National Institute of Arthritis and Musculoskeletal and Skin Diseases
Bisphosphonates with Estrogen Show Additive Benefits Against Osteoporosis

NIH-supported investigators identified the mechanism of action of bisphosphonates, used to treat osteoporosis. Unlike the effects of bisphosphonates and PTH, the effects of bisphosphonates and estrogen are additive; thus, combining these two medications may prove more effective than unpleasant and costly injections of PTH.

Lead Agency:

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)/National Institutes of Health (NIH)

Agency Mission:

The mission of the National Institute of Arthritis and Musculoskeletal and Skin Diseases is to support research into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases, the training of basic and clinical scientists to carry out this research, and the dissemination of information on research progress in these diseases.

Principal Investigators:

Dr. Stavros C. Manolagas

Dr. Joel Finkelstein

Dr. Felicia Cosman

Dr. Dennis Black

Partner Agency:

National Institute on Aging (NIA)
Department of Veterans' Affairs

General Description:

Bisphosphonates with Estrogen Show Additive Benefits Against Osteoporosis
The mechanism by which estrogen decreases cell death in bone forming cells, the osteoblast, has been identified, and new therapies based on this action of estrogen are being designed and tested as a result. However, increasing evidence indicates that the bone-maintaining and primary stress-sensing cell, the osteocyte, also contributes to the mechanical competence of the skeleton. Both estrogen and bisphosphonates, also used to treat osteoporosis, act to prevent death of osteocytes. However, until recently the bisphosphonate mechanism of action was not well understood, and questions remained as to how to optimize this therapy as well as how to best combine it with other osteoporosis therapies in order to achieve the best effect while minimizing drug use and cost.

In a recent study, NIH-supported investigators found that bisphosphonates act through a novel intracellular signaling pathway triggered by opening of special channels in the osteocytes' membranes. Their findings demonstrate that estrogen and bisphosphonates act on osteocytes to prevent cell death via different mechanisms. The effects of the two drugs are additive *in vitro*. Thus, this work helps to explain clinical observations that the combination of these two drugs may be more effective than either drug alone as a treatment for osteoporosis.

Earlier NIH-funded research has provided guidance about using bisphosphonates concurrently with another medication, PTH, which closely resembles human parathyroid hormone. Unlike bisphosphonates and estrogen which slow bone loss by preventing cell death, PTH stimulates bone formation. Many thought that bisphosphonates and PTH combined would be more protective than either taken separately. NIH-supported researchers refuted that belief, demonstrating that not only did the combined regimen of PTH injections and oral bisphosphonate therapy fail to provide more benefit than bisphosphonate alone, combining the oral drug and PTH injections somewhat diminished the therapeutic effect of PTH alone.

Despite its health benefits, patients are reluctant to give themselves daily injections of PTH. Therefore, researchers continued to search for strategies to minimize the cost and burden of PTH therapies—with important results that provide good news for people with osteoporosis. In a subsequent study, women taking PTH for one year were given either no drug in the second year or were switched to bisphosphonate. Those who received no drug after a year of PTH began to lose the bone they had gained during treatment, while those who switched to bisphosphonate in the second year continued to gain bone, demonstrating that the sequential use of PTH as a bone building drug followed by bone-conserving bisphosphonate maximized the bone gain.

In a related study in a different laboratory, researchers found that treatment with PTH does not need to be continuous throughout the year. In fact, cyclic treatment with PTH for three months followed by three months of bisphosphonate alone was as effective in stimulating bone gain as the continuous use of PTH for 12 months. Taking 3-month breaks from PTH not only provides cost benefits, but also improves quality of life for patients who do not need to inject the drug every day.

Excellence: What makes this project exceptional?

This new work demonstrates a novel mechanism of action of bisphosphonates and shows that this mechanism differs from and is additive to the action of estrogen. These new insights open the path for optimizing use of both types of drugs individually and in combination to achieve the best treatment for osteoporosis.

Significance: How is this research relevant to older persons, populations and/or an aging society?

Osteoporosis affects over ten million people in the United States and is a major cause of morbidity, loss of function, and mortality among older adults.

Effectiveness: What is the impact and/or application of this research to older persons?

Physicians and patients can use the results of these studies to strategize for the best therapeutic benefit while minimizing drug use and cost.

Innovativeness: Why is this research exciting or newsworthy?

Optimizing treatments for osteoporosis has the potential to affect quality of life and reduce costs of care for millions of Americans.