Drug Monitor

How Do Drug-Coated Stents Fare in the "Real World"?

In the clinical trial setting, drug-coated stents have shown an advantage over bare metal stents in terms of safe and effective prevention of major cardiac events in patients with vascular disease. But do these advantages carry over into the "real world," where patients typically are older and sicker than those selected for clinical studies?

One-year findings from a study performed at the Erasmus Medical Center, Rotterdam, the Netherlands offer some reassurance. The researchers compared rates of mortality, myocardial infarction (MI), and target vessel revascularization in two "unselected" populations: 508 consecutive patients with de novo lesions who received stents coated with slow-release sirolimus and 450 patients who had received bare stents in the period just before the coated stent protocol was adopted at the hospital.

According to a lead investigator, 68% of the patients wouldn't have met the selection criteria for clinical trials of the coated stent. About half of the patients in both groups had acute coronary syndromes and 16% in each group had diabetes. In general, those in the coated stent group were more likely to have multivessel disease, to have more complicated disease, and to require more stents than patients treated with bare stents.

After one year, only 3.7% of patients who received coated stents needed target vessel revascularization, compared with 10.9% of the patients who received bare stents. The overall rate of major adverse cardiac events (including MI and death, in addition to revascularization) was 9.7% in the coated stent group versus 14.8% in the bare stent group.

The treatment effects were similar across all patient subgroups, the researchers say—for long and short lesions, small vessels, and in various anatomic settings.

Sources: *Circulation.* 2004; 109:190–195.

American Heart Association News Release. December 22, 2003.

New Drug on the Horizon for Intractable Pain

Results of a phase III trial indicate that ziconotide, the synthetic equivalent of a polybasic peptide found in the venom of a marine snail, holds promise as an analgesic alternative for some patients with chronic refractory pain. Initial experimental studies of the drug, the first selective N-type voltage sensitive calcium channel blocker to be tested in clinical trials, showed no evidence of tolerance or addiction. And when given intrathecally, the drug cleared quickly—suggesting that it would distribute and metabolize rapidly in the cerebrospinal fluid.

In an initial feasibility study, 31 men whose chronic pain (related to cancer, AIDS, or other conditions) wasn't controlled adequately with intrathecal opioids were given intrathecal ziconotide. For 19 of the 24 patients who completed the study, Visual Analog Scale of Pain Intensity (VASPI) scores dropped an average of 43% with ziconotide. In addition, 15 patients were able to reduce their concomitant use of opioids by at least half. Adverse central nervous system effects—such as dizziness, confusion, somnolence, and abnormal gait—were diminished or resolved when the researchers slowed the infusion rate or stopped ziconotide treatment altogether.

Based on these encouraging preliminary findings, a international team of researchers conducted a double-blind, placebo-controlled, multicenter, randomized study to establish ziconotide's safety and efficacy. The trial enrolled patients with cancer or AIDS, ranging in age from 24 to 85, who were treated at 32 study centers in the United States, Australia, and the Netherlands from 1996 to 1998. After exclusion, 111 patients remained for randomization.

Intrathecal ziconotide was titrated over five to six days, followed by a five-day maintenance phase for responders. Nonresponders from either group had the option of crossing over to the opposite treatment group. In patients who didn't have previously implanted pumps, the researchers implanted an

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intrathecal catheter and used an external infusion system. Given the risk of infection with such external systems, they limited the total drug infusion time to two weeks. As it was, seven patients developed meningitis—which the researchers attributed to poor physiologic status and the external catheter, not to ziconotide.

In the initial phase of the study, mean VASPI scores improved 53% among the patients given ziconotide, compared with 18% in the placebo group. The drug remained effective over the maintenance phase. Slightly more than half of the ziconotide patients reported at least moderate pain relief, and five of these reported complete pain relief. By contrast, only 18% of the placebo patients reported at least moderate pain relief, and none had their pain completely eradicated. Opioid use decreased in the ziconotide group by 10%, while it increased 5% in the placebo patients.

A total of 31 serious drug-related adverse events were reported in the ziconotide group, compared to only four in the placebo group. In 16 cases (12 in the ziconotide group and all four in the placebo group), these events led to therapy discontinuation. As in the earlier study, the researchers say the most common adverse effects observed with ziconotide (such as confusion, somnolence, and urinary retention) were easily recognizable and reversible.

They point out that subsequent trials using lower dosages and longer durations of treatment should better define the long-term risk-benefit profile of this promising drug. These trials are being conducted in response to the FDA's request for more information prior to drug approval. If all goes well, the drug's manufacturer (Elan Pharmaceuticals, Dublin, Ireland) hopes to bring the drug to market by the first quarter of 2005.

Sources: *JAMA.* 2004;291: 63–70.

Elan Pharmaceuticals News Release. January 7, 2004.

TMP-SMX and Myoclonus

Several reports have described the occurrence of tremors in patients taking trimethoprim-sulfamethoxazole (TMP-SMX), though such adverse central nervous system effects are believed to be very rare. A trio of physicians from the University of Rochester School of Medicine and Dentistry, Rochester, NY, however, suggest that these effects actually may be underdiagnosed.

The physicians report on the case of a 63-year-old woman who developed myoclonus and asterixis while receiving IV TMP-SMX for a *Nocardia asteroides* infection. Her medical history included non-Hodgkin's lymphoma (for which she had been treated 25 years earlier), hypertension, hypercholesterolemia, and transient ischemic attack. A recent course of chemotherapy for acute myelogenous leukemia had resulted in remission of the disease.

The patient was admitted to the hospital and treated with IV trimethoprim 20 mg/kg/day and IV sulfamethoxazole 100 mg/kg/day, given in two doses, along with ceftriaxone 2 g twice daily. Her fever resolved, but after four days of treatment she began having progressively worsening involuntary movements of her head and extremities. Neurologic examination revealed diffuse, multifocal myoclonus and bilateral asterixis, with no other abnormalities.

Cessation of TMP-SMX resulted in a marked decline in involuntary movements the next day. Four days later, the symptoms were gone.

The physicians note that while most previous reports of similar effects with TMP-SMX have involved patients who, like their patient, were immunocompromised (usually due to AIDS), at least one report has described tremors in an immunocompetent patient. In fact, they say, this adverse effect is related to the drug dosage, rather than the patient's immunologic status. They stress the importance of watching out for this possible complication and recommend stopping TMP-SMX treatment before ordering a costly neurologic evaluation in the event that a patient develops tremors or other involuntary movements.

Source: *N Engl J Med*. 2004; 350:88–89 [research letter].

Stronger Bones for Patients with CF

Thanks to advances in treatment, patients with cystic fibrosis (CF) are living decades longer. But with longer lives have come more health problems. Bone disease, for instance, is now a major concern for these patients—it can lead to pathologic fractures and kyphosis and even keep a patient from being a candidate for lung transplantation.

Adults with CF lose bone mineral density (BMD) three to five times faster than healthy adults. The reason for this isn't exactly clear, but recent research suggests that chronic pulmonary infection increases bone resorption and suppresses bone formation through the activity of inflammatory

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cytokines. Other possible etiologic factors include delayed pubertal maturation, malabsorption of vitamin D, poor nutritional status, physical inactivity, hypogonadism, and glucocorticoid therapy.

Bisphosphonates have been shown to improve BMD in several populations, but their safety and efficacy in patients with CF haven't been studied thoroughly. For this reason, researchers from the University of North Carolina at Chapel Hill conducted a double-blind, placebo-controlled, randomized trial comparing 10 mg/day of alendronate (a second-generation oral bisphosphonate) with placebo for one year in 48 patients with CF. All patients received an additional daily 800 IU of cholecalciferol and 1,000 mg of calcium carbonate.

At one year, 100% of the alendronate patients had increased BMD at the spine and 78% had increased BMD at the femur, compared with 50% and 35%, respectively, of the placebo patients. The alendronate group had gained a mean of 4.9% in spine bone density and 2.8% in femur bone density. By contrast, the placebo group had lost 1.8% in spine bone density and 0.7% in femur bone density. Patients with lower baseline T scores, lower body mass index, or diminished lung function responded better to treatment. The alendronate group also showed lower levels of urinary markers of bone resorption.

The researchers believe their findings strongly suggest that bone disease in patients with CF is treatable, despite the frequency of intestinal malabsorption in this population. They found that the long half-life of alendronate had a cumulative protective effect on BMD, which mitigated the absorption issues. They advise clinicians to be aware that the problem starts young—it's important to screen for low BMD and treat it before bones start breaking.

Source: *Am J Respir Crit Care Med*. 2004;169:77–82.

Topical vs. IV Vancomycin for MRSA

The glycopeptide antibiotic vancomycin, which has demonstrated efficacy against methicillin resistant *Staphylococcus aureus* (MRSA), has been used safely as a topical ointment as well as an intravenous solution. In a recent case report, clinicians from Hiroshima University Hospital, Hiroshima, Japan illustrated that, in certain cases, topical administration may succeed where intravenous therapy fails.

A 63-year-old woman developed an MRSA infection at the site of a recent cranioplasty with an autologous bone graft. Initially, IV vancomycin cleared the infection, but after a second cranioplasty with a ceramic artificial bone implant, the MRSA infection returned. This time, IV vancomycin failed to keep the infection at bay. When the patient refused to allow removal of the ceramic implant, the clinicians turned to an experimental option: topical administration of a vancomycin ointment.

After obtaining informed consent from the patient, they began applying the ointment daily to the cavity under the ceramic implant. Two days later, microbiological examination of samples from the cavity yielded no MRSA. Over the next four months, the patient continued to receive daily applications of the ointment and remained afebrile—even with undetectable serum levels of vancomycin. No adverse effects related to the ointment were recorded.

At this point, though the infection was under control, the wound hadn't healed. The clinicians tried switching the vancomycin ointment with bucladesine sodium ointment to encourage formation of granulation tissue. When the MRSA infection reappeared, however, they resumed daily topical vancomycin administration.

Several months later, after the patient underwent placement of a gastronomy tube, she developed a second MRSA infection at the tube site. Once again, IV vancomycin failed but vancomycin ointment succeeded.

Eventually (about three years after initial implantation), the patient became unconscious and her husband consented to have the ceramic implant removed. Following this procedure, the aperture in the left frontal portion closed and no subsequent MRSA infection was detected.

The clinicians say they know of no other reports describing long-term use of topical vancomycin—or use of this ointment to treat an infection at the site of an implant that closes an exposed area of the body. Based on their experience with this patient, however, they suggest the treatment be considered when systemic vancomycin proves ineffective due to low concentration in an infected epidermal area. ●

Source: *Ann Pharmacother*. 2004;38:70–72.

Case Reports Wanted!

Do you have an interesting or unusual case to share with your colleagues? Send your short case report and discussion to:

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