

CLINICAL CAPSULES

Statins Reduce Sepsis Risk

Statins may diminish the risk of sepsis in people with cardiovascular disease, according to the results of a large observational study.

Dr. Daniel G. Hackam of the University of Toronto and his colleagues found that the risk of sepsis was reduced by 19% in patients over the age of 65 years who used statins, compared with those who did not use the drugs (Lancet DOI:10.1016/S0140-6736[06]68041-0, published Jan. 25, 2006).

Statins, widely used as lipid-lowering

agents, also exhibit anti-inflammatory and antioxidant effects and can improve endothelial function and modulate cellular immunity, all of which may help ward off the severe effects of sepsis, the authors wrote.

The researchers identified 173,410 patients at high risk of sepsis. The selection criteria were patients over 65 years who had been treated in a hospital in Ontario, Canada, between 1997 and 2002 for an acute cardiac event, ischemic stroke, or revascularization. Propensity-based matching produced a final cohort of 69,168 pa-

tients, of whom 34,584 were statin users and 34,584 were not.

Monitoring for each patient began on their index date and continued until the patient died or was admitted to the hospital for sepsis, or until the end of the study, if there were no events. In all, there were 1,218 cases of sepsis, of which 551 were in statin-using patients and 667 were in the nonstatin-using control group, a statistically significant difference. The development of severe or fatal sepsis was also less likely in the statin-using group, the authors noted.

Dr. Hackam and his colleagues recommended that statin treatment for patients

with major infections who are already on the drug should be continued, although they should be monitored closely for potential toxic effects. Statins should be considered for patients with a high risk for sepsis, especially those with cardiovascular disease, they wrote.

Waist Size Predicts CVD Risk

Waist circumference of at least 35 inches correlated with major cardiovascular and metabolic risk factors in women, reported Dr. Lori Mosca, director of preventive cardiology at New York-Presbyterian Hospital/Columbia University Medical Center, and her associates.

This finding suggests that measuring the waist can serve as a simple way to identify women at risk for cardiovascular events "who might benefit from further evaluation and intervention," the researchers said (J. Women's Health 2006;15:24-34).

They conducted a free, 1-day cardiovascular disease (CVD) screening program in 12 cities across the country; 6,938 women aged 18-93 years participated, and more than half were racial or ethnic minorities. The women were assessed for waist size, blood pressure, body mass index, and cholesterol and glucose levels.

Waist circumference of at least 35 inches was found in 52%; these women were significantly more likely than those with smaller waists to have high blood pressure, hypercholesterolemia, low HDL cholesterol, and impaired fasting glucose, even after the data were controlled for race and ethnicity, education level, and family history of CVD.

Thus a single, simple waist measurement, even if done by the woman herself, can be valuable in identifying those "who have a clustering of risk factors known to be synergistic with respect to CVD risk," Dr. Mosca and her associates said.

High Fish Intake Cuts CHD Risk

For reducing the risk of coronary heart disease, a diet high in fish is better than a diet with a modest amount of fish, reported Dr. Hiroyasu Iso of the University of Tsukuba, Ibaraki-ken, Japan, and associates.

The investigators conducted a prospective study of healthy Japanese men (19,985) and women (21,593) aged 40-59 years at enrollment during 1990-1992. By follow-up in 2001, there had been 258 incident cases of CHD, including 198 definite MIs, 23 probable MIs, and 37 sudden cardiac deaths. This included 62 fatal and 196 nonfatal cardiac events (Circulation 2006;113:195-202).

CHD risk was 40% lower among people with the highest intake of fish (eight servings per week, or 180 g/day) than among those with the lowest intake (once per week, or 23 g/day). "This implies that a high intake of fish can further reduce the risk of initial coronary heart disease events compared with a moderate fish intake, which has never been tested by previous observational studies in Western countries," Dr. Iso and associates said.

The reduced risk was confined to nonfatal events only, but that may have been because the low number of fatal MIs (62) and sudden cardiac deaths (37) failed to provide enough statistical power to detect an association with those types of events, they added.

—Mary Ann Moon and Giancarlo La Giorgia

BONIVA® (ibandronate sodium) INJECTION

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

CONTRAINDICATIONS

- Known hypersensitivity to BONIVA Injection or to any of its excipients
- Uncorrected hypocalcemia (see PRECAUTIONS: General)

WARNINGS

BONIVA Injection, like other bisphosphonates administered intravenously, may cause a transient decrease in serum calcium values (see PRECAUTIONS). BONIVA Injection must only be administered intravenously. Care must be taken not to administer BONIVA Injection intra-arterially or paravenously as this could lead to tissue damage. Do not administer BONIVA Injection by any other route of administration. The safety and efficacy of BONIVA Injection following non-intravenous routes of administration have not been established.

PRECAUTIONS: General

Mineral Metabolism: Hypocalcemia, hypovitaminosis D, and other disturbances of bone and mineral metabolism must be effectively treated before starting BONIVA Injection therapy. Adequate intake of calcium and vitamin D is important in all patients. Patients must receive supplemental calcium and vitamin D.

Renal Impairment: Treatment with intravenous bisphosphonates has been associated with renal toxicity manifested as deterioration in renal function (ie, increased serum creatinine) and in rare cases, acute renal failure. No cases of acute renal failure were observed in controlled clinical trials in which intravenous BONIVA was administered as a 15- to 30-second bolus. The risk of serious renal toxicity with other intravenous bisphosphonates appears to be inversely related to the rate of drug administration. Patients who receive BONIVA Injection should have serum creatinine measured prior to each dosage administration. Patients with concomitant diseases that have the potential for adverse effects on the kidney or patients who are taking concomitant medications that have the potential for adverse effects on the kidney should be assessed, as clinically appropriate. Treatment should be withheld for renal deterioration. BONIVA Injection should not be administered to patients with severe renal impairment (ie, patients with serum creatinine >200 µmol/L [2.3 mg/dL] or creatinine clearance [measured or estimated] <30 mL/min).

Jaw Osteonecrosis: Osteonecrosis, primarily in the jaw, has been reported in patients treated with bisphosphonates. Most cases have been in cancer patients undergoing dental procedures, but some have occurred in patients with postmenopausal osteoporosis or other diagnoses. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (eg, chemotherapy, radiotherapy, corticosteroids), and co-morbid disorders (eg, anemia, coagulopathy, infection, pre-existing dental disease). Most reported cases have been in patients treated with bisphosphonates intravenously but some have been in patients treated orally. For patients who develop osteonecrosis of the jaw (ONJ) while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Musculoskeletal Pain: In postmarketing experience, severe and occasionally incapacitating bone, joint and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis (see ADVERSE REACTIONS). However, such reports have been infrequent. This category of drugs includes BONIVA (ibandronate sodium) Injection. Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

Information for Patients: BONIVA Injection must be administered intravenously only by a health care professional. Patients should be instructed to read the Patient Information Leaflet carefully before BONIVA Injection is administered and to re-read it each time the prescription is renewed. BONIVA Injection should be administered once every 3 months. If the dose is missed, the injection should be administered as soon as it can be rescheduled. Thereafter, injections should be scheduled every 3 months from the date of the last injection. Do not administer BONIVA Injection more frequently than once every 3 months. Patients must receive supplemental calcium and vitamin D.

Drug Interactions

See FULL PRESCRIBING INFORMATION, CLINICAL PHARMACOLOGY: Drug Interactions

Drug/Laboratory Test Interactions: Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific studies with ibandronate have not been performed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:

In a 104-week carcinogenicity study, doses of 3, 7, or 15 mg/kg/day were administered by oral gavage to Wistar rats (systemic exposures in males and females up to 3 and 1 times, respectively, human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). There were no significant drug-related tumor findings in male or female rats. In a 78-week carcinogenicity study, doses of 5, 20, or 40 mg/kg/day were administered by oral gavage to NMRI mice (exposures in males and females up to 96 and 14 times, respectively, human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). There were no significant drug-related tumor findings in male or female mice. In a 90-week carcinogenicity study, doses of 5, 20, or 80 mg/kg/day were administered in the drinking water to NMRI mice. A dose-related increased incidence of adrenal subcapsular adenoma/carcinoma was observed in female mice, which was statistically significant at 80 mg/kg/day (32 to 51 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). The relevance of these findings to humans is unknown.

Mutagenesis: There was no evidence for a mutagenic or clastogenic potential of ibandronate in the following assays: *in vitro* bacterial mutagenesis assay in *Salmonella typhimurium* and *Escherichia coli* (Ames test), mammalian cell mutagenesis assay in Chinese hamster V79 cells, and chromosomal aberration test in human peripheral lymphocytes, each with and without metabolic activation. Ibandronate was not genotoxic in the *in vivo* mouse micronucleus tests for chromosomal damage.

Impairment of Fertility: In female rats treated from 14 days prior to mating through gestation, decreases in fertility, corpora lutea and implantation sites, and increased preimplantation loss were observed at an intravenous dose of 1.2 mg/kg/day (117 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). In male rats treated for 28 days prior to mating, a decrease in sperm production and altered sperm morphology were observed at intravenous doses ≥0.3 mg/kg/day (≥40 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison).

Pregnancy: Pregnancy Category C: In pregnant rats given intravenous doses of 0.05, 0.15, or 0.5 mg/kg/day from Day 17 post-coitum until Day 20 postpartum, ibandronate treatment resulted in dystocia, maternal mortality, and early postnatal pup loss in all dose groups (≥2 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison).

Reduced body weight at birth was observed at 0.15 and 0.5 mg/kg/day (≥4 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). Pups exhibited abnormal odontology that decreased food consumption and body weight gain at 0.15 and 0.5 mg/kg/day (≥18 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). Periparturient mortality has also been observed with other bisphosphonates and appears to be a class effect related to inhibition of skeletal calcium mobilization resulting in hypocalcemia and dystocia. Exposure of pregnant rats during the period of organogenesis resulted in an increased fetal incidence of RPU (renal pelvis ureter) syndrome at an intravenous dose of 1 mg/kg/day (≥47 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). In this spontaneous delivery study, dystocia was counteracted by perinatal calcium supplementation. In rat studies with intravenous dosing during gestation, fetal weight and pup growth were reduced at doses ≥0.1 mg/kg/day (≥5 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). In pregnant rabbits given intravenous doses of 0.03, 0.07 or 0.2 mg/kg/day during the period of organogenesis, maternal mortality, reduced maternal body weight gain, decreased litter size due to increased resorption rate, and decreased fetal weight were observed at 0.2 mg/kg/day (19 times the recommended human intravenous dose of 3 mg every 3 months, based on cumulative body surface area comparison, mg/m²). Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest that uptake of bisphosphonates into fetal bone is greater than into maternal bone. Therefore, there is a theoretical risk of fetal harm (eg, skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been established. There are no adequate and well-controlled studies in pregnant women. BONIVA Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers: In lactating rats treated with intravenous doses of 0.08 mg/kg, ibandronate was present in breast milk at concentrations of 8.1 to 0.4 mg/mL from 2 to 24 hours after dose administration. Concentrations in milk averaged 1.5 times plasma concentrations. It is not known whether BONIVA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BONIVA Injection is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Of the patients receiving BONIVA Injection 3 mg every 3 months for 1 year (DIVA study), 51% were over 65 years of age. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity in some older individuals cannot be ruled out.

ADVERSE REACTIONS

Daily Oral Tablet: Treatment with BONIVA 2.5 mg daily oral tablet was studied, in over 3900 patients in postmenopausal osteoporosis trials of up to 3 years duration. The overall adverse event profile of BONIVA 2.5 mg once daily tablet in these studies was similar to that of placebo.

Most adverse events were mild or moderate and did not lead to discontinuation. The incidence of serious adverse events was 20% in the placebo group and 23% in the BONIVA 2.5 mg daily oral tablet group. The percentage of patients who withdrew from treatment due to adverse events was approximately 17% in both the BONIVA 2.5 mg daily oral tablet group and the placebo group. Overall, and according to body system, there was no difference between BONIVA daily oral tablet and placebo, with adverse events of the digestive system being the most common reason for withdrawal.

Table 1 lists adverse events from the Treatment and Prevention Studies reported in ≥2% of patients and in more patients treated with BONIVA 2.5 mg daily oral tablet than in patients treated with placebo. Adverse events are shown without attribution of causality.

Table 1: Adverse Events Occurring at a Frequency ≥2% and in More Patients Treated with BONIVA 2.5 mg Daily Oral Tablet than in Patients Treated with Placebo in the Osteoporosis Treatment and Prevention Studies

Body System	Placebo %	BONIVA 2.5 mg daily %
	(n=1134)	(n=1140)
Body as a Whole		
Back Pain	12.2	13.5
Pain in Extremity	6.4	7.8
Infection	3.4	4.3
Asthenia	2.3	3.5
Allergic Reaction	1.9	2.5
Digestive System		
Dyspepsia	9.8	11.9
Diarrhea	5.0	6.8
Tooth Disorder	2.3	3.5
Vomiting	2.1	2.7
Gastritis	1.9	2.2
Metabolic and Nutritional Disorders		
Hypercholesterolemia	4.1	4.8
Musculoskeletal System		
Myalgia	5.2	5.7
Joint Disorder	3.3	3.6
Arthritis	2.7	3.2
Nervous System		
Headache	5.8	6.5
Dizziness	2.6	3.7
Vertigo	2.5	3.0
Nerve Root Lesion	1.9	2.2
Respiratory System		
Upper Respiratory Infection	33.2	33.7
Bronchitis	6.8	10.0
Pneumonia	4.3	5.9
Pharyngitis	1.5	2.5
Urogenital System		
Urinary Tract Infection	4.2	5.5

Quarterly IV Injection: In a 1-year, double-blind, multicenter study comparing BONIVA Injection administered intravenously as 3 mg every 3 months to BONIVA 2.5 mg daily oral tablet in women with postmenopausal osteoporosis, the overall safety and tolerability profiles of the two dosing regimens were similar. The incidence of serious adverse events was 8.0% in the BONIVA 2.5 mg daily group and 7.5% in the BONIVA Injection 3 mg once every 3 months group. The percentage of patients who withdrew from treatment due to adverse events was approximately 6.7% in the BONIVA 2.5 mg daily group and 8.5% in the BONIVA Injection 3 mg every 3 months group.

Table 2 lists the adverse events reported in >2% of patients without attribution of causality.

Table 2: Adverse Events With an Incidence of at Least 2% in Patients Treated with BONIVA Injection (3 mg once every 3 months) or BONIVA Daily Oral Tablet (2.5 mg)

Body System/Adverse Event	BONIVA 2.5 mg Daily (Oral) %	BONIVA 3 mg q 3 mo (IV) %
	(n=465)	(n=469)
Infections and Infestations		
Influenza	8.0	4.7
Nasopharyngitis	6.0	3.4
Cystitis	3.4	1.9
Gastroenteritis	3.4	1.5
Urinary Tract Infection	3.2	2.6
Bronchitis	2.8	2.1
Upper Respiratory Tract Infection	2.8	1.1
Gastrointestinal Disorders		
Abdominal Pain*	5.6	5.1
Dyspepsia	4.3	3.6
Nausea	4.3	2.1
Constipation	4.1	3.4
Diarrhea	2.4	2.8
Gastritis	2.2	1.9
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	8.6	9.6
Back Pain	7.5	7.0
Localized Osteoarthritis	2.4	1.5
Pain in Extremity	2.2	2.8
Myalgia	0.9	2.8
Nervous System Disorders		
Dizziness	2.8	1.9
Headache	2.6	3.6
Vascular Disorders		
Hypertension	7.1	5.3
Psychiatric Disorders		
Insomnia	2.6	1.1
Depression	2.2	1.3
General Disorders and Administration Site Conditions		
Influenza-like illness*	1.1	4.9
Fatigue	1.1	2.8
Skin and Subcutaneous Tissue Disorders		
Rash†	2.8	2.3
Metabolism and Nutrition		
Hypercholesterolemia	4.3	1.5

*Is a combination of abdominal pain and abdominal pain upper.

†Combination of influenza-like illness and acute phase reaction.

‡Combination of rash, rash pruritic, rash macular, dermatitis allergic, exanthem, erythema, rash papular, rash generalized, dermatitis medicamentosa, rash erythematous.

Acute Phase Reaction-like Events: Symptoms consistent with acute phase reaction (APR) have been reported with intravenous bisphosphonate use. The overall incidence of patients with APR-like events was higher in the intravenous treatment group (4% in the BONIVA 2.5 mg daily oral tablet group vs. 10% in the BONIVA Injection 3 mg once every 3 months group). These incidence rates are based on reporting of any of 33 potential APR-like symptoms within 3 days of an IV dose and for a duration of 7 days or less. In most cases, no specific treatment was required and the symptoms subsided within 24 to 48 hours.

Injection Site Reactions: Local reactions at the injection site, such as redness or swelling, were observed infrequently, but at a higher incidence in patients treated with BONIVA Injection 3 mg every 3 months (<2%; 8/469) than in patients treated with placebo injections (<1%; 1/465). In most cases, the reaction was of mild to moderate severity.

Ocular Adverse Events: Bisphosphonates may be associated with ocular inflammation such as uveitis and scleritis. In some cases, these events did not resolve until the bisphosphonate was discontinued.

Laboratory Test Findings: There were no clinically significant changes from baseline values or shifts in any laboratory variable with oral ibandronate. As expected with bisphosphonate treatment, a decrease in total alkaline phosphatase levels was seen with 2.5 mg daily oral ibandronate compared to placebo. There was no difference compared with placebo for laboratory abnormalities indicative of hepatic or renal dysfunction, hypocalcemia, or hypophosphatemia. There also was no evidence that BONIVA Injection 3 mg every 3 months induced clinically significant laboratory abnormalities indicative of hepatic or renal dysfunction compared to BONIVA 2.5 mg daily oral tablet.

OVERDOSAGE: No cases of overdose were reported in premarketing studies with BONIVA Injection. Intravenous overdose may result in hypocalcemia, hypophosphatemia, and hypomagnesemia. Clinically relevant reductions in serum levels of calcium, phosphorus, and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, respectively. Dialysis would not be beneficial unless it is administered within 2 hours following the overdose.

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