

Hip Fracture Risk Higher in Elderly With Diabetes

BY MIRIAM E. TUCKER

Senior Writer

TORONTO — The risk for hip fractures appears to be elevated in elderly men and women with diabetes, Dr. Lorraine L. Lipscombe reported in a poster at the joint annual meeting of the Canadian Diabetes Association and the Canadian Society of Endocrinology and Metabolism.

Whereas previous studies have documented an association between type 1 di-

abetes and osteoporotic fractures, the data on patients with type 2 diabetes have conflicted. Those studies have mostly been small and limited to women. Moreover, bone density is typically normal or high in type 2 diabetes, whereas it is reduced in type 1, leading some to believe that people with type 2 diabetes are somehow “protected,” said Dr. Lipscombe, of the University of Toronto.

In a retrospective cohort study using population-based Ontario health care databas-

es from 1994 to 2003, researchers compared the risk of hip fractures between individuals older than 65 years of age with and without diabetes. After excluding those with prior hip fractures or hip replacements and those on oral corticosteroid treatment, the study population comprised 207,252 diabetics and 414,504 nondiabetics, with an overall mean age of 71.7 years. Information about diabetes type was not available, but it was presumed that most were type 2 because of the age group involved, Dr. Lipscombe said in an interview.

After a mean of 6.1 years, the risk for hip fractures was significantly higher among those with diabetes, at 7.21 per 1,000 person-years, compared with 6.15 per 1,000 person-years among those without diabetes.

Compared with nondiabetics, those with diabetes had more comorbidity, were less likely to have had a bone mineral density test, and were more likely to be taking drugs that affected fall risk and

bone density.

Women had a significantly higher risk for fracture than did men, but diabetes increased the risk in both genders, with hazard ratios of 1.22 for men and 1.19 for women. The increased risk remained significant (1.18 in men and 1.11 in women) after adjustment for age; comorbidity; prior stroke; visual impairment; neuropathy; amputation; treatment with nitrates, statins, anticonvulsants, inhaled corticosteroids, thiazides, or fall-promoting medications; history of a bone mineral density test; estrogen treatment in women; and income quintile in men, Dr. Lipscombe reported.

Insulin use among the patients with diabetes increased the fracture risk, with hazard ratios of 1.34 in women and 1.64 in men, compared with those not using insulin.

Until the phenomenon is better understood, bone fracture risk assessment and enhanced prevention strategies are warranted in all patients with diabetes, she said. ■

Treatment differences depended on baseline BMI or weight such that the effects of AVANDIA and metformin appeared more closely comparable among heavier patients. The median weight gain was 2.8 kg with rosiglitazone and 0.2 kg with metformin (see PRECAUTIONS, General, *Weight Gain*). Fifty four percent of patients treated with rosiglitazone and 32% of patients treated with metformin gained ≥ 2 kg, and 33% of patients treated with rosiglitazone and 7% of patients treated with metformin gained ≥ 5 kg on study. Adverse events observed in this study are described in ADVERSE REACTIONS.

Geriatric Use: Results of the population pharmacokinetic analysis showed that age does not significantly affect the pharmacokinetics of rosiglitazone (see CLINICAL PHARMACOLOGY, Special Populations in the full prescribing information). Therefore, no dosage adjustments are required for the elderly. In controlled clinical trials, no overall differences in safety and effectiveness between older (≥ 65 years) and younger (< 65 years) patients were observed.

ADVERSE REACTIONS: Adult: In clinical trials, approximately 8400 patients with type 2 diabetes have been treated with AVANDIA; 6000 patients were treated for 6 months or longer and 3000 patients were treated for 12 months or longer.

The following adverse events (occurring at rates $\geq 5\%$ in any treatment group) were reported by patients in double-blind clinical trials with AVANDIA as monotherapy (N=2526), compared to events seen in patients treated with placebo (N=601), metformin (N=225) or sulfonylureas (N=626), respectively: Upper respiratory tract infection (9.9%, 8.7%, 8.9%, 7.3%); injury (7.6%, 4.3%, 7.6%, 6.1%); headache (5.9%, 5.0%, 8.9%, 5.4%); back pain (4.0%, 3.8%, 4.0%, 5.0%); hyperglycemia (3.9%, 5.7%, 4.4%, 8.1%); fatigue (3.6%, 5.0%, 4.0%, 1.9%); sinusitis (3.2%, 4.5%, 5.3%, 3.0%); diarrhea (2.3%, 3.3%, 15.6%, 3.0%), and hypoglycemia (0.6%, 0.2%, 1.3%, 5.9%). The sulfonylurea group includes patients receiving glyburide (N=514), glipizide (N=91) or glipizide (N=21).

Overall, the types of adverse experiences reported when AVANDIA was used in combination with a sulfonylurea or metformin were similar to those during monotherapy with AVANDIA. Events of anemia and edema tended to be reported more frequently at higher doses, and were generally mild to moderate in severity and usually did not require discontinuation of treatment with AVANDIA. In double-blind studies, anemia was reported in 1.9% of patients receiving AVANDIA as monotherapy compared to 0.7% on placebo, 0.6% on sulfonylureas and 2.2% on metformin. Reports of anemia were greater in patients treated with a combination of AVANDIA and metformin (7.1%) and with a combination of AVANDIA and a sulfonylurea plus metformin (6.7%) compared to monotherapy with AVANDIA or in combination with a sulfonylurea (2.3%). Lower pre-treatment hemoglobin/hematocrit levels in patients enrolled in the metformin combination clinical trials may have contributed to the higher reporting rate of anemia in these studies (see ADVERSE REACTIONS, Laboratory Abnormalities, Hematologic). In clinical trials, edema was reported in 4.8% of patients receiving AVANDIA as monotherapy compared to 1.3% on placebo, 1.0% on sulfonylureas, and 2.2% on metformin. The reporting rate of edema was higher for AVANDIA 8 mg in sulfonylurea combinations (12.4%) compared to other combinations, with the exception of insulin. Edema was reported in 14.7% of patients receiving AVANDIA in the insulin combination trials compared to 5.4% on insulin alone. Reports of new onset or exacerbation of congestive heart failure occurred at rates of 1% for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with AVANDIA. In postmarketing experience in patients receiving thiazolidinedione therapy, serious adverse events with or without a fatal outcome, potentially related to volume expansion (e.g., congestive heart failure, pulmonary edema, and pleural effusions) have been reported. (See WARNINGS, Cardiac Failure and Other Cardiac Effects.) In controlled combination therapy studies with sulfonylureas, mild to moderate hypoglycemic symptoms, which appears to be dose related, were reported. Few patients were withdrawn for hypoglycemia ($< 1\%$) and few episodes of hypoglycemia were considered to be severe ($< 1\%$). Hypoglycemia was the most frequently reported adverse event in the fixed-dose insulin combination trials, although few patients withdrew for hypoglycemia (4 of 408 for AVANDIA plus insulin and 1 of 203 for insulin alone). Rates of hypoglycemia, confirmed by capillary blood glucose concentration ≤ 50 mg/dL, were 6% for insulin alone and 12% (4 mg) and 14% (8 mg) for insulin in combination with AVANDIA. (See PRECAUTIONS, General, Hypoglycemia and DOSAGE AND ADMINISTRATION, Combination Therapy.)

In postmarketing experience with AVANDIA, rash, pruritus, urticaria, angioedema, and anaphylactic reaction have been reported rarely. Postmarketing reports of new onset or worsening diabetic macular edema with decreased visual acuity have also been received (see PRECAUTIONS, Macular Edema).

Pediatric: AVANDIA has been evaluated for safety in a single, active-controlled trial of pediatric patients with type 2 diabetes in which 99 were treated with AVANDIA and 101 were treated with metformin. In this study, one case of diabetic ketoacidosis was reported in the metformin group. In addition, there were 3 patients in the rosiglitazone group who had FPG of ≥ 300 mg/dL, 2+ ketonuria, and an elevated anion gap. The following adverse events (occurring at rates $\geq 5\%$ of pediatric patients) were reported in a double-blind, active-controlled, clinical trial with AVANDIA as monotherapy (N=99), compared to events seen in pediatric patients treated with metformin as monotherapy (N=101), respectively: Headache (17.2%, 13.9%); influenza (7.1%, 5.9%); upper respiratory tract infection (6.1%, 5.9%); cough (6.1%, 5.0%); hyperglycemia (8.1%, 6.9%); dizziness (5.1%, 2.0%); back pain (5.1%, 1.0%); nausea (4.0%, 10.9%); hypoglycemia (4.0%, 5.0%); nasopharyngitis (3.0%, 11.9%); vomiting (3.0%, 8.9%); abdominal pain (3.0%, 6.9%); pharyngolaryngeal pain (2.0%, 5.0%); diarrhea (1.0%, 12.9%); sinusitis (1.0%, 5.0%); and dysmenorrhea (0%, 6.9%).

Laboratory Abnormalities: Hematologic: Decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in adult patients treated with AVANDIA (mean decreases in individual studies up to 1.0 gram/dL hemoglobin and up to 3.3% hematocrit). The time course and magnitude of decreases were similar in patients treated with a combination of AVANDIA and other hypoglycemic agents or AVANDIA monotherapy. Pre-treatment levels of hemoglobin and hematocrit were lower in patients in metformin combination studies and may have contributed to the higher reporting rate of anemia. In a single study in pediatric patients, decreases in hemoglobin and hematocrit (mean decreases of 0.29 g/dL and 0.95%, respectively) were reported. White blood cell counts also decreased slightly in adult patients treated with AVANDIA. Decreases in hematologic parameters may be related to increased plasma volume observed with treatment with AVANDIA. **Lipids:** Changes in serum lipids have been observed following treatment with AVANDIA in adults (see CLINICAL STUDIES in the full prescribing information). Small changes in serum lipid parameters were reported in children treated with AVANDIA for 24 weeks. **Serum Transaminase Levels:** In clinical studies in 4598 patients treated with AVANDIA encompassing approximately 3600 patient years of exposure, there was no evidence of drug-induced hepatotoxicity or elevated ALT levels. In controlled trials, 0.2% of patients treated with AVANDIA had reversible elevations in ALT > 3 X the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. Hyperbilirubinemia was found in 0.3% of patients treated with AVANDIA compared with 0.9% treated with placebo and 1% in patients treated with active comparators. In the clinical program including long-term, open-label experience, the rate per 100 patient years exposure of ALT increase to > 3 X the upper limit of normal was 0.35 for patients treated with AVANDIA, 0.59 for placebo-treated patients, and 0.78 for patients treated with active comparator agents. In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure. In postmarketing experience with AVANDIA, reports of hepatic enzyme elevations 3 or more times the upper limit of normal and hepatitis have been received (see PRECAUTIONS, General, Hepatic Effects).

OVERDOSAGE: Limited data are available with regard to overdosage in humans. In clinical studies in volunteers, AVANDIA has been administered at single oral doses of up to 20 mg and was well-tolerated. In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status.

DOSAGE AND ADMINISTRATION: The management of antidiabetic therapy should be individualized. All patients should start AVANDIA at the lowest recommended dose. Further increases in the dose of AVANDIA should be accompanied by careful monitoring for adverse events related to fluid retention. (See WARNINGS, Cardiac Failure and Other Cardiac Events.) AVANDIA may be administered either at a starting dose of 4 mg as a single daily dose or divided and administered in the morning and evening. For patients who respond inadequately following 8 to 12 weeks of treatment, as determined by reduction in FPG, the dose may be increased to 8 mg daily as monotherapy or in combination with metformin, sulfonylurea, or sulfonylurea plus metformin. Reductions in glycemic parameters by dose and regimen are described under CLINICAL STUDIES in the full prescribing information. AVANDIA may be taken with or without food. **Monotherapy:** The usual starting dose of AVANDIA is 4 mg administered either as a single dose once daily or in divided doses twice daily. In clinical trials, the 4 mg twice daily regimen resulted in the greatest reduction in FPG and HbA_{1c}. **Combination Therapy:** When AVANDIA is added to existing therapy, the current dose(s) of the agent(s) can be continued upon initiation of AVANDIA therapy. **Sulfonylureas:** When used in combination with sulfonylurea, the usual starting dose of AVANDIA is 4 mg administered as either a single dose once daily or in divided doses twice daily. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased. **Metformin:** The usual starting dose of AVANDIA in combination with metformin is 4 mg administered as either a single dose once daily or in divided doses twice daily. It is unlikely that the dose of metformin will require adjustment due to hypoglycemia during combination therapy with AVANDIA. **Insulin:** For patients stabilized on insulin, the insulin dose should be continued upon initiation of therapy with AVANDIA. AVANDIA should be dosed at 4 mg daily. Doses of AVANDIA greater than 4 mg daily in combination with insulin are not currently indicated. It is recommended that the insulin dose be decreased by 10% to 25% if the patient reports hypoglycemia or if FPG concentrations decrease to less than 100 mg/dL. Further adjustments should be individualized based on glucose-lowering response. **Sulfonylurea Plus Metformin:** The usual starting dose of AVANDIA in combination with a sulfonylurea plus metformin is 4 mg administered as either a single dose once daily or divided doses twice daily. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased. **Maximum Recommended Dose:** The dose of AVANDIA should not exceed 8 mg daily, as a single dose or divided twice daily. The 8 mg daily dose has been shown to be safe and effective in clinical studies as monotherapy and in combination with metformin, sulfonylurea, or sulfonylurea plus metformin. Doses of AVANDIA greater than 4 mg daily in combination with insulin are not currently indicated. **Special Populations: Geriatric:** No dosage adjustments are required for the elderly. **Renal Impairment:** No dosage adjustment is necessary when AVANDIA is used as monotherapy in patients with renal impairment. Since metformin is contraindicated in such patients, concomitant administration of metformin and AVANDIA is also contraindicated in patients with renal impairment. **Hepatic Impairment:** Therapy with AVANDIA should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT > 2.5 X upper limit of normal at start of therapy) (see PRECAUTIONS, General, Hepatic Effects and CLINICAL PHARMACOLOGY, Special Populations, Hepatic Impairment in full prescribing information). Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with AVANDIA and periodically thereafter (see PRECAUTIONS, General, Hepatic Effects). **Pediatric:** Data are insufficient to recommend pediatric use of AVANDIA.

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IV Ibandronate Preferred By Those With Prior GI Intolerance

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TORONTO — Women with postmenopausal osteoporosis who had previously discontinued oral bisphosphonate therapy because of gastrointestinal intolerance preferred an intravenous, every-3-month regimen of ibandronate over a monthly oral regimen, Dr. E. Michael Lewiecki reported at a world congress on osteoporosis.

Complex dosing instructions designed to maximize bioavailability and address tolerability concerns may affect adherence to oral bisphosphonate therapy, and adherence is crucial to clinical efficacy and fracture prevention, Dr. Lewiecki noted.

Adherence was addressed in a 12-month, open-label multicenter study that included 542 patients with osteoporosis or osteopenia who had stopped daily or weekly treatment with oral alendronate or risedronate because of perceived or actual symptoms such as heartburn and acid reflux. All received supplemental vitamin D (400 IU/day) and elemental calcium (1,000 mg/day).

Patients were given the choice of oral ibandronate, 150 mg once monthly, or 3 mg by intravenous injection every 3 months. A total of 396 (73%) of patients chose the intravenous regimen, while 146 (27%) chose the oral route.

They were permitted to switch treatment groups once during the study if they experienced adverse effects, he noted.

Severity and frequency of gastrointestinal symptoms and other side effects were evaluated with surveys administered at baseline and at months 1, 4, 7, and 10.

Available data indicate that adherence to both regimens at 6 months was high, at 94.5%. Actual duration of study medication intake divided by maximum duration of intake and a threshold of 75% or more was used to define adherence, according to Dr. Lewiecki of New Mexico Clinical Research and Osteoporosis Center, Albuquerque.

Among patients receiving the oral drug, adherence was 87.7%, while adherence was 94.9% among those receiving the intravenous formulation, Dr. Lewiecki wrote in a poster session at the meeting, which was sponsored by the International Osteoporosis Foundation.

Among patients who chose intravenous administration, 147 (37.1%) had a history of fracture as an adult, compared with 36 (24.7%) of those who chose the oral drug.

Thus far, 26 patients have switched their route of administration. Eleven switched from oral to intravenous ibandronate because of gastrointestinal intolerance, while 15 switched from intravenous to oral for reasons including influenzalike symptoms and injection-site reactions.

By month 4, 28.1% and 36.6% of patients on the oral and intravenous drugs, respectively, reported improved gastrointestinal tolerance, compared with baseline.

“Based on these findings, it appears that patients who had previously discontinued weekly or daily oral bisphosphonates because of gastrointestinal intolerance prefer intravenous dosing, and that patients with a previous fracture are even more likely to do so than patients without a previous fracture,” Dr. Lewiecki concluded.

The study was sponsored by Roche Laboratories. ■

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