

Use of rapid dosimetry modeling to evaluate the effect of long-term spaceflight on drug disposition

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Spaceflight causes a wide range of physiological changes, some of which can affect the pharmacokinetics (PK) of medications, causing reduced efficacy or adverse effects. Since the astronaut demographic is shifting towards individuals with a broader range of ages, health conditions and physical capabilities, there is an increased risk of PK variability that may impact medical provisions planning for long-haul missions. Therefore, a better understanding of how spaceflight physiology impacts drug PK is needed.

Some studies have tested the efficacy of individual drugs in simulated low gravity environments. However, it is not feasible to investigate the effects of spaceflight stressors on all drugs that may be provided to astronauts. Therefore, this study focused on developing a computational approach to evaluate the effect of low gravity on drug disposition of medications likely to be included in spacecraft medical kits.

The initial modeling approach was based on the US Environmental Protection Agency's High Throughput Toxicokinetics (httk), a physiologically based pharmacokinetic model that estimates chemical exposure doses in the body for thousands of chemicals simultaneously. We adjusted the model to reflect current astronaut demographics and evaluated model sensitivity. The most sensitive model parameters were related to plasma binding, urinary clearance, hepatic metabolism and fraction absorbed. Spaceflight modifiers calculated using published data were applied to these parameters. Metabolic enzyme polymorphisms were incorporated to explore how genetic diversity affects drug PK during spaceflight. Disposition predictions were then compared between terrestrial and spaceflight conditions for 74 drugs. Physiological changes in spaceflight minimally affected steady state blood parent drug concentrations, but did alter acute dosing kinetics.

Genetic susceptibility plays a larger role in steady state blood concentrations. While more data and comprehensive models are needed, these studies demonstrate how predictive approaches can improve personalized medicine in the future of spaceflight. **Disclaimer:** No DoD endorsement implied.

(Note that the abstract, including the disclaimer, is limited to 300 words.)