Drug Monitor

Osteonecrosis and HAART

As patients with HIV live longer, osteonecrosis—also known as avascular necrosis (AVN) of bone—is emerging more frequently as a complication. A variety of explanations for this have been proposed, including a theory that implicates long-term highly active antiretroviral therapy (HAART).

This theory is supported by a case series of six patients from the infectious diseases department of Centres Hospitalo-Universitaires, Reims, France who were diagnosed with AVN between 1999 and 2002. At the time of diagnosis, five of the patients had developed AIDS and all were receiving HAART. Four of the patients were currently taking a protease inhibitor (PI), and the other two had taken a PI in the past. Each of the patients had at least one risk factor for osteonecrosis, such as hyperlipidemia or previous steroid exposure. Nevertheless, analysis using the Naranjo probability scale indicated that HAART was a possible cause of AVN in all six cases.

The authors discussed several mechanisms by which AVN might develop in patients with HIV. Hyperlipidemia has been linked with AVN, and HAART is known to affect lipids. PIs, for instance, can increase serum cholesterol and triglycerides, in turn promoting atherosclerosis and increasing the risk of thrombosis and occlusion of blood vessels in the bone. PIs also might interfere with vitamin D metabolism and bone reorganization by acting directly on metabolic pathways. In addition, HAART may affect humoral immunity in such a way that increases the production of antiphospholipid antibodies, which can predispose patients to intraosseous platelet aggregation and subsequent bone necrosis.

Published reports also have linked AVN to HIV infection itself. HIV can directly stimulate the production of proinflammatory cytokines, which are involved in bone reabsorption. In one review, HIV was the only risk factor for AVN in 33% of the cases.

The authors emphasize that the role of HAART in the development of AVN is still unclear and that the pathogenesis of the condition in patients with HIV may be multifactorial. They advise clinicians to stay alert for unexplained bone pain in HIV-infected patients and to treat any concomitant conditions that might contribute to osteonecrosis before such symptoms develop.

Source: *Ann Pharmacother*. 2004;38:2050–2054.

Epilepsy Drugs and Fracture Risk

The risk of fracture is almost twice as high in patients with epilepsy than in those without the disease, according to a review of 121,455 patient records from a large United Kingdom primary care database. Reporting on findings from their study at the American Epilepsy Society annual meeting, researchers from Utrecht Institute for Pharmaceutical Sciences, the Netherlands also said they found a "striking" increase—more than 20%—in bone disorders and fracture rates among women after age 50. Although menopause may be a contributing factor to low bone mineral density in these patients, they add, antiepileptic drugs clearly exacerbate the hormonal effect on bone loss. The researchers suggest that clinicians treating epileptic patients watch out for bone disorders and encourage patients with low BMD to seek appropriate treatment.

Source: Doctor's Guide News Release. December 13, 2004.

AD and Anticholinergics Don't Mix

Cholinesterase inhibitors, which help salvage acetylcholine and maintain function in the cholinergic system, currently are the mainstay of pharmacotherapy for Alzheimer disease (AD). Unfortunately, these drugs are expensive and have only a small effect on cognition. To get the most from AD therapy, therefore, logic dictates that clinicians should avoid prescribing concurrent medications that have anticholinergic effects. But recent studies indicate that this isn't happening.

Researchers from the University of Iowa, Iowa City; the University of Oklahoma, Oklahoma City; and Laureate Psychiatric

Research Center, Tulsa, OK reviewed Iowa Medicaid pharmacy claims data on 557 patients aged 50 or older who received a cholinesterase inhibitor between 1997 and 2000. They found that 197 (35%) of the patients received a concurrent anticholinergic. Of all the anticholinergics prescribed, 75% were identified as inappropriate for use in elders, and 22% were deemed inappropriate for the condition prescribed. Even more disturbing, instead of seeing a decline in anticholinergic treatment once cholinesterase inhibitors were started, researchers actually found an increase.

So why is this happening? The researchers speculate that, in some cases, prescribers may be unaware of the anticholinergic properties of certain medications, alternatives to a particular anticholinergic may be unavailable, or the anticholinergic may have been prescribed to relieve adverse effects of a cholinesterase inhibitor. Regardless, they recommend that, for patients with AD, avoidance of anticholinergics should be the rule rather than the exception. Even those who aren't taking cholinesterase inhibitors are "exquisitely sensitive" to the cognitive and other adverse psychiatric effects of anticholinergics.

If a patient is already receiving these antagonistic drugs in combination, the researchers advise stopping the anticholinergic or choosing a "less anticholinergic" drug. They caution, however, that such substitution should be done with care: If anticholinergics are withdrawn too abruptly, the patient can develop seizures.

Source: *J Am Geriatr Soc*. 2004;52:2082–2087.

Effects of Statins in Type 2 Diabetes

Two years of statin therapy had no effect on the intima-media thickness (IMT) of carotid and femoral arteries, a marker of atherosclerotic progression, in a randomized, double-blind, placebo-controlled study of 250 patients with type 2 diabetes but no overt coronary artery disease (CAD). On the other hand, it did result in significantly fewer cardiovascular events and diminished low-density lipoprotein levels. The magnitude of these effects were comparable to previous studies in diabetic and nondiabetic populations, say the researchers—from Leiden University Medical Center, Leiden; Diakonessenhuis, Utrecht; and Leyenburg Hospital, the Hague; all in the Netherlands.

Initially, the statin group received cerivastatin 0.4 mg/day. When this drug was withdrawn from the market in August 2001, the researchers switched patients to simvastatin 20 mg/day without unblinding the study. Although they identify this event as a potential limitation of the study, they say that correcting for the duration of cerivastatin treatment didn't alter the results.

An important finding was that IMT didn't change much in either group over the duration of the study. The mean common carotid IMT among placebo patients was 0.780 mm at baseline and 0.774 mm at study's end. In patients receiving statin therapy, it went from 0.763 mm to 0.765 mm. Results were similar for common femoral and other arterial measurements.

According to the researchers, this suggests that, for type 2 diabetic patients without established CAD, the natural history of atherosclerosis progression (as measured by IMT) may be milder than previously postulated. It also indicates that statins may work to prevent cardiovascular disease by mechanisms other than IMT regression, such as through a beneficial effect on plaque vulnerability.

Source: *Diabetes Care*. 2004; 27:2887–2892.

New Warning for Atomoxetine

Based on reports of severe liver injury in a teenager and an adult (both of whom recovered), the FDA has issued a warning regarding the long-term use of atomoxetine hydrochloride, a drug approved to treat attention deficit hyperactivity disorder in children and adults. The actual incidence of liver injury is unknown due to underreporting of postmarketing adverse events.

At the FDA's recommendation, the manufacturer (Eli Lilly, Indianapolis, IN) is adding a bolded warning to the product labeling, sending an informative letter to health professionals, and revising the package insert to include signs and symptoms of liver problems. In addition to alerting clinicians to the potential for liver injury, the warning would mention the possibility of progression to liver failure in a small percentage of patients and recommend drug discontinuation in patients who develop jaundice or laboratory evidence of liver injury.

Source: FDA Talk Paper T04-60. December 17, 2004.