Nitroglycerin Ointment Modestly Raises BMD

BY MARY ANN MOON

FROM JAMA

Topical nitroglycerin ointment raises bone mineral density, cuts resorption, and alters bone structure so that bone strength is increased, according to results of a double-blind trial in 243 women.

The magnitude of improvement equals or exceeds that observed with other therapies, including teriparatide. "Together, these findings suggest that nitroglycerin may significantly decrease the risk of fractures, including fractures in long bones such as the hip, legs, and upper arm, which are largely composed of cortical bone," wrote Dr. Sophie A. Jamal of the University of Toronto and her associates.

In a single-center double-blind clinical trial, they assessed the efficacy of daily application of 2% nitroglycerin ointment over the course of 2 years in increasing bone mineral density (BMD). The study was not large enough to directly determine the drug's effects on fracture risk.

The study subjects were randomly assigned to apply active 15 mg/d nitroglycerin or a matching placebo ointment to a piece of onion skin that was taped to the upper outer arm overnight, every night. The study subjects were women aged 50 years or older (mean age, 62 years) who were at least 1 year past menopause. None had osteoporosis, but all had BMD T scores of 0 to –2.0 at the lumbar spine and higher than –2.0 at the total hip.

A total of 400 women were enrolled, but only 243 remained in the study long enough to be included in the analysis; 126 in the nitroglycerin group and 117 in the placebo group. A total of 106 subjects dropped out because of headache, nausea, or allergic reaction, and another 51 "lost interest" or became ineligible.

After randomization, another 30 subjects in the nitroglycerin group (24%) and 15 in the placebo group (13%) discontinued treatment or were lost to follow-up, including 26 who cited adverse reactions including headache.

VITALS

Major Finding: Compared with placebo, topical nitroglycerin ointment increased bone mineral density in the lumbar spine, total hip, and femoral neck by 7%; decreased bone resorption; and strengthened bone structure to the same or a greater degree than did other available therapies.

Data Source: A single-center, double-blind, placebo-controlled, randomized clinical trial involving 243 postmenopausal women followed for 2 years.

Disclosures: This study was supported by the Canadian Institutes of Health Research and Physicians' Services Inc. Dr. Jamal reported receiving support from Novartis, Amgen, Warner-Chilcott, Genzyme, and Shire, and her associates reported ties to numerous drug, device, and technology companies.

The primary end point was change in lumbar spine areal BMD after 2 years of treatment. Compared with women in the placebo group, those who received active nitroglycerin showed a significant increase of approximately 7% in areal BMD at the lumbar spine.

They also showed comparable increases in areal BMD at the total hip (6%) and femoral neck (7%). Compared with placebo users, the nitroglycerin group also showed increases in volumetric trabecular BMD of 12% at the radius and 8.5% at the tibia; increases in cortical thickness of 14% at the radius and 25% at the tibia; and increases in periosteal circumference of 7% at the radius and 3% at the tibia. The latter finding has not been reported with any other agent, they said (JAMA 2011;305:800-07).

Nitroglycerin therapy also was associated with increases in measures of bone strength, with rises of 11% and 10% in polar section modulus and of 7% and 14.5% in polar moment of inertia at the radius and tibia, respectively. These findings indicate significant improvement in bone bending and twisting strength, which in previous research has correlated with fewer fractures.

Compared with placebo, nitroglycerin treatment was associated with significant increases in bone-specific alkaline phosphatase, a marker of bone formation. This rose 14% at 3 months, 21% at 12 months, and 35% at 24 months. At the same time, urinary N-telopeptide level, a marker of bone resorption, decreased by 20% at 3 months, 33% at 12 months, and 54% at 24 months.

This concomitant change indicates that nitroglycerin uncouples bone formation from bone resorption. Moreover, "the differential effects of nitroglycerin on formation and resorption appear to widen with time, suggesting that its efficacy continues or even increases during 24 months of use. In contrast, the effects of other antiresorptives and teriparatide either plateau or wane with time," Dr. Jamal and her colleagues wrote.

The incidence of serious adverse effects did not differ between the two groups, at 4% in both. However, headaches were much more common with active nitroglycerin, and often led to discontinuation of therapy. The number of headaches markedly declined with time, and no subjects dropped out of the second year of the study because of headache.

"The possibility that different preparations, doses, or schedules of administration would reduce the frequency of headaches without diminishing the effects on bone should be explored in future studies," the researchers said. ■

VIEW ON THE NEWS

Next Step: Assess Fracture Rate

When added to previous research, the findings reported by Dr. Jamal and her associates suggest that nitroglycerin both inhibits bone resorption and stimulates bone formation, which no single drug can do. These results "should set the stage for an adequately powered, larger study using nitroglycerin ointment, with fracture as an outcome," said Dr. Sundeep Khosla.

"If such a study demonstrates efficacy for reducing fractures, clinicians would have a novel and inexpensive therapy for osteoporosis."

The results of the current study also should spur development of other agents that act as nitric oxide donors, preferably drugs with better adverse effect profiles that don't cause so many headaches.

Future research also should report data on any blood pressure changes associated with nitroglycerin therapy, which Dr. Jamal and her associates did not report on, he added.

DR. KHOSLA *is in the endocrine research unit at the Mayo Clinic, Rochester, Minn. He reported serving on a scientific advisory board for Amgen. These remarks were taken from his editorial accompanying Dr. Jamal's report (JAMA 2011;305:826-7).*

Zoledronic Acid Cuts Fractures at All Fracture-Risk Levels

BY MITCHEL L. ZOLER

FROM THE ANNUAL MEETING OF THE AMERICAN SOCIETY FOR BONE AND MINERAL RESEARCH

TORONTO – Among postmenopausal women with osteoporosis, treatment with zoledronic acid had a similar effect on fracture reduction regardless of whether women had a low, intermediate, or high baseline fracture risk, based on a post-hoc analysis of nearly 3,900 women who received the agent in the drug's pivotal trial for fracture prevention.

The analysis showed that rates of vertebral fractures and total clinical fractures fell by roughly similar amounts, regardless of the women's baseline fracture risk, with annual injection of zoledronic acid during 3 years of treatment and follow-up.

The rate of hip fractures showed a greater reduction in women who entered the study in the lowest tertile for fracture risk relative to the placebo group than in women with intermediate or high risk, but this difference failed to reach statistical significance, Jane A. Cauley, Dr.P.H. said at the meeting.

The message is that postmenopausal women with osteoporosis should feel comfortable starting zoledronic acid treatment regardless of the severity of their fracture risk at baseline, said Dr. Cauley, professor of epidemiology at the University of Pittsburgh.

It is not necessary to target treatment to women with an especially elevated fracture risk, such as those with a high FRAX (Fracture Risk Assessment Tool) score, she explained.

The current analysis used data collected in the Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly (HORIZON) pivotal fracture trial, which randomized 7,765 postmenopausal women to either an annual infusion with 5 mg zoledronic acid or placebo for 3 years (N. Engl. J. Med 2007;356:1809-22).

Assessment of the study's primary end point showed that annual treatment with zoledronic acid significantly cut the rate of vertebral and hip fractures as well as total clinical fractures.

To perform the post-hoc analysis, Dr. Cauley and her associates rated the baseline fracture risk of the 3,889 women randomized to receive zoledronic acid using a modification of the Fracture Index developed for the Study of Osteoporotic Fractures (SOF) (Osteoporosis Int. 2001;12:519-28).

The modification calculated a woman's baseline fracture risk using five of the seven variables of the SOF tool available in the HORIZON records: age, femoral neck bone mineral density T score, clinical fracture history, weight, and smoking status. The two SOF tool elements not available were maternal history of hip fracture and the use of arms to stand from a chair.

Analyses by Dr. Cauley and her associates using SOF data showed that calculating a fracture risk score with the five elements had a 98% correlation with the seven-item score, as well as a 64% correlation with women's FRAX scores. To further confirm the validity of the modified SOF score, they calculated scores for the 3,876 women enrolled in the placebo arm of HORIZON.

During 3 years of follow-up, the rate of total fractures per 1,000 person-years was 30, 35, and 45, respectively, in the low-, intermediate-, and high-risk tertiles.

Overall, for every 1-point rise in the modified SOF score, the risk of a fracture among the placebo women during follow-up rose by 11%, a statistically significant difference.

HORIZON was supported by Novartis, the company that markets zoledronic acid. Dr. Cauley said that she has received research funding from and has served as a consultant to Novartis. ■