Acronym: Bisphosphonates

Title: Bisphosphonates as a Countermeasure to Space Flight Induced Bone Loss

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Sponsoring Agency: National Aeronautics and Space Administration (NASA)

Increment(s) Assigned: 17, 18

Mission Assigned:

Brief Research Summary (PAO): Bisphosphonates as a Countermeasure to Space Flight Induced Bone Loss (Bisphosphonates) will determine whether antiresorptive agents, in conjunction with the routine in-flight exercise program, will protect ISS crewmembers from the regional decreases in bone mineral density documented on previous ISS missions.

Research Summary:

- The potential for loss of bone mass is one of the most important medical concerns for long-duration manned space flight with regional losses of 1-2% per month in spite of the fact that crewmembers exercise while in space. The resultant hypercalciuria increases the risk of renal stone formation.

- Bisphosphonates are a group of antiresorptive agents that block breakdown of bone and are used to treat osteoporosis and other disorders related to bone turnover.

- This study will test the effectiveness of two bisphosphonates; alendronate, taken as a pill once per week before and during space flight; and zoledronic acid, given by intravenous infusion once before flight with an effect lasting for the length of the flight.

- If shown to be an effective countermeasure to space flight-induced bone loss, bisphosphonates or other antiresorptive agents could help prevent several bone-related problems for crewmembers on ISS and on future long-duration missions. These problems include loss of bone mineral mass and the possibility of developing renal stones during or after space flight.

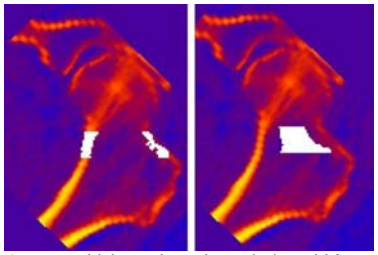
Detailed Research Description:
The purpose of this investigation is to determine whether bisphosphonates, in conjunction with the routine in-flight exercise program, will protect ISS crewmembers from the regional decreases in bone mineral density documented on previous ISS flights. Two dosing regimens will be tested: (1) an oral dose of 70 mg of alendronate taken weekly starting 3 weeks prior to flight and then throughout the flight and (2) an I.V. dose of zoledronic acid, 4 mg, administered just once approximately 45 days before flight. The rationale for including both alendronate and zoledronic acid is that two dosing options will: maximize crew participation, increase the countermeasure options available to flight surgeons, increase scientific opportunities, and minimize the effects of operational and logistical constraints. Operational and logistical constraints may favor one option versus the other. The purpose of this study is not to test one dosing option versus the other. Rather, the intent is to show that bisphosphonates plus exercise will have a measurable effect versus exercise alone in preventing space flight-induced bone loss.

The primary measurement objective of this study will be to obtain preflight and postflight Quantitative Computed Tomography (QCT) scans of the hip. The QCT scans will provide volumetric bone density information of both cortical and trabecular (spongy) bone regions of the hip. This study aims to show that bisphosphonates will significantly reduce bone mineral density loss and the increased risk of renal stone formation documented previously on untreated ISS crewmembers.

Secondary measurement objectives will include: preflight and postflight Dual-energy X-Ray Absorptiometry (DXA) scans of the whole body, spine, hip, and heel; preflight and postflight scans of the tibia using peripheral Quantitative Computed Tomography (pQCT); preflight and postflight blood draws to measure serum markers of bone metabolism, and preflight, inflight, and postflight urine collections to measure urinary markers of bone metabolism. Urine measurements will also be used to look at the risk for developing renal stones before, during and after flight.

Project Type: Payload

Images and Captions:



One mm thick sections through the mid frontal plane of the hip, showing regions of evaluation in white superimposed on a false color image of the Quantitative Computed Tomography (QCT) data. The left hand image shows the cortical region of the femoral neck and the right hand image shows the trabecular bone regions. Courtesy image of NASA.

Operations Location: ISS Inflight

Brief Research Operations:

- While in flight, Alendronate subjects will ingest a pill weekly.
- All subjects will conduct three urine collection sessions.

Operational Requirements: This experiment requires the participation of 10 long duration crewmembers. Subjects will complete DXA and pQCT Scans (L-45, R+5, R+180, and R+360, R+720, R+1080), High Resolution QCT scans (L-45, R+5, R+360), 24-hr urine collections (L-90, L-10, R+0, R+14, R+30, R+180, R+360), and blood draws (L-90, L-10, R+0, R+14, R+30, and R+180, R+360). Alendronate subjects will complete an Alendronate Tolerance Test on L-180, and they will take Alendronate on L-17, L-10, and L-3. Zoledronic Acid subjects will be administered the bisphosphonate on L-45 and will conduct one or more additional blood draws for post-infusion health monitoring.

Operational Protocols: While in flight, Alendronate subjects will ingest a pill weekly. All subjects will conduct three urine collection sessions (flight day 4 weeks, 12 weeks, and 24 weeks). Crewmembers will also take a daily Vitamin D supplement during the duration of the mission.

Category: Human Research and Countermeasure Development for Exploration

Subcategory: Bone and Muscle Physiology in Space

Space Applications: The purpose of this investigation is to determine whether antiresorptive bisphosphonates, in conjunction with the routine in-flight exercise program, will protect ISS crewmembers from the regional decreases in bone mineral density documented on previous ISS flights. If shown to be an effective countermeasure to space flight-induced bone loss, bisphosphonates could prevent or ameliorate several potential bone-related problems identified in NASA's Critical Path Roadmap. If bisphosphonates improve the efficiency of in-flight exercise to maintain bone mass, then more crew time could be made available to ameliorate other problem areas.

Earth Applications: The benefits of this research are primarily for space travelers. Knowledge gained from this investigation may generate useful information applicable to patients on Earth with accelerated bone loss due to disuse (e.g., spinal cord injury patients or those with prolonged immobilization). The timeframe required for relevant knowledge to be transferred to the medical community at large would be an estimated 4-6 years.

Manifest Status: Planned

Availability: Developed for ISS

Supporting Organization: Exploration Systems Mission Directorate (ESMD)

Previous Missions: Bisphosphonates is a unique investigation that has not been conducted in microgravity.

Results:

Results Status:

Results Publications:

Related Publications:
Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, Rodriguez-Portales JA, Downs RW, Gupta J, Santora AC, Liberman UA. Alendronate Phase III Osteoporosis Treatment Study Group. Ten years' experience with alendronate for osteoporosis in postmenopausal women. New England Journal of Medicine. 2004 ;350(12):1189-1199.

LeBlanc A, Schneider V, Shackelford L, West S, Oganov V, Bakulin A, Voronin L. Bone Mineral and lean tissue loss after long duration spaceflight. Journal of Musculoskeletal and Neuronal Interactactions. 2000 ;1(2):157-160.

LeBlanc AD, Driscoll TB, Shackelford LC, Evans HJ, Rianon NJ, Smith SM, Feeback DL, Lai, D. Alendronate as an Effective Countermeasure to Disuse Induced Bone Loss. Journal of Musculoskeletal and Neuronal Interactions. 2002 ;2(4): 335-343.

Shapiro J, Beck TJ, Mustapha B, Ruff CB, Ballard P, BrintzenhofeSzoc K, Caminis J. Zoledronic Acid Counteracts Bone Loss in the Spinal Cord Injury Model of Microgravity. Journal of Bone Mineral Research. 2004 ;19:S445.

Watanabe Y, Ohshima H, Mizuno K, Sekiguchi C, Fukunaga M, Kohri K, Rittweger J, Felsenberg D, Matsumoto T, Nakamura T. Intravenous pamidronate prevents femoral bone loss and renal stone formation during 90-day bed rest. Journal of Bone Mineral Research. 2004 ;19(11):1771-1778.

Web Sites:

Related Payload(s): Subregional Bone