Nitroglycerin Ointment Strengthened Bone

BY MARY ANN MOON

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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.

Of 400 women enrolled, 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 treatment group and 15 in the placebo group discontinued or were lost to follow-up, including 26 who cited adverse reactions including headache.

The primary end point was change in lumbar spine areal BMD after 2 years. Those who received active nitroglycerin showed a significant increase of about 7%, compared with women in the placebo group, in that measure.

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 trabecu-

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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.

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lar 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, the investigators said (JAMA 2011;305:800-7).

Nitroglycerin therapy also was linked 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.

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 was 4% in both groups. However, headaches were much more common with 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 owing to 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 concluded.

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