Alendronate Therapy and Renal Insufficiency: A Prescription for Problems?

Brandon S. Hayes, PharmD, Laurence A. Lavezo, PharmD, and Robert B. Parsons, MD

Although little research has been published on the use of bisphosphonates in patients with severe renal insufficiency, the FDA advises against administering these drugs to such patients for theoretical reasons. Now, a retrospective pilot study challenges the long held notion that reduced renal clearance of alendronate increases adverse drug events.

Osteoporosis, which is defined as having a bone density of 2.5 or more standard deviations below the average adult's peak bone mass, is marked by progressive bone loss. Patients at greatest risk for osteoporosis and resultant fractures include those who are elderly, female, white, or small-framed. According to the National Institutes of Health, of the 10 million Americans with osteoporosis, about eight million are female. Similarly, most osteoporotic fractures occur in women, though nearly 30% of hip fractures occur in men—in whom morbidity and mortality is almost double that of women.[1] All told, osteoporosis causes about 1.5 million fractures a year, with annual national direct care expenditures for osteoporotic fractures ranging from $12.2 billion to $17.9 billion, measured in 2002 dollars.[2] Given these costs, the aging of the veteran population, the growing number of women veterans, the morbidity and mortality of osteoporotic fracture in men, and the prevalence of smoking (a major risk factor for osteoporosis) among veterans,[3] osteoporosis prevention is a high priority in the VHA.

Once a person has received a diagnosis of osteoporosis, treatment options are limited. The bisphosphonate class of drugs—the primary option—actually reverses the loss of bone mass by becoming incorporated into the bone structure and decreasing osteoclasts' bone absorption ability.[4,5] Currently, two oral bisphosphonates are available: alendronate and risedronate. Alendronate is distributed first to soft tissues and then is redistributed rapidly to bone or excreted in the urine.[4] The mean oral bioavailability of alendronate is 0.64% in women and 0.59% in men, after an overnight fast and two hours before a standardized breakfast.[4]

Alendronate is approved for use by individuals with mild to moderate renal insufficiency (those having a creatinine clearance of 35 to 60 mL/min)—and at the usual dose—though alendronate elimination by way of renal excretion is reduced in these individuals, compared with those whose renal function is normal. Alendronate is not, however, approved for use in patients with more severe renal insufficiency (creatinine clearance of less than 35 mL/min). The FDA withheld approval for this patient population because these individuals were excluded from the drug's clinical trials. Little research has been published on the use of risedronate or alendronate in these patients.

Since creatinine clearance decreases with age and tends to be lower in women than in men, the FDA restriction concerning renal insufficiency could limit substantially the use of bisphosphonates and reduce VHA osteoporosis prevention efforts. For this reason, we designed a retrospective pilot study to determine whether there was a link between decreased renal clearance and increased adverse drug events (identified in the package insert as back pain, abdominal pain, arthralgia, joint disorders, gastric ulcers, esophagitis, and, possibly, hypocalemia), which are said to occur at least 1% more often in patients taking alendronate than in those taking placebo.[4]

STUDY DESIGN

We hypothesized that patients with severe renal insufficiency who were undergoing alendronate therapy would not experience a greater number of

At the time of this study, **Dr. Hayes** was a pharmacy practice resident at the New Mexico VA Health Care System (NMVAHCS) in Albuquerque. He is currently a primary care clinical pharmacist at the VA Great Lakes Health Care System in Tomah, WI. **Dr. Lavezo** is a primary care clinical pharmacist and **Dr. Parsons** is an attending physician in the internal medicine service, both at the NMVAHCS.

adverse drug events than patients with normal renal function. Our hypothesis was based on prior experience with alendronate in patients with impaired renal function and on the drug's low bioavailability.

To test our hypothesis, we conducted a retrospective chart review at a VA tertiary care facility, examining the electronic medical records of patients prescribed alendronate for at least one year. We then determined creatinine clearance for each patient, using the Cockcroft-Gault equation, which our facility employs to determine renal function and adjust dosages: calculated creatinine clearance = [(140–age) x lean body weight (kg)] ÷ [serum creatinine (mg/dL) x 72] (the quotient is multiplied by 0.85 for female patients).[6] We included in the study group patients with a creatinine clearance below 35 mL/min and examined their charts for the 12-month period following initiation of alendronate for the following endpoints indicative of adverse drug events: change in use or initiation of nonsteroidal anti-inflammatory drugs, histamine 2 blockers, or proton pump inhibitors; diagnosis of abdominal, muscle, or joint pain; rise in serum creatinine value of 0.5 mg/dL or more; and reduction in serum calcium values to below 7 mg/dL.

For comparison, we analyzed data from a control group, consisting of patients receiving alendronate therapy for at least one year whose creatinine clearance was greater than 35 mL/min and who were matched to the study group by gender, age within five years, and time of clinic visit by six months. The study and control groups contained 24 patients each, almost half of whom were men.

The facility's biostatistician used SAS/STAT software (SAS Institute Inc., Cary, NC) to calculate statistics. Study data were subjected to the Fisher exact test and the *t* test with the Satterthwaite correction. A post hoc power analysis was performed to determine the incidence of joint pain, which develops in about 4% of patients receiving alendronate and 1.5% of those receiving placebo, according to the manufacturer.[4] Determining a clinically significant increase in new onset joint pain is difficult because joint pain is common in elderly patients. If this study were to detect a threefold increase in the rate of joint pain diagnosis (from 4% to 12%) in patients receiving alendronate and have a power of 80%, we would have needed to enroll 134 patients in each arm.

WHAT THE DATA SHOWED

From January 2002 to January 2004, 836 patients in our facility received alendronate therapy. Of these, 40 had a creatinine clearance of less than 35 mL/min when alendronate therapy was initiated, and 25 had received alendronate therapy for at least 12 months—though one patient also had received chemotherapy during this time and was excluded. We then matched the 24 patients remaining in the study group with 24 controls. On average, patients in the study group were shorter and had lower calculated creatinine clearance, higher serum creatinine, and lower lean body weight than those in the control group (Table 1). The two groups did not differ significantly in age or gender distribution.

The two groups demonstrated no significant differences in terms of the proportion of patients whose medical record reflected possible indications of an adverse drug event during the 12 months studied (Table 2). There were no instances of abdominal or muscle pain or reduction in serum calcium in either group. We concluded, therefore, that there were no statistically significant differences in the incidence of adverse events between the two groups.

Although patients in our study group demonstrated a greater rise in serum creatinine than did patients in our control group, the difference did not reach statistical significance. While we cannot account for this finding, one study of alendronate in animals determined that rats with renal failure had a greater concentration of the bisphosphonate in the bone, kidney, and spleen than did rats with normal kidney function.[7] The study did not report whether the increased concentration was harmful to kidney function. Clinicians who

Table 1. Demographic characteristics of patients in the retrospective study

Characteristic	Study group (n = 24)	Control group (n = 24)	*P* value
Gender (% male)	45.8%	45.8%	> .99
Average CC_{Cr}* (mL/min)	30.2	46.3	< .001
Average SCr† (mg/dL)	1.5	1.1	< .001
Average LBW‡ (kg)	53.7	60.0	.020
Average height (in)	61.4	66.4	.004
Average age (years)	77.3	75.7	.528

*CC_{Cr} = calculated creatinine clearance. †SCr = serum creatinine. ‡LBW = lean body weight.

Table 2. Percentage of patients whose medical record reflected possible indications of an ADE* during the study period

Potential ADE indicator	Study group (n = 24)	Control group (n = 24)	*P* value
Change in NSAID† use	20.8	25.0	> .99
Change in H2‡ blocker use	8.3	8.3	> .99
Change in PPI§ use	12.5	4.2	.6
Diagnosis of joint pain	4.2	4.2	> .99
Change in SCr‖	12.5	0.0	.2

*ADE = adverse drug event. †NSAID = nonsteroidal anti-inflammatory drug. ‡H2 = histamine 2. §PPI = proton pump inhibitor. ‖SCr = serum creatinine.

decide to use alendronate in patients with severe renal insufficiency should consider monitoring the patients' kidney function more closely than they typically would.

HYPOTHESIS UPHELD

Our findings supported our hypothesis: Individuals with severe renal insufficiency who used alendronate for osteoporosis were no more likely than individuals without severe renal insufficiency to experience adverse drug events. It should be noted, however, that the post hoc power analysis showed the study to be underpowered. Because medical literature includes few investigations on this topic, our analysis could be considered a pilot study. Through a literature search, we found one other retrospective study on the topic, and its findings were similar to ours.[8] When the study authors reviewed the medical records of 181 patients receiving oral bisphosphonate therapy, 31 of whom had severe renal impairment, they found no significant difference in the incidence of adverse events between the patients with severe renal impairment and those without.[8]

Our study was limited by its retrospective nature, which restricted our data to that which was documented in the patients' medical records. Patients may not have reported adverse events to their physicians or they may have treated adverse events with over-the-counter medications, such as ibuprofen or ranitidine. In fact, since arthritis and gastroesophageal reflux disease are so prevalent among elderly patients, we did not exclude patients with these diagnoses from our study, and these conditions are treated, respectively, with ibuprofen and ranitidine. Finally, we did not examine the possible effect of dosage on incidence of adverse events, though dosages in this study varied widely, from 5 mg daily to 70 mg weekly. It is not known whether higher doses or more frequent dosing could have played a role in the rate of adverse events.

NOT THE LAST WORD

Our study could be used as a stepping stone for future investigations, perhaps with a prospective design. Increasing the number of sites at which the study is conducted would enhance the likelihood of finding an adequate number of eligible patients to give the study sufficient power. This also would allow investigators to examine the effect of different dosages on adverse events, and to use wider inclusion criteria. For example, to ensure follow-up appointments with primary care providers, we excluded patients who were taking alendronate for less than one year. Had we included patients who stopped the medication before a full year had passed, we may have uncovered a greater number of adverse events. ●

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