Are There Differences Between Men and Women Prescribed Bisphosphonate Therapy in Canadian Subspecialty Osteoporosis Practices?

ANNA M. SAWKA, JONATHAN D. ADACHI, ALEXANDRA PAPAIOANNOU, LEHANA THABANE, GEORGE IOANNIDIS, K. SHAWN DAVISON, WOJCIECH P. OLSZYNSKI, JACQUES P. BROWN, DAVID A. HANLEY, TIM M. MURRAY, ROBERT G. JOSSE, ROLF J. SEBALDT, ANNIE PETRIE, ALAN TENENHOUSE, and CHARLES H. GOLDSMITH

ABSTRACT. ***Objective.*** To determine if there are differences between men and women referred for treatment of osteoporosis in Canada.

Methods. We performed an observational study of 1588 patients (163 men, 1425 women), 50 years of age and older, who were prescribed cyclic etidronate or alendronate for treatment of osteoporosis or osteopenia and had at least 2 years of followup registered in the Canadian Database for Osteoporosis and Osteopenia Patients (CANDOO). Comparisons of characteristics between men and women were performed using Pearson chi-square test, Student's t test, or a Kruskal-Wallis test, whichever was most appropriate.

Results. Mean baseline femoral neck and lumbar spine bone mineral densities were significantly higher in men than women at both the femoral neck and lumbar spine ($p < 0.05$, respectively). Men had double the rate of prevalent vertebral fractures (44%, 72/163) compared to women (22%, 315/1425; $p < 0.001$) and triple the rate of multiple prevalent vertebral fractures (10%, 17/163) compared to women (3%, 37/1425, $p < 0.001$). Furthermore, men were twice as likely as women to sustain a fracture within 2 years of starting treatment during observation in the CANDOO study (men: 4%, 7/163, women: 2%, 24/1425, $p = 0.033$).

Conclusion. Osteoporosis may be under-recognized in men until the condition is at an advanced stage. A form of gender bias may exist in recognition and treatment (or referral for treatment) of osteoporosis in men. (J Rheumatol 2004;31:1993–5)

Key Indexing Terms:
OSTEOPOROSIS FRACTURES GENDER DIPHOSPHONATES

Osteoporosis is an important source of morbidity and mortality in men. Approximately 20-30% of all hip fractures occur in men[1-3]. Furthermore, men have an age-adjusted prevalence of vertebral fractures similar to women[4]. Moreover, bisphosphonates have been shown to increase bone mineral density (BMD) at the spine and hip and prevent vertebral fractures in men with osteoporosis[5-7]. Despite this, men are less likely to be treated with a bisphosphonate after hip fracture than women[8]. We compared men and women referred to Canadian specialty osteoporosis practices and prescribed bisphosphonates.

MATERIALS AND METHODS

We studied 1588 patients (163 men, 1425 women), 50 years of age and older, who were prescribed cyclic etidronate or alendronate and had at least 2 years of followup registered in the Canadian Database for Osteoporosis and Osteopenia Patients (CANDOO) Study. The CANDOO study is a collaborative, prospective observational program in which data are collected systematically from routine clinical care by a network of tertiary care specialists in osteoporosis[9]. Further methodologic information about the CANDOO database has been published[9]. Participating study centers included McMaster University, McGill University, Centre Hospitalier de Laval, University of Calgary, University of Saskatchewan, and the University of Toronto. Choice of treatment was at the discretion of the treating physician. Typically, etidronate disodium was prescribed at a dose of 400 mg daily for 14 days, followed by 76 days of calcium carbonate (500 mg of elemental calcium) (Didrocal®, Procter and Gamble), and alendronate was prescribed at a dose of 10 mg daily (Fosamax®, Merck Frosst). All patients were encouraged to consume 1000 mg of elemental calcium and 400-1000 IU of vitamin D daily. Patients were excluded from this study if they were receiving concurrent therapy with one of the above bisphos-

The CANDOO database has been sponsored in part by Procter and Gamble Pharmaceuticals.

From McMaster University, St. Joseph's Healthcare, Centre for Evaluation of Medicines, Hamilton, and the University of Toronto, Toronto, Ontario; the University of Saskatchewan, Saskatoon, Saskatchewan; Centre Hospitalier de Laval, and McGill University, Montreal, Quebec; and the University of Calgary, Calgary, Alberta, Canada.

A.M. Sawka, MD; J.D. Adachi, MD; A. Papaioannou, MD; L. Thabane, PhD, McMaster University, St. Joseph's Healthcare, Centre for Evaluation of Medicines; G. Ioannidis, MSc, St. Joseph's Healthcare; K.S. Davison, PhD, McMaster University; W.P. Olszynski, MD, University of Saskatchewan; J.P. Brown, MD, Centre Hospitalier de Laval; D.A. Hanley, MD, University of Calgary; T.M. Murray, MD; R.G. Josse, MD, University of Toronto; R.J. Sebaldt, MD; A. Petrie, McMaster University, St. Joseph's Healthcare; A. Tenenhouse, MD, McGill University; C.H. Goldsmith, PhD, McMaster University, St. Joseph's Healthcare, Centre for Evaluation of Medicines.

Address reprint requests to Dr. J.D. Adachi, 501-25 Charlton Avenue East, Hamilton, Ontario, L8N 1Y2.

Submitted December 1, 2003; revision accepted April 28, 2004.

phonates in addition to calcitonin: estrogen, raloxifene, oral corticosteroids, pharmacologic doses of vitamin D (more than 1000 IU/day) or fluoride; or if they had diabetes mellitus, primary hyperparathyroidism, chronic renal failure, Paget's disease, osteogenesis imperfecta, multiple myeloma, or inflammatory bowel disease. There was an insufficient number of patients treated with risedronate for meaningful analysis (as the drug had only recently been approved for prescription in Canada) so risedronate-treated patients were also excluded from the analysis.

Comparisons of characteristics between men and women were performed by using a Pearson chi-square test for categorical variables, a Student's t test for normally distributed continuous variables, or a Kruskal-Wallis test for non-normally distributed continuous variables (SPSS 10.0).

RESULTS

From March 1990 to March 2002, 1588 patients were prescribed etidronate or alendronate monotherapy. Men and women were of similar age but men had higher body mass index, alcohol consumption, and smoking rates, and lower exercise rates (Table 1). Mean baseline BMD values were significantly higher in men compared with women at the femoral neck (men: n = 96, mean ± standard deviation, SD, = 0.722 ± 0.123 g/cm^2; women: n = 824, mean ± SD = 0.695 ± 0.109 g/cm^2, p = 0.045) and the lumbar spine (men: n = 83, mean ± SD = 0.951 ± 0.195 g/cm^2; women, n = 787, mean ± SD = 0.891 ± 0.146 g/cm^2, p = 0.008). At time of referral, rates of previous vertebral fracture were twice as high in men (44%, 72/163) compared to women (22%, 315/1425; p < 0.001) and rates of multiple vertebral fractures were 3 times as high in men (10%, 17/163) compared to women (3%, 37/1425; p < 0.001).

Alendronate prescription rates were not significantly different between genders (men 35.0%, 57/163, women 28.9%, 412/1425; chi-square = 2.58, df = 1, p = 0.108). However, men were significantly more likely than women to be prescribed first-line alendronate therapy (without a previous history of etidronate use) (men 21.5%, 35/163, vs women 12.2%, 174/1425; chi-square = 9.82, df = 1, p = 0.003). Men were significantly more likely than women to sustain an incident fracture within 24 months of starting bisphosphonate therapy (men 7/163, 4%, compared to women 24/1425, 2%, chi-square = 5.21, df = 1, p = 0.033).

DISCUSSION

We found that far fewer men than women were referred for bisphosphonate therapy in university-affiliated osteoporosis clinics across Canada. Furthermore, referred male patients presented with more severe degrees of osteoporosis, as reflected by higher rates of prevalent and incident fractures, despite higher areal bone density measurements than women. This may reflect a form of gender bias in recognition and treatment of osteoporosis in men.

This observational study has several limitations. First of all, only subspecialty osteoporosis practice patterns were studied and the results may not be generalizable to that of primary care practices or practices of internal medicine specialists outside the tertiary care setting; confirmation of our findings in a population-based study may be warranted. Second, spinal radiographs formally quantifying arthritic changes, which could affect bone density measurements, were not systematically performed. Osteophytes of degenerative arthritis may have contributed to the falsely elevated lumbar bone density measurements in men, given that the prevalence of lumbar spine osteophytes is known to be higher in men and is known to explain variability of BMD measurements to a greater degree in men than in women[10]. Furthermore, volumetric bone density measurements (as opposed to areal measurements using DXA) may have been preferable in men, but were not performed. Our findings were also limited by missing data, particularly with respect to BMD values; however imputation of series means did not alter our results. Moreover, given a limited number of events (such as incident fractures), we did not have statistical

Table 1. Comparison of baseline characteristics of men and women prescribed bisphosphonates in subspecialty osteoporosis practices.

Variable (n = No. of patients with available data)	Men	Women	P
No. of patients (1588)	163	1425	
[a] Age, years (1588)	65.5 ± 9.4	66.9 ± 8.4	0.081
[a] Body mass index, kg/m^2 (1021)	26.8 ± 3.8	25.5 ± 4.3	0.004
[c] Weekly Alcohol Intake, No. of drinks/week, (n = 977)	2 (0, 14)	0 (0, 0)	< 0.001
[b] No. of smokers (1325)	88 (64%)	390 (33%)	< 0.001
[c] Daily calcium intake, mg (968)	423 (300, 763)	455 (445, 741)	0.267
[c] Exercise at baseline, minutes/week (684)	13 (0, 40)	30 (30, 60)	0.004
[b] Family history of osteoporotic fracture (1259)	17 (13%)	190 (17%)	0.327
[a] Baseline femoral neck bone mineral density, g/cm (920)	0.722 ± 0.123	0.695 ± 0.109	0.045
[a] Lumbar spine bone mineral density L2–L4, g/cm^2 (870)	0.951 ± 0.195	0.891 ± 0.146	0.008
[b] Presence of ≥ 1 vertebral fractures (1588)	72 (44%)	315 (22%)	< 0.001
[b] Presence of multiple vertebral fractures (1588)	17 (10%)	37 (3%)	< 0.001
[b] Discontinued bisphosphonate within 24 months (1588)	13 (8%)	153 (11%)	0.275
[b] Incident fracture within 24 months (1588)	7 (4%)	24 (2%)	0.022

[a] Mean ± standard deviation shown for continuous variables that are normally distributed. [b] Number of patients (percentage) shown for categorical variables. [c] Median and interquartile range shown for continuous variables that are not normally distributed.

power to perform multivariable analyses examining independent associations of clinical covariables with clinical outcomes to make conclusions about causation.

BMD measurements are known to be predictive of fracture risks. BMD testing of men and women with clinical characteristics predisposing to osteoporosis is generally recommended[11,12]. In addition, spinal radiographs should be conducted to investigate vertebral fractures in men with back pain, particularly in the setting of known secondary causes of osteoporosis (such as hypogonadism, corticosteroid use, excessive alcohol consumption, or other predisposing medical conditions). Treatment is generally indicated if one or more prevalent vertebral fractures are found in men or women, particularly if no major trauma causing the fracture is identified.

REFERENCES

1. Cooper C, Campion G, Melton LJ III. Hip fractures in the elderly: a worldwide projection. Osteoporos Int 1992;2:285-9.
2. De Laet CE, Pols HA. Fractures in the elderly: epidemiology and demography. Baillieres Best Pract Res Clin Endocrinol Metab 2000;14:171-9.
3. Diamond TH, Thornley SW, Sekel R, Smerdely P. Hip fractures in elderly men: prognostic factors and outcomes. Med J Aust 1997;167:412-5.
4. Jackson SA, Tenenhouse A, Robertson L. Vertebral fracture definition from population-based data: preliminary results from the Canadian Multicenter Osteoporosis Survey (CaMos). Osteoporos Int 2000;11:680-7.
5. Orwoll E, Ettinger M, Weiss S, et al. Alendronate for the treatment of osteoporosis in men. N Engl J Med 2000;343:604-10.
6. Ringe JD, Orwoll E, Daifotis A, Lombardi A. Treatment of male osteoporosis. Osteoporos Int 2002;13:195-9.
7. Ho YV, Frauman AG, Thompson W, Seeman E. Effects of alendronate on bone mineral density in men with primary and secondary osteoporosis. Osteoporos Int 2000;11:98-101.
8. Kiebzak GM, Beinart GA, Perser K. Ambrose CG, Siff SJ, Heggeness MH. Undertreatment of osteoporosis in men with hip fracture. Arch Intern Med 2002;162:2217-22.
9. Sebaldt RJ, Adachi JD. Canadian database of osteoporosis and osteopenia patients (CANDOO). Canadian Organization for the Advancement of Computers in Healthcare 1996;21:36-9.
10. Liu G, Peacock M, Eilam O, Dorulla G, Braunstein E, Johnston CC. Effect of osteoarthritis in the lumbar spine and hip on bone mineral density and diagnosis of osteoporosis in elderly men and women. Osteoporos Int 1997:7:564-9.
11. Khan AA, Brown JP, Kendler DL, et al. The 2002 Canadian bone densitometry recommendations: take-home messages. CMAJ 2002;167:1141-5.
12. Cummings SR, Bates D, Black DM. Clinical use of bone densitometry: Scientific review. JAMA 2002;288:1889-97.