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Bone drugs' reverse danger

Rare instances of jaw decay are being linked to medicines used to prevent bone loss.

By Linda Marsa

Sue Piervin never suspected the pills she took to strengthen her bones could severely damage her jaw. Twelve years ago, a routine X-ray revealed her bones were thinning, so her doctor prescribed a drug to help stop the erosion of bone density. Then, in 1999, Piervin developed a painful bone spur in her jaw that had decayed to such an extent that it had to be surgically removed.

At the time, doctors were puzzled. But when she had a recurrence last year, they had a pretty good idea what was causing the trouble: Fosamax, the medication she was taking to prevent bone loss.

"I had three oral surgeries to remove all the dead bone," says the 56-year-old Los Angeles resident. "It was not a fun summer."

Since 2001, more than 2,400 patients taking Fosamax and other bone-building medications like it have reported bone death in their jaws, mostly after a minor trauma such as getting a tooth extracted. Most were taking especially potent, intravenously delivered versions of these drugs, which are known as bisphosphonates.

An additional 120 people who were taking bisphosphonates in pill form to prevent bone thinning have been stricken with such incapacitating bone, joint or muscle pain that some were bedridden and others required walkers, crutches or wheelchairs.

The incidence of both these complications is minuscule in comparison with the millions of people taking these medications. More than 36 million prescriptions for oral bisphosphonates, such as Actonel, Fosamax and Boniva, were dispensed in 2005, according to IMS Health, a pharmaceutical information and consulting company. Nearly 3 million cancer patients have been treated with intravenous versions of the medications.

But because at least 90% of drug side effects aren't reported to the Food and Drug Administration, the real number of people stricken with jaw necrosis and other side effects could be higher.

"We've uncovered about 1,000 patients [with jaw necrosis] in the past six to nine months alone, so the magnitude of the problem is just starting to be recognized," says Kenneth M. Hargreaves, chair of the endodontics department at the University of Texas Health Science Center in San Antonio.

With concern growing over the possible side effect, the American Assn. of Endodontists last week released a position statement on the problem. "Until further information is available, it would appear prudent to consider all patients taking bisphosphonates to be at some risk," the group said.

Unreported cases of the pain syndrome may be "considerable," says Diane K. Wysowski of the FDA's Office of Drug Safety, "because physicians may attribute the pain to osteoporosis."

The issue is especially worrisome, says Dr. Susan M. Ott, an osteoporosis expert at the University of Washington in Seattle, because the number of women taking bisphosphonates stands to increase now that women are more reluctant to preserve their bones by taking estrogen after menopause.

In 2002, when a landmark study revealed that hormone replacement therapy carried slight but measurable heart and breast cancer risks, prescriptions for oral bisphosphonates shot up 32%, according to IMS Health.

Bisphosphonate drugs have been used since 1995 to strengthen bone in women who are losing bone density and for nearly 15 years in men and women who have cancer. The medicines act by altering the dynamics of bone, which is constantly being turned over.

Cells called osteoclasts break bone down. Others called osteoblasts build it up. Osteoporosis occurs when formation of new bone does not keep pace with bone destruction.

Debate over risks

Bisphosphonates thwart the action of the osteoclasts, thickening bones and making them less likely to break. Physicians aren't sure why these drugs sometimes do seemingly the opposite and cause jaw death. But they know that osteoclasts are also involved in prompting osteoblasts to form. Consequently, over time, these medications may actually impede rather than promote the creation of new bone.

Christopher Loder, a spokesman for Fosamax maker Merck, points out that osteonecrosis of the jaw with Fosamax is "exceedingly rare." "In all of our controlled clinical trials with Fosamax, which involved more than 17,000 patients, including some that were 10 years in duration, we had no reports" of it, he says.

The risk appears to vary according to the strength of the bisphosphonate being used. Recent studies show that about 80% to 90% of jaw decay occurs in cancer patients who take potent intravenous bisphosphonates (Aredia, Zometa). The drugs replenish bone tissue that is lost when cancer spreads to the bone and can reduce pain and the risk of debilitating fractures.

The rare side effect, called osteonecrosis of the jaw, causes severe infections, swelling and the loosening of teeth. Patients often require long-term antibiotic therapy or surgery to remove the dying bone tissue.

"I've taken off several jaws because of this problem," says Dr. Salvatore Ruggiero, an oral surgeon at Long Island Jewish Medical Center in New York who was among the first to observe this phenomenon in 2001. "Because bone death can't be reversed, there's nothing we can do for these patients except ease their pain and prevent it from spreading."

Patients who have cancer-related bone weakening and pain have few options but to take bisphosphonates. More worrisome for experts are the millions of women such as Piervin who take the weaker bisphosphonate pills to treat osteoporosis, and for many more years than do cancer patients. "Even though the chances of getting this are small, considering there are 23 million women taking this drug, we could be talking about a significant number of people," Ruggiero says. "Risks increase the longer you're on the drugs, and it can take years for the complication to manifest itself."

It's not uncommon for rare side effects to come to light only after a drug has been approved, says Dr. Eric Colman of the FDA's Division of Endocrine and Metabolic Drugs in Silver Spring, Md. Serious adverse reactions that weren't apparent in premarket tests emerge in half of all prescription medications.

"People need to realize there are unknown side effects with every drug, and these medications are no exception," he says.

What patients can do

In the last two years, drug makers have added warnings about bone death to some of the medications' labels and about the pain syndrome to all of them.

But despite an alert sent to physicians by the FDA in 2004, "it's been a battle getting people educated," Ruggiero says. Dentists and oncologists know about the problem, but gynecologists and family doctors, who write many of the prescriptions for oral bisphosphonates, aren't as informed.

Patients need to be vigilant. "Women taking these drugs for osteoporosis should tell their doctor if they develop severe pain," says Dr. Theresa Kehoe, an endocrinologist with the FDA's Division of Endocrine and Metabolic Drugs.

In addition, anyone who uses oral or intravenous bisphosphonates should alert their dentist and oral surgeon if they need an invasive dental procedure. Better yet, says Hargreaves, get dental work done before going on these drugs, although avoiding jaw trauma is no guarantee of protection.

The drugs greatly reduce risks of incapacitating fractures for older women with osteoporosis. Women who don't have osteoporosis but have other risk factors, such as usage of bone-depleting steroids, previous fractures or a family history of the condition can also benefit, says Dr. Charles H. Chestnut III, who heads osteoporosis research at the University of Washington.

But they should be considered far more cautiously by younger women who have less bone thinning and are taking oral bisphosphonates simply to prevent further deterioration. These meds become incorporated into the bone's matrix, where they can linger for five years or more. Their effects are cumulative. And women are expected to take them for the rest of their lives.

"These drugs are still relatively new and problems sometimes take years to show up," says Ott of the University of Washington.

"We're not quite sure what we're dealing with over the long haul. Side effects like this should make ordinary, healthy women think twice."

Piervin still takes calcium and Miacalcin, a nasal spray that helps preserve bone density but isn't nearly as potent as the bisphosphonates. She also walks every day and does weight-bearing exercise three times weekly to help her bones stay stronger — even parks her car eight to 10 blocks from work to fit more walking into her schedule.

She'd take hormones, but she's worried about the risk. She'd exercise more, but she doesn't have the time.

"I'm off Fosamax," she says, "but I'm in limbo regarding future treatment."