Rediscovery of Crystalline Niacin

Niacin is a B-complex vitamin that is present in a wide variety of foods. In pharmacologic dosages of 500 mg or more per day, niacin is an effective agent for control of hyperlipidemia involving increased levels of both cholesterol and triglycerides and for increasing high-density lipoprotein (HDL) cholesterol levels in patients with primary hypo-α (high-density)-lipoproteinemia. Niacin therapy in patients with coronary heart disease has been demonstrated to reduce total mortality by 11% in comparison with that in a placebo group. Combination therapy with niacin and a bile acid sequestrant agent has been shown to decrease the frequency of progression and to increase the frequency of regression of coronary atherosclerosis in angiographic studies.

In this issue of the Proceedings (pages 23 to 28), Etchason and colleagues emphasize the hazards of sustained-release niacin therapy. The safest niacin preparation remains the immediate-release form, which had been used in the past as the sole treatment for hyperlipidemia. Its use had declined because of the undesirable side effects, particularly flushing, and because of the introduction of other antilipid agents. As experience with these newer antilipid agents accumulated, however, it became clear that niacin still had a place in the control of lipid levels, usually in conjunction with bile acid sequestrant resins. Recently, its beneficial effects have been rediscovered, and niacin has been used more widely than in the past to control hyperlipidemia—particularly hypertriglyceridermia—and hypo-α-lipoproteinemia. For 30 years, investigators have known that sustained- or delayed-release forms of niacin are more toxic and often less effective in controlling lipid levels than crystalline or immediate-release niacin. In general, the toxic effects of sustained-release niacin preparations are noted at lower dosages—as low as 1 g/day. With administration of immediate-release niacin, toxic levels associated with hepatic dysfunction usually occur at the higher dosages of 1.5 g or more per day. Whether the toxic side effects are related to the niacin therapy itself or to some contaminant or cofactor present in the sustained-release niacin is unknown. The occurrence of toxic side effects even with crystalline or immediate-release niacin (albeit less frequently and at higher dosages than with sustained-release niacin) suggests that niacin sensitivity is the problem. Why toxic side effects occur more frequently with sustained-release niacin remains an enigma but is an important clinical consideration in the selection of the appropriate niacin preparation for the treatment of hyperlipidemia.

Hepatic dysfunction, in some instances leading to hepatic failure, remains a potentially life-threatening side effect of pharmacologic doses of niacin, particularly of the sustained-release form. Severe hepatic dysfunction rarely occurs with crystalline or immediate-release niacin unless large dosages of the vitamin are used—namely, 3 g or more per day. Baggenstoss and associates reported alterations in the endoplasmic reticulum and an enlargement of the mitochondria evident on electron microscopy of liver biopsy specimens from patients on niacin therapy for hypercholesterolemia. These changes suggested a toxic effect of niacin on the liver even when, clinically, liver function and results of light microscopy studies were normal. The changes noted may have been dose related, but the authors did not analyze for this possible association with the dosage of niacin because the number of patients studied was too small for such an analysis.

Flushing remains the most bothersome side effect of niacin therapy. It was primarily cutaneous flushing that prompted the development of a sustained-release form of niacin to eliminate...
this side effect. Usually, taking niacin with food tends to decrease the flushing effect, particularly with crystalline niacin treatment. Continued administration of niacin results in tolerance of the flushing over time. Aspirin, 80 to 300 mg 1/2 hour before niacin therapy (particularly crystalline niacin), will blunt or eliminate the flushing effect.

Another important side effect of pharmacologic doses of niacin, whether of the immediate-release or the sustained-release variety, is that it may result in deterioration of carbohydrate tolerance. Niacin therapy may aggravate hyperglycemia in patients with diabetes or may unmask diabetes mellitus in potential diabetics. Other side effects such as hyperuricemia, gout, hyperpigmentation, dyspepsia, and aggravation of ulcer symptoms may also occur and need to be monitored while the patient is receiving niacin therapy.

Niacin, particularly crystalline or immediate-release niacin, is an effective agent for the control of lipid levels in patients with primary hyperlipidemia. In addition, niacin effectively increases HDL cholesterol in patients with low levels of HDL cholesterol, even in the presence of serum triglyceride levels of less than 100 mg/dl.

The mechanism or mechanisms whereby niacin decreases serum lipid levels are unknown. Studies suggest that it decreases synthesis of cholesterol and triglycerides through an inhibitory effect on hydroxymethylglutaryl-coenzyme A reductase and on very low-density lipoprotein synthesis, respectively, while promoting production of HDL in the liver.6-11

Although niacin may be purchased as an over-the-counter vitamin, patients should be discouraged from self-administration because of its potential toxicity. It is important to monitor not only the patient’s response to niacin therapy but also the appearance of clinical and laboratory side effects that necessitate adjustment of the niacin dosage or discontinuance of therapy. During niacin therapy, patients may have severe enough hepatic dysfunction to become clinically ill. A return to the use of crystalline or immediate-release niacin should be encouraged, in view of the increasing frequency of reported side effects with sustained-release niacin.

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REFERENCES