Aspirin Plus PPI Safe In Barrett's Patients

BY FRAN LOWRY
Orlando Bureau

ORLANDO — Early findings from the Aspirin Esomeprazole Chemoprevention Trial indicate that therapy with aspirin and esomeprazole is safe and well tolerated for preventing the progression of Barrett's esophagus to adenocarcinoma.

Since the start of the randomized Aspirin Esomeprazole Chemoprevention Trial (AspECT) in September 2005, 1,192 (83%) of the 1,436 patients have remained on their medication, and just 33 adverse events have been reported, said lead investigator Dr. Janusz Jankowski, professor of medicine, Oxford University (England), at a meeting on gastrointestinal cancers sponsored by the American Society of Clinical Oncology.

AspECT is an ambitious, 10-year clinical trial being conducted in the United Kingdom. The trial's primary aim is to determine whether treatment with the proton pump inhibitor esomeprazole (Nexium, AstraZeneca) and aspirin can stop Barrett's metaplasia from progressing to adenocarcinoma. The investigators are also trying to determine whether this therapy will prevent or reduce myocardial infarction.

The United Kingdom is fertile ground for such a study, Dr. Jankowski said at the symposium, also sponsored by the AGA Institute, the American Society for Therapeutic Radiology and Oncology, and the Society of Surgical Oncology.

"The U.K. has the highest incidence of esophageal adenocarcinoma in the world—up to four times greater than that of other countries in Europe," he said in an interview.

Being able to show that aspirin "is incredibly well tolerated" is very gratifying, Dr. Jankowski said, because many people were skeptical that it could be done. "People thought we were mad and dangerous, and that we would kill patients with low-dose aspirin."

The first planned efficacy analysis is scheduled for 2010, and the final analysis is due in 2016. The trial is funded by Cancer Research UK, Oxford University, and AstraZeneca. Dr. Jankowski disclosed that he is a consultant to and receives research funding from AstraZeneca. ■

Carvedilol Beats Band Ligation for Variceal Bleed

BOSTON — Carvedilol is more effective than band ligation in preventing the first bleed from esophageal varices, Dr. Dhiraj Tripathi said at the annual meeting of the American Association for the Study of Liver Diseases.

Because the drug is also well tolerated, "it should be the first line of treatment for primary prophylaxis in these patients," said Dr. Tripathi of the Royal Infirmary, Edinburgh.

His randomized, controlled trial included 152 patients with esophageal varices of grade II or larger that had not previously bled. The patients' mean age was 54 years, and 72% had cirrhosis due to alcoholic liver disease. The mean Child-Pugh Score was 8.

Patients were randomized to variceal band ligation performed twice weekly until eradication (77 patients) or to carvedilol at 6.25 mg/day for 1 week, up to 12.5 mg/day or as tolerated (75 patients).

By 24 months, a significantly higher percentage of the patients on carvedilol were free from a first variceal bleed (87% vs. 78%, respectively). No significant differences were seen in overall mortality or mortality from variceal bleeding.

Three patients did not tolerate the carvedilol dose escalation, and 10 withdrew from that arm because of side effects, mostly gastrointestinal effects and shortness of breath. Dr. Tripathi noted that the 10% withdrawal rate was significantly lower than the 30% rate that had been seen in studies of propranolol for variceal bleeding prophylaxis (Gastroenterology 2002;123:735-44).

Variceal eradication with banding was successful in 57% of patients. Dr. Tripathi said banding ligation remains a good option "for patients who can't tolerate β-blockers, or who would have problems with compliance."

Dr. Tripathi had no disclosures related to the study drug.

—Michele G. Sullivan

THE EFFECTIVE PHYSICIAN

Esophageal Varices

BY WILLIAM E. GOLDEN, M.D., AND ROBERT H. HOPKINS, M.D.

Background

Substantial progress in the understanding of the physiology of esophageal varices has clarified treatment options as outlined in recent guidelines from the American Association for the Study of Liver Diseases and the American College of Gastroenterology.

Conclusions

Patients with cirrhosis develop varices at the rate of 8% per year. While 50% of patients with cirrhosis have varices, they are present in 85% of patients with Child C cirrhosis.

Variceal hemorrhage occurs at a rate of 5%-15% per year, with higher rates in patients with larger varices.

Portal hypertension is an important predictor of hemorrhage risk and long-term survival.

Portal hypertension reflects an increased resistance to blood flow secondary to regenerative nodules and fibrotic changes seen in cirrhosis. In addition, reduced endogenous nitric oxide promotes intrahepatic vasoconstriction, which also raises portal pressure.

Portal hypertension creates portosystemic collaterals that fail to reduce elevated pressure because the collaterals have higher resistance than does normal hepatic circulation. In addition, the shunts promote an increase in portal venous inflow secondary to splanchnic arteriolar vasodilatation.

Portal hypertension can be measured by the wedged hepatic venous pressure determined by a balloon catheter placed in the hepatic vein. This measurement requires correction for the increased intra-abdominal pressure of ascites. A normal portal venous pressure gradient is 3-5 mm Hg. Patients with cirrhosis and esophageal varices have hepatic venous pressure gradients of 10-12 mm Hg.

Of all variceal hemorrhages, 40% resolve spontaneously, but such hemorrhages are associated with a 20% mortality at 6 weeks. A hepatic venous pressure gradient of more than 20 mm Hg 24 hours after a variceal hemorrhage predicts higher rates of bleeding and 1-year mortality. Variceal hemorrhage can be prevented by reducing hepatic venous pressure to below 12 mm Hg. Rebleeding can also be reduced if the hepatic venous pressure gradient is lowered by 20% or more from baseline.

Nonselective β-blockers (propranolol, nadolol) lower portal pressures by lowering heart rate and producing splanchnic vasoconstriction, which reduces portal blood flow. Nevertheless, these agents do not prevent the development of varices and have significant side effects. Selective β-blockers (metoprolol, atenolol) are less effective in reducing portal hypertension and should not be used for primary prophylaxis of variceal hemorrhage.

Implementation

Patients with cirrhosis and no varices should not receive prophylactic therapy because of the high incidence of side effects. Patients with small varices and a high risk of bleeding because of advanced cirrhosis can benefit from prophylactic therapy with nonselective β-blockers.

Esophagogastroduodenoscopy (EGD) is the preferred strategy to identify the 15%-25% of patients who have varices of sufficient size to warrant prophylactic therapy. Patients without varices should have repeat EGD 2-3 years after the baseline study. Patients with small varices and those with decompensated cirrhosis without varices should have repeat studies on a nearly annual basis.

Starting doses of nonselective β-blockers include propranolol 20 mg twice a day and nadolol 40 mg once a day. Because hemorrhage risk increases with cessation of therapy, prophylactic nonselective β-blockers should be continued indefinitely.

Combining endoscopic variceal ligation with nonselective β-blockade can reduce first variceal hemorrhage, but use of this technology should be based on patient risk and local expertise.

Combining isosorbide mononitrate with nonselective β-blockers does not improve outcomes and can increase side effects. Spironolactone when added to β-blockers does not reduce the rates of first variceal hemorrhage. Shunt surgery and transvenous intrahepatic portosystemic shunt (TIPS) procedures reduce portal hypertension but substantially increase encephalopathy and should not be used for primary prevention of variceal hemorrhage. Sclerotherapy is inferior to ligation techniques and should not be used for primary prevention.

Patients with acute hemorrhage should have airway protection, modest fluid resuscitation, and transfusion to keep their hemoglobin level at 8 g/dL. More aggressive fluid management can worsen ascites and elevate portal pressures, which can thwart hemorrhage management. Recombinant factor VIIa has not been shown to be superior to standard therapy.

Prophylactic antibiotics with oral norfloxacin or intravenous ceftriaxone improve survival for patients with cirrhosis and acute variceal hemorrhage because of their high risk of sepsis from intestinal flora.

β-Blockers should not be started during acute hemorrhage episodes because the drugs impair the physiologic response to volume loss. Vasopressin is a potent splanchnic vasoconstrictor, but it has substantial, dangerous side effects.

Octreotide inhibits release of vasodilatory peptides such as glucagon and produces local vasoconstrictive effects. It can be used safely for up to 5 days but has limited effectiveness because of tachyphylaxis.

EGD should be performed promptly during a hemorrhage event to determine whether variceal ligation should be undertaken. Endoscopic variceal ligation is superior to sclerotherapy and benefits from concomitant octreotide infusion after the procedure.

A hepatic venous pressure gradient above 20 mm Hg 24 hours after presentation is highly predictive of treatment failure in patients with variceal hemorrhage. Bleeding that cannot be controlled or is recurrent can be managed by shunt procedures as rescue therapy.

Reference

Garcia-Tsao G., et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Am. J. Gastroenterol. 2007;102: 2086-102.

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