Why Aren't We Using More Niacin?

RECENT YEARS have witnessed a tremendous increase in interest in the role that lipid disorders play in the development of atherosclerosis. Both primary prevention trials (the Lipid Research Clinics Coronary Primary Prevention Trial[1] and the Helsinki Heart Study[2]) and secondary prevention trials (eg, the Cholesterol Lowering Atherosclerosis Study[3,4] and the Familial Athersoclerosis Treatment Study[5]) have afforded the hope that atherosclerotic morbidity and mortality rates can be favorably impacted by aggressive efforts to alter lipid levels. Indeed, the suggestion that it may sometimes be possible to induce the actual regression of atherosclerotic lesions has led to the widespread and often uncritical use of lipid-lowering medications.

One important lipid-lowering agent has been largely neglected in the rush to pharmacotherapy for lipid disorders. This agent is nicotinic acid, also commonly known as niacin. Niacin has a tremendous disadvantage in that it is not being promoted by any of the major pharmaceutical firms. Because niacin is a widely available generic agent, no pharmaceutical company stands to generate any significant amount of revenue from marketing this drug. Thus, niacin has not enjoyed the frequent and intensive exposure that competing lipid-lowering agents have richly benefited from, particularly gemfibrozil and the growing number of hepatic hydroxymethylglutaryl coenzyme A reductase inhibitors. An audit by US Food and Drug Administration (FDA) officials that was published in 1990 showed that niacin accounted for only 7.9% of all lipid-lowering prescriptions.[6] Even allowing for underreporting because niacin is also available over the counter, it seems beyond dispute that niacin is not widely recommended by physicians. Yet there are many reasons why niacin should be used far more widely than it currently is.

The lipid-lowering efficacy of niacin was first reported in the mid 1950s with the demonstration that niacin could lower cholesterol levels both in normal individuals[7] and in hypercholesterolemic subjects.[8,9] By the late 1950s it was known that nicotinic acid lowers β-lipoprotein cholesterol levels as well as total cholesterol levels.[10,11] We now know that niacin is also very effective in lowering triglyceride levels and Lp(a) lipoprotein, as well as in increasing high-density lipoprotein (HDL) levels.

The Coronary Drug Project demonstrated in the mid 1970s that niacin had a modest beneficial effect in reducing recurrent nonfatal myocardial infarctions.[12] A subsequent 15-year follow-up showed a reduction in the mortality rate in those individuals who had previously taken niacin during the actual study period of the Coronary Drug Project.[13] Similarly, a Swedish group has reported reduced mortality rate in a secondary prevention trial using combined treatment with clofibrate and niacin.[14]

Two major atherosclerosis regression trials, the Cholesterol Lowering Atherosclerosis Study[3] and the Familial Atherosclerosis Treatment Study,[5] included niacin as a major component of the pharmacologic intervention. Niacin was combined with colestipol in the Cholesterol Lowering Atherosclerosis Study and with either lovastatin or colestipol in the Familial Atherosclerosis Treatment Study. In both studies, the niacin was relatively well tolerated and played an important role in producing the lipid reductions that were seen in those individuals who were randomized to drug therapy.

Niacin was recognized as a first-line therapy in the management of hyperlipidemia by the National Cholesterol Education Program (NCEP) Expert Panel in 1988.[15] This occurred despite the fact that the NCEP chose to de-emphasize the role of HDL because of a concern over the reliability of the HDL determinations performed in the field. Fortunately, HDL levels received considerably more emphasis in the updated NCEP recommendations that were issued in June 1993.[16] It is now recommended that an HDL level be obtained along with the total cholesterol measurement in the initial screening assessment. Even if the total cholesterol level is acceptable, an

HDL level of less than 0.91 mmol/L (35 mg/dL) becomes an indication for continued monitoring and possible intervention.

Although prospective studies have not yet confirmed the value of raising HDL levels pharmacologically, there is considerable clinical interest in intervening to elevate HDL levels. Niacin is clearly the most potent pharmacologic agent available for increasing HDL levels, assuming that lifestyle modifications have failed to produce a sufficient increase. Yet many clinicians seem to prefer gemfibrozil over niacin in this setting. Gemfibrozil, however, is far less potent than niacin in its ability to increase HDL levels. A full 1200-mg daily dose of gemfibrozil affords no more than a mean 10% increase in HDL levels.[17] In contrast, the rise in HDL levels seen in the Cholesterol Lowering Atherosclerosis Study was 37%, almost entirely attributable to niacin rather than to the accompanying colestipol.[4] It is, therefore, not surprising that gemfibrozil continues to be relegated to the status of "other drugs" in the updated NCEP guidelines.

NIACIN continues to suffer from the widespread perception among clinicians that it is a very difficult and, indeed, somewhat dangerous medication. Some physicians may avoid it because of medicolegal concerns. There is considerable hand-wringing over the virtually universal phenomenon of flushing, which typically occurs 20 to 30 minutes after the drug is taken. Fortunately, tachyphylaxis to the flushing phenomenon develops within a few weeks in most patients if they are compliant with regular dosing, and proper patient education can markedly reduce the anxiety associated with the flushing. Some have recommended taking an aspirin one-half hour before the niacin, but others have considered this an unnecessary nuisance that reduces compliance. Tachyphylaxis to the flushing phenomenon sometimes fails to develop in very fair-skinned individuals, and hence, they must discontinue the medication. Other occasional side effects of niacin include gastric irritation, nausea, pruritus, skin rash, and modest elevations of hepatic enzyme levels within the reference range. The drug should be used only with extreme caution in diabetics or in individuals with impaired glucose tolerance because of its consistent effect of exacerbating glucose intolerance. It should also be avoided in patients with preexisting liver disease or elevations in liver function test levels.

Niacin should also be used with extreme caution, if at all, in individuals with a known history of gouty attacks because of its effect of precipitating gout in predisposed individuals. The most dreaded side effects of niacin, namely, retinal damage and fulminant hepatic toxicity,[18] are fortunately only very rarely encountered. Nonetheless, liver function tests should be monitored 3 weeks after each dose increase and then regularly at 3- to 4-month intervals. The likelihood of incurring a serious side effect does increase with higher doses of niacin. Although toxic side effects are definitely dose related, they most certainly can be seen at doses in the usual therapeutic range. The potential for hepatic toxic side effects is greater when niacin is used in combination with other hepatotoxic drugs, including lipid-lowering agents such as gemfibrozil and hepatic hydroxymethylglutaryl coenzyme A inhibitors, as well as other classes of drugs, such as isoniazid.

Niacin is a reasonably benign preparation when used appropriately by informed practitioners. Physicians at the Atherosclerosis Detection and Prevention Clinic at the University of Alabama, Birmingham, reported that 83% of 65 nontransplantation patients tolerated the drug well at a mean dosage of 2.5 ± 0.9 g/d.[19] No cases of hepatitis were noted in the patients taking immediate-release niacin. However, the prevalence of hepatitis was very high in individuals taking sustained-release niacin (eight of 15 patients). This is similar to the experience of Etchason et al[18] at the Mayo Clinic, Rochester, Minn, who reported that almost all cases of niacin-induced hepatitis were due to the sustained-release rather than the immediate-release preparation.

A recent study of patients attending clinics at a Veterans Affairs hospital, who are often considered a group with significant compliance problems related to low educational and socioeconomic levels, also demonstrated that niacin was very well tolerated in nearly three quarters (73%) of all veterans receiving the medication.[20] Those who were unable to tolerate the drug discontinued its use because of flushing, rash, pruritus, fatigue, nausea, headache, abdominal pain, or diarrhea.

The recently released NCEP guidelines continue to endorse niacin as a major drug that is appropriate for use as a first-line pharmacologic therapy in lipid disorders.[16] The NCEP expert panel noted that "nicotinic acid is effective in lowering total cholesterol and triglyceride levels and in raising HDL cholesterol levels." The panel went on to say that "nicotinic acid is valuable in treating high blood cholesterol in patients with low HDL cholesterol levels, or when combined hyperlipidemia (elevated cholesterol and triglycerides) is present."[16] In view of the remarkable potency and efficacy of niacin, it will be prudent for all physicians attempting to manage lipid disorders to become very familiar with this medication.

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