

# Microgravity and drug effects on bone

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Microgravity changes the metabolic environment of bone leading to site-specific alterations in bone remodeling: bone formation is decreased and bone resorption is increased resulting in significant bone loss with an attendant increase in fracture risk. The pelvis and lower extremities show the greatest loss of bone that may amount to as much as 5% in the lumbar spine and 10% in the proximal femur after spaceflight of 6 months duration<sup>1</sup>. Multiple drugs have been employed during manned spaceflight to combat a variety of flight-related medical disorders such as space motion sickness, sleeplessness, nasal congestion, headache, back pain and constipation. The list includes antibiotics, sleep medications, drugs for nasal congestion, antiarrhythmics, and muscle relaxants<sup>2</sup>. However, to date, only exercise has been employed to counter bone loss: the effects of different regimens have not proven protective of bone.

It is appreciated that the response of bone to drugs will be different in extended spaceflight as compared to responses on the ground<sup>3</sup>. Extended bed rest studies on earth have not focused on pharmacodynamics of bone active drugs. The few reported observations that involving drugs such as acetaminophen and promethazine indicate that microgravity has potentially profound effects on drug actions when compared to earth<sup>4</sup>. Furthermore, drug action in microgravity may be affected by factors such as gender, which is not considered a primary fact when assessing drug actions on earth, but which may assume greater importance in microgravity<sup>5</sup>.

Microgravity will alter drug pharmacokinetics through several mechanisms:<sup>6-8</sup>

- Oral availability: Alterations in agent dissolution rate, absorption, hepatic first pass metabolism, and in intestinal blood flow.

- Drug distribution: changes in total body water and plasma volume, muscle loss
- Alterations in receptor number and receptor affinity
- Altered drug metabolism leading to increased or decreased drug activity
- Altered tissue binding
- Altered pulmonary absorption: altered aerosol dispersion
- Altered renal clearance due to changes in renal perfusion due to drug toxicity
- Altered drug elimination via skin, the GI tract and the pulmonary tract.

The pharmacologic approach to the preservation of bone mass during spaceflight is complex because of the multiplicity of factors affecting bone metabolism, which are affected by microgravity exposure. Additional factors specific to bone that potentially alter the response to drugs are: alterations in fluid shear forces at the cellular level, alterations in the composition of osteoblast and osteoclast populations and changes in several hormones and cytokines including decreased levels of PTH, elevations in ionized serum calcium, decreased levels of 25(OH) and 1,25(OH) vitamin D, depressed levels of IGF-1 and growth hormone, elevated plasma cortisol levels and alterations in diurnal rhythms.

Drugs that act primarily on bone have not been tested during spaceflight. The use of the oral and intravenous bisphosphonates, alendronate and zoledronic acid, is currently under consideration for flight testing. Animal experiments provide only limited insight into the potential actions of these agents during extended duration spaceflight. Alendronate, and pamidronate have been studied in the chronic bed rest model and zoledronic acid has been studied in individuals with spinal cord injury<sup>9,10</sup>; each has been shown to protect bone mass suggesting their potential for limiting bone loss in microgravity<sup>11</sup>. However, when estimating the response during flight, one must consider experiments on earth that demonstrate the importance of inter-subject variation in drug absorption as well as the different effects of age and gender on bisphosphonate pharmacodynamics<sup>12</sup>.

Future studies may involve newer pharmacologic countermeasures to bone loss. Among these may be anti-resorptive agents such as Rank Ligand inhibitors, or agents designed to

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increase osteoblastic bone formation such as PTH analogues<sup>13</sup>. The potential role for cathepsin K inhibitors, integrin inhibitors or hormone receptor agonists such as SERMs is untested.

Microgravity exposure increases bone resorption. An important consideration is the maintenance of coupled bone formation following prolonged treatment with anti-resorptive agent, during a 6-month flight to Mars. However, the use of newer pharmacologic agents in the future may permit better maintenance of coupled bone formation and resorption under varying conditions of microgravity as would be experienced during long-duration spaceflight.

Programs should be developed to test the pharmacokinetic, pharmacodynamic and pharmacogenetic characteristics of drugs during microgravity with the goal of maintaining the integrity of bone during extended exposure to a microgravity environment.

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