

Intensive BP Therapy May Cut Fracture Risk

BY RICHARD M. KIRKNER

FROM THE ANNUAL MEETING OF THE AMERICAN SOCIETY OF HYPERTENSION

NEW YORK – Intensive therapy to control systolic blood pressure did not appear to be associated with more falls and fractures in a study of patients under age 80 years with hypertension and type 2 diabetes, based on a report presented at the meeting.

The finding was noted in a subgroup analysis of ACCORD-BONE, an ancillary study of skeletal health in ACCORD study participants. The subgroup analysis looked at ACCORD-BONE participants in the ACCORD Blood Pressure Clinical Trial arm of ACCORD.

For the subgroup analysis, the researchers examined data from 3,282 people who were randomly assigned to standard systolic blood pressure goals of

130-139 mm Hg or to intensive systolic goals of less than 120 mm Hg.

“Intensive control of systolic blood pressure did not result in an increased risk of falls,” reported Dr. Karen Margolis of the Health Partners Research Foundation in Minneapolis. “And fewer intensive than standard group patients developed nonspinal fractures.”

Average blood pressure at entry was 138/75 mm Hg. Those in the intensive

therapy group received a thiazide-type diuretic in combination with another class of antihypertensive drug to a goal of 120 mm Hg. The standard intervention group used the same drugs and combinations, but the systolic goal was 130-135 mm Hg and treatment was only intensified if systolic blood pressure rose above 160 mm Hg, according to Dr. Margolis.

Systolic blood pressure averaged 133 mm Hg in the standard treatment group and 119 mm Hg in the intensive treatment group. Subjects' average age was 62 years, and patients over age 80 years were excluded; 44% were women; 66% were white, 26% were black, and 2% Latino. Patients' average body mass index was 32.5 kg/m².

With an average follow-up of almost 5 years, ACCORD-BONE study results bucked conventional wisdom about risk of falls, according to Dr. Margolis. “About 20% in the intensive group and 21% in the standard group fell,” she said. The intensive group had a 0.81 relative risk of falling, compared with the standard group. The study found no differences across age, sex, ethnicity, or status of baseline diabetes.

The overall rate of self-reported falls was 70/100 person-years, Dr. Margolis said. “This also was lower in the intensive group at 62/100 person-years vs. the standard group at 74/100.

“With regard to nonspinal fractures, the study identified 273 individuals with at least one fracture, including 63 ankle, 34 humerus, 29 foot, 25 wrist, and 19 hip,” said Dr. Margolis. “Overall, fracture risk was significantly lower in the intensive vs. the standard blood pressure group with a hazard ratio of 0.78,” she said.

Dr. Margolis acknowledged the ACCORD-BONE study had some limits. “One of the most striking findings from the blood pressure treatment data was that there was a very, very large difference in thiazide use – thiazides being known to improve bone density – so that’s a very suggestive mechanism,” she said.

Dr. Joseph L. Izzo of the University of Buffalo, N.Y., remarked about obesity in the study group, noting the high average BMI. “I’m not sure that overweight people aren’t protected in some way against blood pressure-related falls,” Dr. Izzo said.

Physical activity might also explain why those on intensive therapy were less prone to falls and fractures, noted Dr. Bryan Williams of the University of Leicester, England. “To some extent, falls are not always due to just people getting possible hypotension; they’re related to amount of activity,” he said.

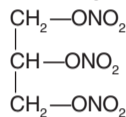
Dr. Margolis said that a substudy would further investigate physical activity in this population.

The National Heart, Lung, and Blood Institute and National Institute of Diabetes and Digestive and Kidney Diseases funded the ACCORD-BONE study. Dr. Margolis had no other disclosures to report.

Nitrolingual® Pumpspray

(nitroglycerin lingual spray)
400 mcg per spray, 60 or 200 Metered Sprays

DESCRIPTION: Nitroglycerin, an organic nitrate, is a vasodilator which has effects on both arteries and veins. The chemical name for nitroglycerin is 1,2,3-propanetriol trinitrate (C₃H₅N₃O₉). The compound has a molecular weight of 227.09. The chemical structure is:



Nitrolingual® Pumpspray (nitroglycerin lingual spray 400 mcg) is a metered dose spray containing nitroglycerin. This product delivers nitroglycerin (400 mcg per spray, 60 or 200 metered sprays) in the form of spray droplets onto or under the tongue. Inactive ingredients: medium-chain triglycerides, dehydrated alcohol, medium-chain partial glycerides, peppermint oil.

CLINICAL PHARMACOLOGY: The principal pharmacological action of nitroglycerin is relaxation of vascular smooth muscle, producing a vasodilator effect on both peripheral arteries and veins with more prominent effects on the latter. Dilation of the post-capillary vessels, including large veins, promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure (pre-load). Arteriolar relaxation reduces systemic vascular resistance and arterial pressure (after-load). The mechanism by which nitroglycerin relieves angina pectoris is not fully understood. Myocardial oxygen consumption or demand (as measured by the pressure-rate product, tension-time index, and stroke-work index) is decreased by both the arterial and venous effects of nitroglycerin and presumably, a more favorable supply-demand ratio is achieved. While the large epicardial coronary arteries are also dilated by nitroglycerin, the extent to which this action contributes to relief of exertional angina is unclear.

Nitroglycerin is rapidly metabolized *in vivo*, with a liver reductase enzyme having primary importance in the formation of glycerol nitrate metabolites and inorganic nitrate. Two active major metabolites, 1,2- and 1,3-dinitroglycerols, the products of hydrolysis, although less potent as vasodilators, have longer plasma half-lives than the parent compound. The dinitrates are further metabolized to mononitrates (considered biologically inactive with respect to cardiovascular effects) and ultimately glycerol and carbon dioxide.

Therapeutic doses of nitroglycerin may reduce systolic, diastolic and mean arterial blood pressure. Effective coronary perfusion pressure is usually maintained, but can be compromised if blood pressure falls excessively or increased heart rate decreases diastolic filling time.

Elevated central venous and pulmonary capillary wedge pressures, pulmonary vascular resistance and systemic vascular resistance are also reduced by nitroglycerin therapy. Heart rate is usually slightly increased, presumably a reflex response to the fall in blood pressure. Cardiac index may be increased, decreased, or unchanged. Patients with elevated left ventricular filling pressure and systemic vascular resistance values in conjunction with a depressed cardiac index are likely to experience an improvement in cardiac index. On the other hand, when filling pressures and cardiac index are normal, cardiac index may be slightly reduced.

In a pharmacokinetic study when a single 0.8 mg dose of Nitrolingual® Pumpspray was administered to healthy volunteers (n = 24), the mean C_{max} and T_{max} were 1,041 pg/mL · min and 75 minutes, respectively. Additionally, in these subjects the mean area-under-the-curve (AUC) was 12,769 pg/mL · min.

In a randomized, double-blind single-dose, 5-period cross-over study in 51 patients with exertional angina pectoris significant dose-related increases in exercise tolerance, time to onset of angina and ST-segment depression were seen following doses of 0.2, 0.4, 0.8 and 1.6 mg of nitroglycerin delivered by metered pumpspray as compared to placebo. Additionally the drug was well tolerated as evidenced by a profile of generally mild to moderate adverse events.

INDICATIONS AND USAGE: Nitrolingual® Pumpspray is indicated for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS: Allergic reactions to organic nitrates are rare. Nitroglycerin is contraindicated in patients who are allergic to it. Nitrolingual® Pumpspray is contraindicated in patients taking certain drugs for erectile dysfunction (phosphodiesterase inhibitors), as their concomitant use can cause severe hypotension. The time course and dose-dependency of this interaction are not known.

WARNINGS: Amplification of the vasodilatory effects of Nitrolingual® Pumpspray by certain drugs (phosphodiesterase inhibitors) used to treat erectile dysfunction can result in severe hypotension. The time course and dose dependence of this interaction have not been studied. Appropriate supportive care has not been studied, but it seems reasonable to treat this as a nitrate overdose, with elevation of the extremities and with central volume expansion. The use of any form of nitroglycerin during the early days of acute myocardial infarction requires particular attention to hemodynamic monitoring and clinical status.

PRECAUTIONS: (General) Severe hypotension, particularly with upright posture, may occur even with small doses of nitroglycerin. The drug, therefore, should be used with caution in subjects who may have volume depletion from diuretic therapy or in patients who have low systolic blood pressure (e.g., below 90 mm Hg). Paradoxical bradycardia and increased angina pectoris may accompany nitroglycerin-induced hypotension.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy. Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and anti-anginal effects of nitrates has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. In industrial workers continuously exposed to nitroglycerin, tolerance clearly occurs. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In various clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of nitroglycerin is not known.

PRECAUTIONS: (INFORMATION FOR PATIENTS) Physicians should discuss with patients that Nitrolingual® Pumpspray should not be used with certain drugs taken for erectile dysfunction (phosphodiesterase inhibitors) because of the risk of lowering their blood pressure dangerously.

DRUG INTERACTIONS: Alcohol may enhance sensitivity to the hypotensive effects of nitrates. Nitroglycerin acts directly on vascular muscle. Therefore, any other agents that depend on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending upon the agent.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and oral controlled-release nitroglycerin were used in combination. Dose adjustments of either class of agents may be necessary.

Concomitant use of nitric oxide donors (like Nitrolingual® Pumpspray) and certain drugs for the treatment of erectile dysfunction (phosphodiesterase inhibitors) can amplify their vasodilatory effects, resulting in severe hypotension. The concomitant use of these drugs is contraindicated (see **CONTRAINDICATIONS**) and alternative therapies should be used to treat acute angina episodes.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Animal carcinogenesis studies with sublingual nitroglycerin have not been performed. Rats receiving up to 434 mg/kg/day of dietary nitroglycerin for 2 years developed dose-related fibrotic and neoplastic changes in liver, including carcinomas, and interstitial cell tumors in

testes. At high dose, the incidences of hepatocellular carcinomas in both sexes were 52% vs. 0% in controls, and incidences of testicular tumors were 52% vs. 8% in controls. Lifetime dietary administration of up to 1056 mg/kg/day of nitroglycerin was not tumorigenic in mice. Nitroglycerin was weakly mutagenic in Ames tests performed in two different laboratories. Nevertheless, there was no evidence of mutagenicity in an *in vivo* dominant lethal assay with male rats treated with doses up to about 363 mg/kg/day, p.o., or in *in vitro* cytogenetic tests in rat and dog tissues.

In a three-generation reproduction study, rats received dietary nitroglycerin at doses up to about 434 mg/kg/day for six months prior to mating of the F₀ generation with treatment continuing through successive F₁ and F₂ generations. The high dose was associated with decreased feed intake and body weight gain in both sexes at all matings. No specific effect on the fertility of the F₂ generation was seen. Infertility noted in subsequent generations, however, was attributed to increased interstitial cell tissue and aspermatogenesis in the high-dose males. In this three-generation study there was no clear evidence of teratogenicity.

PREGNANCY: Pregnancy Category C – Animal teratology studies have not been conducted with nitroglycerin-pumpspray. Teratology studies in rats and rabbits, however, were conducted with topically applied nitroglycerin ointment at doses up to 80 mg/kg/day and 240 mg/kg/day, respectively. No toxic effects on dams or fetuses were seen at any dose tested. There are no adequate and well-controlled studies in pregnant women. Nitroglycerin should be given to pregnant women only if clearly needed.

NURSING MOTHERS: It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Nitrolingual® Pumpspray is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness of nitroglycerin in pediatric patients have not been established.

ADVERSE REACTIONS: Adverse reactions to oral nitroglycerin dosage forms, particularly headache and hypotension, are generally dose-related. In clinical trials at various doses of nitroglycerin, the following adverse effects have been observed: Headache, which may be severe and persistent, is the most commonly reported side effect of nitroglycerin with an incidence on the order of about 50% in some studies. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop. Occasionally, an individual may exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) may occur even with therapeutic doses. Drug rash and/or exfoliative dermatitis have been reported in patients receiving nitrate therapy. Nausea and vomiting appear to be uncommon.

Nitrolingual® Pumpspray given to 51 chronic stable angina patients in single doses of 0.4, 0.8 and 1.6 mg as part of a double-blind, 5-period single-dose cross-over study exhibited an adverse event profile that was generally mild to moderate. Adverse events occurring at a frequency greater than 2% included: headache, dizziness, and paresthesia. Less frequently reported events in this trial included (≤2%): dyspnea, pharyngitis, rhinitis, vasodilation, peripheral edema, asthenia, and abdominal pain.

OVERDOSAGE: Signs and Symptoms: Nitrate overdosage may result in: severe hypotension, persistent throbbing headache, vertigo, palpitation, visual disturbance, flushing and perspiring skin (later becoming cold and cyanotic), nausea and vomiting (possibly with colic and even bloody diarrhea), syncope (especially in the upright posture), methemoglobinemia with cyanosis and anorexia, initial hyperpnea, dyspnea and slow breathing, slow pulse (dicrotic and intermittent), heart block, increased intracranial pressure with cerebral symptoms of confusion and moderate fever, paralysis and coma following the clonic convulsions, and possibly death due to circulatory collapse.

Methemoglobinemia: Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates. The formation of methemoglobin is dose-related and in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrates could produce harmful concentrations of methemoglobin.

Treatment of Overdosage:

Keep the patient recumbent in a shock position and comfortably warm. Passive movement of the extremities may aid venous return. Administer oxygen and artificial ventilation, if necessary. If methemoglobinemia is present, administration of methylene blue (1% solution), 1-2 mg per kilogram of body weight intravenously, may be required. If an excessive quantity of Nitrolingual® Pumpspray has been recently swallowed gastric lavage may be of use.

WARNING: Epinephrine is ineffective in reversing the severe hypotensive events associated with overdosage. It and related compounds are contraindicated in this situation.

DOSE AND ADMINISTRATION: At the onset of an attack, one or two metered sprays should be administered onto or under the tongue. No more than three metered sprays are recommended within a 15-minute period. If the chest pain persists, prompt medical attention is recommended. Nitrolingual® Pumpspray may be used prophylactically five to ten minutes prior to engaging in activities which might precipitate an acute attack.

Each metered spray of Nitrolingual® Pumpspray delivers 48 mg of solution containing 400 mcg of nitroglycerin after an initial priming of 5 sprays. It will remain adequately primed for 6 weeks. If the product is not used within 6 weeks it can be adequately reprimed with 1 spray. Longer storage periods without use may require up to 5 repriming sprays. There are 60 or 200 metered sprays per bottle. The total number of available doses is dependent, however, on the number of sprays per use (1 or 2 sprays), and the frequency of repriming.

The transparent container can be used for continuous monitoring of the consumption. **The end of the pump should be covered by the fluid level.** Once fluid falls below the level of the center tube, sprays will not be adequate and the container should be replaced. As with all other sprays, there is a residual volume of fluid at the bottom of the bottle which cannot be used.

During application the patient should rest, ideally in the sitting position. The container should be held vertically with the valve head uppermost and the spray orifice as close to the mouth as possible. The dose should preferably be sprayed onto the tongue by pressing the button firmly and the mouth should be closed immediately after each dose. **THE SPRAY SHOULD NOT BE INHALED.** The medication should not be expectorated or the mouth rinsed for 5 to 10 minutes following administration. Patients should be instructed to familiarize themselves with the position of the spray orifice, which can be identified by the finger rest on top of the valve, in order to facilitate orientation for administration at night.

HOW SUPPLIED: Each box of Nitrolingual® Pumpspray contains one glass bottle coated with red transparent plastic which assists in containing the glass and medication should the bottle be shattered. Each bottle contains 4.9 g or 12 g (Net Content) of nitroglycerin lingual spray which will deliver 60 or 200 metered sprays containing 400 mcg of nitroglycerin per spray after priming. Nitrolingual® Pumpspray is available as:

- 60-dose (4.9 g) single bottle NDC 24338-300-65
- 200-dose (12 g) single bottle NDC 24338-300-20

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Note: Nitrolingual® Pumpspray contains 20% alcohol. Do not forcefully open or burn container after use. Do not spray toward flames. Rx Only.



Manufactured for
Arbor Pharmaceuticals, Raleigh, North Carolina 27609
by G. Pohl-Boskamp GmbH & Co. KG,
25511 Hohenlockstedt, Germany

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