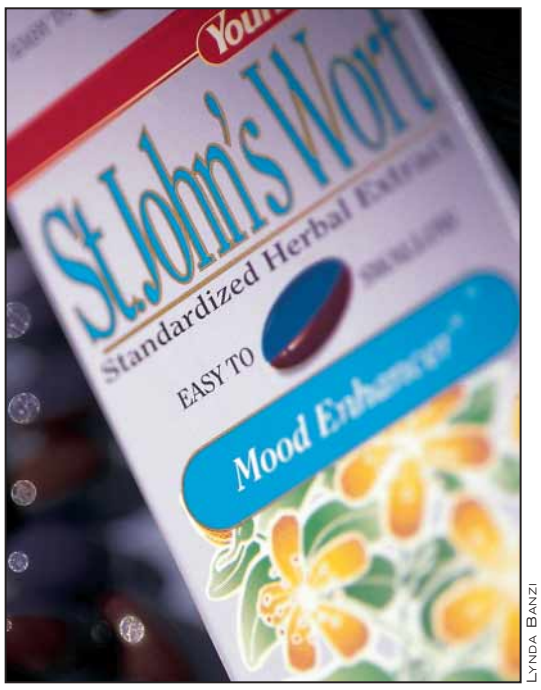
St. John's Wort Can Reverse Resistance to Clopidogrel

BY BRUCE JANCIN
Denver Bureau

ORLANDO, FLA. — St. John's wort converts clopidogrel-resistant patients into responders, Wei C. Lau, M.D., reported at the annual meeting of the American College of Cardiology.

The mechanism by which the herbal product enhances clopidogrel's antiplatelet effect and transforms clopidogrel nonresponders into responders lies in the fact that St. John's wort boosts hepatic cytochrome P450 3A4 metabolic activity. Clopidogrel (Plavix) is activated by this hepatic enzyme. Individuals having inherently low P450 3A4 activity will show clopidogrel resistance. So will patients taking drugs that are cytochrome P450 3A4 inhibitors, explained Dr. Lau, an anesthesiologist at the University of Michigan, Ann Arbor.



LYNDA BANZI

St. John's wort is said to boost the metabolic activity of hepatic cytochrome P450 3A4.

He told this newspaper he would recommend using St. John's wort "with discretion" to convert clopidogrel-resistant patients into responders rather than increasing the dosage of the antiplatelet agent to 600 mg/day or more, as some physicians now do in an effort to overcome the resistance despite the expense and increased bleeding risk.

He added that the need for care in using St. John's wort for this purpose stems from the fact that doing so will speed up the metabolism of any other drugs the patient might be taking that are dependent upon the cytochrome P450 3A4 enzyme pathway. One such very widely used drug is atorvastatin. The St. John's wort/atorvastatin interaction would render any given dose of the statin equivalent to a considerably lesser dose.

In an earlier study, he showed that clopidogrel resistance, as defined by relative inhibition of adenosine diphosphate–induced platelet aggregation, is quite common. Indeed, in a group of 57 subjects, of whom 25 were healthy volunteers and 23 had coronary artery disease, 19% were clopidogrel-resistant while another 23% were clopidogrel low-responders. Dr. Lau further showed that clopidogrel's antiplatelet effect correlated inversely with cytochrome P450 3A4 activity (Circulation 2004;109:166-71).

Having previously observed anecdotally that clopidogrel-resistant patients taking St. John's wort seemed to lose their resistance, Dr. Lau and coinvestigators set about in the new study to find the mechanism of benefit. He had six healthy clopidogrel-resistant subjects take 300 mg of St. John's wort three times daily for 2 weeks. Then he measured platelet aggregation by point-of-care whole blood aggregometry prior to a single 450-mg dose of clopidogrel and again 2, 4, and 6 hours later.

The subjects were converted to clopidogrel responders, showing marked enhancement of platelet inhibition at 4 and 6 hours compared with testing done prior to taking St. John's wort. Moreover, erythromycin breath test measurements of hepatic cytochrome P450 3A4 activity performed 4 hours after taking clopidogrel showed a greater than 1.5-fold increase in conjunction with the use of St. John's wort. ■

Patients on Long-Term Clopidogrel Need Not Stop Drug for Surgery

BY MITCHEL L. ZOLER
Philadelphia Bureau

WASHINGTON — Patients on long-term clopidogrel treatment don't need to stop the drug before surgery, Richard E. Kuntz, M.D., said at a meeting sponsored by the Cardiovascular Research Institute at Washington Hospital Center.

"There is growing experience that it's safe to perform surgery on a patient taking clopidogrel. At our institution, surgeons will operate on these patients. There is no significant difference in morbidity and mortality" during surgery, said Dr. Kuntz, a cardiologist at Brigham and Women's Hospital in Boston.

"Surgeons make more of a big deal about clopidogrel than they need to," he added.

This approach to dealing with patients on long-term treatment with the antiplatelet drug clopidogrel (Plavix) was endorsed also by Ron Waksman, M.D., of the division of cardiology at the Washington Hospital Center.

"If we push our surgeons, they'll do surgery without waiting to stop clopidogrel," said Dr. Waksman, who chaired the meeting.

The issue of when to stop clopidogrel recently became critical for patients who take the medication after they have received drug-eluting coronary stents.

A report last year detailed four anecdotal cases of patients who developed clinically significant coronary thrombosis within a drug-eluting stent after their clopidogrel and aspirin regimens were stopped (Lancet 2004;364:1519-21). In three of these cases, patients had stopped their antiplatelet medications before undergoing surgery.

These reports have made many experts wary about discontinuing the use of aspirin and clopidogrel in their patients.

Although standard practice when placing drug-eluting coronary stents is to treat patients with clopidogrel for 2-3 months (for sirolimus-eluting stents) or 6 months (for paclitaxel-eluting stents), Dr. Kuntz recommended continuing the drug even longer.

To prevent stent thrombosis, patients with a drug-eluting stent should continue clopidogrel "as long as possible, as long as they can afford it," Dr. Kuntz said.

Intensive Statin Therapy Most Effective in Elderly Patients

BY MITCHEL L. ZOLER
Philadelphia Bureau

ORLANDO, FLA. — Intensive statin treatment produced a bigger benefit in elderly patients at high risk for coronary artery disease than in younger patients, based on an analysis from the PROVE IT-TIMI 22 study.

Intensive statin treatment that lowered serum levels of LDL cholesterol to less than 70 mg/dL also was safe in elderly patients, leading to no increased rate of liver enzyme or muscle abnormalities, Kausik K. Ray, M.D., reported at the annual meeting of the American College of Cardiology.

These findings show that the updated guidelines of the National Cholesterol Education Program, which suggested lowering LDL-cholesterol levels to less than 70 mg/dL in patients with a very high risk of coronary disease, are applicable to patients who are aged at least 70 years, said Dr. Ray, a cardiologist at Brigham and Women's Hospital in Boston.

To assess the role of age in intensive LDL-cholesterol reduction, Dr. Ray and his associates used data collected in the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial (N. Engl. J. Med. 2004;350:1495-504). This study randomized more than 4,000 patients with acute coronary syndrome to treatment with either an intensive (80 mg of atorvastatin daily) or moderate (40 mg of pravastatin daily) lipid-lowering regimen, and showed that patients whose LDL-cholesterol levels dropped below 70 mg/dL had better outcomes during 2 years of follow-up compared with patients who had higher levels of LDL cholesterol.

The new analysis focused on the 3,784 patients (91% of the total study cohort) who were free from death, MI, or unstable angina 30 days after they started treatment. This group included 634 patients aged at least 70 years, and 3,150 patients who were younger than age 70.

During the remaining 23 months of follow-up, patients aged 70 or older who were in the intensive-treatment group had a 20% reduced risk of death, MI, or unstable angina compared with similarly aged patients in the moderate-treatment group.

The benefit from aggressive treatment was virtually identical in younger patients. Those younger than 70 years in the aggressive arm had a 21% drop in events compared with similarly aged patients in the moderate-treatment group.

Another way to assess the outcomes was to focus on how patients fared if their LDL-cholesterol level dropped below 70 mg/dL after the first 30 days on treatment, regardless of which treatment arm they were in. By this measure, older patients got more bang for their statin buck than did younger patients.

Among the older patients, those whose cholesterol had dropped below 70 mg/dL after the first 30 days of treatment had a 13.5% rate of death, MI, or unstable angina during the following 23 months. In contrast, older patients whose LDL-cholesterol level was 70 mg/dL or higher after the first 30 days had a 21.5% event rate, a statistically significant 8% absolute difference, reported Dr. Ray.

In contrast, among younger patients, those whose LDL-cholesterol level dropped below 70 mg/dL had a subsequent 8.1% event rate, compared with a 10.4% rate among younger patients who failed to achieve this LDL-cholesterol target. The difference between these groups was also statistically significant, but the absolute difference was only 2.3%

Safety measures were similar in the older and younger patients. The incidence of abnormal liver-function tests, an aspartate aminotransferase level at three times or more above the upper limit of normal, occurred in 2% of all patients regardless of their age. The incidence of elevations in creatinine kinase, a marker of muscle abnormalities, was 6% in younger patients and 3% in older patients. ■