Dose Tracker Application for Collecting Medication Use Data from International Space Station Crew

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INTRODUCTION: There are knowledge gaps in spaceflight pharmacology with insufficient in-flight data to inform future planning. This effort directly addressed in-mission medication use and also informed open questions regarding spaceflight-associated changes in pharmacokinetics (PK) and/or pharmacodynamics (PD).

METHODS: An iOS application was designed to collect medication use information relevant for research from volunteer astronaut crewmembers: medication name, dose, dosing frequency, indication, perceived efficacy, and side effects. Leveraging the limited medication choices aboard allowed a streamlined questionnaire. There were 24 subjects approved for participation.

RESULTS: Six crewmembers completed flight data collection and five completed ground data collection before NASA's early study discontinuation. There were 5766 medication use entries, averaging 20.6 $\pm$ 8.4 entries per subject per flight week. Types of medications and their indications were similar to previous reports, with sleep disturbances and muscle/joint pain as primary drivers. Two subjects treated prolonged skin problems. Subjects also used the application in unanticipated ways: to note drug tolerance testing or medication holiday per research protocols, and to share data with flight surgeons. Subjects also provided usability feedback on application design and implementation.

DISCUSSION: The volume of data collected (20.6 $\pm$ 8.4 entries per subject per flight week) is much greater than was collected previously (<12 per person per entire mission), despite user criticisms regarding app usability. It seems likely that improvements in a software-based questionnaire application could result in a robust data collection tool that astronauts find more acceptable, while simultaneously providing researchers and clinicians with useful data.

KEYWORDS: pharmacy, pharmaceutical, astronaut, space, software.

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During spaceflight, the body undergoes a number of physiological changes that would be expected to result in altered interactions with administered medications. From basic pharmacokinetics (PK = how the body handles administered medications) and pharmacodynamics (PD = how administered medications act upon the body) principles, this potential seems high because:

- Fluid shifts could alter absorption and distribution of administered medications (PK) and thus alter perceived efficacy.
- Changes in the amounts or activities of enzymes that metabolize drugs (PK) could alter perceived efficacy or severity of untoward effects.
- Tissue remodeling could change expression of drug targets (PD), which could also alter perceived efficacy.

Supporting evidence from human spaceflight experiments includes changes in gastrointestinal transit time,[11] calcium absorption,[2] and, in rat studies, in the amounts of liver enzymes involved in drug metabolism.[7–9] Regarding pharmacodynamics, tissue remodeling may alter cell phenotypes and expression of cell membrane receptors that serve as drug targets; it is well-demonstrated that human bone[12] and rat muscle[10] exhibit significant remodeling during spaceflights.

Two dedicated spaceflight PK studies[3,6] showed conflicting results. In a pilot study on flight days 0–3, all three subjects exhibited changes in absorption and elimination of acetaminophen

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as measured in salivary samples, although no conclusion could be drawn because each subject exhibited a unique pattern of change (two exhibited decreased peak concentration, while one was increased; one subject each showed various delayed, accelerated, and unchanged absorption rates).[3] A slightly larger study ($N = 5$) showed delayed absorption (by over 1 h) and elimination of acetaminophen (measured in blood samples). This report did not include elapsed mission time or include error bars or other measure of variability for the data.[6]

Certain previous studies[13] included data from mission medical records and physician notes from in-flight private medical conferences (PMC), which are collected by flight surgeons. These only included data deemed pertinent to maintenance of crew health by flight surgeons and did not address important research questions for the evaluation of medication PK/PD changes. A retrospective analysis of crew medication records[13] included 24 crewmembers on 20 missions over a 10-yr period. There were 277 reports of medication use (<12 per person). This study revealed limitations in the available data with regards to addressing PK/PD changes: frequent ambiguity regarding number of doses taken, 38% of reports described perceived efficacy, and only 5% of reports described side effects occurrence or severity.

There have been many undocumented anecdotal reports of astronauts using medications in flight without incident. However, evidence regarding possible therapeutic failures were reported in the areas of sleep aids and treatments for skin rash. A comprehensive study of thousands of mission nights showed that 75% of crewmembers reported use of sleep promoting medications,[1] roughly 10-fold higher than healthy adults on Earth.[5] Furthermore, on 19% of nights when sleep aids were used, two doses were reported; that is, individuals woke earlier than desired and used an additional sleep aid in the same night.[1] A case report that tracked symptomology, medication use, and research immunology findings for a crewmember over 191 flight days described a rash that never fully resolved during a 6-mo flight onboard the International Space Station (ISS).[4] The rash was nonresponsive to multiple treatments: topical hydrocortisone cream, topical terbinafine, topical triamcinolone acetonide, and a variety of antihistamines, the last of which did improve concurrent rhinitis symptoms, but provided minimal improvement of the rash. Oral steroids (methylprednisolone, prednisone) improved symptoms, but the rash still never fully resolved until shortly after landing. This report highlighted the need for higher fidelity medication use data so that pharmacy planning for future missions can be improved; this subject exhausted the hydrocortisone stocked onboard within the first 60 d of symptoms.

The unknowns about PK/PD in flight, coupled with the gap in medication use data collection, prompted the originally planned research study that aimed to: develop an iOS application (app) for collection of medication usage data from crewmember participants during their missions, and employ the application to collect in-flight medication usage data applicable to studying in-flight pharmacokinetic changes (alterations in how the body absorbs, distributes, metabolizes or excretes a medication) or data that suggest in-flight pharmacodynamic changes. Given the limited subject number, however, this report is presented as an observational case series.

METHODS

Subjects

This study was approved by the Institutional Review Boards at Johnson Space Center (JSC) and Baylor College of Medicine. Participation was open to ISS astronauts who elected to provide consent. Astronaut subjects logged medication usage information for analysis by research staff. Due to limited potential astronaut subject numbers, a within-subject study design was planned, with data collection on the ground serving as each subject's control. Six subjects participated.

Equipment and Materials

An iOS application was designed to ask specific questions regarding medication use, somewhat different from the typical questions that clinicians would ask regarding patient health. Desired data were: medication name, dose, dosing frequency, indication, perceived efficacy, and perceived side effects. Subjects who wanted to use a personal iPad were assisted in a secure software download to their device. Subjects without a personal iPad were loaned study hardware loaded with app software. Several models of Apple iPads were used to run the app.

A tablet-based platform was used for app development to enable a convenient user experience. The data collection process was streamlined by using a custom-made, flexibly programmed computerized survey application that leveraged the limited medication choices aboard, the doses available, typical dosing frequency, and side effects associated with each medication to provide an individualized short questionnaire for each medication use by the crewmember. The app was preloaded with the ISS medical kit medication list as a default.

Feedback on draft versions of the app was received from the JSC Pharmacy, a flight surgeon, and an astronaut. The app was tested in four 1-wk Human Research Exploration Analog (HERA) missions at JSC prior to use with spaceflight crew. Since HERA subjects were not permitted to use medications, the study team provided each HERA subject written prompts directing them to simulate self-treatment for some minor condition. The subjects were then instructed to enter simulated medication uses and outcomes into the app.

As a result of the testing process, additional options for app personalization were incorporated. These included the ability for users to prepopulate recurring medication doses, (useful for daily medication uses) and the ability to add medications outside of the ISS formulary.

Procedure

Subjects were trained in app use and study requirements before their data collections were scheduled to begin. Subjects were asked to choose a 4-digit personal identifier for their data, trained in app use, and then asked to complete data collection

at least weekly, ±1 d to permit operational flexibility. Flight data collection was desired for the entire duration of the subject's spaceflight mission, plus the first week after landing to capture landing-related medication uses. Control ground data collection was requested for an equivalent duration and could be scheduled before or after the mission at the subject's convenience.

App software was available only in the NASA App Store to invited individuals, which was limited to the study team, the subjects, and ISS Medical Projects staff. Data were stored with each subject's personal identification number and encrypted. Decryption required use of the app software, which had tightly controlled distribution. During control ground data collection, encrypted data files were sent to the Principal Investigator via weekly secure email. During missions, encrypted files were downlinked via an ISS secure server, where they were retrieved by the study team. Data were not shared with medical staff or NASA personnel involved in future flight assignments, except in the case of one subject who requested data sharing with their flight surgeon. That request was confirmed by the subject and the flight surgeon and approved by the JSC IRB.

Statistical Analysis

Medication use data were decrypted, maintaining de-identification of astronaut subjects, and transformed into Excel and SAS files for analysis. Repeated measures ANOVA analyses were planned, within and between subjects, but could not be accomplished due to the small number of subjects who ultimately finished the study. Due to the small number of subjects who completed data collection, analysis was limited to a case series style report of observations collected in the app with some limited descriptive statistics.

RESULTS

Six subjects completed flight data collection, but only five completed control ground data collection. The study was terminated after only 6/24 subjects were recruited due to concerns regarding the usability and function of the application software. Overall, 5766 records of medication use were collected. These included 49 wk of confirmed "no medication usage." On average, subjects reported somewhat higher medication usage in flight compared to on Earth (see **Table I**): 20.6 ± 8.4 entries per subject per flight week; 15.6 ± 4.6 per ground week (mean ± SEM, $N = 6$ flight, $N = 5$ ground).

Two subjects reported about twofold more medication use during their missions compared to a similar duration on Earth, while two others reported that medication usage was about the same. One subject reported > threefold more medication uses on Earth compared to during the mission. This was due to near-daily use of loratadine (noted for seasonal allergies) and vitamin D. Neither of these medications were reported used during the mission. The sixth subject did not collect control data on Earth and thus was not included in this analysis. The small number of subjects precluded more detailed flight/ground analysis.

Table I. Numbers of Medication Use Entries Collected.

	ENTRIES/WEEK	
SUBJECT	FLIGHT	GROUND
A	2.1	7.0
B	1.2	1.6
C	22.0	20.6
D	3.6	(none)
E	40.3	18.5
F	54.7	30.5
Mean	20.6	15.6
SD	20.7	10.2
N	6	5
SEM	8.4	4.6

One subject reported use of zolpidem in stretches of 1–3 d at a time over weeks 10–24 of their mission and reported no use of sleep aids on the ground. Another reported eight uses of zaleplon during their mission and none on Earth. A third reported 40 uses of zolpidem during their mission and only 8 during a similar duration of ground reporting, a fivefold increase. This same individual reported using zaleplon on 19 flight nights and only 1 ground night. Another subject reported 10 uses of zaleplon during their flight and 3 on the ground. A fifth subject report a single use of zolpidem in flight.

Three subjects used pain relievers. One used ibuprofen in flight and naproxen on the ground for elbow, muscle, and back pain. Another used ibuprofen for EVA-related sprains/strains and for headache, while acetaminophen was used for headache and pain related to a urinary tract infection. Another used celecoxib on many ground days, noting treadmill running and spacewalk training as the reasons. The same subject reported use of lorazepam after back pain associated with resistance exercise device use in flight. One subject reported using mometasone furoate nasal spray on most flight days and another reported using fexofenadine on most flight days, for treatment of congestion/allergy symptoms and rash.

In addition to prophylactic use of scopolamine/dexamethasone prior to launch, one subject reported use of several doses of scopolamine/dexamethasone in the first 2 flight days. This was followed by a dose of meclizine. At landing, this subject used several doses of meclizine. Another subject used three doses of promethazine. All of these uses were restricted to a few days around launch or landing. One subject reported medication uses for cold sores, twice on Earth and seven times during the mission. The same subject reported mission-long treatments for rash, including fluocinonide.

Small numbers of medication uses to prevent future discomfort were reported. Most were associated with launch or landing (scopolamine/dexamethasone in two subjects, ibuprofen in one subject, and meclizine in two subjects). Use of aspirin was reported prior to extravehicular activity (EVA) by one subject. One subject used chronic treatments for skin problems and two others used chronic treatments for cholesterol control and cardiovascular disease prevention.

Three subjects reported using vitamin D supplements on most flight days. One subject reported use of a multivitamin

product daily, both during the mission and on Earth. Another subject reported using a multivitamin for iron deficiency postflight.

One subject reported using over the counter (OTC) piracetam (marketed as a cognition enhancer but not evaluated by the U.S. Food and Drug Administration for this purpose) nearly every day postflight. During the mission, this subject reported using a jellyfish aquaporin-based OTC reputed cognition enhancer.

Subjects reported a range of medication efficacy and few side effects. Perceived efficacy was reported by 1–3 subjects for 32 medications. Most medications were considered partially effective. Two subjects evaluated efficacy in both flight and Earth environments: one found valcyclovir to provide "complete relief, but required continued dosing" in both situations, and another found zaleplon to provide complete relief in a single dose. One subject reported the absence of side effects during both flight and ground use for eight medications.

Crewmember subjects were asked about their experience with the study during debriefs. Some users had no comments. Some users found the app to be inconvenient for a variety of reasons: multiple login pins and IDs, app icon placement and appearance, and app organization. Each of these negatively affected usability for subjects.

Two subjects noted medication use for drug tolerance testing conducted on the ground prior to missions. The app provided a way to document date and time of testing, as well as the occurrence or absence of side effects.

One subject used the app to note "no medication use" for 2 d, clearly indicating that daily medications had been stopped for this period. Notes included state that this was done to follow the research protocol for another flight experiment.

One subject found the app to be useful, performed data collection for more weeks than requested, and requested that their flight surgeon be given access to the data. Part of the initial consent process was that researchers would not share this private medical information so that subjects could feel confident that their study data would not be used to inform future career assignments. Accommodating this request required specific subject request, flight surgeon request, and approval by the JSC IRB.

DISCUSSION

The volume of data collected during this study is greater than was collected through medical records or postmission questionnaires used previously. The data show a total of 5766 medication use entries with an average of 20.6 $\pm$ 8.4 entries per subject per flight week. In contrast, an earlier examination of medical records from 24 crewmembers on 20 missions over a 10-yr period yielded a total of 277 medication use reports, $<$ 12 per person per entire mission.[13] This is despite user criticisms regarding the function and usability of the app and iOS system. It seems likely that changes in the use and function of a software-based questionnaire application would result in a data collection tool that astronauts find acceptable, while still providing researchers with data that permits evaluation of research questions in an unobtrusive fashion.

Sleep was the indication linked to the most subject-initiated medication uses, excluding scheduled uses like vitamin supplements or medications prescribed for health maintenance. Pain associated with EVA or exercise also remained a significant reason for medication use. Sleep difficulties and pain associated with EVA and exercise equipment were also the chief drivers of medication use in a previous study of crew medication use.[13] Improvements and advances in technology and operational changes could lead to decreased crewmember reliance on symptomatic treatments.

Multiple (but not all) subjects reported some level of dissatisfaction with the app user interface, organization, or implementation. Subjects indicated that NASA-required security measures (multiple login pins and IDs) decreased the usability of this tool. Some subjects were asked to download additional files to perform updates for iOS registration or software bug fixes; security regarding these updates also burdened the user. Subjects provided opinions on size, shape, location, and color of certain icons on the app display, but the study team was bound by NASA software standards and could not incorporate all user suggestions.

In the app design phase of the study, the project team would have benefited from additional flight surgeon and crew input, whose feedback was extremely valuable. Additional communication to the study team regarding operational file transfer protocols could have prevented some of the issues identified by users. It is also clear to the study team that additional app testing prior to initiation of the study with subjects would have been beneficial. Use of test subjects from the general population as opposed to HERA participants (who were not permitted to use medications) might have been more useful.

The subjects of this study used the app in three ways that were unexpected: to document ground preflight drug tolerance testing, to document the medication holiday required for a research study protocol, and to share data with medical personnel. The fact that subjects developed their own uses of the app underscores the need for crew to have better methods for documenting their medication uses and experiences.

In 2018, the PI was notified that the research study would not be continued but that NASA recognized the value of the data collected for both research and clinical purposes. As a result, NASA is planning a transition-to-operations of a redesigned tool for collection of astronaut medication use data, one that incorporates the lessons learned from this effort. Gathering additional data in this fashion will help to address open spaceflight pharmacology-related research gaps.

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