Effects of simulated microgravity on the anesthetic properties of propofol:
A prospective randomized crossover study evaluating safety and efficacy as well as pharmacokinetics, pharmacodynamics and metabolism in human volunteers

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Introduction

Despite careful health screening by NASA, astronauts adapted to microgravity may require the administration of anesthesia for a variety of surgical conditions not only in the highly autonomous environments of space habitation or Mars-type missions but also for immediate surgical care after evacuation from low orbital missions. Physiologic adaptation to weightlessness (e.g., changes in blood and plasma volume, fraction of cardiac output directed to brain, autonomic nervous system activity) can be expected to markedly alter the in vivo behavior and characteristics of anesthetics/hypnotics. A suitable anesthetic technique for microgravity has not been devised. Furthermore, independent external review of the experience with primates on BION 11 has led to the conclusion that “...there was an unexpected mortality risk associated with anesthesia ...following return from space ...”

Total intravenous anesthesia (TIVA) is probably the most practical and cost-effective method of rendering subjects insensate during surgery under microgravity conditions. Equipment for TIVA is light, compact, and self-contained. Among the TIVA agents in use today, propofol (2, 6-diisopropylphenol) is the best single agent suitable for use in space. Propofol has several key properties that make it a suitable anesthetic in a space environment: 1) rapid induction of and emergence from anesthesia, 2) ability to adjust the dose to achieve anesthetic states ranging from conscious sedation to general anesthesia, 3) minimal drug accumulation in the body, even during long procedures, 4) significant anti-emetic properties, and 5) a simple and reliable means for assessing the depth of anesthesia/hypnosis, the bispectral index (BIS), derived from the electrical activity of the brain.

Hypotheses:
1. Adaptation to microgravity increases the hypnotic/anesthetic effect of propofol by changing its pharmacokinetics (PK), but not pharmacodynamics (PD).
2. Adaptation to microgravity does not change the recovery of cognitive function after propofol anesthesia.

Specific Aims:
- Determine the changes in clearance, volume of distribution, mean residence time and half-life and pattern of metabolites of propofol caused by adaptation to microgravity.
- Relate propofol plasma concentrations to clinical and electrophysiological measures of anesthetic drug effect during normal gravity and adaptation to microgravity
- Assemble the pharmacokinetic and pharmacodynamic information to provide guidelines for dosing requirements for sedation and anesthesia in microgravity
- Determine changes caused by adaptation to microgravity in the time course of the recovery of cognitive function after propofol anesthesia
- Assess whether the adaptation to microgravity causes delayed postoperative cognitive dysfunction.

These hypotheses and aims focus on questions of autonomous medical care, specifically risks number 18, 19 and to a lesser extent 22 as they relate to the capabilities/knowledge background required to provide anesthesia care specifically and pharmacotherapy in general.
Research Plan

The evaluation of the effects of simulated microgravity on the anesthetic properties of propofol was conducted sequentially in two groups of subjects. The first group was exposed to a dose escalation protocol to characterize the changes in pharmacodynamics caused by adaptation to microgravity and to identify any prominent, unexpected and novel safety concerns. The second group served to characterize the pharmacokinetics and pharmacodynamics as they apply to a clinical anesthetic as well as the neuro-cognitive recovery after an anesthetic titrated to comparable anesthetic depth in subjects adapted to either normal or microgravity. The dosing of the anesthetic in the second group was guided by the information from the first group and aimed to provide a clinically relevant scenario. Both groups used a randomized cross-over design. That is, each subject received the same dosing protocol of propofol twice in random order, either adapted to normal gravity or after 48 hours of antiorthostatic bed rest to simulate adaptation to microgravity. The hemodynamic effects of the antiorthostatic bed rest were studied by obtaining complete blood counts and transthoracic echocardiograms before and after the 48 hour bed rest. A third group of 10 subjects controlled for changes in the neuro-cognitive test scores that may occur by repeat administration or learning of tested tasks. This group was matched to the volunteers in health status and test intervals but neither underwent neither anesthesia nor adaptation to simulated microgravity. Timeline and study design are summarized in table 1 and figure 1, respectively.

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<td>Safety Monitoring Report</td>
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Table 1: Time course of the proposed project. A, annual renewal of regulatory approval. R, report of the Data Safety Monitoring Committee to the IRB.

**Group I** Propofol was administered at doses of 25, 50, 100, and 200 µg/kg/min for 15 minutes each to achieve sub-clinical drug effect, light conscious sedation, deep conscious sedation and general anesthesia, respectively. The response to this dosing protocol was assessed by sampling blood for the determination of propofol plasma concentrations and by assessing anesthetic drug effect with the bispectral index (BIS)
derived from the electroencephalogram, scoring sedation on a sedation scale and by repeatedly assessing neuro-cognitive function during recovery.

**Group II** Propofol was administered at doses that led to BIS scores of 40-50 for the last 15 minutes of the anesthetic regardless of whether the subject was adapted to microgravity or not. This BIS score reflects a state of general anesthesia. General anesthesia may cause airway obstruction. Therefore, subjects were instrumented with a laryngeal mask airway (LMA Proseal™). Because no muscle relaxants were used, ventilation was adequate as monitored continuously by pulse oximetry and capnography.

![Figure 1: Basic study design. The Anesthesia protocol differs between group I and II.](image)

**Results**

Twenty volunteers were enrolled to receive propofol anesthesia, ten volunteers for each of the two groups. Basic demographic information is presented in Table 2.

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<td>Weight (kg)</td>
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Table 2: Demographic information of the subjects in Groups I and II. Subjects in the neurocognitive control group were not different from subjects in the propofol groups (data not shown).

Of the 20 volunteers in the propofol groups 18 completed the study without complications. Two anesthetics in Group II were stopped, one because of persistent coughing – likely a residual from a respiratory tract infection - and one because of regurgitation without aspiration – most likely caused by inadequate anesthesia. Independent review of all anesthetics by a panel of 4 anesthesiologists as part of Data Safety Monitoring oversight did agree with the investigators that no unexpected novel...
safety concerns were raised by the study anesthetics. Antiorthostatic bed rest led to hemoconcentration and typical mild symptoms of back pain or a sensation of fullness of the head/ headache. Figure 2 illustrates the magnitude of the changes in the hemogram caused by 48 hours of anti-orthostatic bedrest.

![Figure 2](image1.png)

**Figure 2:** Change in a values of a complete blood count from baseline caused by 48 hours of head down bed rest (n=19; one subject in Group II withdrawn prior to bed rest).

For both propofol groups the anesthetic effect of propofol was similar in normal gravity and simulated microgravity. The clinical assessment by the modified observer’s assessment of alertness/sedation scale was corroborated by BIS monitoring (Figures 3 and 4).

![Figure 3](image2.png)

**Figure 3:** Effect of propofol on the bispectral index score (BIS) in normogravity and simulated microgravity in Group I (n=10). The dose escalation protocol led to sedation (BIS 70-85) and general anesthesia (BIS < 60) as planned. Adaptation to microgravity did not change the effect of propofol.
Specifically, in the group treated with escalating doses of propofol the time spent unconscious was 16.4±8.5 and 18.1±6.3 minutes in normal and microgravity, respectively (P=0.42, paired t-Test). More importantly, this small change induced by simulated microgravity is far smaller than the normal inter-individual variation in the time spent unconscious, which ranged from 8-26.5 minutes.

![Graph showing MOAA/S score over time and propofol infusion](image)

**Modified Observer's Assessment of Alertness/Sedation (MOAA/S)**

- 5 Responds readily to name spoken in normal tone
- 4 Lethargic response to name spoken in normal tone
- 3 Responds only after name is called loudly and/or repeatedly
- 2 Responds only after mild prodding or shaking
- 1 Responds only after painful trapezius squeeze
- 0 No response after painful trapezius squeeze

Figure 4: Clinical assessment of the anesthetic effect of propofol. Although sedation and anesthesia were achieved as planned through the dosing regimen, simulated microgravity did not change the effect of propofol.

As intended, subjects in group II underwent clinically equivalent anesthetics in normo- and simulated microgravity (see figures 5 and 6). Consistent with the expected hemoconcentration, but unexpected from the clinical course, these anesthetics resulted in propofol plasma concentrations for up to 60 minutes after the anesthetic that were higher in simulated microgravity than in normogravity (p<0.05, repeated measures ANOVA, figure 7). The mean doses of propofol delivered were 12.26±3.54 and 12.55±4.03 mg/kg for the 60-minute anesthetic in normo- and simulated microgravity, respectively (P=0.63, t-test, n=8).
Sedation Score during Propofol Anesthesia

Figure 5: Clinical assessment of sedation in Group II.

Bispectral Index during Propofol Anesthesia

Figure 6: EEG effects of propofol in Group II are identical for normo- and simulated microgravity as intended by the anesthesia protocol (n=8).
Average Measured Plasma Concentrations of Propofol

Figure 7: Plasma concentrations of propofol during the final 15 minutes of the anesthetic and the initial recovery period. Adaptation to simulated microgravity causes higher plasma concentrations for a given level of anesthesia in Group II.

While propofol impaired aspects of cognitive function early after the anesthetic, the recovery was the same for normal and simulated microgravity (Figure 8). There was no evidence of delayed postoperative cognitive dysfunction.

Figure 8: Recovery of neurocognitive function after one hour of propofol anesthesia. Data from groups I and II were combined, because neither propofol doses nor clinical
effects of propofol were different between normo- and simulated microgravity. The time points for testing were baseline (1), and 30, 120 and 240 minutes after the end of propofol administration (2, 3, and 4). Only 30 minutes after propofol administration were test scores significantly lower than at baseline. Test scores were normalized to z-scores and expressed as reliable change scores to control for practice effects, as determined with the neurocognitive control group.

Detailed pharmacokinetic analysis is currently underway, but complicated by the fact that the clinically relevant but heterogeneous dosing of subjects in group II makes the analysis more complex. Results are expected by August 2007.

Discussion

The revised CPR and NASA’s focus around the Exploration Spirals continues to put great emphasis on applied research that aims to solve mission-critical problems. For any mission beyond spiral 1 autonomous medical care requirements represent an important component. In the case of anesthesia care the critical need for further information is even more pressing, because of the anesthesia-related morbidity and mortality of the primates on BION 11.

Our results suggest only a minor impact of the adaptation to weightlessness on the pharmacodynamic/pharmacokinetic profile of propofol. While our results are still preliminary, because the final pharmacokinetic analysis is still ongoing, the responses to the two anesthesia regimes were as clinically expected and well within what can be considered normal inter-individual variability. The finding that clinically equivalent anesthetics (figures 5 and 6) would be caused by slightly different plasma concentrations of propofol is surprising. The slight difference in plasma levels can be expected because equal doses of propofol were given during both anesthetics even though plasma volume is reduced in both antiorthostatic bed rest and adaptation to microgravity. Why then does the higher plasma level not lead to a “deeper” anesthetic? Several explanations are plausible: first antiorthostatic bed rest diminishes the transfer of propofol to its effector site in the central nervous system. Second, the discomfort and bodily symptoms associated with antiothostatic bed rest provide an arousing input of sufficient magnitude to require a higher dose of anesthesia for an equivalent “anesthetic depth”. It is well known that perceived anesthetic “depth” is the balance between noxious input and dose of anesthetic and that, therefore, an increase in noxious input either requires additional anesthetic or causes arousal. Finally, it could be that the assessments of anesthetic drug effect were not sensitive enough to detect such a small difference in plasma level. The latter possibility seems remote because clinical equivalency was evident from repeated clinical assessments as well as well defined time points such as return of consciousness as well as three clinically validated monitors of cortical anesthetic drug effect (BIS, Patient State Index, and Entropy).

A second important finding of our study was the absence of novel safety concerns caused by adaptation to microgravity, especially since both primates on BION 11 experienced complications that were thought to be caused by anesthesia. In this context the two
anesthetics that were aborted deserve special consideration. The first was a control anesthetic in a subject, who reported a recent upper airway infection (URI) that had completely resolved by the time she presented for the study. Even active URIs are no longer considered contraindications to anesthesia/surgery, because the rate of complications is not increased. Lower respiratory tract infections, in contrast, lower the threshold to trigger airway reflexes. This lowered threshold may persist for weeks beyond the resolution of clinical symptoms. Therefore, when the subjects coughing did not subside with deepening anesthesia, the investigators elected to stop drug administration and withdraw the subject from the study. The second anesthetic was aborted in a subject randomized to simulated microgravity. After induction and airway instrumentation with an LMA, she regurgitated gastric contents, while retching and moving purposefully. Clinical signs, induction dose and EEG based monitors were consistent with the interpretation of inadequate anesthesia. To prevent harm to the subject, propofol administration was discontinued and the anesthesia protocol was modified to allow for propofol dosing more in line with the investigators clinical practice. A less likely explanation for this episode of regurgitation is the fact that gastric emptying is decreased in simulated and actual microgravity, in turn increasing the risk of regurgitation.

There are important limitations to our study. First, adaptation to microgravity was only brief, i.e. simulated by 48 hours of antiorthostatic bed rest. While this duration is sufficient to cause the changes in blood volume and blood flow characteristic of microgravity, and thereby simulates microgravity-induced changes in distribution and elimination of drugs, it falls short of reproducing the clinical scenario of anesthesia care after a medical evacuation from ISS or autonomous care on a long-term mission. Second, anesthesia was studied in the absence of surgery and surgical disease. Both alter the neuro-humeral milieu and may profoundly influence the patient’s response to an anesthetic.

Specific CPR questions addressed by this project are:

18a What are the essential technologies, resources, procedures, skills, and training necessary to provide effective prevention strategies to mitigate each of the conditions listed in the SMCCB-approved Space Medicine Condition List (catalogued in the online Patient Condition Database)? [ISS 3, Lunar 1, Mars 1]

Our research would suggest that initial preparations for administration of anesthesia can be patterned after training, procedures, requirements and technologies used on earth. These same preparations should extend to anesthesia-related aspects of the following questions

18d What resources are required for telemedical consultation, diagnosis, and management of major trauma? [ISS 3, Lunar 2, Mars 1]

18ah What resources and procedures are needed for the surgical management of major illness, injury, and trauma? [ISS 3, Lunar 1, Mars 1]

18ak What are effective regional and local anesthesia strategies in reduced G? [ISS TBD, Lunar TBD, Mars TBD]

23a What are the necessary clinical skills/knowledge for a space medicine physician? [ISS 4, Lunar 1, Mars 1]

22a What decision support technologies are needed to support clinical care? [ISS 4, Lunar 2, Mars 1]
On a separate level, our study addresses aspects of the PK/PD changes caused by adaptation to microgravity as stated in question by studying a drug with well defined rapid effects in a strict crossover design. This question is raised in the CPR as question: 19a What are the effects of space flight and reduced-G on the absorption, distribution, metabolism, clearance, excretion, clinical efficacy, side effects and drug interactions for medications used in primary, secondary and tertiary prevention of conditions stated in the Space Medicine Condition List? [ISS 2, Lunar 2, Mars 1] Our results suggest small changes in PK/PD that fall within the spectrum of normal inter-individual variability are caused by adaptation to microgravity at least for drugs that are administered intravenously and relatively lipophilic.

**Other Information and Materials**

*Presentations*


Anesthesia During and Immediately After Spaceflight. (Invited presentation for a pharmacodynamics panel) 27th Annual International Gravitational Physiology Meeting, 4/23-28/2006, Osaka, Japan

Effects of simulated microgravity on the anesthetic properties of propofol: Clinical observations from a randomized cross-over study, NASA Life Sciences Investigator Workshop, Houston TX 2/2007

Effects of simulated microgravity on the anesthetic properties of propofol. (Invited presentation for the panel on space pharmacology) Aerospace Medical Association Meeting, New Orleans 5/2007

*Published Articles*


*Paper in preparation:*