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Early statin withdrawal can endanger patients with acute coronary syndrome

Pharmacists should be aware of 'rebound' effect

The benefits of statins on acute coronary outcomes are rapidly lost and outcomes worsened if statins are discontinued during a patient's hospitalization for an acute coronary syndrome, report researchers at Nova Southeastern University in Fort Lauderdale-Davie, FL.

"Withdrawal of statin therapy in the first 24 hours of hospitalization for non-ST-elevation myocardial infarction increased the hospital morbidity and mortality rate versus continued therapy," the report in *Pharmacotherapy* said. [1]

Lead researcher **Luigi Cubeddu**, MD, PhD, of the Nova Southeastern University departments of Pharmaceutical Sciences and Pharmacy Practice, tells *Drug Formulary Review* his research was in response to the "well-known fact that high levels of LDL cholesterol are associated with increased risk for adverse cardiovascular events, specifically all events related or due to atherosclerotic vascular disease."

Statins are the medications that have shown the greatest efficacy in lowering serum cholesterol, and that they have been seen to decrease adverse cardiovascular events, he adds. They have good safety profiles and are used extensively, he says.

For many drugs, according to Cubeddu, abruptly discontinuing therapy is often associated with rebound symptoms and complications that are often opposite to what the drugs are indicated for. "When we started thinking about this problem and reviewed the literature for information concerning this aspect, we decided that a review article on statin discontinuation was needed and could make practitioners further aware of the problem," he says.

The literature review the researchers performed found that short-term discontinuation of statin therapy in patients with stable cardiac conditions may not substantially increase risk of acute coronary syndromes. But in patients who already have acute coronary syndrome, the rapid increase in risk of an event may result not only from the lost benefits of the therapy,

but also from rebound inhibition of vascular protective substances and activation of vascular deleterious substances. Thus, researchers concluded, in the absence of data from randomized controlled trials, current information suggests that statin therapy should be continued and possibly boosted during hospitalization for an acute coronary syndrome. "Because statins are discontinued during the early hospitalization of many patients, practitioners must ensure that statins are not omitted, unless contraindicated, from the treatment of patients with acute coronary syndromes," they said.

Many have high cholesterol

Nearly 105 million American adults have total blood cholesterol levels of 200 mg/dl or higher, and some 42 million of them have levels of 240 mg/dl or higher and are considered to be at high risk. Individuals with preexisting coronary heart disease or risk equivalents are also at high risk and require aggressive lipid lowering. Statins have assumed the central role in treating high cholesterol because of their superior ability to reduce levels of low-density lipoprotein cholesterol (LDL). Statins reduce coronary heart disease frequency by 21% to 43% and are effective in the primary and secondary prevention of coronary heart disease.

Although statins are generally well tolerated, nearly 1.5% of subjects receiving them develops complications and requires either dosage reduction and/or discontinuation of therapy. Drug-induced muscle weakness, myositis, and rhabdomyolysis with or without acute renal failure were observed with statin use. FDA's MedWatch system recorded 3,339 cases of statin-associated rhabdomyolysis reported between January 1, 1990, and March 31, 2002. Withdrawal of Baycol from the U.S. market in August 2001, after it was associated with some 100 rhabdomyolysis-related deaths, underscores the risk, Cubeddu says.

Less serious adverse effects such as muscle pain and weakness affect some 1% to 5% of patients. Liver toxicity is another important cause of statin discontinuation.

The researchers said that in addition to adverse drug reactions, statins' high cost and their long-term use may negatively affect patient compliance. At six to seven months after the drug was initially supplied, discontinuation rates for statins average 30% and were similar for all statins. Researchers said they are not aware of any guidelines for discontinuing statin therapy, and said discontinuation of therapy may not be without risk. Acute statin discontinuation may reduce endothelial dysfunction and increase risk of cardiovascular events.

Discontinuation raises risks

The researchers found that statin therapy should be continued during a patient's hospitalization for acute coronary syndrome unless contraindicated. Discontinuing statins in patients with acute coronary syndrome appeared to increase the risk for cardiovascular events. A similar increase in risk was not seen in patients with stable cardiac conditions, whose low baseline of events might not have provided enough power to observe significant differences between statin withdrawal and statin continuation. A sudden discontinuation of statin therapy appears to lead to a rapid loss of its vascu-

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Editor: **John Hope**.
Senior Vice President/Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@ahcmedia.com).
Associate Publisher: **Coles McKagen**, (404) 262-5420, (coles.mckagen@ahcmedia.com).
Managing Editor: **Gary Evans**, (706) 310-1727, (gary.evans@ahcmedia.com).
Senior Production Editor: **Ami Sutaria**.

Editorial Questions

Questions or comments? Call **Gary Evans** at (706) 310-1727.

lar protective effects and, in some instances, vascular deleterious and prothrombotic activity may increase above baseline levels. Given those findings, the researchers said from their review of literature on statin withdrawal in healthy subjects, baseline active vascular disease seems to be needed for clinically significant vascular adverse events to develop after statin withdrawal.

"In the trials discussed, an alarmingly high number of patients who took statin therapy had their statin discontinued during early hospitalization for an acute coronary event," Cubeddu wrote. "Motives for discontinuation were not documented and could have been associated with other factors leading to poor hospital outcomes. Equally distressing was the finding that many individuals admitted with an acute coronary syndrome were not receiving statins…. Factors and conditions that make a specific patient susceptible to adverse cardiovascular events after the withdrawal of statins are not understood…. A pressing issue then becomes what to use in place of statins in patients with an acute coronary event who require discontinuation. Investigators found that the vasodilatory effect of nitroglycerin was unaffected during statin withdrawal in mice. The administration of drugs that deliver nitric oxide and/or increase its production, such as organic nitrates, L-arginine, and nebivolol, could theoretically be of value in these patients. In addition, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, and drugs that reduce the generation of oxygen free radicals and proinflammatory and proatherogenic substances could be used. However, we know of no studies that directly addressed this aspect."

Cubeddu tells *Drug Formulary Review* his retrospective analyses of databases was for the purpose of determining whether subjects hospitalized for an acute coronary event (sick subjects who should never have stopped statin treatment), abrupt statin discontinuation would worsen the disease course. He says the data were collected at a time at which the role of statins in primary and secondary prevention was just emerging. Consequently, practitioners were less knowledgeable about the need to continue the statins. Currently, he says, unless it happens inadvertently, physicians are not stopping statins in patients with acute coronary events. "We hope that our article has helped to nail in this concept," he says. "There was a suggestion on the data analyses that events may get worse and be more frequent after statin discontinuation [like a rebound worsening]. The other type of data derives from analyses in subjects who had the disease [chronic] and that stopped the statins for some reason. It was found out that these subjects lose the gained benefits of the treatment. Data on otherwise healthy subjects, who take statins because of high lipids, but not because of cardiovascular disease, suggest that stopping statins does not lead to serious cardiovascular events."

Pharmacists' role in promoting awareness

Asked about the role pharmacists can play in bringing about a different approach to statin use in hospitalized patients, Cubeddu says they should develop a surveillance plan to detect and thus prevent statin discontinuation in subjects admitted with an acute coronary syndrome or cardiovascular event such as a stroke. If the statin the hospital formulary uses is different from the one the patient has been taking, he says, the best approach would be to ask the patient and his or her relatives for the same statin. Absent that, he suggests providing at least an equivalent dose of the other statin. He says practitioners could even consider increasing the dose for the first week, until steady state levels of the new statin have been reached.

Physicians, nurses, and pharmacists should be educated on the problem and share responsibility for changing the approach to statin continuation in some hospitalized patients, Cubeddu emphasizes. He acknowledges pinpointing responsibility for change is a difficult issue. "Obviously, the physician should be the one with the greatest responsibility," he says. "But perhaps pharmacists should play the greatest role." In terms of future research that is needed, Cubeddu says determining the therapy to be used with discontinuing a statin is a must in subjects with an acute coronary event. For example, he says, a patient is destroying his muscle mass [rhabdomyolysis] as a consequence of a statin treatment. In that case, the statin must be discontinued. "We need to provide other meds to control his or her cholesterol," he says, "but in addition we need to protect for a possible worsening of the coronary event."

[Editor's note: Contact Dr. Cubeddu at lcubeddu@nova.edu.]

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Hospitalized patients also at risk for VTE

May warrant consideration for prophylaxsis

Research conducted by Policy Analysis, Inc., Brookline, MA, and reported in the *American Journal of Health-System Pharmacy*, found that the risk of clinical venous thromboembolism (VTE) among medically ill patients admitted to a hospital, although less than that of patients undergoing major surgery, is not negligible.[1] The authors report that patients with a history of recent VTE or surgery, those who are admitted to an intensive care unit, those with an admitting diagnosis of heart failure, and those with acute cancer are at especially high risk of VTE and deserve increased consideration for prophylaxis.

Deep-vein thrombosis (DVT) and pulmonary embolism (PE)—referred to together as venous thromboembolism—are important causes of disability and death, according to corresponding author **Gerry Oster**, PhD, Policy Analysis vice president. Most VTE cases occur among people living in the community, and not in nursing homes, but risk for VTE is more than 260-fold higher among those who are hospitalized. Although a recent major surgery is the greatest risk factor for VTE, the number of cases among medical and surgical patients is roughly equal, as there are far more medical than surgical admissions.

In research supported by drug company Sanofi-Aventis, Oster and colleagues conducted a retrospective cohort study to estimate the risk of VTE in hospitalized medically ill patients. They identified all persons age 40 and older who were admitted to a hospital between January 1, 1998, and June 30, 2002, for reasons other than traumatic injury and who did not undergo surgery. Patients were followed for 90 days from the date of their earliest such hospital admission for the occurrence of clinical VTE.

The researchers characterized the study population in terms of selected demographic and clinical characteristics at index admission, including age, gender, principal diagnosis group (based on a classification scheme from the U.S. National Hospital Discharge Survey), geographical region, and payer type. The presence of several established VTE risk factors during the index admission was also noted, including acute coronary syndrome, stroke, chronic obstructive pulmonary disease, heart failure, and admission to an ICU. Study subjects were further characterized according to whether they had any of these additional established VTE risk factors at the index admission or during the immediately preceding six month period: cancer, post-thrombotic syndrome (but not as principal diagnosis at the index admission), and neurological disorders with plegia, paresis, or paralysis. Finally, any diagnosis of DVT or PE during the six month history period before the index admission was obtained.

Primary study endpoint

The researchers said their primary measure of interest was the occurrence of clinical VTE between the index admission and the end of the 90 day follow-up period.

A total of 92,162 patients met all inclusion criteria for the study. Mean age was 71 years. Some 54% of study subjects were women. About one-half had a principal diagnosis involving either the circulatory or respiratory system. During the index admission or the previous six months, 2.25% of study subjects had a recorded principal or secondary diagnosis of post-thromboting syndrome. And during the index admission, 10.5% of patients had a diagnosis of acute coronary syndrome; 9.7%, stroke; and 15%, heart failure. One-half of all study patients were admitted to an ICU or critical care unit (CCU).

The cumulative incidence of clinical VTE at 90 days was 1.59%, with 18% of the cases occurring post-discharge. Inpatient mortality (unadjusted) was 42% higher for patients who developed VTE than for those who did not. Significant risk factors for VTE included peripheral arterial disease during admission; chronic obstructive pulmonary disease during index admission; any diagnosis of post-thrombotic syndrome, neurological disease with paresis or paralysis, cancer, or heart failure; a diagnosis of VTE during the six-month history period; admission to an ICU or CCU; and an operating room procedure during the 30 days before the index admission.

The researchers said that while most cases of clinical VTE among hospitalized medically ill patients occur during hospitalization, almost one in five events occurred post-discharge. "To the best of our knowledge," they said, "our study is the first to examine VTE risk following hospital discharge among these patients. In studies of hip and knee arthroplasty patients, in contrast, 49% to 81% of all cases of clinical VTE have been reported

to occur during the three months following hospital discharge. While the risk of post-discharge VTE appears to be lower in medical patients than in those who have undergone major orthopedic surgery, it nonetheless should be of concern."

Risk factors that the researchers found to be independent predictors of VTE such as a history of cancer, history of VTE within six months of index admission, an operating room procedure within 30 days of index admission, and a diagnosis of heart failure or peripheral artery disease during index admission are generally well known, the researchers said. The only exception is peripheral artery disease during the index admission, but they said that finding could reflect a diagnostic bias based on increased scrutiny of the lower extremities in the disease. The researchers said they did not find that other variables previously reported to be important predictors such as stroke and acute coronary syndrome were related to VTE risk. In fact, they said, a diagnosis of coronary artery disease was found to be associated with a decreased risk of VTE, a finding that probably reflects the widespread use of antithrombotic agents for preventing and treating arterial thrombosis.

[Editor's note: Contact Dr. Oster at goster@pai2.com.]

Reference

1. Oster, G. Risk of Venous Thromboembolism Among Hospitalized Medically Ill Patients. *Am J Health-Syst Pharm.* 2006;63(20):S16-S22. ■

Setting record straight on VA pharmacy system

Both praise, blame stem from misconceptions

Department of Veterans Affairs chief pharmacy officer **Michael Valentino**, R.Ph., says much of the praise and criticism his organization's pharmacy system has received in terms of it being considered a model for potential changes to Medicare Part D arise out of misconceptions about VA pharmacy.

Valentino spoke at a Washington, DC, briefing hosted by the American Enterprise Institute and reported on at the American Society of Health-System Pharmacists (ASHP) web site. Among the myths that Valentino sought to dispel was that the VA formulary covers just 1,300 drugs, or less than one-third of the products typically available through a Part D drug plan. "The fact is that VA dispenses 4,778 drugs" from the formulary, he told the briefing. He said the 1,300 figure represents the individual chemical compounds on the VA formulary, some of which are represented by multiple products. "Also, we dispense an additional 1,400 drugs not on the formulary," he said. "If you look at it this way, we offer more drugs" than are typically available through a Part D drug plan.

The VA's track record of negotiating low prices from drug manufacturers has caught the attention of policymakers. Recent government data indicate that VA's costs for commonly prescribed drugs were just 42% of the products' average wholesale price, while costs for Part D plans averaged 73% of average wholesale price. Legislation has been proposed that would allow the federal government to directly negotiate with drug manufacturers to obtain volume based discounts on Part D covered drugs for Medicare beneficiaries, as VA does for its enrollees. Opponents of the legislation have said that negotiation by Medicare would actually be a price-controlling mechanism that would destabilize the prescription drug marketplace and drive up costs outside of Medicare.

Former Centers for Medicare and Medicaid Services administrator **Mark McClellan**, MD, now an American Enterprise Institute visiting fellow, said VA's system behaves like a staff model HMO that is efficient but cannot be directly compared to most Part D plans. "If you wanted to get costs down for Part D right away, one way to do it would be to get everybody into coordinated care plans—staff model HMOs or one of the PPOs or other coordinated care plans in Medicare," McClellan said. Nearly eight million Medicare beneficiaries were enrolled in Medicare Advantage managed care plans or PPOs at the end of 2006, and some 17.5 million beneficiaries had signed up for standalone drug coverage, according to federal figures.

How VA negotiates prices

McClellan also emphasized that VA obtains good discounts on formulary drugs by limiting the number of products in certain therapeutic classes like statins to get better prices on preferred brands. "The tighter the formulary, the more you can drive down prices in negotiations,"

he said, also noting that Part D enrollees are "choosing plans with broad formularies" instead of more restrictive plans. Valentino acknowledged that Pfizer's statin Lipitor, the most commonly prescribed drug for seniors in the U.S., is not on VA's national formulary. Rather, he said, VA's formulary includes Merck's Zocor, generic lovastatin (Merck's Mevacor), and Novartis' Lescol. But Valentino also reiterated that VA patients can obtain nonformulary drugs.

"We use evidenced based criteria for use of nonformulary drugs to make sure they're available for people that need them," he said. He said that in the case of Lipitor, VA pharmacies dispensed more than 700,000 30-day prescriptions for the drug last year. Valentino said the VA system scores well in customer satisfaction surveys, and that the majority of veterans are satisfied with the system. McClellan said the same is true for Part D plans.

But the two had differing perspectives on reports that some one million veterans have left the VA system for Part D. "It's not that they're not using the VA coverage at all, but they're also using Medicare coverage when it's more convenient or maybe a different kind of medication, but they're definitely using Medicare coverage as well," McClellan said. But Valentino said the idea of one million VA defections to Plan D is a myth. "We looked at our 4.4 million VA pharmacy users and matched that to CMS data," he said. "There are about 2.5 million VA pharmacy users who are dually eligible for Part D. As it turns out, about 650,000 patients that are using VA have enrolled in Part D, and 400,000 of those were auto enrolled by someone else. They didn't choose to enroll. It was either because they were in Medicaid, other low income subsidy, or their employer enrolled them in a plan. That leaves about 250,000 roughly that appear to have consciously enrolled in Part D. The next step, after we have a year's worth of data for Part D, is to take that cohort and check their reliance on Part D, VA, or both and see what's actually happening." ■

Pharmacists help with ED smoking cessation efforts

Many smokers seek primary care in EDs

Smoking cessation is a timely topic and efforts to curb tobacco use are widely discussed in the medical literature. MLC Solutions principals **Charlotte Kenreigh**, Pharm.D., and **Linda Timm Wagner**, Pharm.D., wrote in a Viewpoint column at the Medscape pharmacist web page that emergency department smoking interventions could make use of pharmacists by calling on them to help educate patients about available smoking cessation products.

Kenreigh and Wagner commented on a report in the *Annals of Emergency Medicine* that provided a joint statement of emergency medicine organizations on tobacco control interventions in the emergency department. The statement reported that smoking is considered a leading cause of preventable death, with nearly 20% of all U.S. deaths related to tobacco use. Despite the knowledge that the effects of smoking are catastrophic, it said, people continue to smoke. The nicotine in tobacco is addictive, and breaking the cycle of this addiction can be difficult.

While national practice guidelines offer specific recommendations to help clinicians and healthcare systems fight tobacco use, the study authors noted the guidelines fail to target actions for hospital emergency departments. Because more than 115 million patients pass through emergency departments each year, targeting tobacco interventions at that level has the potential to affect a large population.

A task force representing major emergency medicine professional organizations sought to test feasibility of emergency department based tobacco control, review the evidence, and propose a research and educational agenda for tobacco intervention in the emergency department setting. A literature review indicated that tobacco use among emergency department patients exceeds that of the general population, indicating that interventions in the emergency department population could reach a significant number of smokers. Studies have shown that emergency department physicians are likely to inquire about a patient's smoking status, but are not likely to assess patients' interest in quitting or raise the possibility of tobacco cessation.

Barriers to emergency department tobacco control that were identified include insufficient time with patients, perceived lack of interest on the part of patients, the belief that the emergency department is an inappropriate setting for preventive health services, perceived ineffectiveness of counseling, lack of training in tobacco cessation techniques, difficulties with followup, lack of reimbursement for screening

and referral, and the administrative burden of screening if smoking is not perceived to be the cause of the emergency department visit.

Large potential effect

Kenreigh and Wagner say that even if an emergency department based tobacco control program were not highly efficacious, it still could reach a large number of smokers if delivered to a large population.

For example, about 85 million of the annual emergency department visits include adults and children age 15 and older. If one-third of those individuals smoke, that would translate to an estimated 20 million smoker emergency department visits per year. The task force estimated that even with a low-efficacy program, 1% of the smokers could be persuaded to quit, meaning there would be an additional 200,000 people who quit smoking each year who might not have been reached by any other tobacco intervention program.

The task force provided several recommendations, including:

- Educate all faculty and emergency medicine residents about the burden of smoking and the potential for emergency department cessation programs.
- Identify the most effective emergency department based strategies for urban, suburban, and rural emergency departments, and assist in adopting them.
- Conduct research on novel approaches to emergency department based smoking cessation.
- Identify funds to encourage emergency department-based research and demonstration projects on smoking cessation.

Kenreigh and Wagner said that while pharmacists could be useful in educating patients about smoking cessation products, the costs of the aids would likely be a concern for patients without healthcare coverage and studies on how to make smoking cessation aids affordable should be included in the research agenda. ■

FDA moving to strengthen drug safety program

Canadian pharmacists increase safety as well

The U.S. Food and Drug Administration have asked Congress to make changes as part of reauthorization of the Prescription Drug User Fee Act (PDUFA) that would significantly broaden and upgrade the agency's drug safety program.

The user fee program was first authorized in 1992. It adds industry funds to congressional appropriations to FDA to help the agency's human drug review program achieve performance goals by paying for additional staff. Over the years, the PDUFA programs have enabled the agency to dramatically reduce the review time for drugs and biological medications while increasing scientific consultations, clarifying issues involving drug development, and increasing oversight of postmarket safety.

FDA is requesting an increase of $29.3 million in user fees for a major boost to activities to ensure the safety of medications after they are on the market. The increased funds would be available for FDA drug safety activities for marketed medications throughout as long as they remain on the market and would increase FDA's drug safety capacity for surveillance, including hiring an additional 82 employees to perform post market safety work.

The agency also has recommended eliminating a statutory provision under which PDUFA fees may be used to assess safety issues only during the first three years after a product's approval. FDA also would use the added resources to adopt new scientific approaches and improve the utility of existing tools for detecting and preventing adverse events, such as obtaining access to the best available databases to better analyze drug safety signals.

Meanwhile, the Canadian Society of Hospital Pharmacists and the Institute for Safe Medication

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- Documenting pharmacist interventions via PDA
- Drug-related hospitalizations

Practices Canada have signed a memorandum of understanding on their mutual commitment to collaborate to advance safe medication practices within the larger scope of patient safety.

The two organizations said they will collaborate to reduce the potential for medication-related adverse events by (1) raising awareness of issues relating to medication safety, (2) identifying and addressing system issues related to medication safety in hospitals, and (3) providing tools, information, and education pertaining to safe medication practices.

Steps to be taken

The agreement commits the two groups to working together to:

• Promote best pharmacy practices based on the best research evidence on the optimization of medication use systems such as involving pharmacists in direct patient care; implementing safe drug distribution systems; expanding use of computer technology and automation; reviewing drug orders; using drug formulary systems; standardizing medication policies and guidelines; providing drug information/education to patients and healthcare providers; and reporting to the Canadian Medication Incident Reporting and Prevention System.

• Provide recommendations to key stakeholders for system changes required to improve patient safety, such as packaging and labeling issues related to pharmaceuticals and error-prone medication use systems and procedures.

• Provide timely information to hospital pharmacists on issues related to medication safety.

• Deliver educational programs pertaining to safe medication practices to hospital pharmacists.

• Undertake specific medication safety initiatives as appropriate.

• Establish consistency in initiatives and messaging pertaining to safe medication use in hospitals.

Representatives of the two organizations are to meet at least annually to discuss areas of cooperation, identify priority areas, tackle safety issues, and review progress on common goals. ■

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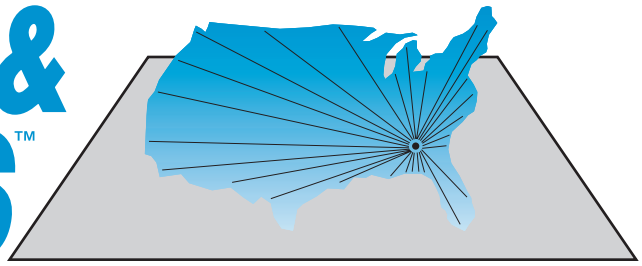

Bad to the (jaw) bone:

Avoiding ADRs in cancer patients receiving IV bisphosphonates

By **Brandy Puet**, PharmD Candidate, Auburn (AL) University

Physician, dentist collaboration necessary

The recent appearance of osteonecrosis of the jaw in cancer patients receiving intravenous (IV) bisphosphonates is a painful reminder of the condition that struck match factory workers over a hundred years ago.

In the mid-1800s to early 1900s, cases of osteonecrosis of the jaw began to appear in workers who were involved in the production of matches dipped in white phosphorus throughout Europe and the United States. At least 150 cases were reported from 15 different match factories in the U.S during this time period. These workers suffered from pain, an odorous discharge, and often disfigurement. Lacking the modern advantage of antibiotics, this condition was fatal in approximately 20% of cases.[1]

Today, bisphosphonate induced osteonecrosis appears to be linked to nitrogen-containing bisphosphonates, with a 2-12 % incidence occurring in patients taking these medications.[2] The only bisphosphonates in the U.S. not containing a nitrogen moiety are Didronel (etidronate disodium) and Skelid (tiludronate disodium).[3] Aredia (pamidronate disodium) and Zometa (zoledronic acid) -- the main bisphosphonates used in cancer patients -- are responsible for the majority of cases of osteonecrosis, with zolendronic acid having a higher incidence.[3,4] In a review by Marx et. al. of 119 patients with osteonecrosis, approximately 97% of patients were receiving either zoledronate or pamidronate.[5] Another review by Woo et. al. involving 368 cases of bisphosphonate-associated osteonecrosis revealed that 94% of these patients had been treated with IV bisphosphonates (mainly zoledronic acid and pamidronate).[3]

Adverse drug reactions surface

Despite the fact that bisphosphonates have been in use for over 30 years, with an indication for IV use in bone metastasis for over ten years, the occurrence of osteonecrosis was not reported until 2003.[4,6] In 2004, oncologists and maxillofacial surgeons were warned of the adverse drug reaction (ADR) by letters sent out by Novartis, the manufacturer of the two main causative agents. Dental health professionals were not warned of this potential ADR until May of 2005.[6] Now that healthcare professionals are becoming aware of the connection between osteonecrosis and bisphosphonate use, reports are likely to increase.

Intravenous bisphosphonates are highly advantageous in the treatment of cancer patients, treating and preventing complications in these patients such as pain, fractures, spinal cord compression, and hypercalcemia of malignancy. Cancer patients receiving intravenous bisphosphonates are those patients with hypercalcemia of malignancy, those with prostate, lung, or breast cancer with or at risk of bone metastases, and those with multiple myeloma.[3-6] Bisphosphonates act by osteoclast inhibition and apoptosis, thus hindering resorption of bone. They are also suspected to have antiangiogenic properties.[4,6]

How does a drug that prevents fractures also cause osteonecrosis? The exact pathophysiology behind this is unclear. One theory stresses the importance of the body being able to remodel its bones after the daily stress put on them. The jaw especially undergoes constant use and abuse resulting in the collection of microfractures. The body's normal response is to use its osteoblasts

and osteoclasts to repair these microfractures. The osteoblasts perform their normal function of bone mineralization; however, due to the bisphosphonate concentration in the bone, the osteoclasts are unable to remove the damaged bone. If you add in the possible antiangiogenic properties, which will take away much needed blood flow to the bone to heal, the main result is a bone that cannot repair itself. Add in patients who are immunosuppressed and unable to fight off the millions of bacteria that live in the mouth and who are undergoing such treatments as chemotherapy, the end result is a perfect atmosphere for osteonecrosis of the bone to occur.[4]

Dental procedure may proceed onset

Although bisphosphonate induced osteonecrosis can present spontaneously, its presentation typically occurs after a dental procedure such as an extraction or after a recent dental infection.[3,6] This is likely due to an inability of the bone to heal from the procedure and concomitant bacterial invasion. In the review by Woo et. al., 60% of cases were related to dental procedures.[3] In a web based survey performed by the International Myeloma Foundation, 81% of patients with myeloma and 69% of patients with breast cancer who had osteonecrosis of the jaw had a history of recent dental problems such as infection or a recent tooth extraction.[7] In most cases, the initial presentation is an area of exposed bone in the maxilla or mandible. Some patients are otherwise asymptomatic; others may complain of pain. Other symptoms are a nonhealing dental procedure site, ulcer, purulent discharge, and inflammation and swelling of the gums. In later stages, other sites may become affected and surrounding teeth may become loosened. Some patients may only complain of pain with no evidence of exposed bone.[4,6,8]

Many of the risks of bisphosphonate induced osteonecrosis have already been alluded to in this article. The main risks are associated with the specific type of bisphosphonate (nitrogen containing), the intravenous route of the bisphosphonate, the type of patient (cancer), inappropriate dental hygiene, and dental procedures.[4] Other risk factors involve the use of other medications that affect the bone such as corticosteroids and medications that lead to bacterial invasion of the osteonecrotic site such as immunosuppressants.[8] A longer duration of bisphosphonate use also increases a patient's risk. [6]

Of all these risk factors, the most preventable are those associated with dental care. Patients are at an increased risk if they have dental disease, dental surgery (including extractions), oral trauma, periodontitis, or poor dental hygiene.[9] Bisphosphonate induced osteonecrosis is comparable to osteoradionecrosis (bone necrosis caused by radiation). Patients receiving head and neck radiation are referred to a dentist to take care of any dental problems before the procedure to decrease the risk of osteoradionecrosis. Cancer patients receiving IV bisphosphonates should be no different.[10] Upon dental evaluation, current infections can be treated and future risky procedures can be prevented by planning ahead and performing those procedures before bisphosphonate therapy.[2,5,6,8-10] If dental referral cannot be made before bisphosphonate therapy is initiated due to the urgency of the patient's condition, patients should still seek a dental evaluation as soon as possible.

Patient education recommended

Patients should be counseled about the risk of osteonecrosis, and the importance of good dental hygiene and regular checkups should be stressed. It is important that patients also understand the importance of making their dentist aware that they are receiving IV bisphosphonates. If dentists are aware of a patient's bisphosphonate use, they will know to try to avoid procedures that may be risky in this type of patient. Physician and dentist collaboration is necessary to provide optimal care for cancer patients taking bisphosphonates. Pharmacists can also play a role by helping other health professionals become aware of this adverse drug reaction and by encouraging appropriate dental care when involved in the distribution of these medications to the patient.

For those patients on IV bisphosphonate therapy whose condition necessitates a dental procedure such as an extraction, it is debatable whether or not to discontinue the bisphosphonate therapy before and after the procedure. There is no evidence that discontinuing the bisphosphonate around the time of the procedure decreases the risk of osteonecrosis. It is even debatable if bisphosphonates should be discontinued in cancer patients once osteonecrosis has already occurred.[2,3,5,8,9] Debate exists because much is unknown about how long it takes to decrease osteoclast suppression once discontinuing bis-

phosphonate treatment, and bisphosphonates may significantly improve a cancer patient's quality of life. Due to a current lack of evidence based medicine on this subject, careful consideration of the necessity of the bisphosphonate treatment and collaboration between the dentist or oral surgeon and the physician will determine the decision to continue or discontinue bisphosphonate therapy.

May not respond to standard treatments

Despite its resemblance to a more familiar from of jaw necrosis, osteoradionecrosis, bisphosphonate-induced osteonecrosis is not as likely to have a response to standard treatments such as surgical debridement and hyperbaric oxygen. Bisphosphonate-induced osteonecrosis is typically treated with oral rinses and antibiotic treatment, with surgical removal of bone being a last line option.[3-6,10]

Although osteonecrosis is most prevalent in cancer patients receiving IV bisphosphonates, a small percentage of the millions of patients receiving oral bisphosphonates for osteoporosis have also developed osteonecrosis of the jaw. Cases reported to drug companies producing these agents report 170 cases with Fosamax (alendronate), 20 with Actonel (risedronate), and one with Boniva (ibandronate) as of early 2006. This is a small number considering the millions of patients receiving oral bisphosphonates for osteoporosis. Despite the small risk in patients receiving oral bisphosphonates, patients should also be referred for dental evaluation before treatment is initiated and have current dental problems treated before initiation of therapy. These patients should also be made aware of the risk of osteonecrosis and encouraged to maintain proper oral hygiene.[11] In contrast to patients receiving IV bisphosphonates, dental surgeries are not contraindicated in patients receiving oral bisphosphonates; however, some dental health professionals are recommending discontinuing the oral bisphosphonate around the time of the procedure.

Drop drugs before, after dental surgery

The American Association of Oral and Maxillofacial Surgeons (AAOMS) recently released a position paper that recommends discontinuing oral bisphosphonate therapy three months before and three months after a dental surgery if the patient has been on a bisphosphonate for greater than three years or has been receiving corticosteroids concomitantly. AAOMS also suggests that discontinuing oral bisphosphonates for 6 -12 months after the occurrence of osteonecrosis improves patient outcomes.[12]

Due to the importance of bisphosphonate therapy, the most valuable step healthcare professionals can take is prevention of adverse drug reactions. Healthcare professionals from the Mayo Clinic have already arisen to this challenge through recommendations made in their guidelines for bisphosphonate use in multiple myeloma patients. In these guidelines, "proactive communication" between the physician and the dental health professional is encouraged and prescribing of pamidronate over zoledronic acid is recommended due to a higher incidence of osteonecrosis in patients receiving zoledronic acid.[13] Healthcare professionals from other institutions can become involved in preventing bisphosphonate ADRs by developing guidelines for appropriate bisphosphonate use and educating other healthcare professionals. Guidelines and education should stress the importance of collaboration of healthcare professionals, patient awareness, and appropriate monitoring.

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New FDA Approvals

FDA recently approved these drugs:

• Connetics' Olux-E (clobetasol propionate) foam, 0.05%, was approved for treating inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. FDA noted the company has already fulfilled the pediatric study requirement for the application, and reminded the company of its commitments to perform two post-marketing studies: a dermal carcinogenicity study and a photocarcinogenicity study.

• Shire's Lialda (mesalamine) delayed release tablets, 1.2g, was approved for induction of remission in patients with active, mild to moderate ulcerative colitis. FDA said Lialda's safety and effectiveness beyond eight weeks has not been established. The company is required to perform a post-marketing pediatric study for treating ulcerative colitis in children of all ages. ■

CE Questions

Pharmacists participate in this continuing education program by reading the article, using the provided references for further research, and studying the CE questions. Participants should select what they believe to be the correct answers.

Participants must complete a post-test and evaluation form provided at the end of each semester (June and December) and return them in the reply envelopes provided. A statement of credit requires a passing score of 70% or higher. When a passing test and evaluation form are received, a statement of credit and answer guide will be mailed to the participant.

This CE program will improve participants' ability to:

- **Compare** the clinical efficacy and safety of one therapeutic agent over another used in the same setting.
- **Assess** clinical trial data and explain how the results influence formulary decision making.
- **Perform** cost-effectiveness analyses.

9. Cases of osteonecrosis of the jaw began to appear in workers involved in the production of what product?

A. candles.
B. dentures.
C. matches.
D. glass.

10. Pamidronate disodium and zoledronic acid are responsible for the majority of cases of osteonecrosis today.

A. True
B. False

11. Cancer patients typically receiving intravenous-bisphosphonates are those patients with hyper calcemia of malignancy, including those with cancer of the:

A. prostate.
B. lung.
C. breast.
D. All of the above

12. Although bisphosphonate inducedosteonecsis can present spontaneously, its presention typically occurs after a nondental surgical procedure or infection.

A. True
B. False