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# TICLOPIDINE: NEW OPTION FOR STROKE PREVENTION

TICLOPIDINE, a potent inhibitor of platelet aggregation, is superior to asprin in the prevention of stroke, according to the results of two recent multicenter studies. Until recently, aspirin was the only drug that showed conclusive evidence of risk reduction compared to other therapies used for stroke prevention.

Aspirin remains the standard preventive therapy, despite some questions about its efficacy and safety. The Physicians' Health Study, for example, in which aspirin was shown to help prevent recurrent myocardial infarction (MI), also demonstrated an increased number of hemorrhagic strokes in the aspirin group, although the difference between the aspirin and control groups was not significant. A meta-analysis of 189 studies, in which aspirin was used for a variety of indications, assessed 268 hemorrhagic strokes that occurred in a population of more than 100,000 people. Although the frequency of hemorrhagic stroke was 19% higher in the treated group, the difference was not significant.

## ACTS IN ADP PATHWAY

Ticlopidine, which is awaiting approval by the Food and Drug Administration, apparently acts in the ADP pathway. This step occurs earlier than the cyclooxygenase pathway, where aspirin has its effect. At a dosage of 250 mg bid, the drug exerts its effect within 24 to 48 hours, with the peak effect occurring after 3 to 5 days. The drug is 90% absorbed from the gut and rapidly metabolized in the kidney. Although trough levels are slightly elevated in patients with mild to moderate renal insufficiency, the half-life is unchanged, so these patients do not require dosage reductions.

## EFFICACY

The Ticlopidine Aspirin Stroke Study (TASS) compared ticlopidine with aspirin in the primary prevention of vascular endpoints—especially stroke or death from any cause—in 3,069 patients who had had transient ischemic events. The Canadian American Ticlopidine Study (CATS) compared ticlopidine with placebo in the secondary prevention of a combination of endpoints, including stroke, MI, and vascular death, in 1,072 patients who had survived a recent thromboembolic stroke.

Both studies showed significant preventive benefit associated with ticlopidine. In the efficacy analysis of TASS, ticlopidine reduced the relative risk of stroke or stroke death by 17% compared to aspirin. In the intent-to-treat analysis, the risk reduction was 19%; but during the first year of treatment, when risk is highest, the risk of stroke or stroke death in the ticlopidine group was 47.6% less than in the aspirin group. The CATS data showed that ticlopidine reduced the risk of stroke, MI, and death from any cause by 24.1% and the risk of stroke and stroke death by 33.5%.

More than 2,000 patients received ticlopidine for up to 6 years; among these individuals, diarrhea was the most frequently reported side effect. Although the incidence of serious adverse events was similar in all groups (1.37% among ticlopidine patients and 1.38% with aspirin) the types of effects were different. Significant neutropenia developed in 16 patients within the first 3 months of ticlopidine therapy and resolved spontaneously on withdrawal of the drug. Gastrointestinal bleeding was more common with aspirin therapy and, although more common in the first 6 months, bleeding occurred unpredictably throughout the course of the TASS.

## COST *v* BENEFIT

When approved, ticlopidine will be relatively expensive therapy. However, the benefits (33.5% risk reduction in patients patients at high risk because of completed stroke; 19% to 47.6% risk reduction in patients who have had transient ischemic events) weigh heavily against the cost of hospitalization and rehabilitation following a stroke.

Data based on subgroup analyses from TASS suggest that ticlopidine may be more effective in women than in men, and in blacks than in whites or Orientals; that patients with carotid events may respond better than those with vertebrobasilar events; and that patients

with greater than 70% carotid stenosis may respond better to aspirin than to ticlopidine. No difference in cardiac outcome between ticlopidine- and aspirin-treated patients was observed, suggesting that the two drugs are approximately equal in the prevention of cardiac events in stroke-prone patients.

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# TREATING HIGH CHOLESTEROL: EVERYDAY APPLICATIONS OF THE NATIONAL GUIDELINES

The National Cholesterol Education Program guidelines vary, depending on the patient's history and laboratory evaluations. The following case histories show how this information influences treatment decisions.

## BORDERLINE CHOLESTEROL, NO RISK FACTORS

A 54-year-old woman participated in a cholesterol screening at a local mall, where a total cholesterol of 300 mg/dL was discovered. A subsequent evaluation revealed a total cholesterol of 310 mg/dL; triglycerides, 89 mg/dL; HDL cholesterol, 75 mg/dL; and LDL cholesterol, 221 mg/dL. Her family history for hypercholesterolemia and premature heart or vascular disease was negative, as was her medical history for risk factors.

Although the use of malls and drugstores for cholesterol screening is controversial, this patient's actions demonstrate an appropriate use of these screening measures; ie, she obtained another measurement as well as an evaluation for cardiovascular risk factors.

According to the NCEP guidelines, this patient is a candidate for diet therapy, with a target LDL threshold of 160 mg/dL. Some might argue with this approach. For example, it is unresolved whether treatment is indicated when the HDL is acceptably high, as in this patient's case. In both men and women, HDL and the incidence of coronary artery disease are inversely related; overall mortality from heart disease is very low in people whose HDL levels exceed 65 mg/dL, even with LDL-C levels in this range.

Because this patient was considered low risk, we opted for diet counseling, which she followed aggressively. The strategy would change in the presence of risk factors, where the goal would be to lower the LDL to less than 130 mg/dL, even if the HDL were high.

## IMPORTANCE OF TRIGLYCERIDES

A 68-year-old diabetic man weighed 170 pounds at 5'5" and had a history of myocardial infarction and coronary artery bypass surgery. He had hypertension that was controlled with a calcium channel blocking agent. His lipid profile revealed a markedly elevated triglyceride level of 1,456 mg/dL; total cholesterol, 408 mg/dL; HDL, 26 mg/dL; and LDL, 136 mg/dL. Other studies showed a blood glucose of 253 mg/dL and hemoglobin A1C of 10.3%.

The NCEP guidelines recommend screening with total cholesterol. Screening in this patient could lead to the false assumption that he has a disturbance of cholesterol metabolism when, in fact, the primary abnormality is disturbed triglyceride metabolism. The triglyceride level is related to high very-low-density lipoprotein (VLDL) particles which also contain cholesterol; 20 to 25% of VLDL particles are made up of cholesterol esters. Therefore, patients who have markedly elevated plasma triglyceride levels can have concomitant elevations in total cholesterol. With correction of the triglyceride level, the cholesterol comes down. A high triglyceride level by itself is not a proven cardiovascular risk factor, but a strong inverse relationship exists between triglyceride and HDL levels. Correction of elevated triglyceride is often enough to increase the HDL. Furthermore, when the triglyceride level is higher than 1000 mg/dL, the risk of pancreatitis increases substantially.

A high triglyceride level is often caused by obesity (as little as 10 to 15 pounds excess weight), diabetes, or excess alcohol intake. Drugs such as certain beta blockers, thiazides, isotretinoin, and estrogens also can be responsible. Treatment requires correction of the underlying problem—eg, achieving ideal body weight or controlling diabetes. Exercise by itself has little effect on the total cholesterol, but it can lower the triglyceride level by as much as 30%.

This patient's course demonstrates the power of weight reduction. In 8 weeks, he reduced his weight from 170 to 154 pounds and achieved normal blood