Drug Monitor

Better Odds with Intensive Statins?

Having set out to establish the equivalence of two statin therapies, researchers from the Thrombolysis in Myocardial Infarction (TIMI) Study Group were surprised to find that for patients with a recent history of acute coronary syndrome, early, intensive lipid lowering statin treatment appeared to offer significantly better protection against death or major cardiovascular events than did standard treatment.

At 349 international sites, the researchers randomly assigned 4,162 adults (mean age, 58 years) who had been hospitalized with an acute coronary syndrome to receive either the standard regimen of pravastatin 40 mg/day or the more intensive regimen of atorvastatin 80 mg/day. At the time of double-blind randomization (a median of seven days after the index event), the median low-density lipoprotein (LDL) cholesterol level of all patients was 106 mg/dL.

The benefit of high dose atorvastatin emerged as early as 30 days, the researchers say, and was consistent throughout the study period. They also observed a continued benefit of atorvastatin therapy throughout the follow-up period of two and a half years, though it was unclear whether the advantage was due to ongoing intensive treatment or to the stabilization of vulnerable plaques soon after the acute event.

LDL levels in the atorvastatin group dropped to a median of 62 mg/dL, compared with 95 mg/dL in the pravastatin group. By 30 days, among the 2,985 patients who had never taken statins prior to the trial, the median LDL levels fell by 51% in the atorvastatin group compared with 22% in the pravastatin group.

At two years, the primary endpoint—a composite of death by any cause, myocardial infarction (MI), rehospitalization for unstable angina, revascularization within 30 days of randomization, or stroke—occurred in 26.3% of patients taking standard dose pravastatin and 22.4% of those taking high dose atorvastatin. This represents a significant 16% reduction in the hazard ratio. Similarly, high dose atorvastatin reduced the risk of MI, revascularization, or death from coronary heart disease by 14%.

The pattern favoring high dose atorvastatin continued in nearly all of the individual components of the primary endpoint: This regimen reduced the need for revascularization by 14%, the risk of recurrent unstable angina by 29%, and the rates of death from any cause and of death or MI, by 28% and 18%, respectively.

The benefits of high dose atorvastatin were consistent across all prespecified subgroups, including men and women, patients with unstable angina, patients with MI, and patients with and without diabetes. They appeared to be greatest among patients with a baseline LDL level of at least 125 mg/dL, who experienced a 34% reduction in hazard ratio, compared with only 7% among patients with baseline LDL levels below this threshold.

The researchers found both treatments to be well tolerated, but significantly more liver-related adverse events occurred in the intensive therapy group. They also note that these results were obtained in a carefully selected and monitored study population, and advise clinicians to take care when applying these results to a broader patient population. An accompanying editorial calls for more trials pitting the different statins against one another in order to help health care providers reap "the full benefit of this remarkable class of medicines."

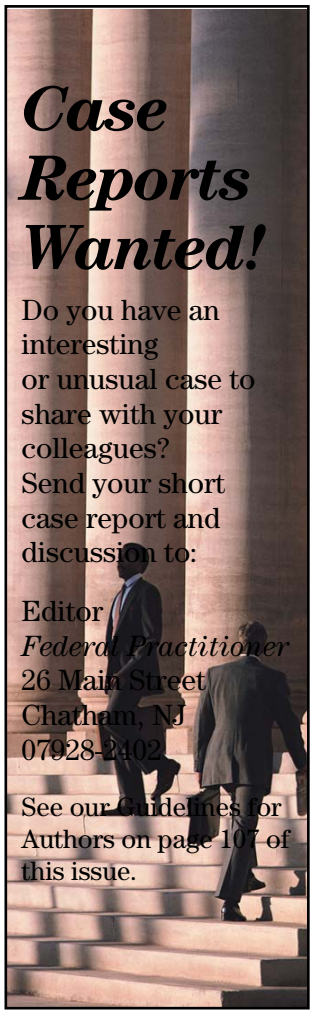
Source: *N Engl J Med.* 2004; 350:1495–1504, 1562–1564.

Zoledronic Acid and Interferon Alfa: A Call for Caution

The combination of zoledronic acid and interferon alfa could spell trouble for some patients, say physicians from the Loyola University Stritch School of Medicine, Maywood, IL and the Edward Hines, Jr. VA Hospital, Hines, IL. They report on the case of a patient with a metastatic carcinoid tumor who developed severe hypocalcemia and acute renal fail-

ure after zoledronic acid was added to his anticancer regimen.

The 39-year-old, male patient had received subcutaneous, long-acting octreotide and interferon alfa for six months without any significant adverse events. His physicians added zoledronic acid—a bisphosphonate that inhibits osteoclastic activity and skeletal calcium release—to his regimen after they had detected multiple bony metastases.



The first monthly infusion (4 mg, given over 30 minutes) went well, but after a second infusion the following month, the patient became lethargic and confused. When he was brought to the hospital four days after his infusion, he was disoriented and appeared dehydrated. His serum chemistry indicated hyperkalemia, hypocalcemia, and acute renal failure. Urinalysis revealed granular casts and few red and white blood cells. An electrocardiogram showed tall T waves and prolonged QT intervals.

The health care team stopped the patient's medications and took vigorous steps to correct his electrolyte imbalance. They administered oral calcitriol 0.25 µg and both oral and IV calcium supplementation. His electrolytes and mental status improved, but his serum calcium level continued to drop until a week after admission, when it returned to normal. Although his renal function improved substantially, it didn't return to baseline.

The adverse effects of zoledronic acid were unexpected: The physicians say their experience includes many instances in which the drug was prescribed to patients with solid tumors—even those with mild renal insufficiency—without the type of complications this patient developed. As of January 2004, they add, there were no reports in medical literature linking zoledronic acid with simultaneous severe hypocalcemia and acute renal failure in patients with solid tumors. The only similar situation involved a patient with multiple myeloma who was also taking thalidomide.

The physicians say that such factors as tumor lysis syndrome and preexisting vitamin D deficiency can cause severe calcium deficiency in patients with metastatic cancer, but none of these applied to their patient. There have been rare instances, however, of hypocalcemia induced by zoledronic acid. And since interferon alfa can inhibit osteoclastic bone resorption, the physicians suggest that the combination of the two drugs might have had an additive effect on the patient's calcium levels.

As for the renal dysfunction, the physicians note that though interferon alfa can sometimes cause immune-mediated nephropathy, their patient had received the drug for more than six months without any renal changes. Zoledronic acid is associated more frequently with nephrotoxicity—especially in higher doses or if it's infused too quickly. Despite the fact that the patient's infusion was given slowly at the recommended dose, the physicians suggest that dehydration (possibly brought on by reduced fluid intake due to the confusion and lethargy resulting from hypocalcemia) might have put him at higher risk for renal complications of zoledronic acid treatment.

Source: *Ann Pharmacother.* 2004;38:418–421.

Carnitines vs. Testosterone for "Male Climacteric"

For decades, controversy has swirled around the concept of a "male climacteric," a time in an aging man's life marked by reduced levels of free and albumin-bound testosterone. Symptoms of the syndrome include decreased libido and erectile quality, depressed mood, inability to concentrate, irritability, and fatigue.

Exogenous testosterone has been the standard treatment, but a pair of Italian researchers have patented a new treatment: a combination of acetyl-L-carnitine and propionyl-L-carnitine. In a randomized study of 120 male patients (mean age, 66 years), these researchers—along with three colleagues from the Società Italiana di Studi di Medicina della Riproduzione, Bologna and Fermo, Italy and Ferrara University, Ferrara, Italy—tested their carnitine therapy against both

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testosterone and placebo and found that it compared favorably in the treatment of sexual dysfunction, depression, and fatigue.

They divided the patients into three groups. For six months, group 1 was given testosterone undecanoate 160 mg/day; group 2 received propionyl-L-carnitine 2 g/day plus acetyl-L-carnitine 2 g/day; and group 3 was given placebo.

Both testosterone and carnitines significantly improved several variables, including erectile function, depression, fatigue, peak systolic velocity, end-diastolic velocity, and nocturnal penile tumescence. Carnitines were significantly better at improving erectile function and nocturnal penile tumescence, while testosterone significantly increased prostate volume and free and total testosterone levels and significantly lowered serum luteinizing hormone. Efficacy wasn't diminished over the course of active administration for either testosterone or carnitines, but as soon as the drugs were stopped, nearly all parameters returned to baseline. The exception was prostate volume, which remained significantly greater than baseline in group 1 patients for at least six months after testosterone suspension. None of these patients had a rise in prostate-specific antigen, displayed prostatic symptoms, or had any suspicious areas detected by digital rectal examination.

The researchers note that several aging mechanisms may share an increase in reactive oxygen species (ROS), membrane damage, and cell death. Carnitines, which previously have demonstrated efficacy in treating such other age-related conditions as Alzheimer's disease and intermittent claudication, restore the ROS physiologic concentration by acting on the Krebs cycle. In both humans and experimental models, carnitines have stabilized cell membrane fluidity by regulating phospholipid levels and have reduced ceramide production and insulin-like growth factor, preventing cellular death and apoptosis.

Source: *Urology*. 2004;63: 641–646.

More Beta-Blockers, Please

Not enough high risk surgical patients are being given perioperative beta-blockers, according to researchers from Baystate Medical Center, Springfield, MA and Tufts University School of Medicine, Boston, MA. After reviewing the records of 72 patients who developed myocardial infarction (MI) after surgery, they found that 70 (97%) could have been identified as being at increased risk for cardiac complications and 58 (81%) were ideal candidates for perioperative beta-blocker therapy. Only 30 patients, however, actually received such drug therapy before the MI. Beta-blockers, the researchers say, could have prevented as many as 40% of postoperative MI cases.

Most of the patients had undergone vascular, general, or orthopedic surgery. Ideal candidates for perioperative beta-blockade were defined as those who had no contraindications against such therapy and who scored 1 or more on the Revised Cardiac Risk Index or had two or more risk factors for coronary artery disease (such as ischemic heart disease, cerebrovascular disease, renal insufficiency, diabetes mellitus, and high risk surgical procedures).

The median interval between surgery and postoperative MI was two days. Of the ideal candidates who received beta-blockers before their MI, four died—compared with nine who didn't receive a beta-blocker before their MI. Although this difference wasn't statistically significant, the researchers say it indicates that even when beta-blockers don't prevent MI, they may reduce the impact of the event.

For almost two decades, the researchers point out, it's been known that the administration of beta-adrenergic blockers can reduce the incidence of myocardial ischemia associated with the stress of surgery. One of the reasons perioperative beta-blockers aren't used more widely, they say, may be that surgeons performing many major noncardiac procedures aren't completely comfortable prescribing the drugs. The researchers, therefore, suggest implementing novel strategies, such as having surgeons and internists comanage the care of patients undergoing major surgery.

Source: *Arch Intern Med*. 2004; 164:762–766.

New Answer to Acute Hypomobility in Parkinson's Disease

Until recently, the only available treatments for the debilitating and often unpredictable episodes of hypomobility that occur in 10% of patients with Parkinson's disease (PD) were long-term oral medications taken to decrease the amount of time patients spent in this state. But now, the FDA has approved the first acute treatment for such episodes: apomorphine, an injectable nonergoline dopamine agonist.

Marketed as Apokyn (Mylan Bertek Pharmaceuticals Inc., Research Triangle Park, NC), the drug has an unknown mecha-

nism of action—though researchers believe it works by stimulating the postsynaptic dopamine D_2 receptors within the brain. It's administered subcutaneously at the onset of a hypomobility episode using a multiple dose injector pen. It must be taken with an approved antiemetic, such as trimethobenzamide (if taken alone, it causes severe nausea and vomiting). Care should be taken when selecting the antiemetic, however, since apomorphine is contraindicated with $5HT_3$ agonists due to resultant profound hypotension and loss of consciousness.

Apomorphine's approval was based on three randomized, controlled trials. In the first, a parallel-group study comparing subcutaneous apomorphine to placebo, 18 of the 20 patients given apomorphine achieved a therapeutic response within 20 minutes, compared to none of the nine patients given placebo. The second trial was a crossover study in which 17 patients who had been using apomorphine for three months either continued receiving apomorphine or switched to placebo. Mean changes in Unified PD Rating Scale (UPDRS) scores from baseline at 20 minutes were 20 and 3 in the apomorphine and placebo groups, respectively.

In the third trial, 62 patients who had been taking apomorphine for three months were assigned to one of four groups: apomorphine at usual dose, placebo matching the apomorphine usual dose, apomorphine at the usual dose plus 2 mg, and placebo matching the apomorphine usual dose plus 2 mg. Mean changes in UPDRS scores from baseline at 20 minutes were 24.2 and 7.4 for the pooled apomorphine groups and the pooled placebo groups, respectively. This study revealed that the higher apomorphine dose yielded no significant improvement, though there was an increased incidence of adverse events. Doses above 6 mg weren't found to be of clinical benefit and aren't recommended.

Overall, 89% of patients who've been given apomorphine in controlled clinical trials have experienced at least one adverse event. The most common were yawning, dyskinesias, nausea or vomiting, somnolence, dizziness, rhinorrhea, hallucinations, edema, chest pain, increased sweating, flushing, and pallor. Patients older than 65 were more likely than younger patients to discontinue apomorphine due to adverse effects. ●

Source: FDA Talk Paper T04-09. April 21, 2003.

Apokyn prescribing information. Mylan Bertek Pharmaceuticals Inc. April 2004.