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REVIEW ARTICLE

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

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As human spaceflight progresses with extended mission durations, the demand for effective and safe drugs will necessarily increase. To date, the accepted medications used during missions (for space motion sickness, sleep disturbances, allergies, pain, and sinus congestion) are administered under the assumption that they act as safely and efficaciously as on Earth. However, physiological changes have been documented in human subjects in spaceflight involving fluid shifts, muscle and bone loss, immune system dysregulation, and adjustments in the gastrointestinal tract and metabolism. These alterations may change the pharmacokinetics (PK) and pharmacodynamics of commonly used medications. Frustratingly, the information gained from bed rest studies and from in-flight observations is incomplete and also demonstrates a high variability in drug PK. Therefore, 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 research gaps.

KEYWORDS
animal studies, bed rest studies, therapeutic drugs, drug formulation, pharmacokinetics, pharmacotherapy in space, real evidence in space, space stressor

Abbreviations: AUC, area under the drug-time curve; BR, bed rest; Cl, clearance; C_{max}, peak concentration; HBR, horizontal bed rest; HDT, head down tilt; ISS, International Space Station; LEO, low Earth orbit; SMS, space motion sickness; $t_{1/2}$, half-life time; T_{max}, time to peak concentration; V_d, apparent distribution volume.

1 | INTRODUCTION

When exposed to the space environment, all physiological systems and organs undergo adaptations that can affect drug pharmacokinetics (PK) and thus affect drug safety and efficacy (Czarnik & Vernikos, 1999; Derendorf, 1994; Graebe et al., 2004; Kast et al., 2017; Putcha & Cintrón, 1991; Strollo et al., 2018). Beside weightlessness, a number of 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 rhythm misalignments, and exposure to artificial light as well as to onboard noises can profoundly affect astronauts' mood and central nervous system well-being, with attendant consequences on all the organs and physiological systems. Reduced sanitation as well as exposure to radiation can alter human microbial balance, can increase the risk of DNA damage, and may compromise immune system function (Pavez Loriè et al., 2021; Williams et al., 2009). Relatively mild, yet chronic, hypoxia also can be a further stressor.

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

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 (Kast et al., 2017; Pavez Loriè et al., 2021; Wotring, 2015). These conditions often require pharmacotherapy and, accordingly, 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 necessarily 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 need for repeated dosing to achieve adequate pharmacological effects (Crucian et al., 2016; Pool & Nicogossian, 1983; Wotring, 2015; Wotring & Smith, 2020). The reasons behind this reported variability have not been 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 have not been sufficiently validated as a surrogate. The need to investigate the effects of drugs in detail under space conditions, as outlined from 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. Concerted efforts have been made by space agencies to develop tracking systems of crews' intake of medications and to standardize the reporting procedures, to allow for accurate data collection and monitoring of drug use by astronauts during space missions (Wotring & Smith, 2020). In-flight data are particularly relevant to understand critical differences between the way drugs act in space as opposed to on Earth (Blue, Bayuse, et al., 2019).

Within this framework, we have carried out an extensive literature review on the topic of 'physiological changes that impact drug PK' with the following 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, and mainly in two distinct phases. During the early phase, that is, 72–96 h, symptoms such as SMS, sleep disturbances, nasal congestion, headache, and back pain have been reported (Dijk et al., 2001; Lakin et al., 2007). Changes in bone and muscle mass and in central nervous system function occur later during the adaptive phase, in a time span from weeks to months (Demertzi et al., 2016).

Following is a description of the main organs and systems whose alterations can change the absorption, distribution, metabolism, and excretion (ADME) of drugs. Figure 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 with the common experience on Earth. Gastric emptying is slower and more variable in microgravity, in part due to the loss of gravity-dependent size and density effects on ingested matter (Amidon et al., 1991). Intestinal transit rate through the small intestine is faster and more variable. These changes can affect the dissolution rate of tablets/capsules and the stability of drugs in the stomach.

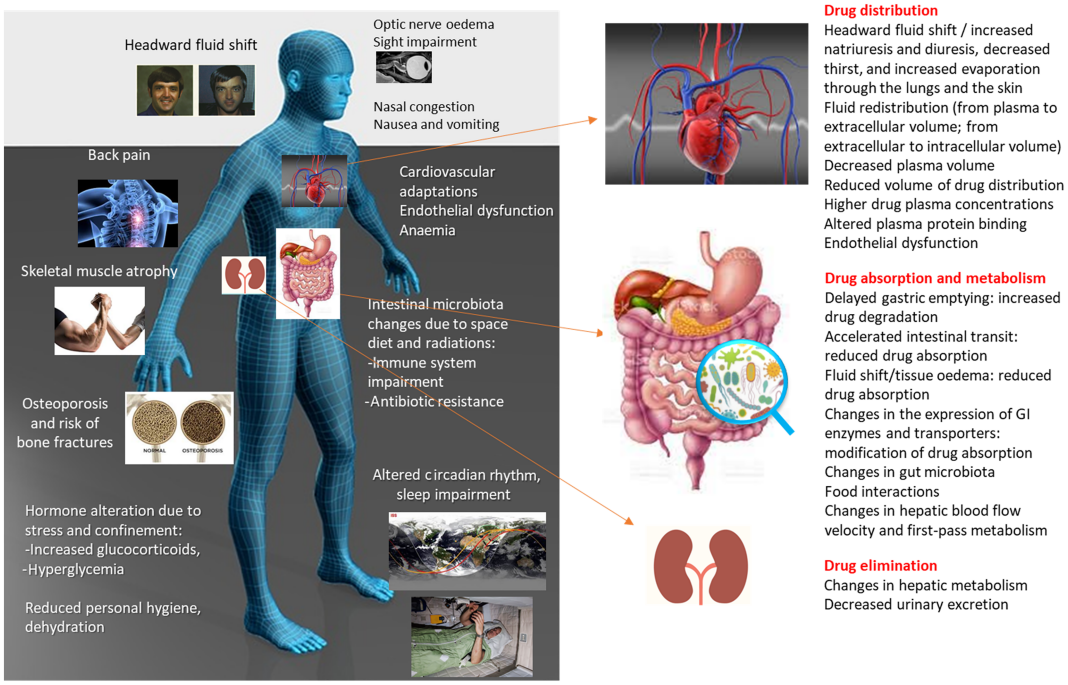

FIGURE 1 Schematic representation of the main physiological adaptations to space environment and their relevance on drug ADME. The right part of the figure represents a summary of the main alterations described for drug absorption, distribution, metabolism and excretion (ADME), resulting from organ and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

Although it is not known if motility is directly affected by microgravity, gastrointestinal (GI) transit time is certainly affected by SMS drug treatments, mainly with **scopolamine** and **promethazine**, which are used to counteract the activation of the **muscarinic receptor system** (Davis, Jennings, & Beck, 1993; Davis, Jennings, Beck, & Bagian, 1993; Wood et al., 1987, 1990). Weakly acidic drugs may show increased absorption because their presence in the stomach is prolonged, but for most medications, particularly basic ones, absorption occurs in the more basic regions of the intestine. Treatment with anti-muscarinic drugs will delay drug absorption, even by the order of hours, or can 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 expression of epithelial transport systems together with altered blood flow experienced in a hypoxic environment, as is typical at high altitude (Bailey et al., 2018; Zhou et al., 2018), may occur in spaceflight.

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

The alterations in gut microbiota in space (Turroni et al., 2020; Voorhies et al., 2019) can contribute to some the above events, both in terms of the quality and quantity of the faecal mass, and for the spectrum of enzymatic activities involved in gastrointestinal metabolism and elimination of xenobiotics. In general, it is beyond doubt that the microflora can affect drug absorption (Fleisher et al., 1999; Schneeman, 2002); however, it has not yet been determined whether the changes reported during spaceflight can significantly affect drug 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 implementation of effective therapeutic countermeasures

to ensure safety and health of the crewmembers during these high-risk expeditions (LaPelusa 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 the enteric level, as well as the overall influence of the shift in gut microbiota in the processing and absorbption 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 parts of the body and a subsequent adjustment and then decrease in blood volume (Charles & Bungo, 1991; Charles & Lathers, 1991; Leach, Inners, et al., 1991; Montgomery 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 et al., 1998). Mild hypoxia can further aggravate the condition, by causing vasogenic brain swelling and oedema, as described at high altitude (Lafuente et al., 2016; Turner et al., 2021). An 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 (Charles & Bungo, 1991; Charles & Lathers, 1991; Leach et al., 1988, 1996; Natochin et al., 1975). However, further studies report that the baroreceptor-kidney loop does not contribute in the same way to fluid-volume regulation in microgravity as it does on Earth (Hargens & Richardson, 2009). Despite these conflicting results and hypotheses, the final outcomes are a 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 a prolonged permanence in space (Leach, 1981). Total body mass declines during spaceflight, mostly as a reduction in the lean body mass. Thus for a given dosage, drug concentration in the bloodstream is expected to be higher. The latest data describing the extent of chronic dehydration typically seen in spaceflight show around a 1 to 2% reduction in body mass, with only transient increases at launch. Fluid redistribution is not only related to the whole cardiovascular system but also to extracellular and intracellular water movements. One study suggests that the volume of intracellular fluid increases (Leach et al., 1996). Additionally, other available data have confirmed that a redistribution of fluids occurs during spaceflight (from plasma volume to the extracellular compartment, and then from the extracellular to the intracellular volume), more than a loss of total body water due to dehydration or increased diuresis. Other blood components, that is, red cells and proteins, such as albumin, also reduce in the first few days, so that final blood concentrations return to normal, but the overall blood volume is a little lower (Smith et al., 2019). The drug apparent distribution volume (V_d) would thus be lower, and effective drug concentrations would be higher in space in comparison to Earth.

Other cardiovascular changes occur during spaceflight, such as decreased left ventricular end-diastolic volume and stroke volume indexes, with compensatory accelerated heart rate for the maintenance of cardiac output (Mulvagh et al., 1991). All these adjustments create the phenomenon of cardiovascular deconditioning (Antonutto & di Prampero, 2003). In addition, nonfatal cardiac arrhythmias have been reported during space missions, particularly with an increased risk during long explorations. Several factors may trigger cardiac rhythm alterations, including prolongation of the QT interval, hypokalaemia, exposure to radiation leading to myocardial damage, and psychological stressors (Anzai et al., 2014). Fluctuations in cardiovascular parameters can affect the PK of drugs, thus affecting their safety and efficacy. However, these cardiovascular changes undergo adaptation after few days of spaceflight, and crewmembers typically do not report long-term fluid problems, because the body seems to adapt to environmental changes (Hargens & Watenpaugh, 1996). The problem with fluctuations of cardiovascular parameters however manifests upon return to Earth. Taken together, these results provide support for a model that includes a fluid shift on flight days 1 and 2, upwards in the body and from the plasma, interstitial, and extracellular spaces and into the intracellular spaces. There is no convincing evidence regarding the distribution of drugs during or after such fluid shifts. No additional distribution evidence from in-flight studies has been described, other than in Wotring's report (2011).

Drug binding to plasma proteins, lipids, and erythrocytes is probably altered, but only a few direct studies on these parameters have been carried out. Plasma albumin and HDL cholesterol are known to decrease 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), as well as accelerated clearance, but also to the possible worsening of adverse effects. Concerning hematologic indices, results are contrasting, due to different time-points for blood sampling. Red blood cell mass, that is, haemoglobin and number of erythrocytes, but not haematocrit (Grigoriev et al., 1991; Leach & Johnson, 1984; Leonard et al., 1983; Tavassoli, 1982) has been reported to be reduced after short duration spaceflights. Erythropoietin levels have been found to decrease throughout the flight (Alfrey, Udden, Huntoon, & Driscoll, 1996; Alfrey, Udden, Leach-Huntoon, et al., 1996), which could be the cause of the increased neocytolysis, that is, the destruction of young red blood cells (Trial et al., 2001). On the contrary, red blood cells and haemoglobin were reported to be elevated during long-term spaceflights (Kunz et al., 2017). It is thus mandatory to evaluate the correlation among hematologic parameters and altered free drug concentration during long permanence in space, because these values change throughout mission phases.

Endothelial cells are very sensitive to the absence of gravity (Morbidelli et al., 2005); therefore, a state of endothelial dysfunction can result in spaceflight, accompanied by vascular oxidative stress and a mild chronic inflammatory state (Kapitonova et al., 2012; Maier et al., 2015). Spaceflight-induced disturbance of the blood–brain barrier (Mao et al., 2020), due to chronic mild inflammation and redox imbalance, can be responsible for brain impermeable drugs entering the brain, thus causing adverse toxic effects. 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, and for the permeability status of the endothelium within an 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 et al., 2001). During spaceflights of long duration, there is a loss of bone and muscle mass, as well as a loss of muscle strength. Drug tissue binding may be altered as a result of an important muscle protein loss (Leonard et al., 1983) and of scant perfusion. Although an intensive physical training plan can effectively reduce bone loss (Hargens et al., 2013; Iwamoto et al., 2005), 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

The cytochrome P450 superfamily constitutes the largest family of phase I enzymes responsible for the metabolism of drugs and xenobiotics. Cytochrome variations can lead to either increased or decreased metabolism, as well as leading to a different profile for drug and xenobiotic metabolites. All these changes can result in the appearance of unwanted pharmacological effects or therapeutic failure. Significant changes in hepatic content of P-glycoprotein and of metabolic enzymes belonging to the cytochrome P450 family have been described in experimental animals maintained under microgravity conditions (Lu et al., 2002; Merrill et al., 1990; Moskaleva et al., 2015). In rats flown to space for 14 days, morphological analysis showed that hepatocytes were larger than those in control animals, although the livers themselves were not larger in size (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 space station, reductions were detected in the amount of the liver enzymes catalase and glutathione (GSH) reductase, both of which are involved in general antioxidant activity, as well as a reduction in GSH sulphurtransferase (Hollander et al., 1998). Activation of the lipotoxic pathway has been demonstrated in mice after a 13-day spaceflight mission (Jonscher et al., 2016). This finding suggests the onset of progressive liver damage and a predisposition towards non-alcoholic fatty liver disease (NAFLD). However, it remains to be shown if enzyme protein concentrations, or their absolute amounts, correlate directly with hepatic enzymatic activity during prolonged spaceflight.

The decreased hepatic metabolism during spaceflight is broadly consistent with a decreased hepatic blood flow due to hypovolaemia. Nevertheless, conflicting data have been reported in the literature. In fact, hepatic blood flow has been found to increase in spaceflight in some cases, hypothesizing that more drug would be delivered to the liver and processed by first-pass metabolism, thus reducing its circulatory level (Saivin et al., 1995). Consistently, a slight increase in liver size and liver filling has been reported after 9 months of spaceflight (Grigoriev et al., 1991).

An hypoxic environment can influence xenobiotic metabolism. Human studies during high altitude hypoxia indicate that the metabolism of most drugs is reduced (Bailey et al., 2018). In particular, cytochrome P450 monooxygenase activity is diminished because oxygen is a pivotal cofactor. Recently, changes in the PK of **acetaminophen** and **metformin hydrochloride** have been observed in rats under simulated high altitude hypoxic conditions. These modifications were driven by a significant decrease in the transcription of **uridine diphosphate glucuronosyltransferase 1A1** (UGT1A1) and **organic cation transporter 2** (OCT2) (Zhu et al., 2021). A fine control of the major liver enzymes, or the levels of circulating metabolites of drugs with a 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 future spaceflight studies (Berrios et al., 2021).

In conclusion, metabolic enzyme systems are not equally affected by spaceflight. More detailed experiments on identified genes and enzymes should be performed, especially those involving enzymes that metabolize the common 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 et al., 2015). On top of this, data on drug–drug, drug–diet, and drug–physical countermeasure interactions in the space environment are lacking (Berman & Eyal, 2019).

2.4 | Excretion of drugs

Changes in organ perfusion, including kidneys, and in renal function have been reported to influence 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. Because all drug-binding macromolecules in the blood are decreased, the drug-free fraction is increased, which should lead to an increased renal clearance. However, renal plasma flow, glomerular filtration rate (GFR), and urine production were shown to be unchanged in space (Drummer et al., 1993; Drummer, Gerzer, et al., 2000; Drummer, Hesse, et al., 2000), contrary to previous data from simulated microgravity models that suggested increased GFR and diuresis (Norsk et al., 2001). Instead of increased natriuresis, an increased sodium reabsorption was observed in flight (Norsk et al., 2000), resulting in a positive sodium balance. In addition, under hypoxia, alterations in capillary pressure, urinary epithelial biochemistry, and transport carrier expression and function may be responsible for an increased half-life time ($t_{1/2}$) and area under the drug-time curve (AUC), and a reduced clearance rate (Cl) as found at high altitude

(Bailey et al., 2018). It cannot excluded that these changes also happen in space environment.

Since the D-2 Spacelab mission reports of the early 90s, direct studies on renal blood flow are absent in the literature (Kuipers, 1996). In-flight measurements indicated a slight reduction in total body water for the first few days of spaceflight (Leach, Inners, et al., 1991). 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 et al., 1996). Abrupt cessation of large muscle group activity may also contribute to decreased plasma volume (Christensen et al., 2001). This decrease would be expected to reduce renal blood flow and, therefore, drug excretion. Indeed, a compensatory increase in plasma **renin** activity and **anti-diuretic hormone** were detected in short-duration spaceflights (Leach, 1991; Leach, Cintrón, et al., 1991). A 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 showed no studies reporting on drug excretion in microgravity or during spaceflight (see further details in the present review). The ability to have at hand a simple and immediate system to check the elimination of drugs and/or their metabolites in the urine could help to optimize the dosage of drugs used in space.

3 | DRUG PK STUDIES IN SPACE AND IN 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 safety and efficacy 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 of the PubMed database (accessed on 02 January 2022), as detailed in Figure 2a. A total of 43 papers were selected for this review. Among them, there were 24 reviews and two editorials, which account for 60.5% of the selected publications, as well as a further four in-flight studies, 12 research studies carried out on ground-based experimental models of microgravity, and one recent publication reporting both in-flight PK and ground-based data (Figure 2a). As shown in Figure 2b, the majority of studies, that is 33/43 (76.4%), were published between years 1986 and 2007. Since then, only two original articles on drug PK in human spaceflights have appeared in the literature. The most commonly used experimental model of microgravity for PK studies is the BR model, either in the horizontal position (HBR), that is, six articles published between years 1976 and 1992, or the head-down tilt (HDT) BR, that is, six articles published between years 1995 and 2011 and one publication in 2021 (Polyakov et al., 2021). Despite the number of review articles on drug PK in space available in the literature, this is the first time that a critical approach has been 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 et al., 2021), directly shows a paucity of original results on drug PK in space and a 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 and (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 mostly has been derived from crewmembers involved in the Space Shuttle Flight programme. As shown in Table 1, there were five publications that reported drug PK data obtained in-flight, including one study on the oral administration of scopolamine and **dextroamphetamine** (scop/dex) and four studies on oral acetaminophen alone (Table 1). The PK of oral scop/dex (0.4 mg/5 mg) was investigated in-flight for three crewmembers involved in two different Space Shuttle missions. This study also tested the feasibility of performing PK studies in space using saliva samples. First, a saliva/plasma ratio was determined in healthy volunteers on the ground. This ratio was reported to be constant amongst the entire scopolamine disposition profile after both intravenous and oral administration, although the raw data have not been openly published. Thereafter, PK data for scopolamine in space were obtained using saliva specimens collected at specific time points over a period of 12 h, although no corresponding measurements of dextroamphetamine concentrations were presented (Cintrón 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 to have either increased or decreased in comparison to ground values in the three astronauts tested, thus precluding any robust conclusions. 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 et al., 1987b). These data therefore underlie the difficulties in performing drug PK studies in space. Saliva sampling and the PK analysis were carried out one time per each astronaut in space, although repeated twice for one astronaut, at mission days 0–1 and 2–3, with inconsistent results. Physiological adaptations to space conditions vary over time, suggesting that the time of testing can variably affect predictions on 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, & Beck, 1993). 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 et al., 1987b) contributed to the reduced efficacy of oral scop/dex observed in-flight (Davis, Jennings, & Beck, 1993). On the other hand, since its first use for the symptomatic treatment of one male

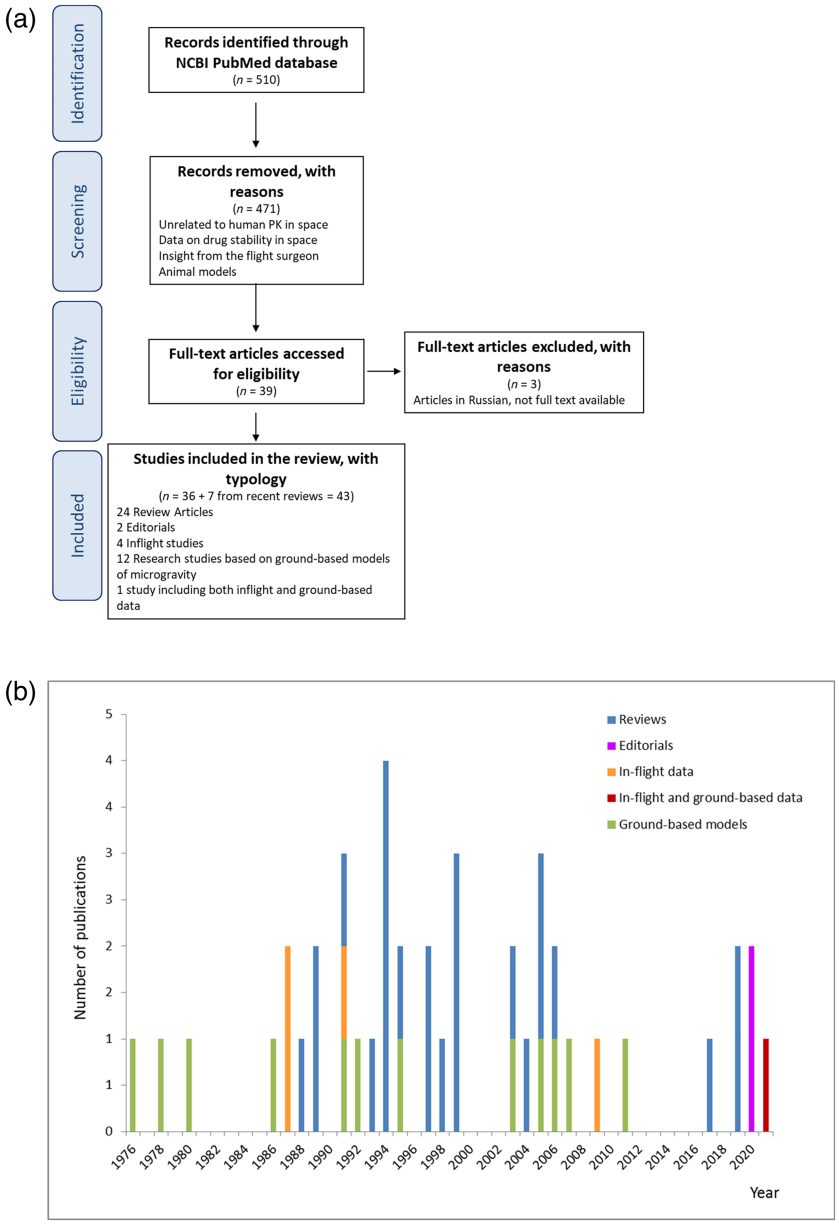

FIGURE 2 Search strategy and flow diagram followed for the literature review and timeline of the distribution of studies concerning PK in space. (a) The diagram shows the search strategy adopted to select papers related to PK in space. A total 450 papers were retrieved using 'pharmacokinetics' OR 'pharmacotherapy' 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 January 02, 2022 compared with the first search carried out on 08 May 2021. Based on the abstracts, 36 articles related to drug PK in space were selected, excluding three articles in Russian and 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 (Eyal & Derendorf, 2019; Kast et al., 2017), for a total of 43 papers. Among them, there were 24 reviews and two editorials, a further four 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 (four publications), results from ground-based models of microgravity, including six publications using the supine bed rest model and six 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)

crewmember developing severe SMS (Bagian, 1991), i.m. promethazine, at the dose of 25–50 mg mostly as single injection, has proved to be highly effective and well tolerated (Bagian & Ward, 1994; Davis, Jennings, & Beck, 1993; Davis, Jennings, Beck, & Bagian, 1993). Hence, alternative routes of drug administration can possibly overcome PK variability observed after oral dosing and, consequently, could increase drug efficacy in space. However, no PK studies were carried out in space using i.m. promethazine to prove this hypothesis. Nevertheless, this drug has become standard treatment for SMS on the Space Shuttle flights.

The PK of acetaminophen has been studied in-flight using saliva samples, in a study involving five different astronauts participating in three different Space Shuttle missions. The study confirmed higher variability of acetaminophen PK in-flight versus on the ground. Significant changes in the absorption phase were reported, with increased C_{max} and reduced T_{max} in two subjects for sampling done at mission day 2. Opposite effects were observed at mission day 4, when physiological adaptation to weightless conditions was 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 drug concentrations observed (Cintrón et al., 1987a). We calculated the average C_{max} and T_{max} values compiling data from these five astronauts, although sampling was performed at different mission days, and found a modest trend in these astronauts towards increased C_{max} and T_{max}, as shown in Table 1. In a subsequent report that included data from 12 subjects on seven different flights after oral administration of 650 mg of acetaminophen, an increase in T_{max} on mission days 0 and 1 versus preflight measurements was revealed. 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

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 intersubject variability. C_{max} (mean, SD, *n*)[a]: Control (406.33 pg·ml^{-1}, 169.09, 3) In-flight (375.25 pg·ml^{-1}, 194.38, 4); T_{max}, (mean, SD, *n*)[a]: Control (2 h, 0.82, 3) In-flight (2.5 h, 1.06, 4)	Cintrón et al., 1987b
N02BE01	Acetaminophen	os	2 × 325 - tablets	5	Acetaminophen PK profile affected in space. Large intersubject variability. C_{max} (mean, SD, *n*)[a]: Control (10.78 mg·ml^{-1}, 1.68, 5) In-flight (11.40 mg·ml^{-1}, 4.23, 5); T_{max}, (mean, SD, *n*)[a]: Control (0.5 h, 0, 5) In-flight (0.7 h, 0.37, 5)	Cintrón 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 2 h post administration) observed in space. C_{max} (mean, SD, *n*): Control (5.13 μm·ml^{-1}, 0.74, 5) In-flight (4.80 μm·ml^{-1}, 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}, 1.60, 5) In-flight (19.79 μg·h·ml^{-1}, 3.15, 5) In addition: ↑ relative absorption rate (124.45% ± 24.27) ↑ relative bioavailability (126.72% ± 24.04) in space vs. on earth	Kovachevich 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^{-1}, 0.75, 5) In-flight (4.17 μm·ml^{-1}, 0.60, 5); T_{max}, (mean, SD, *n*): Control (0.90 h, 0.06, 5) In-flight (0.60 h[b], 0.06, 5) $AUC_{0-\infty}$ (mean, SD):	

(Continues)

TABLE 1 (Continued)

ATC code	Drug	Administration route	Dose (mg) - Formulation	Subjects (*n*)	PK results	References
					Control (14.81 μg·h·ml^{-1}, 3.13, 5) In-flight (17.23 μg·h·ml^{-1},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 vs. on Earth	
			625 - film-coated tablets	8[c]	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}, 1.3, 8) In-flight (5.4 μg·ml^{-1}, 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, n): Control (45.5 μg·h·ml^{-1}, 3.71, 8) In-flight (19.8 μg·h·ml^{-1},2.8, 5). In addition: ↑[d] $t_{1/2}$ No changes in the relative absorption rate (98.31% ± 25.9) ↓[e] relative bioavailability (48.02% ± 8.07) in space vs. on Earth	Polyakov et al., 2021

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.

[a]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.

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

[c]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.

[d]Statistically significant differences ($p < 0.05$) compared with background (data obtained on Earth, 2 months before the space mission).

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

mission days 0 and 1 and increase on mission days 2 and 3, while T_{max} tended to increase (Putcha & Cintrón, 1991). Data from these two studies could not be combined because the average values (± standard errors) for C_{max} and T_{max} were only provided in the graphs from the second study (Putcha & Cintrón, 1991). In addition, it is not clearly stated if the second analysis included data from the first five astronauts evaluated in the previous report (Cintrón et al., 1987a). A third PK study of acetaminophen was carried out on 10 healthy crewmembers involved in ISS expeditions. Participants were divided into two test groups of five men. Two different formulations of acetaminophen were tested, that is, 500 mg of acetaminophen as either tablets or capsules (Table 1). PK was studied in-flight as well as 2 months before the space mission under normal 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 that seen on Earth (Table 1). Moreover, two peak concentrations were detected. When given as 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 terrestrial evaluations. Other PK parameters, including elimination $t_{1/2}$, retention time and V_d were significantly increased. No significant changes in the relative absorption rate and drug bioavailability were reported (Kovachevich 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 et al., 2009), in longer duration spaceflight (127–414 days) (Polyakov et al., 2021). This study was carried out applying a similar protocol, using saliva samples and included data from crewmembers that participated in space missions to the MIR orbital station. These data confirmed the delay in drug absorption (increased T_{max}), as basically reported in all previous studies on acetaminophen in space (Cintrón et al., 1987a; Kovachevich et al., 2009; Putcha & Cintrón, 1991). 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 values (Table 1). With respect to the data reported by Kovachevich and collaborators (Kovachevich et al., 2009), the authors suggested that the differences observed in several PK parameters among the two studies can be explained by differences in (i) the manufacturing process (and the composition of excipients in the administered formulations), (ii) the dose (625 mg vs. 500 mg in the Kovachevich's study) of acetaminophen, and (iii) different durations of spaceflight (127–414 days vs. 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). Considering that the PK evaluations on ground were carried out using blood samples and on a different cohort of subjects, we cannot use these unpaired 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 quasi-comparative analysis between BR and in-flight data was provided by the authors.

3.2 | The horizontal bed rest (HBR) model

The HBR model was initially used as a physiological analogue of spaceflight, to mimic the effect of prolonged exposure to microgravity in human subjects (Hargens & Vico, 2016). The recumbent position produces 0 Gz gravitational 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, thus providing a direct validation of the HBR model, although only related to cardiovascular adaptations (Moore et al., 1994). As shown in Table 2, six PK studies were carried out using the HBR between years 1976 and 1992, which was before the conclusive validation of this experimental model. All studies were performed according to a crossover design and included between six and 12 healthy volunteers. Apart from one study that enrolled subjects with mean age of 50.2 years (Kates et al., 1980), all 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 five females (Elfström & Lindgren, 1978; Kates et al., 1980; Renwick et al., 1992; Rumble et al., 1986, 1991). 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 focussed on anti-inflammatory drugs and pain relievers.

From these studies, it emerged that the absorption of orally administered **pivmecillinam** is delayed and reduced in the supine position compared with the orthostatic position. A slight reduction of drug bioavailability was observed in the supine position, as shown by the pivmecillinam serum AUC (Andrews et al., 1976). No significant differences were detected in mean plasma concentrations when similar antibiotic drugs were administered intravenously. This was observed for **benzylpenicillin** given i.v. at the dose of 600 mg after 1-day HBR (Rumble 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 et al., 1980). The urinary blood flow appeared to be significantly higher during HBR, but it did not alter the clearance of benzylpenicillin (Rumble et al., 1986). In both studies, the mean plasma concentration tended to be lower during HBR in comparison to the orthostatic position; however, these differences in drug concentration were not statistically significant. In addition, no significant differences in other PK parameters were induced by HBR, including $t_{1/2}$, Cl, V_d, and AUC (Kates et al., 1980; Rumble 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.

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	200 × 2 – capsules	6	↑T_{max}; ↓C_{max}; ↓ AUC (supine vs. ambulant)	Andrews et al., 1976
J01CE01	Benzylpenicillin	i.v.	600	7[a]	No significant differences (1 day BR)	Rumble 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 et al., 1980
N01BB02	Lidocaine	i.v. over 15 min	100		No significant differences in PK parameters	Kates et al., 1980
N02BB01	Phenazone	os i.v	10/kg - gelatine capsules 10/kg	6[b]	No consistent changes in drug absorption and bioavailability	↑ elimination rate constant ↑ Cl ↓ V_d	Elfström & Lindgren, 1978
N02BE01	Acetaminophen	os	500 - not specified	8[b]	↑ T_{max}; no difference in AUC	Rumble et al., 1991
			1000 - soluble	8[c]	↓ T_{max} ambulant and right vs. left	Renwick et al., 1992
C08CA05	Nifedipine	os	2 × 10 – capsules		↓ T_{max} ambulant and right vs. left; ↑ C_{max} and ↑AUC right and ambulant vs. left	Renwick et al., 1992

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

[a]Four males and 3 females enrolled.

[b]All males enrolled.

[c]Six males and 2 females enrolled.

Consistent with this hypothesis, delayed absorption of orally administered acetaminophen was reported in another study (Rumble 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 et al., 1992). In this study, subjects were given 1 g of acetaminophen and two capsules of 10 mg **nifedipine** during three different visits, after overnight fasting. At each visit, subjects were randomly requested to maintain one specific posture for 4 h, including lay down on the right or on the left side, or in a standing position (Renwick et al., 1992). Similarly, the absorption of orally administered nifedipine was more rapid in ambulant subjects and subjects lying on the right side compared with lying on the left side. Moreover, the C_{max} and AUC of nifedipine were significantly increased in subjects lying on the right side or standing compared with subjects lying on the left side (Renwick 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 that included six subjects, it was shown that the elimination rate and clearance of the NSAID drug phenazone were increased during bed rest, whereas V_d was reduced. Conversely, the supine position did not significantly affect the absorption and bioavailability of phenazone (Elfström & Lindgren, 1978). Finally, no significant changes in the clearance of **lidocaine** were observed during HBR, as well as in other PK parameters (Kates 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 also 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 is currently regarded as the model of choice to mimic microgravity on the ground, particularly when investigating cardiac and muscle atrophy, orthostatic intolerance, and bone loss due to microgravity and when developing specific countermeasures (Hargens & Vico, 2016). Subjective and empirical in-flight observations that fluid shift towards 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 et al., 2016), in line

with in-flight data. Later, the HDT BR 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 et al., 2013). As shown in Table 3, the PK of several drugs was investigated by mostly using the 6° HDT BR model, including studies on 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, that is, drug administered after 2-days of 6° HDT BR. The PK curves showed slightly reduced C_{max} and increased T_{max} due to 6° HDT BR compared with the orthostatic position. Slightly lower muscle tissue penetration of ciprofloxacin was observed in simulated microgravity (Schuck et al., 2005). This is in line with the hypothesis that tissue perfusion may be altered in space due to the lack of mechanical pressure and a 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 a sedation score and the bispectral index (an electro-encephalograph-derived measure of 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 compared with the orthostatic position. However, despite these physiological changes, no significant effects were observed on the bispectral index after i.v. administration of propofol in the dose range of 25–200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 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 $\mu g \cdot kg^{-1} \cdot min^{-1}$, a dose that gave a 40–50 bispectral index in the previous trial. Propofol plasma concentrations were increased by exposure to 6° HDT bed rest, up to 60 min after the anaesthetic withdrawal. However, mean dose delivered was similar in both groups, recovery time was the same, and no evidence was detected for delayed postoperative cognitive dysfunction (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 $mg \cdot kg^{-1}$, appeared to decrease from 130.69 ± 47.65 $mg \cdot min \cdot L^{-1}$ on day 1 to 92.51 ± 21.43 $mg \cdot min \cdot L^{-1}$ on day 5. Subjects were ambulant on day 1 and then were exposed to 6° HDT BR between day 2 and 5 and were again ambulant on day 7. A total of eight subjects were enrolled in this study. Breakfast without lipid and juice was provided before drug administration, and 200 ml of water was allowed 4 h 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 V_d 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 significantly different, due to the variability observed on the first day (Saivin et al., 1995).

The PK of acetaminophen was studied in subjects exposed to 6° HDT BR for different times, including 1, 18, and 80 days. Subjects laid on their back for 6 h 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 h after drug administration, and a full meal was provided 6 h 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 with the length of BR (Gandia et al., 2003). These data therefore suggest that the rate of drug absorption is increased during 6° HDT BR, in contrast to that observed using the HBR (Renwick et al., 1992; Rumble et al., 1991). The PK of acetaminophen was recently studied in a group of seven male subjects exposed to 2 days of 8° HDT BR (Polyakov et al., 2021). The study showed relevant differences in the profile of the averaged PK curves for 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 were 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 subjects 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 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 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 V_d. The relative bioavailability of etacizine was increased during HDT BR (Polyakov et al., 2021). Finally, no relevant differences in PK parameters were observed for orally administered **ibuprofen** after 1-day of HDT BR (angle not-specified) (Idkaidek & Arafat, 2011), whereas 30% increased exposure to promethazine was found after 2-days of 6° HDT BR, especially when the drug was administered per os (Gandia 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 et al., 2009). Again, the main gap in PK studies involves the lack of in-flight validation of 6° HDT BR data.

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[b] observed in the following PK parameters: ↑ T_{max}; ↓C_{max}; ↑ V_d; ↓ absorption rate (HDT-BR vs. background). ↓[c] relative absorption rate (80.70% ± 19.67) ↑[c] relative bioavailability (139.90% ± 26.62) during HDT-BR	Polyakov 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. ↓[c] relative absorption rate (80.19% ± 5.10) and ↑[c] relative bioavailability (112.70% ± 6.22) during HDT-BR	Polyakov 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. ↑[c] relative absorption rate (157.85% ± 47.52)↓[c] relative bioavailability (95.21% ± 13.10) during HDT-BR	Polyakov 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. ↑[c] relative absorption rate (141.55% ± 28.62) and ↑[c] relative bioavailability (122.91% ± 17.50) during HDT-BR	Polyakov et al., 2021
J01MA02	Ciprofloxacin	os	250 mg - tablets	6[d]	6° HDT BR (2 days)	Total plasma concentration not affected; slight ↓ C_{max} and ↑ T_{max}. ↓ muscle tissue penetration	Schuck et al., 2005
N01AX10	Propofol (2, 6-diisopropylphenol)	i.v. (15 min)	25, 50, 100, and 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$	20[e]	6° HDT BR (2 days)	↑ plasma concentration. Similar efficacy. Mean dose delivered was similar.	Seubert, 2007
N01BB02	Lidocaine	i.v.	1 $mg \cdot kg^{-1}$	8[a]	6° HDT BR (2–7 days)	↓ AUC from day 1 to day 5 ↓ C_{max} at day 2 vs. day 1, then <20% difference ↑ Cl and V_d at day 2 vs. day 1, then stable ↓ $t_{1/2}$ between day 1 and 7 High variability/differences not significant	Saivin et al., 1995

TABLE 3 (Continued)

ATC code	Drug	Administration route	Dose (mg) - Formulation	Subjects (*n*)	Experimental model	PK results	References
N02BE01	Acetaminophen	os	1 g with 200 ml water - not specified	18[a]	6° HDT BR (1 day; 18 days; 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 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. ↑[c] relative absorption rate (125.68% ± 47.52) and ↓[c] relative bioavailability (87.85% ± 1.36) during HDT-BR	Polyakov et al., 2021
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 et al., 2006

Abbreviations: AUC, area under the curve; Cl, clearance; C_{max}, peak 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 peak concentration; V_d, distribution volume.

[a]All males enrolled.

[b]Statistically significant differences ($P < 0.05$) compared with background.

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

[d]Five males and 1 female enrolled.

[e]Ten males and 10 females enrolled.

3.4 | Parabolic flight

Parabolic flight has been viewed as a spaceflight analogue and used experimentally to generate alternating periods of free fall (reduced gravity) at high gravitoinertial force level (~1.8–2G), each parabola lasting 20–25 s. A flight usually consists of 30 consecutive parabolas and motion sickness is scored according to a number of 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 outcomes the resolution of motion sickness symptoms and prevention of nausea or vomiting at touchdown. Scopolamine was the most investigated drug used in this experimental model of SMS. In particular, the pharmacological effects of scopolamine were evaluated in two different studies, involving to two different modalities of administration. In the first study involving 47 subjects, scopolamine (0.43–0.5 mg) was administered i.m. during parabolic flight to severely sick subjects, usually at a time 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 a lower dose of 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 beneficial pharmacological effects of these drugs. However, no PK data are available from parabolic flights. Scopolamine was effective when administered as a buccal pouch at the dose of 1 mg and retained in the mouth between parabolas 5 and 30. The therapeutic drug level was estimated to be reached by the time of parabola 10, based on previous investigations on the PK of buccal scopolamine (Norfleet et al., 1992). This study was carried out according to a crossover design; thus, subjects were studied in two different sets of parabolic flights and were generally less sick during the second set of flights. Despite this variability, buccal scopolamine significantly reduced by 31% the severity of nausea and by 50% for the total number of parabolas with vomiting (Norfleet 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 with a reduction in the sedative effects of scopolamine. In a PK study performed on the ground on the more 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 et al., 2007). This variability may contribute to the lack of efficacy sometimes reported during spaceflights. Finally, oral **metoclopramide** administered prophylactically 75 min before parabolic flights did not show any beneficial effect (Kohl, 1987) and is not used in real microgravity.

Despite the above data on the efficacy of anti-motion sickness drugs, we could not find PK studies carried out on these drugs using the parabolic flight experimental model. Overall, parabolic flight seems unsuitable and probably impractical for this kind of investigation.

4 | RESEARCH GAPS IN DRUG RELATED PK STUDIES

Relevant physiological changes occur during spaceflight that may impact on 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 dating 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 operational until 23 March 2001 (https://www.nasa.gov/feature/20-years-ago-space-station-mir-reenters-earth-s-atmosphere), we can hypothesize that the above PK study was carried out before this time and that data were only recently made available through the international literature. Similarly, it has not yet been determined whether those changes in physiological processes occurring by exposure to space environment can significantly affect drug PK. This includes, for example, changes in the expression and functioning of transport system at the 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 on the distribution of active principles or their metabolites during and after fluid shift caused by spaceflight. Also, the effects of changes in bone and muscle mass and of 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, such 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 concerns the changes in haematological parameters, including the plasma protein levels, which can influence the free drug concentration and could precipitate unwanted adverse reactions. An extensive and complete study on the liver enzymatic pattern is still lacking, including also the polymorphic character of metabolic pathways (Pavez Loriè et al., 2021). Drug excretion is a further parameter that merits further detailed study in light of now dated studies and their controversial results. In addition, drug–drug interactions and drug–diet interactions remain to be assessed in-flight to maximize the efficacy of drugs and to guarantee the safety of prescribed medications.

Spaceflight research in this field can benefit from recent developments in wearable sensors which allow the continuous measurements of physiological functions (Li et al., 2017). In particular, the real-time monitoring of heart rate, physical activity and sleep can be relevant in the evaluation of drug PK. In addition, intense

research activity is currently ongoing towards the development of wearable biosensors or implantable devices that would enable continuous drug monitoring (Bian et al., 2021; Gowers 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 difficulties in carrying out multiple blood sampling in real microgravity and a 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 of these drugs for a range of plasma concentrations and over the disposition profile was established on the ground, but no in-flight corroborative studies were performed. It is still unknown whether a consistent saliva/plasma ratio measured on the 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 frequency of using medicines during human spaceflight is measurably greater than the use of the same 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 subject ($n = 5$) 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 standardized procedures on Earth, despite the occurrence of physiological adaptations in space, together with potential alterations in drug stability due to radiation exposure. The extent of such modifications is currently not well determined, and ground-based models cannot be used successfully to answer all the open questions 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, and thus be able to better inform drug prescription. This is particularly relevant for future crewed explorations beyond LEO, which will not permit a rapid return to Earth in the event of a medical emergency.

5.1 | 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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AUTHOR CONTRIBUTIONS

Conceptualization, methodology, investigation, writing-original draft preparation, writing—C.D.R., L.M., T.B.; review and editing—M.M., V.W., V.Y., L.S.; supervision—C.D.R., L.M. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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 organizations engaged with supporting research.

DATA AVAILABILITY STATEMENT

N/A, as this is a review.

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