromising immune system function (Williams, Kuipers et al., 2009; Pavez Loriè, Baatout et al., 2021). Relative mild chronic hypoxia can be a further stressor.

When given orally (os), by intravenous (i.v.) or intramuscular (i.m.) injection, intranasally or rectally, or as a patch, a drug must be absorbed, distribute through the body, act on receptors or other targets, be metabolized and excreted. When circulating in blood, it can variably bind to plasma proteins or red blood cells. All the above steps are influenced by the chemical features of the drug, the formulation, its ability to cross membranes and barriers, and time of contact with them. However, these last features can be significantly altered by microgravity and other space environmental stressors leading to potential modifications of drug efficacy and safety in space (Wotring, 2011; Wotring, 2018; Eyal & Derendorf, 2019; Eyal, 2020). In particular, space radiation can affect drug stability, which is an additional factor that can variably contribute to modifications of drug effects in space and whose magnitude is difficult to predict (Blue, Chancellor et al., 2019a).

Common medical conditions observed during the short-duration Space Shuttle flights and longer space missions on the International Space Station (ISS) are space motion sickness (SMS), sleep problems, pain, such as headache, back pain, joint and muscle pain, allergies, skin rashes and dermatitis, sinus congestion and infectious diseases (Wotring, 2015; Kast, Yu et al., 2017; Pavez Loriè, Baatout et al., 2021). These conditions often require pharmacotherapy and drugs are prescribed and used in space under the assumption that they act in a similar manner as on Earth. However, evidence gathered both from single case reports as well as from the analysis of astronaut medical records suggests that this is not the case. Drugs act differently in space and perhaps are less effective, as indicated by the observation of delayed onset of

action, lack or reduction of beneficial effects, and the need of repeated dosing to achieve pharmacological effects (Pool & Nicogossian, 1983; Crucian, Johnston et al., 2016; Wotring, 2015; Wotring & Smith, 2020). The reasons behind this variability are not fully elucidated. Drug PK may be altered in space due to physiological adaptations to the space environment, thus impacting on drug efficacy and safety. On the other hand, it is possible that ground-based experimental models are not sufficiently validated as surrogate. The need to investigate in detail the effects of relevant drugs under space conditions, outlined since the first observation of such variability (Pool & Nicogossian, 1983), remains an important issue in space medicine, particularly in the present times with long lasting human spaceflight missions beyond the low Earth orbit (LEO) already planned by space agencies and private corporations. Continuous efforts have been made by space agencies to develop tracking systems of crews' intake of medications and to standardize the reporting procedures allowing for accurate data collection and monitoring of drug use by astronauts during space missions (Wotring & Smith, 2020). In-flight data are relevant to understand critical differences between the way drugs act in space in comparison to Earth (Blue, Bayuse et al., 2019b).

In this framework, we carried out an extensive literature review on the topic '*physiological changes that impact drug PK*' with the aims: i) to describe the impact of the space environmental stressors on human physiology in relation to PK (Section 2); ii) to provide the state of the art on experimental data, through the identification of drugs whose PK was studied either in space and/or in ground-based models (Section 3); *iii*) to summarize data on the validation of ground-based models for PK studies (Section 3); and *iv*) to identify possible experimental and research gaps (Section 4).

2. Impact of space environment on human physiology in relation to drug PK

Various physiological changes occur during spaceflight mainly in two distinct phases. During the early phase, *i.e.*, 72-96 hours, symptoms such as SMS, sleep disturbances, nasal congestion, headache and back pain are reported (Dijk, Neri et al., 2001; Lakin, Stevens et al., 2007). Changes in bone and muscle mass and central nervous system function develop later during the adaptive phase in a time span from weeks to months (Demertzi, Van Ombergen et al., 2016).

Following is a description of the main organs and systems whose alterations can change absorption, distribution, metabolism and excretion (ADME) of drugs. Fig. 1 depicts those adaptations and how they influence the single aspects of ADME.

2.1 Gastrointestinal tract and drug absorption

Changes in gastric emptying and intestinal transit time due to SMS may affect the absorption of oral drugs, with significant differences compared to what occurs on Earth. Gastric emptying is slower and more variable in microgravity, in part due to loss of gravity-dependent size and density effects of ingested matter (Amidon, DeBrincat et al., 1991). Intestinal transit rate through the small intestine is instead faster and again more variable. These changes can affect the dissolution rate of tablets/capsules and the stability of drugs in the stomach. Although it is not known if motility is directly affected by microgravity, gastrointestinal (GI) transit time is

certainly affected by SMS treatments, mainly scopolamine and promethazine, used to counteract the activation of the muscarinic receptor system (Wood, Wood et al., 1987; Wood, Stewart et al., 1990; Davis, Jennings et al., 1993a,b). Weakly acidic drugs may show increased absorption as their permanence in the stomach is prolonged, but for most medications, particularly basic ones, absorption occurs in the more basic regions of the intestine. Treatment with antimuscarinic drugs will delay, even in the order of hours, drug absorption, or even reduce it, due to degradation in the strong acidic environment of the stomach, as a consequence of delayed gastric emptying. In addition, it is possible that alterations in gastric pH and in the expression of epithelial transport systems together with altered blood flow described in hypoxic environment as the one typical of high altitude (Bailey, Stacey et al., 2018; Zhou, Nian, et al., 2018) may occur also in spaceflight.

The presence of food in the gut affects absorption of orally administered drugs through several mechanisms. Specific foods can affect the rate of gastric emptying, and the quality of food in space, *i.e.*, ingredients and consistency, differs from Earth (https://www.nasa.gov/content/space-food-systems). Changes in nutrition, reduced or inadequate caloric intake, alterations in nutrients ingestion, together with several other stressors associated with space missions, may significantly impact the composition and function of the gut microbiota (for a recent review, please refer to Turroni, Magnani et al., 2020). In addition, absorption at intestinal level or in other organs is affected by the general re-distribution of fluids, which is responsible for tissue oedema (see the section on cardiovascular system adaptations). Additional factors affecting drug absorption include changes in the expression and activity of epithelial and intraluminal enzymes and of transluminal transport systems in the intestine, also due to hypoxia. As far as metabolism is concerned, alterations in the composition of intestinal microflora, and differences in hepatic blood flow velocity and first-pass metabolism will also play a role in drug absorption and bioavailability. In experimental studies under microgravity conditions, changes in the expression profile of multiple proteins in Caco-2 cells, a cell line used as a model to evaluate drug permeability, and therefore the absorption of drugs through the intestinal wall, have recently been reported (La Barbera, Capriotti et al., 2017). Furthermore, decreased activity of lipid-hydrolysing enzymes, activation of proteolytic enzymes and impaired hepatic secretion of the biliary lipid complex have been observed in spaceflight (Smirnov, 1986).

The alterations in gut microbiota in space (Voorhies, Mark Ott, C. et al., 2019, Turroni, Magnani et al., 2020) can contribute to the above events both for the quality and quantity of the faecal mass, and for the spectrum of enzymatic activities involved in the gastrointestinal metabolism and elimination of the xenobiotics. In general, it is clear that microflora can affect drug absorption (Fleisher, Li et al., 1999; Schneeman, 2002); however, it has not yet been determined whether the changes that have been seen during spaceflight significantly affect a medicine's absorption. Human microbiome research is therefore an essential topic in the agenda of space agencies, especially in consideration of long-duration human space missions beyond LEO. These data will enable the adoption of effective countermeasures to ensure safety and health of the crewmembers during these high-risk expeditions (LaPelusa, Donoviel et al., 2021).

To summarize, the main gaps which remain to be explored in spaceflight include changes in the expression and functioning of transport systems and metabolic enzymes at enteric level and the overall influence of gut microbiota shift in processing and absorption of medicines.

2.2 Cardiovascular system and drug distribution

The physiological gradients of arterial, venous and microcirculatory pressure are no longer present in microgravity, which causes a shift of fluid from the lower to the upper part of the body and a decrease in blood volume (Charles & Bungo, 1991; Charles & Lathers, 1991; Leach, Inners et al., 1991a; Montgomery, Parmet et al., 1993). This headward fluid shift distends the central vasculature containing the primary sensors for the cardiovascular system (*i.e.*, stretch receptors, baroreceptors, and volume receptors) (Strollo, Norsk et al., 1998). Mild hypoxia can aggravate the condition by causing vasogenic brain swelling and oedema as described at high altitude (Lafuente, Bermudez, et al., 2016; Turner and Gattener et al., 2021). The expanded central volume is detected as a "fluid-volume overload". Thus, the body responds by increasing natriuresis and diuresis, decreasing thirst, and increasing evaporation through the lungs and the skin (Natochin, Kozyrevskaya et al., 1975; Leach, Johnson et al. 1988; Leach, Alfrey et al., 1996; Charles & Bungo, 1991; Charles & Lathers, 1991). However, further studies report that the baroreceptor-kidney loop does not participate in fluid volume regulation in microgravity the way it does on Earth (Hargens & Richardson, 2009). Despite these conflicting results and hypotheses, the final outcomes are decrease in plasma volume and an overall fluid deficit.

Concerning drug distribution, total body water has been reported to be decreased by approximately 3% after long permanence in space (Leach, 1981). Total body mass declines during spaceflight as lean body mass. Thus, for a given dosage, drug concentration in the bloodstream is expected to be higher. The last data document that the extent of chronic dehydration typically seen in spaceflight is about 1 to 2 % of body mass, with only transient increases at launch. Fluid redistribution is not only related to the whole cardiovascular system, but also to extra- and intracellular water movements. One study suggests that the volume of intracellular fluid increases (Leach, Alfrey et al., 1996). In addition, other available data would confirm that a redistribution of fluids occurs during spaceflight (from plasma volume to the extracellular compartment, from the extracellular to the intracellular volume) more than a loss of total body water due to dehydration or increased diuresis. Other blood components, *i.e.*, red cells and proteins, like albumin, also reduce in a few days, so that final blood concentrations return to normal, but overall blood volume is a little lower (Smith, Lane et al., 2019). The drug apparent distribution volume (Vd) would thus be lower, and effective drug concentrations would then be all higher in space in comparison to Earth.

There are also other cardiovascular changes that occur during spaceflight, such as decreased left ventricular end-diastolic volume and stroke volume indexes, with compensatory increased accelerated heart rate for the maintenance of cardiac output (Mulvagh, Charles et al., 1991). All these alterations bring to the phenomenon of cardiovascular deconditioning (Antonutto & di Prampero, 2003). In addition, non-fatal cardiac arrhythmias have been reported during space

missions, with increased risk during longer explorations. Several factors may trigger cardiac rhythm's alterations, including prolongation of the QT interval, hypokalaemia, exposure to radiations leading to myocardial damage, and psychological stressors (Anzai, Frey et al., 2014). Fluctuations in cardiovascular parameters can affect the PK of drugs, thus their efficacy and safety. However, these cardiovascular changes undergo adaptation after few days of spaceflight, and crewmembers typically do not report long-term fluid problems, since the body seems to adapt to this new condition (Hargens & Watenpaugh, 1996). The problem of new fluctuations of these phenomena however manifests upon return to Earth. Taken together, these results provide support for a model that includes a fluid shift on flight day 1-2, upward in the body and from the plasma, interstitial, and extracellular spaces into the intracellular spaces. There is no convincing evidence regarding the distribution of drugs during or after any fluid shifts. No additional distribution evidence from in-flight studies has been described after publication of V.E. Wotring's report (Wotring, 2011).

Drug binding to plasma proteins, lipids and erythrocytes is probably altered, but only a few direct studies on these parameters have been performed. Plasma albumin and HDL cholesterol are known to be decreased in spaceflight. As a consequence, the percentage of circulating free drug is higher, thus leading to increased availability of the drug for its target(s), accelerated clearance, but also to possible worsening of adverse effects. Concerning hematologic indices, results are contrasting, due to different time-points for blood sampling. Red blood cell mass, *i.e.*, haemoglobin and number of erythrocytes, but not haematocrit (Tavassoli, 1982; Leonard, Leach et al., 1983; Leach & Johnson, 1984; Grigoriev, Bugrov et al., 1991) have been reported to be reduced after short duration spaceflights. Erythropoietin levels have been found decreased throughout the flight (Alfrey, Udden et al., 1996a,b), which could be the cause of the increased neocytolysis, *i.e.*, destruction of young red blood cells (Trial, Rice et al., 2001). On the contrary, red blood cells and haemoglobin were reported to be elevated during long-term spaceflights (Kunz, Quiriarte et al., 2017). It is thus mandatory to evaluate the correlation among hematologic parameters and altered free drug concentration during long permanence in space, since they change during the different mission phases.

Endothelial cells are very sensitive to the absence of gravity (Morbidelli, Monici et al., 2005), therefore a state of endothelial dysfunction can result, accompanied by vascular oxidative stress and a mild chronic inflammatory state (Kapitanova, Muid et al., 2012; Maier, Cialdai et al., 2015). Spaceflight induced disturbance of the brood brain barrier (Mao and Nishiyama et al., 2020), due to chronic mild inflammation and redox unbalance, can be responsible for brain impermeable drugs to enter the brain, thus causing toxic adverse effect. No specific information on the functions of the transport system in the absence of gravity has been reported for the microvascular and/or lymphatic endothelium, as well as for the permeability status of the endothelium within the organism, both phenomena being involved in the absorption and distribution of drugs to and through the body tissues.

In space, there is no compression of peripheral vessels, and the peripheral hemodynamic performance does not favour tissue perfusion (Regnard, Heer et al., 2001). During spaceflights of long duration, there is a loss of bone and muscle mass, as well as of muscle strength. Drug tissue binding may be altered as a result of massive protein loss (Leonard, Leach et al., 1983)

and scarce perfusion. Although an intensive physical training plan can effectively reduce bone loss (Iwamoto, Takeda et al., 2005; Hargens, Bhattacharya et al., 2013), reduced muscle mass can affect the distribution and storage of drugs within this tissue. Again, no direct studies on this topic are present in the literature.

2.3 Drug Metabolism

Cytochromes P450 constitute the largest family of phase I enzymes responsible for the metabolism of drugs and xenobiotics. Cytochrome variations can lead to an increased or decreased metabolism, as well as a different profile of drug and xenobiotic metabolites. All this could result in the appearance of unwanted pharmacological effects or therapeutic failure. Significant changes in hepatic content of metabolic enzymes belonging to the cytochrome P450 family and P-glycoprotein have been described in experimental animals maintained under microgravity conditions (Merril, Hoel et al., 1990; Lu, Bai et al., 2002; Moskaleva, Moysa et al., 2015). In rats flown to space for 14 days, morphological analysis showed that hepatocytes were larger than those of control animals, although the livers themselves were not larger (Racine & Cormier, 1992). In rats flown on Spacelab 3 (for 7 days), a decrease of ~50% was seen in total cytochrome P450 enzymatic activity, whereas no change occurred in the Phase II enzyme glutathione S-transferase (Hargrove & Jones, 1985). In rats, after an 8-day flight on STS-63, a reduction in the amount of the liver enzymes catalase and glutathione (GSH) reductase, both involved in general antioxidant activity, as well as GSH sulphur-transferase was found (Hollander, Gore et al., 1998). Activation of lipotoxic pathway has been demonstrated in mice after a 13-day spaceflight mission (Jonscher, Alfonso-Garcia et al., 2016). This suggests a progressive liver damage and a predisposition to non-alcoholic fatty liver disease. It is however not known if protein concentration or amount correlates with enzymatic activity in these conditions.

The decreased hepatic metabolism during spaceflight is consistent with the decreased hepatic blood flow due to hypovolemia. Nevertheless, conflicting data have been reported in the literature. Hepatic blood flow has been found to be increased in spaceflight, hypothesizing that more drug is delivered to the liver and processed by first-pass metabolism, thus reducing its circulatory level (Saivin, Pavy-Le Traon et al., 1995). At the same time, a slight increase in liver size and liver filling has been reported after 9 months of spaceflight (Grigoriev, Bugrov et al., 1991).

Hypoxic environment can influence xenobiotic metabolism. Human studies on high altitude hypoxia indicated that the metabolism of most drugs is reduced (Bailey, Stacey et al., 2018). In particular cytochrome P450 monooxygenase activity can diminish since oxygen is a pivotal substrate. Recently, changes in the PK of acetaminophen and metformin hydrochloride have been observed in rats under simulated high altitude hypoxia conditions. These modifications were driven by a significant decrease in the transcription of uridine diphosphate glucuronyltransferase 1A1 and organic cation transporter 2(Zhu, Yang et al., 2021).

A fine control of either the major liver enzymes or the levels of circulating metabolites of drugs with low therapeutic index is therefore mandatory for the definition of safe and effective

therapy. The innovative approach of metabolomics could meet this need. NASA's GeneLab database (https://genelab.nasa.gov/) will support this medical need by collecting and providing access to the genomic, transcriptomic, proteomic and metabolomic data from spaceflight studies (Berrios, Galazka et al., 2021).

In conclusion, metabolic enzyme systems are not equally affected by spaceflight. More detailed experiments on these identified genes and enzymes should be performed, especially those involving the enzymes that metabolize the drugs used in spaceflight. Interestingly, approximately 31% of all drugs in the ISS pharmacy are metabolized by polymorphic liver enzymes, which can significantly contribute to variability in drug PK, efficacy, and safety (Stingl, Welker et al., 2015). On top of this, data on drug-drug, drug-diet, and drug-physical countermeasure interactions in the space environment are also lacking (Berman & Eyal, 2019).

2.4 Excretion of drugs

Changes in organ perfusion, including kidneys, and in renal function are reported, with an influence on the parameters related to the secretion and elimination of drugs and/or their metabolites. In space, there is a decreased urinary excretion secondary to blood volume contraction. Since all drug-binding macromolecules in the blood are decreased, the drug free fraction is increased, which increases its renal clearance. However, renal plasma flow, glomerular filtration rate (GFR), and urine production were shown to be unchanged in space (Drummer, Heer et al., 1993; Drummer, Gerzer et al., 2000a; Drummer, Hesse et al., 2000b), contrary to previous data from simulated microgravity models that suggested increased GFR and diuresis (Norsk, Drummer et al., 2001). Instead of increased natriuresis, an increased sodium reabsorption was observed in flight (Norsk, Christensen et al., 2000), resulting in a positive sodium balance. In addition, under hypoxia altered capillary pressure and urinary epithelial biochemistry and transport carrier expression and function may be responsible for increased half-life time ($t_{1/2}$) and area under the drug-time curve (AUC), and reduced clearance rate (Cl) found at high altitude (Bailey, Stacey, et al., 2018). It is not excluded that this happens also in space environment.
Direct studies on renal blood flow are absent from the literature since the D-2 Spacelab mission (Kuipers, 1996). In-flight measurements indicate a slight reduction in total body water for the first few days of spaceflight (Leach, Inners et al., 1991a). There is also the indication that in weightlessness, fluid moves from the blood to the tissues, probably caused by the decrease in the mechanical pressures over tissues and organs (Leach, Alfrey et al., 1996). Abrupt cessation of large muscle group activity may also contribute to decreased plasma volume (Christensen, Drummer et al., 2001). This would be expected to reduce renal blood flow and drug excretion. Indeed, plasma renin activity and antidiuretic hormones were increased in short-duration spaceflights (Leach, Cintrón et al., 1991b; Leach, 1991c). Reduced intake of fluids and fresh food has been proposed as an explanation for reduction in plasma volume (Norsk, 2005). A search of the literature shows no studies reporting on drug excretion in microgravity or during spaceflight (see further details in the present review). Being able to have simple and immediate systems to check the elimination of drugs and/or their metabolites in the urine could help to optimize the dosage of drugs in space.

3. Drug PK studies in space and surrogate models of microgravity

Important physiological adjustments, as outlined in Section 2, occur during spaceflight with a potential impact on drug PK, thus also on efficacy and safety of medicines in space. Studies that have investigated drug PK directly in spaceflight or in surrogate experimental models, mainly the bed rest (BR) model, were identified through a search on the PubMed database (accessed on Jan 02, 2022), as detailed in Fig. 2A. A total of 43 papers were selected for this review. Among them, there were 24 reviews and 2 editorials, which account for 60.5% of the selected publications, 4 in-flight studies, 12 research studies carried out on ground-based experimental models of microgravity, and 1 recent publication reporting both in-flight PK and ground-based data (Fig. 2A). As shown in Fig. 2B, the majority of studies, that is 33/43 (76.4%), were published between years 1986 and 2007. Since then, only two original articles concerning drug PK in human spaceflights became available in the literature. The most commonly used experimental model of microgravity for PK studies is the BR, either in the horizontal position (HBR), *i.e.*, 6 articles published between years 1976 and 1992, or the head-down tilt (HDT) BR, *i.e.*, 6 articles published between years 1995 and 2011 and one publication in 2021 (Polyakov, Svistunov et al., 2021). Despite the elevated number of review articles on drug PK in space available in the literature, this is the first time that a critical approach was undertaken in presenting these data. By estimating the number and type of publications in the field over time, our analysis, which also includes the most recent in-flight data on drug PK (Polyakov, Svistunov et al., 2021), directly shows the paucity of original results on drug PK in space and the lack of consistency among different studies on the same drug. In addition, we sought to analyse the reasons behind this evidence and provide means to facilitate drug PK studies in space.

Based on published original articles, we provide in the following sections information on: *i*) drugs whose PK was studied either in spaceflight and/or in ground-based models; *ii*) data on validation of ground-based models for PK studies. Data are presented according to the different experimental conditions adopted.

3.1 In-flight observations.

In-flight information on drug PK is mostly derived from crewmembers involved in the Space Shuttle Flight program. As shown in Table 1, there were 5 publications that reported drug PK data obtained in-flight, including 1 study on the oral administration of scopolamine and dextroamphetamine (scop/dex) and 4 studies on oral acetaminophen (Table 1). The PK of oral scop/dex (0.4 mg/5 mg) was investigated in-flight in 3 crewmembers involved in two different Space Shuttle missions. This study also tested the feasibility of performing PK studies in space using saliva samples. First, it was determined a saliva/plasma ratio in healthy volunteers on the ground. This ratio was found to be constant along the entire scopolamine disposition profile after both intravenous and oral administration, although data were not shown. Then PK data for scopolamine were obtained in space using saliva specimens collected at specific time points over a period of 12 hours, whereas no measurements of dextroamphetamine concentrations were reported (Cintrón, Putcha et al., 1987b). Relevant interindividual variability in the PK profile of scopolamine was observed both on Earth and in-flight. In space, the scopolamine

peak concentration (C_{max}) and time to peak concentration (T_{max}) were found either increased or decreased in comparison to ground values in the 3 astronauts, thus precluding any robust conclusion. We calculated the average C_{max} and T_{max} values from the original data and found a modest trend towards reduced C_{max} and increased T_{max} in these astronauts, as reported in Table 1. Notably, the PK profiles lacked several time points due to inadequate sampling (Cintrón, Putcha et al., 1987b). These data therefore underlie the difficulties of performing drug PK studies in space. Saliva sampling and the PK analysis were carried out once in space, although repeated twice for one astronaut, at mission day 0-1 and 2-3, with different results. Physiological adaptations to space conditions vary over time suggesting that can variably affect drug absorption and disposition. Interestingly, reduced efficacy of oral scop/dex for the treatment of SMS was reported by Davis and collaborators in comparison to i.m. promethazine (Davis, Jennings et al, 1993a). Although no direct assessments of drug PK were performed in this study, it can be hypothesized that the variability in drug PK observed after oral dosing of scopolamine (Cintrón, Putcha et al., 1987b) contributed to the reduced efficacy of oral scop/dex observed in-flight (Davis, Jennings et al, 1993a). On the other hand, since its first use for the symptomatic treatment of one male crewmember that developed severe SMS (Bagian, 1991), i.m. promethazine, at the dose of 25-50 mg mostly as single injection, proved to be highly effective and well tolerated (Davis, Jennings et al., 1993a; Davis, Jennings et al., 1993b; Bagian & Ward, 1994). Hence, alternative routes of drug administration can possibly overcome PK variability observed after oral dosing and increase drug efficacy in space. However, no PK studies were carried out in space using i.m. promethazine that proved this hypothesis. Nevertheless, the drug became standard treatment for SMS on the Space Shuttle flights.

The PK of acetaminophen was also studied in-flight using saliva samples in a study involving 5 different astronauts participating in 3 different Space Shuttle missions. The study confirmed higher variability of acetaminophen PK in-flight *versus* ground. Significant changes in the absorption phase were reported, with increased C_{max} and reduced T_{max} in 2 subjects with sampling done at mission day 2. Opposite effects were observed at mission day 4, when physiological adaptation to weightless conditions were assumed to have reached an equilibrium. In one subject both C_{max} and T_{max} increased, and an erratic PK profile was detected at mission day 3. This crewmember experienced severe SMS symptoms, which possibly contributed to the abnormal salivary concentrations observed (Cintrón, Putcha et al., 1987a). We calculated the average C_{max} and T_{max} values compiling data from these 5 astronauts, although sampling was performed at different mission days, and found a modest trend towards increased C_{max} and T_{max} in these astronauts, as reported in Table 1. In a subsequent report including data from 12 subjects on 7 different flights, after oral administration of 650 mg of acetaminophen, an increase in T_{max} on mission day 0-1 *versus* pre-flight measurements was shown. Consistent with previous evidence, salivary concentrations over time were highly variable in the same subject on different flight days. However, C_{max} tended to decrease on mission day 0-1 and increase on mission day 2 and 3, while T_{max} tended to increase (Putcha & Cintrón, 1991). Data from these two studies could not be combined since in the second study the average values (± standard errors) for C_{max} and T_{max} were only provided in the graphs (Putcha & Cintrón, 1991). In addition, it is not clearly stated if the second analysis included data from the first 5 astronauts evaluated in the previous report (Cintrón, Putcha et al., 1987a).

A third PK study of acetaminophen was carried out including 10 healthy crewmembers involved in ISS expeditions. Participants were divided into two parallel groups of 5 men. Two different formulations of acetaminophen were tested, *i.e.*, 500 mg of acetaminophen in tablets or capsules (Table 1). PK was studied in-flight and two months before the space mission under usual living conditions. On Earth, a delay in the rate of acetaminophen absorption was observed when the drug was administered in tablets, without any significant changes in drug bioavailability observed among the two formulations. The PK curves were practically identical during the elimination phase for both formulations when the PK was studied on Earth. On the other hand, in-flight PK data indicated that drug absorption was delayed after the administration of tablets in comparison to what occurred on Earth (Table 1). Moreover, two peak concentrations were detected. When given in tablets, the relative absorption rate and bioavailability tended to increase in space in comparison to Earth (Table 1). For the encapsulated formulation, a significant decrease in the T_{max} was observed in space in comparison to the terrestrial evaluations. Other PK parameters, including elimination $t_{1/2}$, retention time and Vd were significantly increased. No significant changes in the relative absorption rate and drug bioavailability were reported (Kovachevich, Kondratenko et al., 2009). Based on these results, the authors concluded that encapsulated acetaminophen was preferred to the tablet form in space. A recent report largely confirmed the PK data obtained on the ISS using the tablet formulation of acetaminophen (Kovachevich, Kondratenko et al., 2009), in longer duration spaceflight (127-414 days) (Polyakov, Svistunov et al., 2021). The study was carried out applying a similar protocol, using saliva samples and including data from crewmembers that participated to space missions to the MIR orbital station. These data confirmed the delay in drug absorption (increased T_{max}) basically reported in all previous studies on acetaminophen in space (Cintrón, Putcha et al., 1987a; Putcha & Cintrón, 1991; Kovachevich, Kondratenko et al., 2009). However, in this analysis the authors found a significant reduction in the acetaminophen C_{max} and in the overall drug bioavailability in space in comparison to Earth (Table 1). With respect to the data reported by Kovachevich and collaborators (Kovachevich, Kondratenko et al., 2009), the authors suggested that the differences observed in several PK parameters among the two studies can be explained by differences in the manufacturing process (excipients' compositions of the administered formulations) and in the dose (625 mg *versus* 500 mg in the Kovachevich's study) of acetaminophen, and different duration of spaceflight (127-414 days *versus* 76-152 days in the Kovachevich's study). Interestingly, Polyakov and collaborators also presented data on the comparison between the PK profile of acetaminophen during normal ambulatory conditions *versus* anti-orthostatic hypokinesia (as reported in section 3.3). However, considering that the PK evaluations on ground were carried out using blood samples and on a different cohort of subjects, we cannot use these data as a proof of validation of the ground-based model for studying drug PK in space. We believe that the data are not fully comparable, although a comparative analysis between BR and in-flight data is provided by the authors.

3.2 The horizontal bed rest model

The HBR model was initially used as a physiological analogue of spaceflight to investigate the effect of prolonged exposure to microgravity in human subjects (Hargens & Vico, 2016). The recumbent position produces 0 Gz force on the human body (Watenpaugh, 2016). A study published in 1994 showed that similar cardiovascular changes occur during HBR (0° head-down tilt, HDT) and after spaceflights of similar duration, providing a direct validation of the model, although only related to cardiovascular adaptations (Moore, Charles et al., 1994). As shown in Table 2, six PK studies were carried out in the HBR between years 1976 and 1992, thus before the actual validation of the experimental model. All studies were performed according to a crossover design and included between 6 and 12 healthy volunteers. Apart from one study that enrolled subjects with mean age of 50.2 years (Kates, Harapat et al., 1980), all the other studies recruited younger subjects, aged between 20 and 36 years. The sex was specified in five studies enrolling a total of 41 subjects, 36 of which were males and 5 females (Elfstrom & Lindgren, 1978; Kates, Harapat et al., 1980; Rumble, Roberts et al., 1986; Rumble, Roberts et al., 1991; Renwick, Ahsan et al., 1992). None of these studies included a direct comparison of drug PK between HBR and spaceflights of similar duration. Three studies focused on antibiotics, whereas others were mostly on anti-inflammatory drugs and pain relievers.

From these studies, it emerges that the absorption of orally administered pivmecillinam is delayed and reduced in the supine position in comparison to the orthostatic position. A slight reduction of drug bioavailability was observed in the supine position, as shown by the pivmecillinam serum AUC (Andrews, Kendall et al., 1976). No significant differences were detected in mean plasma concentrations when similar drugs were administered intravenously. This was observed for benzylpenicillin given i.v. at the dose of 600 mg after 1-day HBR (Rumble, Roberts et al., 1986) as well as for penicillin administered i.v. as a rapid bolus at a dose of 1,000,000 U after 6-day HBR (Kates, Harapat et al., 1980). The urinary blood flow appeared to be significantly higher during HBR, but it did not alter the Cl of benzylpenicillin (Rumble, Roberts et al., 1986). In both studies, mean plasma concentrations tended to be lower during HBR in comparison to the orthostatic position, however differences were not significant. In addition, no significant differences in other PK parameters including $t_{1/2}$, Cl, Vd, and AUC were induced by HBR (Kates, Harapat et al., 1980; Rumble, Roberts et al., 1986). From these data, we can hypothesize that the recumbent position may interfere with drug absorption, leaving largely unaltered other physiological functions relevant to drug disposition.

Consistent with this hypothesis, delayed absorption of oral administered acetaminophen was also reported in another study (Rumble, Roberts et al., 1991). However, this effect did not significantly modify drug exposure, as shown by drug AUC. In contrast, absorption of acetaminophen was more rapid in subjects lying on the right side or ambulant in comparison to subjects laying on the left side. However, no relevant changes in other PK parameters were reported (Renwick, Ahsan et al., 1992). In this study, subjects were given 1 g of acetaminophen and 2 x 10 mg of nifedipine during three different visits, after overnight fasting. At each visit, subjects were randomly requested to maintain one specific posture for 4 hours, including lay down on the right and on the left side, and standing position (Renwick, Ahsan et al., 1992).

Similarly, the absorption of orally administered nifedipine was more rapid in ambulant subjects and subjects lying on the right side in comparison to the left side. Moreover, the C_{max} and AUC of nifedipine were significantly increased in subjects lying on the right side or standing in comparison to left side recumbent position (Renwick, Ahsan et al., 1992). It should be noted that PK data are commonly derived from subjects adopting a supine position during the initial period of assessment of orally administered drugs. Gastric emptying is increased when lying on the right position and further enhanced by standing or ambulation. On the other hand, renal blood flow and liver blood flow are higher in recumbent patients, and this can account for more rapid drug elimination. In a study including 6 subjects, it was shown that the elimination rate and Cl of phenazone were increased during bed rest, while Vd was reduced. Conversely, the supine position did not significantly affect the absorption and bioavailability of phenazone (Elfstrom & Lindgren, 1978). Finally, no significant changes in the Cl of lidocaine were observed during HBR, as well as in other PK parameters (Kates, Harapat et al., 1980).

These HBR studies varied in length and in the standardization of other parameters, including food intake, fasting, and blood sampling. Conflicting results are possibly due to the characteristics of different drugs tested. The main gap is the lack of in-flight validation of HBR data for PK studies, at variance with the evaluation of bone loss due to microgravity for which comparative data are available (Hargens & Vico, 2016).

3.3 The head-down tilt bed rest model.

The HDT BR model, using various angles (see below), has extensively replaced the HBR and it is currently regarded as the model of choice to mimic microgravity on the ground, particularly to investigate cardiac and muscle atrophy, orthostatic intolerance and bone loss due to microgravity and develop specific countermeasures (Hargens & Vico, 2016). Subjective and empirical in-flight observations that fluid shift toward the upper part of the body exceeded that seen with HBR led to this further development. The HDT angles used range from 4° to 15°, but 6° became the most common angle used. This 6° tilt down angle produces approximately -0.1 Gz force on human body (Watenpaugh, 2016). Interestingly, cardiac rhythm alterations have been reported during long-term 6° HDT BR (Caiani, Martin-Yebra et al., 2016), in line with in-flight data. Later, the HDT model has been adapted to study lunar gravity level. A lunar gravity component parallel to the long-axis of the body is achieved by using ~ 9.5° tilt angle (Cavanagh, Rice et al., 2013). As shown in Table 3, the PK of several drugs was investigated by using mostly the 6° HDT BR model, including antibiotics, anaesthetics, pain relievers and anti-motion drugs, with conflicting results.

For example, it was shown that total plasma concentrations of ciprofloxacin were not significantly affected by simulated microgravity, *i.e.*, drug administered after 2-day 6° HDT BR. The PK curves showed slightly reduced C_{max} and increased T_{max} due to 6° HDT BR in comparison to the orthostatic position. Slightly lower muscle tissue penetration of ciprofloxacin was observed in simulated microgravity (Schuck, Grant et al., 2005). This is in line with the hypothesis that tissue perfusion may be altered in space due to lack of mechanical pressure and decreased plasma volume, as summarized in Section 2.2. Another study was carried out to evaluate the PK/PD (pharmacodynamics) profile of the anaesthetic propofol in

simulated microgravity. Plasma samples were collected during and after anaesthesia, and the therapeutic response of propofol was monitored by the sedation score and the bispectral index, an electro-encephalograph-derived measure for the state of anaesthesia (Seubert, 2007). This study showed that 2-day 6° HDT BR caused significant haemoconcentration, including increased haemoglobin, haematocrit, platelet, and white cell blood counts in comparison to the orthostatic position. However, despite these physiological changes, no significant effects were observed on bispectral index after i.v. administration of propofol in the dose range of 25-200 µg/kg/min to subjects exposed to 2-day 6° HDT BR. No significant differences in time spent unconscious were observed in comparison to subjects not exposed to bed rest. PK was evaluated in the final 15 min of drug administration at 200 µg/kg/min, a dose that gave 40-50 bispectral index in the previous trial. Propofol plasma concentrations were increased by exposure to 6° HDT bed rest, up to 60 minutes after the anaesthetic withdrawal. However, mean dose delivered was similar in both groups, recovery time was the same and no evidence of delayed postoperative cognitive dysfunction was detected (Seubert, 2007). These data would therefore suggest that the observed changes in drug PK due to BR did not affect drug efficacy. In contrast, during 6° HDT BR, the AUC of lidocaine, administered i.v. at 1 mg/kg, appeared decreased from 130.69 ± 47.65 mg·min/L on day 1 to 92.51 ± 21.43 mg·min/L on day 5. Subjects were ambulant on day 1, then were exposed to 6° HDT BR between day 2 and 5 and were ambulant on day 7. A total of 8 subjects were enrolled in this study. Breakfast without lipid and juice was provided before drug administration and 200 mL of water was allowed 4 hours after drug administration. Consistently, lidocaine C_{max} was reduced at day 2 *versus* day 1 when subjects were in 6° HDT BR, then stabilized during the following days. No more than 20% difference was observed during day 2 up to day 7. Lidocaine Cl and Vd were increased on day 2 *versus* day 1, then stabilized or returned near to basal level. Drug $t_{1/2}$ regularly decreased between day 1 and 7. However, these differences were not significant due to the variability observed on the first day (Saivin, Pavy-Le Traon et al., 1995).

The PK of acetaminophen was studied in subjects exposed to 6° HDT BR for different times, including 1 day, 18 days and 80 days. Subjects were lying on the back for 6 hours after drug administration then other positions were allowed but always supine. Acetaminophen was orally administered at the dose of 1 g with 200 mL water after overnight fasting. Liquids were allowed 4 hours after drug administration and a full meal was provided 6 hours after administration. A 30% increase of C_{max} was observed after 1 day of 6° HDT BR in comparison to control level measured in ambulant conditions. Consistently, T_{max} was reduced by 44%. A trend to increased AUC and reduced $t_{1/2}$ was also observed. Similar findings were reported after 18 days and 80 days of 6° HDT BR, with differences increasing in parallel to the length of BR (Gandia, Bareille et al., 2003). These data therefore suggest that the rate of drug absorption is increased during 6° HDT BR, in contrast to what observed using the HBR (Rumble, Roberts et al., 1991; Renwick, Ahsan et al., 1992). The PK of acetaminophen was recently studied in a group of 7 male subjects exposed to 2 days of 8° HDT BR (Polyakov, Svistunov et al., 2021). The study showed relevant differences in the profile of the averaged PK curves of acetaminophen among normal motion conditions (background) and 8° HDT BR. Although the authors did not report any statistically significant variation in specific PK parameters (Table 3), a significant increase in the relative rate of drug absorption and reduced bioavailability was observed in the anti-

orthostatic conditions in comparison to normal motion. The latter is consistent with data obtained during long-term spaceflight, although the magnitude of the reduction in drug bioavailability was larger in space than in subject exposed to short-term HDT BR. However, as mentioned above, different cohorts of subjects and different specimens were used to assess acetaminophen PK in these two settings thus precluding solid conclusions (Polyakov, Svistunov et al., 2021). In the same study, the authors also considered the PK of different antiarrhythmic drugs, namely verapamil, propranolol and etacizine, in part previously published (Polyakov, Svistunov et al., 2020), and the diuretic furosemide. As summarized in Table 3, the exposure to 8° HDT BR for 2 days significantly impacted only on the PK of etacizine, with a significant delay in the absorption, reduced peak concentrations and increased Vd. The relative bioavailability of etacizine was increased during HDT BR (Polyakov, Svistunov et al., 2021). Finally, no relevant differences in PK parameters were observed for orally administered ibuprofen after 1-day HDT BR (angle not-specified) (Idkaidek & Arafat, 2011), whereas 30% increased exposure to promethazine was found after 2-day 6° HDT BR especially when the drug was administered *per os* (Gandia, Saivin et al., 2006).

As outlined for HBR, variability in drug PK observed using the HDT BR model, mostly at -6°, may depend on the characteristics of the drugs and lack of standardization of the studies. In this regard, the NASA Flight Analogs Projects was specifically set out to standardize the experimental conditions in BR studies, with data on cardiovascular adaptation occurring during long-term 6° HDT BR available in the literature (Platts, Martin et al., 2016). Again, the main gap in PK studies is the lack of in-flight validation of 6° HDT BR data.

3.4 Parabolic flight

This spaceflight analogue has been experimentally used to generate alternating periods of free fall (reduced gravity) and high gravitoinertial force level (~1.8-2G), each lasting 20-25 sec. A flight usually consists of 30 consecutive parabolas and motion sickness is scored according to different rating systems (Graybiel & Lackner, 1987; Kohl, 1987). This experimental model of microgravity/hypergravity has been used to study the efficacy of different anti-motion sickness medications, considering as beneficial effects the resolution of motion sickness symptoms and prevention of nausea or vomiting at touchdown. Scopolamine was the most investigated drug using this experimental model. In particular, the pharmacological effects of scopolamine were evaluated in two different studies according to two different modalities of administration. In a first study including 47 subjects, scopolamine (0.43-0.5 mg) was administered i.m. during parabolic flight to severely sick subjects, usually between parabolas 5 and 29. The drug resulted in beneficial effects in 72% of cases (Graybiel & Lackner, 1987). Similarly, i.m. promethazine at 50 mg was effective in 78% of subjects, whereas it was not beneficial at 25 mg (Graybiel & Lackner, 1987). Meclizine administered i.m. at 50 mg did not exert any therapeutic effect (Graybiel & Lackner, 1987). These data would further support the hypothesis that the i.m. administration route can reduce variability in drug absorption due to SMS thus favouring the pharmacological effects of these drugs. However, no PK data are available from parabolic flights. Scopolamine was also effective when administered in a buccal pouch at the dose of 1 mg and maintained in the mouth between parabolas 5 and 30. Therapeutic drug level was estimated to be reached after parabola 10, based on previous investigations on the PK of buccal

scopolamine (Norfleet, Degioanni et al., 1992). This study was carried out according to a crossover design, thus subjects were studied in two different parabolic flights and were generally less sick during the second flight. Despite this variability, buccal scopolamine significantly reduced by 31% the severity of nausea and by 50% the total number of parabolas with vomiting (Norfleet, Degioanni et al., 1992). As mentioned above, scopolamine, alone or in combination with dextroamphetamine, has been widely used to treat SMS during Space Shuttle flights. The drug was often dispensed as custom dosage formulation in gelatine capsules alone or in combination with dextroamphetamine. The latter is associated to reduce the sedative effects of scopolamine. In a PK study, performed on the ground, on the most commonly used formulations of scopolamine during NASA operations, it was shown that drug absorption is delayed when the drug is formulated in gelatine capsules and bioavailability is significantly reduced when the drug is administered in combination with dextroamphetamine (Boyd, Du et al., 2007). This variability may contribute to the lack of efficacy sometimes observed during spaceflights. Finally, oral metoclopramide administered prophylactically 75 min before parabolic flights did not show any beneficial effect (Kohl, 1987) and it is not used in real microgravity.

However, we could not find PK studies carried out using the parabolic flight experimental model, which overall seems unsuitable for this kind of investigation.

4. Research gaps in drug related PK studies

Relevant physiological changes occur during spaceflight that may impact drug PK, thus highlighting the need for controlled studies on drug PK in space. However, despite general agreement on this priority, as reported in several review articles published over time, data on drug PK obtained in-flight are still limited to seminal observations dated back to 1987-1993 with only two more recent studies, one carried out on the ISS in 2009 and one reporting data obtained on the MIR orbital space station. Considering that the MIR orbital space station was in operation until March 23, 2001 (https://www.nasa.gov/feature/20-years-ago-space-station-mir-reenters-earth-s-atmosphere), we can hypothesize that this study was carried out before this time and data were only recently made available through the international literature. Similarly, it has not yet been determined whether changes in physiological processes occurring by exposure to space environment significantly affect drug PK. This includes for example changes in the expression and functioning of transport system at enteric level or the influence of gut microbiota shift in drug processing and absorption. Moreover, no direct studies on drug distribution, metabolism and elimination are present in the literature. There is no convincing evidence about the distribution of active principles or their metabolites during and after any fluid shift due to spaceflight. Also, the effects of changes in bone and muscle mass and endocrine rearrangements on drug distribution and bioavailability remain to be established. Only sporadic reports are available on the effect of real microgravity on the structure and function of blood and lymphatic endothelium, as cell viability, permeability and exposure of metabolizing enzymes or transport systems, to be put in relation to medicine absorption and distribution in the critical organs. Another important gap regards the changes in haematological parameters, including the plasma protein levels, which can influence the free drug concentration and precipitate unwanted adverse reactions. An extensive and complete study on

the liver enzymatic pattern is still lacking, also including the polymorphic character of these metabolic pathways (Pavez Loriè, Baatout, et al., 2021). Drug excretion is a further parameter that merits to be studied in detail due to dated studies and controversial results. In addition, drug-drug interactions and drug-diet components interactions remain to be assessed in-flight to maximize the efficacy and guarantee the safety of medications.

Spaceflight research in this field can benefit from recent developments in wearable sensors allowing continuous measurements of physiological functions (Li, Dunn et al., 2017). In particular, the real-time monitoring of heart rate, physical activity and sleep can be relevant to the evaluation of drug PK. In addition, intense research activity is currently ongoing towards the development of wearable biosensors or implantable devices enabling continuous drug monitoring (Bian, Zhu et al., 2021; Gowers, Freeman et al., 2019). These devices will certainly have a favourable impact on drug PK studies in space. In fact, the lack of comprehensive drug PK studies is probably due to the difficulty of carrying out multiple blood-sampling in real microgravity and lack of simple and immediate systems to check the elimination of drugs and/or their metabolites in the urine. The use of alternative specimens for PK studies is limited to saliva and to the study of scopolamine and acetaminophen PK in-flight. A consistent saliva/plasma ratio for these drugs on a range of plasma concentrations and over the disposition profile was established on the ground but no validation in-flight was performed. It is unknown whether the consistent saliva/plasma ratio measured on ground is maintained in space. Therefore, in order to use saliva samples for in-flight PK studies, an evaluation of the correlation between drug concentration in saliva and blood should be performed in space. In addition, ground-based models of microgravity appear insufficiently validated as predictive models of drug PK in space. There is a substantial lack of comparative studies on drug PK between experimental models of microgravity and real microgravity.

5. Conclusions

The use of medicines during human spaceflight is on average increased in comparison to the use of drugs on Earth, as suggested by a recent study in which data on medicine usage on the ISS were collected from six astronauts through an iOS application (Wotring & Smith, 2020). An average of 20.6 ± 8.4 medication entries per subjects (n=5) per flight week was observed, significantly higher than data obtained through medical notes of flight surgeons (Wotring, 2015). However, medicines are currently used in space based on the assumption that they work in a similar manner to what is standardized on Earth, despite relevant physiological adaptations that occur in space, together with potential alterations in drug stability due to radiation exposure. The extent of such modifications is well supported by in-flight data, and ground-based models cannot be used to answer all the open question because they do not adequately reproduce the spaceflight environment. Despite the compelling need to assess how drugs work in spaceflight, available in-flight data are only limited to few seminal studies. For this kind of evaluation, it is mandatory to determine PK parameters for medications frequently used in spaceflight in two different settings: on Earth and during spaceflights, together with similar studies evaluating drug efficacy in-flight *versus* on Earth. Only with such data we can have a more comprehensive knowledge of pharmacology in space, thus be able to better inform drug

prescription. This is particularly relevant for future crewed explorations beyond LEO, which will not allow rapid return to Earth in the event of a medical emergency.

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Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22 (151-157).

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Ethics and Integrity Statements

Declaration of transparency and scientific rigour

This Declaration acknowledges that this paper adheres to the principles for transparent reporting and scientific rigour of preclinical research as stated in the *BJP* guidelines for Design and Analysis, and as recommended by funding agencies, publishers and other organisations engaged with supporting research.

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Reference list

Alfrey, C. P., Udden, M. M., Huntoon, C. L., & Driscoll, T. (1996a). Destruction of newly released red blood cells in space flight. *Medicine and science in sports and exercise*, *28* (10 Suppl), S42-S44. https://doi.org/10.1097/00005768-199610000-00032

Alfrey, C. P., Udden, M. M., Leach-Huntoon, C., Driscoll, T., & Pickett, M. H. (1996b). Control of red blood cell mass in spaceflight. *Journal of applied physiology (Bethesda, Md.: 1985)*, *81*(1), 98-104. https://doi.org/10.1152/jappl.1996.81.1.98

Amidon, G. L., DeBrincat, G. A., & Najib, N. (1991). Effects of gravity on gastric emptying, intestinal transit, and drug absorption. *Journal of clinical pharmacology*, *31*(10), 968-973. https://doi.org/10.1002/j.1552-4604.1991.tb03658.x

Andrews, J., Kendall, M. J., & Mitchard, M. (1976). Factors influencing the absorption and disposition of mecillinam and pivmecillinam in man. *British journal of clinical pharmacology*, *3*(4), 627-632. https://doi.org/10.1111/j.1365-2125.1976.tb04886.x

Antonutto, G., & di Prampero, P. E. (2003). Cardiovascular deconditioning in microgravity: some possible countermeasures. *European journal of applied physiology*, *90*(3-4), 283-291. https://doi.org/10.1007/s00421-003-0884-5

Anzai, T., Frey, M. A., & Nogami, A. (2014). Cardiac arrhythmias during long-duration spaceflights. Journal of Arrhythmia. 30, 139-149. https://doi.org/10.1016/j.joa.2013.07.009

Bagian J. P. (1991). First intramuscular administration in the U.S. Space Program. *Journal of clinical pharmacology*, *31*(10), 920. https://doi.org/10.1002/j.1552-4604.1991.tb03649.x

Bagian, J. P., & Ward, D. F. (1994). A retrospective study of promethazine and its failure to produce the expected incidence of sedation during space flight. *Journal of clinical pharmacology*, *34*(6), 649-651. https://doi.org/10.1002/j.1552-4604.1994.tb02019.x

Bailey, D. M., Stacey, B. S., & Gumbleton, M. (2018). A Systematic Review and Meta-Analysis Reveals Altered Drug Pharmacokinetics in Humans During Acute Exposure to Terrestrial High Altitude-Clinical Justification for Dose Adjustment?. *High altitude medicine & biology*, *19*(2), 141–148. https://doi.org/10.1089/ham.2017.0121

Berman, E., & Eyal, S. (2019). Drug Interactions in Space: a Cause for Concern?. *Pharmaceutical research*, *36*(8), 114. https://doi.org/10.1007/s11095-019-2649-9

Berrios, D. C., Galazka, J., Grigorev, K., Gebre, S., & Costes, S. V. (2021). NASA GeneLab: interfaces for the exploration of space omics data. *Nucleic acids research*, *49*(D1), D1515-D1522. https://doi.org/10.1093/nar/gkaa887

Bian, S., Zhu, B., Rong, G., & Sawan, M. (2021). Towards wearable and implantable continuous drug monitoring: A review. *Journal of pharmaceutical analysis*, *11*(1), 1–14. https://doi.org/10.1016/j.jpha.2020.08.001

Blue, R. S., Chancellor, J. C., Antonsen, E. L., Bayuse, T. M., Daniels, V. R., & Wotring, V. E. (2019a). Limitations in predicting radiation-induced pharmaceutical instability during long-duration spaceflight. *NPJ microgravity*, *5*, 15. https://doi.org/10.1038/s41526-019-0076-1

Blue, R. S., Bayuse, T. M., Daniels, V. R., Wotring, V. E., Suresh, R., Mulcahy, R. A., & Antonsen, E. L. (2019b). Supplying a pharmacy for NASA exploration spaceflight: challenges

and current understanding. *NPJ microgravity*, *5*, 14. https://doi.org/10.1038/s41526-019-0075-2

Boyd, J. L., Du, B., Vaksman, Z., Locke, J. P., & Putcha, L. (2007). Relative bioavailability of scopolamine dosage forms and interaction with dextroamphetamine. *Journal of gravitational physiology: a journal of the International Society for Gravitational Physiology*, 14(1), P107-P108.

Caiani, E. G., Martin-Yebra, A., Landreani, F., Bolea, J., Laguna, P., & Vaïda, P. (2016). Weightlessness and Cardiac Rhythm Disorders: Current Knowledge from Space Flight and Bed-Rest Studies. *Frontiers in Astronomy and Space Sciences*. *3*(27), 1-27. https://doi.org/10.3389/fspas.2016.00027

Cavanagh, P. R., Rice, A. J., Licata, A. A., Kuklis, M. M., Novotny, S. C., Genc, K. O., Englehaupt, R. K., & Hanson, A. M. (2013). A novel lunar bed rest analogue. *Aviation, space, and environmental medicine*, *84*(11), 1191-1195. https://doi.org/10.3357/asem.3472.2013

Charles, J. B., & Bungo, M. W. (1991). Cardiovascular physiology in space flight. *Experimental gerontology*, *26*(2-3), 163-168. https://doi.org/10.1016/0531-5565(91)90008-a

Charles, J. B., & Lathers, C. M. (1991). Cardiovascular adaptation to spaceflight. *Journal of clinical pharmacology*, *31*(10), 1010-1023. https://doi.org/10.1002/j.1552-4604.1991.tb03665.x

Christensen, N. J., Drummer, C., & Norsk, P. (2001). Renal and sympathoadrenal responses in space. *American journal of kidney diseases : the official journal of the National Kidney Foundation*, *38*(3), 679-683. https://doi.org/10.1053/ajkd.2001.27758

Cintrón, N. M., Putcha, L., & Vanderploeg, J. M. (1987a) Inflight pharmacokinetics of acetaminophen in saliva. In: Bungo MW, Bagian TM, Bowman MA, Levitan BM (eds.) Results of the Life Science DSOs Conducted Aboard the Space Shuttle 1981–1986. Houston: Space Biomedical Research Institute, Johnson Space Center, 19-23. https://ntrs.nasa.gov/api/citations/19870017063/downloads/19870017063.pdf

Cintrón N.M., Putcha L., & Vanderploeg J.M. (1987b) Inflight salivary pharmacokinetics of scopolamine and dextroamphetamine. In: Bungo MW, Bagian TM, Bowman MA, Levitan BM (eds.) Results of the Life Science DSOs Conducted Aboard the Space Shuttle 1981–1986. Houston: Space Biomedical Research Institute, Johnson Space Center, 25-29. https://ntrs.nasa.gov/api/citations/19870017063/downloads/19870017063.pdf

Crucian, B., Johnston, S., Mehta, S., Stowe, R., Uchakin, P., Quiriarte, H., Pierson, D., Laudenslager, M. L., & Sams, C. (2016). A case of persistent skin rash and rhinitis with immune system dysregulation onboard the International Space Station. *The journal of allergy and clinical immunology. In practice*, *4*(4), 759-762.e8. https://doi.org/10.1016/j.jaip.2015.12.021

Czarnik, T. R., & Vernikos, J. (1999). Physiological changes in spaceflight that may affect drug action. *Journal of gravitational physiology: a journal of the International Society for Gravitational Physiology*, *6*(1), P161-P164.

Davis, J. R., Jennings, R. T., & Beck, B. G. (1993a). Comparison of treatment strategies for Space Motion Sickness. *Acta astronautica*, *29*(8), 587-591. https://doi.org/10.1016/0094-5765(93)90074-7.

Davis, J. R., Jennings, R. T., Beck, B. G., & Bagian, J. P. (1993b). Treatment efficacy of intramuscular promethazine for space motion sickness. *Aviation, space, and environmental medicine*, *64*(3 Pt 1), 230-233.

Demertzi, A., Van Ombergen, A., Tomilovskaya, E., Jeurissen, B., Pechenkova, E., Di Perri, C., Litvinova, L., Amico, E., Rumshiskaya, A., Rukavishnikov, I., Sijbers, J., Sinitsyn, V., Kozlovskaya, I. B., Sunaert, S., Parizel, P. M., Van de Heyning, P. H., Laureys, S., & Wuyts, F. L. (2016). Cortical reorganization in an astronaut's brain after long-duration spaceflight. *Brain structure & function*, *221*(5), 2873-2876. https://doi.org/10.1007/s00429-015-1054-3

Derendorf H. (1994). Pharmacokinetic/pharmacodynamic consequences of space flight. *Journal of clinical pharmacology*, *34*(6), 684–691. https://doi.org/10.1002/j.1552-4604.1994.tb02024.x

Dijk, D. J., Neri, D. F., Wyatt, J. K., Ronda, J. M., Riel, E., Ritz-De Cecco, A., Hughes, R. J., Elliott, A. R., Prisk, G. K., West, J. B., & Czeisler, C. A. (2001). Sleep, performance, circadian rhythms, and light-dark cycles during two space shuttle flights. *American journal of physiology. Regulatory, integrative and comparative physiology*, *281*(5), R1647-R1664. https://doi.org/10.1152/ajpregu.2001.281.5.R1647

Drummer, C., Heer, M., Dressendörfer, R. A., Strasburger, C. J., & Gerzer, R. (1993). Reduced natriuresis during weightlessness. *The Clinical investigator*, *71*(9), 678-686. https://doi.org/10.1007/BF00209720

Drummer, C., Gerzer, R., Baisch, F., & Heer, M. (2000a). Body fluid regulation in micro-gravity differs from that on Earth: an overview. *Pflugers Archiv: European journal of physiology*, *441*(2-3 Suppl), R66-R72. https://doi.org/10.1007/s004240000335

Drummer, C., Hesse, C., Baisch, F., Norsk, P., Elmann-Larsen, B., Gerzer, R., & Heer, M. (2000b). Water and sodium balances and their relation to body mass changes in microgravity. *European journal of clinical investigation*, *30*(12), 1066-1075. https://doi.org/10.1046/j.1365-2362.2000.00766.x

Elfström, J., & Lindgren, S. (1978). Influence of bed rest on the pharmacokinetics of phenazone. *European journal of clinical pharmacology*, *13*(5), 379-383. https://doi.org/10.1007/BF00644612

Eyal, S., & Derendorf, H. (2019). Medications in Space: In Search of a Pharmacologist's Guide to the Galaxy. *Pharmaceutical research*, *36*(10), 148. https://doi.org/10.1007/s11095-019-2679-3

Eyal S. (2020). How do the pharmacokinetics of drugs change in astronauts in space?. *Expert opinion on drug metabolism & toxicology*, *16*(5), 353-356. https://doi.org/10.1080/17425255.2020.1746763

Fleisher, D., Li, C., Zhou, Y., Pao, L. H., & Karim, A. (1999). Drug, meal and formulation interactions influencing drug absorption after oral administration. Clinical implications. *Clinical pharmacokinetics*, *36*(3), 233-254. https://doi.org/10.2165/00003088-199936030-00004

Gandia, P., Bareille, M. P., Saivin, S., Le-Traon, A. P., Lavit, M., Guell, A., & Houin, G. (2003). Influence of simulated weightlessness on the oral pharmacokinetics of acetaminophen as a gastric emptying probe in man: a plasma and a saliva study. *Journal of clinical pharmacology*, *43*(11), 1235-1243. https://doi.org/10.1177/0091270003257229

Gandia, P., Saivin, S., Le-Traon, A. P., Guell, A., & Houin, G. (2006). Influence of simulated weightlessness on the intramuscular and oral pharmacokinetics of promethazine in 12 human volunteers. *Journal of clinical pharmacology*, *46*(9), 1008-1016. https://doi.org/10.1177/0091270006291032

Gowers, S., Freeman, D., Rawson, T. M., Rogers, M. L., Wilson, R. C., Holmes, A. H., Cass, A. E., & O'Hare, D. (2019). Development of a Minimally Invasive Microneedle-Based Sensor for Continuous Monitoring of β-Lactam Antibiotic Concentrations in Vivo. *ACS sensors*, *4*(4), 1072–1080. https://doi.org/10.1021/acssensors.9b00288

Graebe, A., Schuck, E. L., Lensing, P., Putcha, L., & Derendorf, H. (2004). Physiological, pharmacokinetic, and pharmacodynamic changes in space. *Journal of clinical pharmacology*, *44*(8), 837-853. https://doi.org/10.1177/0091270004267193

Graybiel, A., & Lackner, J. R. (1987). Treatment of severe motion sickness with antimotion sickness drug injections. *Aviation, space, and environmental medicine*, *58*(8), 773-776.

Grigoriev, A. I., Bugrov, S. A., Bogomolov, V. V., Egorov, A. D., Kozlovskaya, I. B., Pestov, I. D., Polyakov, V. V., & Tarasov, I. K. (1991). Preliminary medical results of the Mir year-long mission. *Acta astronautica*, *23*, 1-8. https://doi.org/10.1016/0094-5765(91)90092-j

Hargens, A. R., & Watenpaugh, D. E. (1996). Cardiovascular adaptation to spaceflight. *Medicine and science in sports and exercise*, *28*(8), 977-982. https://doi.org/10.1097/00005768-199608000-00007

Hargens, A. R., & Richardson, S. (2009). Cardiovascular adaptations, fluid shifts, and countermeasures related to space flight. *Respiratory physiology & neurobiology*,*-169 Suppl 1*, S30-S33. https://doi.org/10.1016/j.resp.2009.07.005

Hargens, A. R., Bhattacharya, R., & Schneider, S. M. (2013). Space physiology VI: exercise, artificial gravity, and countermeasure development for prolonged space flight. *European journal of applied physiology*, *113*(9), 2183-2192. https://doi.org/10.1007/s00421-012-2523-5

Hargens, A. R., & Vico, L. (2016). Long-duration bed rest as an analog to microgravity. *Journal of applied physiology (Bethesda, Md.: 1985)*, *120*(8), 891-903. https://doi.org/10.1152/japplphysiol.00935.2015

Hargrove, J. L., & Jones, D. P. (1985). Hepatic enzyme adaptation in rats after space flight. *The Physiologist*, *28*(6 Suppl), S230.

Hollander, J., Gore, M., Fiebig, R., Mazzeo, R., Ohishi, S., Ohno, H., & Ji, L. L. (1998). Spaceflight downregulates antioxidant defense systems in rat liver. *Free radical biology & medicine*, *24*(2), 385-390. https://doi.org/10.1016/s0891-5849(97)00278-5

Idkaidek, N., & Arafat, T. (2011). Effect of microgravity on the pharmacokinetics of Ibuprofen in humans. *Journal of clinical pharmacology*, *51*(12), 1685-1689. https://doi.org/10.1177/0091270010388652

Iwamoto, J., Takeda, T., & Sato, Y. (2005). Interventions to prevent bone loss in astronauts during space flight. *The Keio journal of medicine*, *54*(2), 55-59. https://doi.org/10.2302/kjm.54.55

Jonscher, K. R., Alfonso-Garcia, A., Suhalim, J. L., Orlicky, D. J., Potma, E. O., Ferguson, V. L., Bouxsein, M. L., Bateman, T. A., Stodieck, L. S., Levi, M., Friedman, J. E., Gridley, D. S., & Pecaut, M. J. (2016). Spaceflight Activates Lipotoxic Pathways in Mouse Liver. *PloS one*, *11*(4), e0152877. https://doi.org/10.1371/journal.pone.0152877

Kapitonova, M. Y., Muid, S., Froemming, G. R., Yusoff, W. N., Othman, S., Ali, A. M., & Nawawi, H. M. (2012). Real space flight travel is associated with ultrastructural changes, cytoskeletal disruption and premature senescence of HUVEC. *The Malaysian journal of pathology*, *34*(2), 103-113.

Kast, J., Yu, Y., Seubert, C. N., Wotring, V. E., & Derendorf, H. (2017). Drugs in space: Pharmacokinetics and pharmacodynamics in astronauts. *European journal of pharmaceutical sciences: official journal of the European Federation for Pharmaceutical Sciences*, *109S*, S2-S8. https://doi.org/10.1016/j.ejps.2017.05.025

Kates, R. E., Harapat, S. R., Keefe, D. L., Goldwater, D., & Harrison, D. C. (1980). Influence of prolonged recumbency on drug disposition. *Clinical pharmacology and therapeutics*, *28*(5), 624-628. https://doi.org/10.1038/clpt.1980.213

Kohl R. L. (1987). Failure of metoclopramide to control emesis or nausea due to stressful angular or linear acceleration. *Aviation, space, and environmental medicine*, *58*(2), 125-131.

Kovachevich, I. V., Kondratenko, S. N., Starodubtsev, A. K., & Repenkova, L. G. (2009). Pharmacokinetics of acetaminophen administered in tablets and capsules under long-term space flight conditions. *Pharmaceutical chemistry journal*, *43*(3), 130-133. https://doi.org/10.1007/s11094-009-0255-6

Kuipers A. (1996). First results from experiments performed with the ESA Anthrorack during the D-2 Spacelab mission. *Acta astronautica*, *38*(11), 865-875. https://doi.org/10.1016/s0094-5765(96)00072-0

Kunz, H., Quiriarte, H., Simpson, R. J., Ploutz-Snyder, R., McMonigal, K., Sams, C., & Crucian, B. (2017). Alterations in hematologic indices during long-duration spaceflight. *BMC hematology*, *17*, 12. https://doi.org/10.1186/s12878-017-0083-y

La Barbera, G., Capriotti, A. L., Michelini, E., Piovesana, S., Calabretta, M. M., Zenezini Chiozzi, R., Roda, A., & Laganà, A. (2017). Proteomic analysis and bioluminescent reporter gene assays to investigate effects of simulated microgravity on Caco-2 cells. *Proteomics*, *17*(15-16), 10.1002/pmic.201700081. https://doi.org/10.1002/pmic.201700081

Lafuente, J. V., Bermudez, G., Camargo-Arce, L., & Bulnes, S. (2016). Blood-Brain Barrier Changes in High Altitude. CNS & neurological disorders drug targets, 15(9), 1188–1197. https://doi.org/10.2174/1871527315666160920123911

Lakin, W. D., Stevens, S. A., & Penar, P. L. (2007). Modeling intracranial pressures in microgravity: the influence of the blood-brain barrier. *Aviation, space, and environmental medicine*, *78*(10), 932-936. https://doi.org/10.3357/asem.2060.2007

LaPelusa, M., Donoviel, D., Branzini, S. E., Carlson, P. E., Jr, Culler, S., Cheema, A. K., Kaddurah-Daouk, R., Kelly, D., de Cremoux, I., Knight, R., Krajmalnik-Brown, R., Mayo, S. L., Mazmanian, S. K., Mayer, E. A., Petrosino, J. F., & Garrison, K. (2021). Microbiome for Mars: surveying microbiome connections to healthcare with implications for long-duration human spaceflight, virtual workshop, July 13, 2020. *Microbiome*, *9*(1), 2. https://doi.org/10.1186/s40168-020-00951-5

Leach C. S. (1981). An overview of the endocrine and metabolic changes in manned space flight. *Acta astronautica*, *8*(9-10), 977-986. https://doi.org/10.1016/0094-5765(81)90068-0

Leach, C. S., & Johnson, P. C. (1984). Influence of spaceflight on erythrokinetics in man. *Science (New York, N.Y.)*, *225*(4658), 216-218. https://doi.org/10.1126/science.6729477

Leach, C. S., Johnson, P. C., & Cintrón, N. M. (1988). The endocrine system in space flight. *Acta astronautica*, *17*(2), 161-166. https://doi.org/10.1016/0094-5765(88)90017-3

Leach, C. S., Inners, L. D., & Charles, J. B. (1991a). Changes in total body water during spaceflight. *Journal of clinical pharmacology*, *31*(10), 1001-1006. https://doi.org/10.1002/j.1552-4604.1991.tb03663.x

Leach, C. S., Cintrón, N. M., & Krauhs, J. M. (1991b). Metabolic changes observed in astronauts. *Journal of clinical pharmacology*, *31*(10), 921-927. https://doi.org/10.1002/j.1552-4604.1991.tb03650.x

Leach C. S. (1991c). Metabolism and biochemistry in hypogravity. *Acta astronautica*, *23*, 105-108. https://doi.org/10.1016/0094-5765(91)90105-e

Leach, C. S., Alfrey, C. P., Suki, W. N., Leonard, J. I., Rambaut, P. C., Inners, L. D., Smith, S. M., Lane, H. W., & Krauhs, J. M. (1996). Regulation of body fluid compartments during short-term spaceflight. *Journal of applied physiology (Bethesda, Md.: 1985)*, *81*(1), 105-116. https://doi.org/10.1152/jappl.1996.81.1.105.

Leonard, J. I., Leach, C. S., & Rambaut, P. C. (1983). Quantitation of tissue loss during prolonged space flight. *The American journal of clinical nutrition*, *38*(5), 667-679. https://doi.org/10.1093/ajcn/38.5.667

Li, X., Dunn, J., Salins, D., Zhou, G., Zhou, W., Schüssler-Fiorenza Rose, S. M., Perelman, D., Colbert, E., Runge, R., Rego, S., Sonecha, R., Datta, S., McLaughlin, T., & Snyder, M. P. (2017). Digital Health: Tracking Physiomes and Activity Using Wearable Biosensors Reveals Useful Health-Related Information. *PLoS biology*, *15*(1), e2001402. https://doi.org/10.1371/journal.pbio.2001402

Lu, S. K., Bai, S., Javeri, K., & Brunner, L. J. (2002). Altered cytochrome P450 and P-glycoprotein levels in rats during simulated weightlessness. *Aviation, space, and environmental medicine*, *73*(2), 112-118.

Maier, J. A., Cialdai, F., Monici, M., & Morbidelli, L. (2015). The impact of microgravity and hypergravity on endothelial cells. *BioMed Research International*, *2015*, 434803. https://doi.org/10.1155/2015/434803

Mao, X. W., Nishiyama, N. C., Byrum, S. D., Stanbouly, S., Jones, T., Holley, J., Sridharan, V., Boerma, M., Tackett, A. J., Willey, J. S., Pecaut, M. J., & Delp, M. D. (2020). Spaceflight induces oxidative damage to blood-brain barrier integrity in a mouse model. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology*, 34(11), 15516–15530. https://doi.org/10.1096/fj.202001754R

Merrill, A. H., Jr, Hoel, M., Wang, E., Mullins, R. E., Hargrove, J. L., Jones, D. P., & Popova, I. A. (1990). Altered carbohydrate, lipid, and xenobiotic metabolism by liver from rats flown on Cosmos 1887. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology*, *4*(1), 95-100. https://doi.org/10.1096/fasebj.4.1.2295381

Montgomery, L. D., Parmet, A. J., & Booher, C. R. (1993). Body volume changes during simulated microgravity: auditory changes, segmental fluid redistribution, and regional hemodynamics. *Annals of biomedical engineering*, *21*(4), 417-433. https://doi.org/10.1007/BF02368634

Morbidelli, L., Monici, M., Marziliano, N., Cogoli, A., Fusi, F., Waltenberger, J., & Ziche, M. (2005). Simulated hypogravity impairs the angiogenic response of endothelium by up-regulating apoptotic signals. *Biochemical and biophysical research communications*, *334*(2), 491-499. https://doi.org/10.1016/j.bbrc.2005.06.124

Moore, A. D., Jr, Charles, J. B., Lee, S. M., Siconolfi, S. F., & Greenisen, M. C. (1994). Does bed rest produce changes in orthostatic function comparable to those induced by space flight?. *Acta astronautica*, *33*, 57-67. https://doi.org/10.1016/0094-5765(94)90109-0

Moskaleva, N., Moysa, A., Novikova, S., Tikhonova, O., Zgoda, V., & Archakov, A. (2015). Spaceflight Effects on Cytochrome P450 Content in Mouse Liver. *PloS one*, *10*(11), e0142374. https://doi.org/10.1371/journal.pone.0142374

Mulvagh, S. L., Charles, J. B., Riddle, J. M., Rehbein, T. L., & Bungo, M. W. (1991). Echocardiographic evaluation of the cardiovascular effects of short-duration spaceflight. *Journal of clinical pharmacology*, *31*(10), 1024-1026. https://doi.org/10.1002/j.1552-4604.1991.tb03666.x.

Natochin, Y. V., Kozyrevskaya, G. I., & Grigor'yev, A. I. (1975). Study of water-salt metabolism and renal function in cosmonauts. *Acta astronautica*, *2*(3-4), 175-188. https://doi.org/10.1016/0094-5765(75)90088-0.

Norfleet, W. T., Degioanni, J. J., Calkins, D. S., Reschke, M. F., Bungo, M. W., Kutyna, F. A., & Homick, J. L. (1992). Treatment of motion sickness in parabolic flight with buccal scopolamine. *Aviation, space, and environmental medicine*, *63*(1), 46-51.

Norsk, P., Christensen, N. J., Bie, P., Gabrielsen, A., Heer, M., & Drummer, C. (2000). Unexpected renal responses in space. *Lancet (London, England)*, *356*(9241), 1577-1578. https://doi.org/10.1016/s0140-6736(00)03135-4

Norsk, P., Drummer, C., Christensen, N. J., Cirillo, M., Heer, M., Kramer, H. J., Regnard, J., & De Santo, N. G. (2001). Revised hypothesis and future perspectives. *American journal of kidney diseases : the official journal of the National Kidney Foundation*, *38*(3), 696-698. https://doi.org/10.1053/ajkd.2001.27769

Norsk P. (2005). Cardiovascular and fluid volume control in humans in space. *Current pharmaceutical biotechnology*, *6*(4), 325-330. https://doi.org/10.2174/1389201054553734

Pavez Loriè, E., Baatout, S., Choukér, A., Buchheim, J. I., Baselet, B., Dello Russo, C., Wotring, V., Monici, M., Morbidelli, L., Gagliardi, G.,Stingl J., Surdo, L, Yip, V.L.M. (2021) The Future of Personalized Medicine in Space: from Observations to Countermeasures. *Frontiers in Bioengineering and Biotechnology* 9:739747. https://org/10.3389/fbioe.2021.739747

Polyakov, A. V., Svistunov, A. A., Kondratenko, S. N., Kovachevich, I. V., Repenkova, L. G., Savelyeva, M. I., & Kukes, V. G. (2020). Peculiarities of Pharmacokinetics and Bioavailability of Some Cardiovascular Drugs under Conditions of Antiorthostatic Hypokinesia. *Bulletin of experimental biology and medicine*, *168*(4), 465–469.

Polyakov, A. V., Svistunov, A. A., Kondratenko, S. N., Kovachevich, I. V., Repenkova, L. G., Savelyeva, M. I., Shikh, E. V., & Badriddinova, L. Y. (2021). Study of the pharmacokinetics of various drugs under conditions of antiorthostatic hypokinesia and the pharmacokinetics of acetaminophen under long-term spaceflight conditions. *Drug metabolism and personalized therapy*, 10.1515/dmdi-2021-0159.

Pool, S. L., & Nicogossian, A. (1983). Biomedical results of the Space Shuttle orbital flight test program. *Aviation, space, and environmental medicine*, *54*(12 Pt 2), S41-S49.

Platts, S. H., Martin, D. S., Stenger, M. B., Perez, S. A., Ribeiro, L. C., Summers, R., & Meck, J. V. (2009). Cardiovascular adaptations to long-duration head-down bed rest. *Aviation, space, and environmental medicine*, *80*(5 Suppl), A29–A36. https://doi.org/10.3357/asem.br03.2009

Putcha, L., & Cintrón, N. M. (1991). Pharmacokinetic consequences of spaceflight. *Annals of the New York Academy of Sciences*, *618*, 615-618. https://doi.org/10.1111/j.1749-6632.1991.tb27292.x

Racine, R. N., & Cormier, S. M. (1992). Effect of spaceflight on rat hepatocytes: a morphometric study. *Journal of applied physiology (Bethesda, Md.: 1985), 73*(2 Suppl), 136S-141S. https://doi.org/10.1152/jappl.1992.73.2.S136

Regnard, J., Heer, M., Drummer, C., & Norsk, P. (2001). Validity of microgravity simulation models on earth. *American journal of kidney diseases: the official journal of the National Kidney Foundation, 38*(3), 668-674. https://doi.org/10.1053/ajkd.2001.27753

Renwick, A. G., Ahsan, C. H., Challenor, V. F., Daniels, R., Macklin, B. S., Waller, D. G., & George, C. F. (1992). The influence of posture on the pharmacokinetics of orally administered nifedipine. *British journal of clinical pharmacology, 34*(4), 332-336. https://doi.org/10.1111/j.1365-2125.1992.tb05639.x

Rumble, R. H., Roberts, M. S., & Scott, A. R. (1986). The effect of posture on the pharmacokinetics of intravenous benzylpenicillin. *European journal of clinical pharmacology, 30*(6), 731-734. https://doi.org/10.1007/BF00608225

Rumble, R. H., Roberts, M. S., & Denton, M. J. (1991). Effects of posture and sleep on the pharmacokinetics of paracetamol (acetaminophen) and its metabolites. *Clinical pharmacokinetics, 20*(2), 167-173. https://doi.org/10.2165/00003088-199120020-00007

Saivin, S., Pavy-Le Traon, A., Cornac, A., Güell, A., & Houin, G. (1995). Impact of a four-day head-down tilt (-6 degrees) on lidocaine pharmacokinetics used as probe to evaluate hepatic blood flow. *Journal of clinical pharmacology, 35*(7), 697-704. https://doi.org/10.1002/j.1552-4604.1995.tb04110.x

Schneeman B. O. (2002). Gastrointestinal physiology and functions. *The British journal of nutrition, 88 Suppl 2*, S159-S163. https://doi.org/10.1079/BJN2002681.

Schuck, E. L., Grant, M., & Derendorf, H. (2005). Effect of simulated microgravity on the disposition and tissue penetration of ciprofloxacin in healthy volunteers. *Journal of clinical pharmacology, 45*(7), 822-831. https://doi.org/10.1177/0091270005276620

Seubert, C. N. (2007). Effects of Simulated Microgravity on the Anesthetic Properties of Propofol (NNJ04HF74G, Accessed 17/11/2016) https://lsda.jsc.nasa.gov/lsda_data/dataset_inv_data/NNJ04HF74G__2340957670.pdf_BRC_NNJ04HF74G_2011_234_100857.pdf

Smirnov, K. V. (1986). Role of the gravitation factor in the development of changes in the digestive system. *Fiziologicheskii zhurnal SSSR imeni I. M. Sechenova, 72*(4), 484-489.

Smith, S. M., Lane, H. W., & Zwart, S. R. (2019) Spaceflight Metabolism and Nutritional Support. In: Barratt, M. R. et al. (eds.), Principles of Clinical Medicine for Space Flight, Springer Science+Business Media, LLC, part of Springer Nature, 413-439. https://doi.org/10.1007/978-1-4939-9889-0_13

Stingl, J. C., Welker, S., Hartmann, G., Damann, V., & Gerzer, R. (2015). Where Failure Is Not an Option - Personalized Medicine in Astronauts. *PloS one, 10*(10), e0140764. https://doi.org/10.1371/journal.pone.0140764

Strollo, F., Norsk, P., Roecker, L., Strollo, G., Morè, M., Bollanti, L., Riondino, G., & Scano, A. (1998). Indirect evidence of CNS adrenergic pathways activation during spaceflight. *Aviation, space, and environmental medicine, 69*(8), 777-780.

Strollo, F., Gentile, S., Strollo, G., Mambro, A., & Vernikos, J. (2018). Recent Progress in Space Physiology and Aging. *Frontiers in physiology, 9*, 1551. https://doi.org/10.3389/fphys.2018.01551

Tavassoli M. (1982). Anemia of spaceflight. *Blood*, *60*(5), 1059-1067.

Trial, J., Rice, L., & Alfrey, C. P. (2001). Erythropoietin withdrawal alters interactions between young red blood cells, splenic endothelial cells, and macrophages: an in vitro model of neocytolysis. *Journal of investigative medicine: the official publication of the American Federation for Clinical Research*, *49*(4), 335–345. https://doi.org/10.2310/6650.2001.33899

Turner, R., Gatterer, H., Falla, M., & Lawley, J. S. (2021). High altitude cerebral edema - its own entity or end-stage acute mountain sickness?. Journal of applied physiology (Bethesda, Md.: 1985), https://doi.org/10.1152/japplphysiol.00861.2019.

Turroni, S., Magnani, M., Kc, P., Lesnik, P., Vidal, H., & Heer, M. (2020). Gut Microbiome and Space Travelers' Health: State of the Art and Possible Pro/Prebiotic Strategies for Long-Term Space Missions. *Frontiers in physiology*, *11*, 553929. https://doi.org/10.3389/fphys.2020.553929

Voorhies, A. A., Mark Ott, C., Mehta, S., Pierson, D. L., Crucian, B. E., Feiveson, A., Oubre, C. M., Torralba, M., Moncera, K., Zhang, Y., Zurek, E., & Lorenzi, H. A. (2019). Study of the impact of long-duration space missions at the International Space Station on the astronaut microbiome. *Scientific reports*, *9*(1), 9911. https://doi.org/10.1038/s41598-019-46303-8

Watenpaugh D. E. (2016). Analogs of microgravity: head-down tilt and water immersion. *Journal of applied physiology (Bethesda, Md.: 1985)*, *120*(8), 904-914. https://doi.org/10.1152/japplphysiol.00986.2015

Williams, D., Kuipers, A., Mukai, C., & Thirsk, R. (2009). Acclimation during space flight: effects on human physiology. *CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne*, *180*(13), 1317-1323. https://doi.org/10.1503/cmaj.090628

Wood, M. J., Wood, C. D., Manno, J. E., Manno, B. R., & Redetzki, H. M. (1987). Nuclear medicine evaluation of motion sickness and medications on gastric emptying time. *Aviation, space, and environmental medicine*, *58*(11), 1112-1114.

Wood, C. D., Stewart, J. J., Wood, M. J., Manno, J. E., Manno, B. R., & Mims, M. E. (1990). Therapeutic effects of antimotion sickness medications on the secondary symptoms of motion sickness. *Aviation, space, and environmental medicine*, *61*(2), 157-161.

Wotring, V. E. (2011) Evidence Report: Risk of Therapeutic Failure Due to Ineffectiveness of Medication. National Aeronautics and Space Administration Lyndon B. Johnson Space Center Houston, Texas. https://humanresearchroadmap.nasa.gov/Evidence/reports/Pharm.pdf

Wotring V. E. (2015). Medication use by U.S. crewmembers on the International Space Station. *FASEB journal: official publication of the Federation of American Societies for Experimental Biology*, *29*(11), 4417-4423. https://doi.org/10.1096/fj.14-264838

Wotring, V. E. (2018) Space Pharmacology: How Space Affects Pharmacology. In: Hock, F., Gralinski, M. (eds.), Drug Discovery and Evaluation: Methods in Clinical Pharmacology. Springer, Cham. https://doi.org/10.1007/978-3-319-56637-5_68-1

Wotring, V. E., & Smith, L. K. (2020). Dose Tracker Application for Collecting Medication Use Data from International Space Station Crew. *Aerospace medicine and human performance*, *91*(1), 41-45. https://doi.org/10.3357/AMHP.5392.2020

Zhou, X., Nian, Y., Qiao, Y., Yang, M., Xin, Y., & Li, X. (2018). Hypoxia Plays a Key Role in the Pharmacokinetic Changes of Drugs at High Altitude. Cdm 19, 960–969. doi:10.2174/1389200219666180529112913

Zhu, J. B., Yang, J. X., Nian, Y. Q., Liu, G. Q., Duan, Y. B., Bai, X., Wang, Q., Zhou, Y., Wang, X. J., Qu, N., & Li, X. Y. (2021). Pharmacokinetics of Acetaminophen and Metformin Hydrochloride in Rats After Exposure to Simulated High Altitude Hypoxia. *Frontiers in pharmacology*, *12*, 692349. https://doi.org/10.3389/fphar.2021.692349

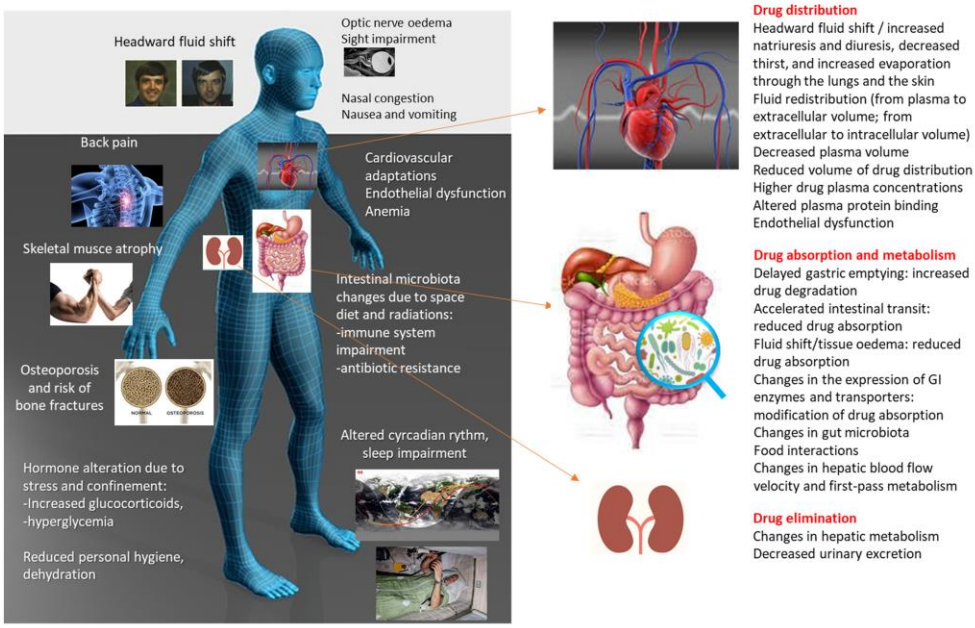
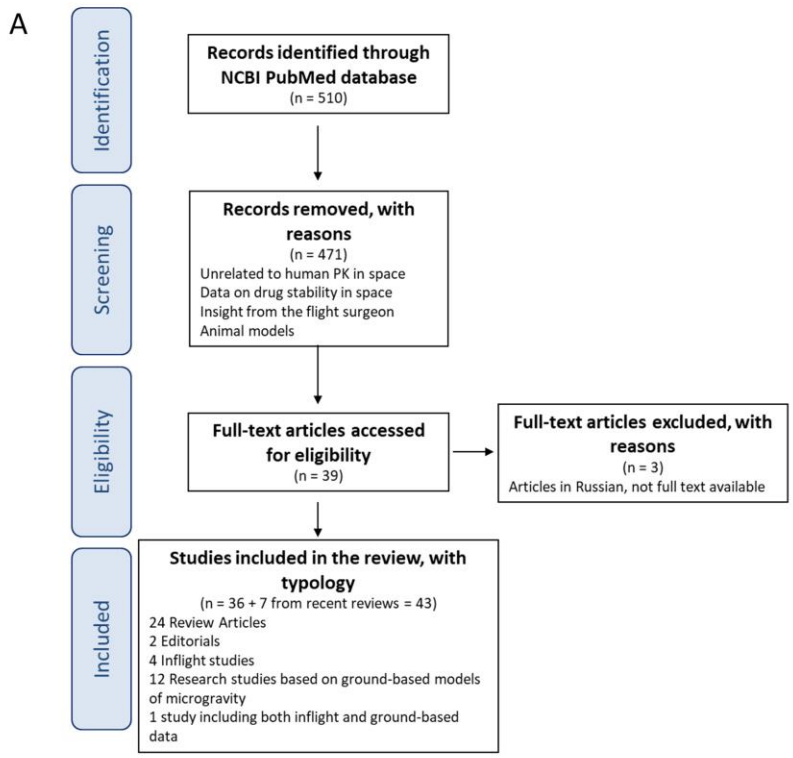


Fig 1. Schematic representation of the main physiological adaptations to Space environment and their relevance on ADME. The right part of the figure represents a summary of the main alterations described for drug absorption, distribution, metabolism and excretion, resulting from organ and tissue adaptation to unloading, stress, confinement and radiation.



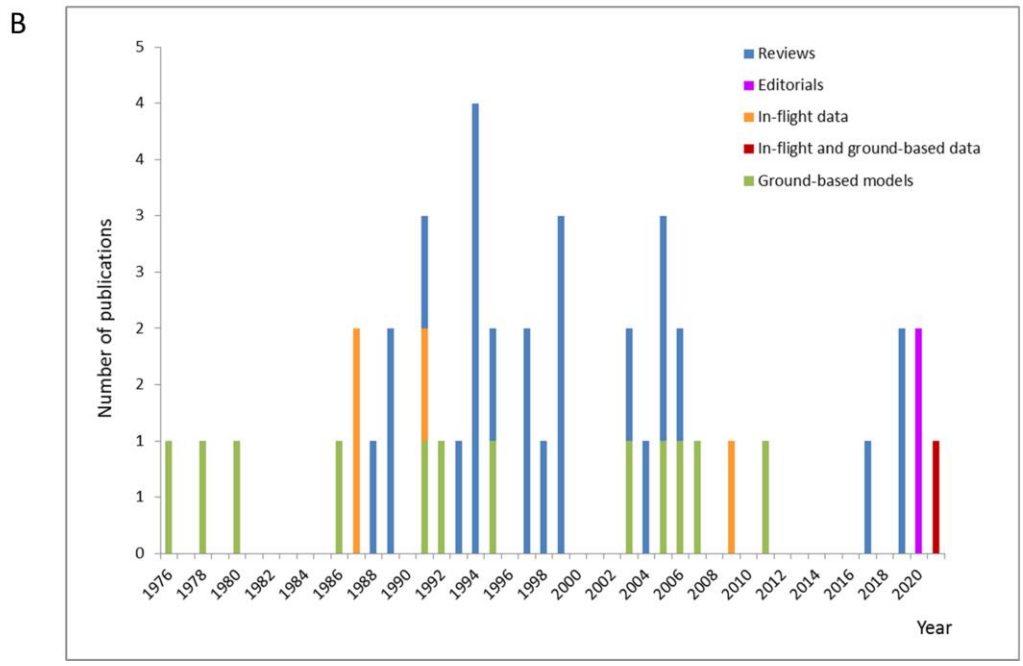


Fig. 2. ***Search strategy and flow diagram followed for the literature review and timeline of the distribution of studies concerning PK in space.*** **(A)** The diagram shows the search strategy adopted to select papers related to PK in space. A total 450 papers were retrieved using

'pharmacokinetics' OR 'pharmacotherapy' AND 'spaceflight' as keywords. An additional 60 studies, not-overlapping with the previous search, were identified using 'bed rest' AND 'pharmacokinetics' OR 'drug disposition' as keywords. A total of 12 new articles were found on Jan 02, 2022 in comparison to the first search carried out on May 08, 2021. Based on the abstracts, 36 articles related to drug PK in Space were selected, excluding three articles in Russian for which full texts were not available. Seven studies, reporting in-flight data or results obtained via ground-based models, were selected through recent review articles (Kast, Yu et al., 2017; Eyal & Derendorf, 2019), for a total of 43 papers. Among them, there were 24 reviews and 2 editorials, 4 in-flight studies and 12 research studies based on ground-based experimental models of microgravity. In addition, one recent publication reported both in-flight pharmacokinetic data and data obtained using the HDT BR model of microgravity. **(B)** The graph reports the number of papers published per year, related to drug PK in Space. Articles were grouped in Editorials, Reviews and Original papers. The latter were divided in publications reporting in-flight data (4 publications), results from ground-based models of microgravity, including 6 publications using the supine bed rest model and 6 studies employing the head-down tilt bed rest model, and one publication with both (in-flight data and data obtained using the HDT BR model of microgravity).

Table 1. List of drugs investigated in spaceflights.

ATC Code	Drug	Administration route	Dose (mg) - Formulation	Subjects (n)	PK results	References
A04AD01 / N06BA02	Scopolamine/ Dextroamphetamine	os	0.4/5 - capsules	3	Scopolamine absorption affected in space. Large inter-subject variability. C_{max} (Mean, SD, n)[b]: Control (406.33 pg/ml, 169.09, 3) In-flight (375.25 pg/ml, 194.38, 4); T_{max}, (Mean, SD, n)[b]: Control (2 h, 0.82, 3) In-flight (2.5 h, 1.06, 4)	Cintrón, Putcha et al., 1987b
N02BE01	Acetaminophen	os	2 x 325 - tablets	5	Acetaminophen PK profile affected in space. Large inter-subject variability. C_{max} (Mean, SD, n)[b]: Control (10.78 mg/ml, 1.68, 5) In-flight (11.40 mg/ml, 4.23, 5); T_{max}, (Mean, SD, n)[b]: Control (0.5 h, 0, 5) In-flight (0.7 h, 0.37, 5)	Cintrón, Putcha et al., 1987a
			650 - not specified	12	↓C_{max} at MD0-1; ↑ C_{max} at MD2-3; ↓ C_{max} at MD4; ↑ T_{max} at MD0-4	Putcha & Cintrón, 1991

			500 - tablets	5	Delayed absorption and 2 peak concentrations (at 0.5 h and 2h post administration) observed in space. C_{max} (Mean, SD, n): Control (5.13 µm/ml, 0.74, 5) In-flight (4.80 µm/ml, 1.06, 5); T_{max}, (Mean, SD, n): Control (1.12 h, 0.37, 5) In-flight (1.80 h, 0.64, 5) $AUC_{0-\infty}$(Mean, SD, n): Control (16.21 µg·h/ml, 1.60, 5) In-flight (19.79 µg·h/ml, 3.15, 5) In addition: ↑ relative absorption rate (124.45% ± 24.27) ↑ relative bioavailability (126.72% ± 24.04) in space *versus* on Earth	Kovachevich, Kondratenko et al., 2009
			500 capsules	5	Similar PK profiles both on Earth and in space, although ↓ plasma concentrations in space. C_{max} (Mean, SD, n): Control (5.00 µm/ml, 0.75, 5) In-flight (4.17 µm/ml, 0.60, 5); T_{max}, (Mean, SD, n): Control (0.90 h, 0.06, 5) In-flight (0.60 h[c], 0.06, 5) $AUC_{0-\infty}$ (Mean, SD):	

					Control (14.81 µg·h/ml, 3.13, 5) In-flight (17.23 µg·h/ml ,3.82, 5) In addition: No changes in the relative absorption rate (93.22% ± 10.27) No changes in the relative bioavailability (119.26% ± 16.35) in space *versus* on Earth	
			625 film-coated tablets	8[a]	Significant differences in the PK profile in space in comparison to normal motion (background). Statistically significant differences[d] observed in the following PK parameters: C_{max} (Mean, SD, n): Control (11.5 µg/ml, 1.3, 8) In-flight (5.4 µg/ml, 1.2, 5); T_{max}, (Mean, SD, n): Control (0.78 h, 0.07, 8) In-flight (1.80 h, 0.20, 5) $AUC_{0-\infty}$ (Mean, SD): Control (45.5 µg·h/ml, 3.71, 8) In-flight (19.8 µg·h/ml ,2.8, 5). In addition: ↑[d] $T_{1/2}$ No changes in the relative absorption rate (98.31% ± 25.9)	Polyakov AV, Svistunov AA et al., 2021

					↓[e] relative bioavailability (48.02% ± 8.07) in space *versus* on Earth	

Notes:

[a], the study group included 7 males and 1 female for the baseline analysis on the ground (Control) carried out approximately 2 months before mission, and 4 males and 1 female for the in-flight PK study. The latter was carried out during 127-414 day long spaceflight.

[b], Mean C_{max} and T_{max} values and standard deviations were calculated based on the absolute values reported in the original papers for each astronaut.

[c], Reported as '*Statistically reliable differences compared with administration of this same drug form under usual conditions*' (Kovachevich, Kondratenko et al., 2009)

[d], statistically significant differences ($p<0.05$) compared to background (data obtained on Earth, two months before the space mission)

[e], the differences were considered statistically significant by the authors, since the mean values and confidence intervals for these parameters were outside '*the acceptable limits*'.

Abbreviations: AUC, area under the curve; C_{max}, peak concentration; os, oral administration; MD, mission day; PK, pharmacokinetics; T_{max}, time to peak concentration; SD, standard deviation.

Table 2. List of drugs investigated using the bed rest experimental model, in the horizontal/supine position.

ATC Code	Drug	Administration route	Dose (mg) - Formulation	Subjects (n)	PK results		References
J01CA08	Pivmecillinam	os	200x2 – capsules	6	↑ T_{max}; ↓C_{max}; ↓AUC (supine *versus* ambulant)		Andrews, Kendall et al., 1976
J01CE01	Benzylpenicillin	i.v.	600	7[a]	No significant differences (1 day BR)		Rumble, Roberts et al., 1986
J01CE02	Penicillin	i.v.	1,000,000 U	12[b]	No significant differences (6 day BR); ↑ urinary blood flow, but no effect on drug Cl.		Kates, Harapat et al., 1980
N01BB02	Lidocaine	i.v. over 15 min	100		No significant differences in PK parameters		Kates, Harapat et al., 1980
N02BB01	Phenazone	os i.v	10/kg - gelatine capsules 10/kg	6[b]	No significant differences in PK parameters	↑ elimination rate constant ↑ Cl ↓ Vd	Elfstrom & Lindgren, 1978
N02BE01	Acetaminophen	os	500 - not specified	8[b]	↑ T_{max}; no difference in AUC		Rumble, Roberts et al., 1991
N02BE01	Acetaminophen	os	1000 - soluble	8[c]	↓ T_{max} ambulant and right *versus* left		Renwick, Ahsan et al., 1992
C08CA05	Nifedipine	os	2 x 10 – capsules		↓ T_{max} ambulant and right *versus* left;		Renwick, Ahsan et al., 1992

					↑ C_{max} and ↑AUC right and ambulant *versus* left	

Notes:

[a], 4 males and 3 females enrolled.

[b], all males enrolled.

[c], 6 males and 2 females enrolled.

Abbreviations: AUC, area under the curve; BR, bed rest; Cl, clearance; C_{max}, maximum concentration; i.v., intravenous administration; os, oral administration; PK, pharmacokinetics; T_{max}, time to maximum concentration; Vd, distribution volume.

Table 3. List of drugs investigated using the head-down tilt bed rest experimental model.

ATC Code	Drug	Administration route	Dose (mg) - Formulation	Subjects (n)	Experimental Model	PK results	References
C01BC09	Etacizine (Ethacizine)	os	100 mg with 100-150 mL water - tablets	9[a]	8° HDT BR (2 days)	Significant differences in the PK profile during HDT-BR in comparison to normal motion (background). Statistically significant differences[d] observed in the following PK parameters: ↑ T_{max}; ↓C_{max}; ↑ V_d; ↓ absorption rate (HDT-BR *versus* background). ↓[e] relative absorption rate (80.70% ± 19.67) ↑[e] relative bioavailability (139.90% ± 26.62) during HDT-BR	Polyakov AV, Svistunov AA et al., 2021

C03CA01	Furosemide	os	40 mg with 100-150 mL water - tablets	6[a]	8° HDT BR (2 days)	Similar PK profile during HDT-BR in comparison to normal motion (background). No significant differences in PK parameters. ↓[e] relative absorption rate (80.19% ± 5.10) and ↑[e] relative bioavailability (112.70% ± 6.22) during HDT-BR	Polyakov AV, Svistunov AA et al., 2021
C07AA05	Propanolol	os	80 mg with 100-150 mL water - tablets	8[a]	8° HDT BR (2 days)	Identical PK profile during HDT-BR in comparison to normal motion (background). No significant differences in PK parameters. ↑[e] relative absorption rate (157.85%± 47.52)↓[e] relative bioavailability (95.21% ± 13.10) during HDT-BR	Polyakov AV, Svistunov AA et al., 2021

C08DA01	Verapamil	os	80 mg with 100-150 mL water - tablets	8[a]	8° HDT BR (2 days)	Similar PK profile during HDT-BR in comparison to normal motion (background). No significant differences in PK parameters. ↑[e] relative absorption rate (141.55% ± 28.62) and ↑[e] relative bioavailability (122.91% ± 17.50) during HDT-BR	Polyakov AV, Svistunov AA et al., 2021
J01MA02	Ciprofloxacin	os	250 mg – tablets	6[b]	6° HDT BR (2 days)	Total plasma concentration not affected; slight ↓ C_{max} and ↑ T_{max}. ↓muscle tissue penetration	Schuck, Grant et al., 2005
N01AX10	Propofol (2, 6-diisopropylphenol)	i.v. (15 min)	25, 50, 100 and 200 µg/kg/min	20[c]	6° HDT BR (2 days)	↑ plasma concentration. Similar efficacy. Mean dose delivered was similar.	Seubert, 2007
N01BB02	Lidocaine	i.v.	1 mg/kg	8[a]	6° HDT BR (2-7 days)	↓ AUC from day 1 to day 5 ↓ C_{max} at day 2 *versus* day 1, then <20% difference	Saivin, Pavy-Le Traon et al., 1995

						↑ Cl and Vd at day 2 *versus* day 1, then stable ↓ $t_{1/2}$ between day 1 and 7 High variability/differences not significant	
N02BE01	Acetaminophen	os	1 g with 200 mL water - not specified	18[a]	6° HDT BR (1 day; 18days; and 80 days)	Day 1: ↓ 44% T_{max}; ↑30% C_{max}; trend ↑AUC; trend ↓ $t_{1/2}$. Similar changes at day 18 and 80, with differences increasing in parallel to the length of bed rest. Opposite results in comparison to supine BR	Gandia, Bareille et al., 2003
			625 mg with 100-150 mL water - Film coated tablets	7[a]	8° HDT BR (2 days)	Different PK profile during HDT-BR in comparison to normal motion (background). No significant differences in PK parameters. ↑[e] relative absorption rate (125.68% ±	Polyakov AV, Svistunov AA et al., 2021

						47.52) and ↓[e] relative bioavailability (87.85% ± 1.36) during HDT-BR	
M01AE01	Ibuprofen	os	600 mg with 240 mL water - tablets	6[a]	Angle not specified (1 day)	No relevant differences after 1 day	Idkaidek & Arafat, 2011
R06AD02	Promethazine	os i.m.	25 mg - tablets 50 mg	12[a]	6° HDT BR (2 days)	↑ 30% exposure (especially per os)	Gandia, Saivin et al., 2006

Notes:
[a], all males enrolled.
[b], 5 males and 1 female enrolled.
[c], 10 males and 10 females enrolled.
[d], statistically significant differences ($p<0.05$) compared to background
[e], the differences were considered statistically significant by the authors, since the mean values and confidence intervals for these parameters were outside '*the acceptable limits*'.
Pharmacokinetics

Abbreviations: AUC, area under the curve; Cl, clearance; C_{max}, maximum concentration; HDT-BR, head tilted down bed rest; i.m., intramuscular administration; i.v., intravenous administration; os, oral administration; PK, pharmacokinetics; $t_{1/2}$, half-life; T_{max}, time to maximum concentration; Vd, distribution volume;