Hypercholesterolemia

Use of Niacin and Niacin Combinations in Therapy

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• **Niacin or niacin combinations were administered in dosage of 1.0 to 6.0 gm. to 31 hypercholesterolemic patients for periods up to three years. Eighty per cent were able to continue medication for long periods without significant side effects. Jaundice, apparently due to nicotinic acid, occurred in one patient. Liver toxicity will probably be a hazard in the use of this therapy.**

Significant and maintained serum cholesterol depression was achieved in 80 per cent of the patients who were able to take adequate dosage. Reduction in xanthomata was observed with cholesterol reduction. In some cases, when larger doses were not tolerated or were unsuccessful, combining 1.5 gm of niacin with small doses of estrogen or triparanol achieved the desired effect. Aluminum nicotinate had no important advantage over plain niacin.

NIACIN ADMINISTERED in daily dosage of 3 to 6 grams brings about a definite reduction in serum cholesterol in most subjects. The precise mechanism of this effect remains to be explained. Both increased and decreased hepatic synthesis have been reported, depending on the experimental animal used and the conditions of the study.[8,11,18,19] In man there does not appear to be any increase in bile acid or sterol excretion in the stool.[6] It has been suggested that in rats and rabbits nicotinic acid achieves its results only by inducing anorexia.[5] The clinical usefulness and potential toxicity of long-term treatment are still in doubt.

This is a report concerning 31 patients treated for periods up to three years with niacin, aluminum nicotinate,* or combinations of aluminum nicotinate and estrogen† or triparanol.‡

METHODS AND MATERIALS

Patients were all male Veterans Administration out-patients or private patients who had cholesterol levels before treatment greater than 270 mg. per 100 cc. of blood. The age range was from 6 to 62 years. Twenty-three had had myocardial infarction while the others had cholesterol deposits in the skin or tendons, or were known to have familial hypercholesterolemia.

In light of known vagaries in determination of serum lipids,[17] measurements were performed at least three times, each time in duplicate, over at least a two-month period to establish the level before treatment—the control level. Because of the great variability in lipid levels in the two months following myocardial infarction,[16] no control measurements were included for this period. Determinations of lipids were carried out again at 2 to 6 week intervals after the start of therapy.

The Kingsley technique[10] was used for total serum cholesterol measurement. At present we achieve a reproducibility of ± 8 mg. of 100 cc. with this method. A comparison of this method with the Abell method on 50 samples over a wide range indicated that the amount as determined by the Kingsley method averages 14 per cent higher. A modification of the Jencks and Durrum[9] technique was used for electrophoresis and staining.[16] Except for the two patients noted, diets were stable during the treatment period. Also, with one exception, weight did not vary more than 5 per cent during the study period.

RESULTS*

A. Niacin alone

Nineteen patients were given plain niacin in 3 gm. to 6 gm. doses daily. Sixteen of them were able to continue the drug in adequate dosage with the following results:

1. *Lipid changes.* Thirteen subjects maintained reductions of serum cholesterol of 20 per cent or more below the control level, six having reductions greater than 30 per cent. It should be emphasized that these are persisting decrements and that the lowest single cholesterol level achieved during the therapy was often more than 50 per cent below the control. When niacin was temporarily discontinued in four patients there was a return to control levels in one month. Of the three unresponding patients, one had idiopathic hyperlipemia, one

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*Aluminum nicotinate supplied as Nicalex® by Walker Laboratories, Inc., Mt. Vernon, N. Y.

†Estrogen supplied as SC 9263 (which is 16-alpha-chloro-1,3,5-estratrien-17-one-) by G. D. Searle Co., Chicago.

‡Triparanol supplied as MER/29® by Merrell Co., Cincinnati.

*Tables containing specific data may be obtained from the author.

familial hypercholesterolemia and the other had had an uncomplicated myocardial infarct.

Ten of the 13 patients who had favorable cholesterol effect also had changes to normal in their alpha:beta lipoprotein ratio, either by increased alpha, decreased beta, or both.

2. *Xanthomata.* Six patients had xanthoma tuberosum, tendinosum or xanthelasma at the start of therapy. In one, the xanthelasma completely disappeared and in two there was measurable reduction of the tendon deposits. One man had xanthomata removed before therapy was begun and at last report, after nearly two years, there had been no return.

3. *Angina, intermittent claudication and peripheral pulses.* There was no change in the single patient with absence of leg pulses even though cholesterol was maintained below 200 mg. per 100 cc. for two years. Although a decrease in angina was reported by a few patients, no convincing evidence of change was noted.

B. Aluminum nicotinate

Thirteen patients were given this medication. Three patients who could not tolerate niacin because of nausea and vomiting were also unable to tolerate aluminum nicotinate. Eight subjects were able to maintain therapy. Of these, four had maintained cholesterol depressions of greater than 20 per cent, along with favorable lipoprotein alteration. Three of the nonresponders were children of a hypercholesterolemic family who were unable to tolerate more than 1 gm. daily.

No effect on the peripheral pulses or exercise tolerance of one peripheral atherosclerotic patient was noted despite good cholesterol depression.

C. Aluminum nicotinate plus estrogen (designated SC 9263, which is 16-alpha-chloro-1,3,5,-estratrien-17-one-)

Two patients were started on this combination as their initial therapy; five were so treated when the full dose of niacin was not tolerated or when niacin alone either failed to reduce the cholesterol or to increase the alpha:beta lipoprotein ratio. Dosage of aluminum nicotinate was 1.5 gm. or 3 gm. daily, and of SC 9263 5 mg. daily. Four patients had persisting cholesterol reductions of more than 20 per cent and 5 had lipoprotein shifts.

D. Niacin plus triparanol (MER/29®)

Two patients were given MER/29®, 250 mg. daily with niacin 1.5 gm. daily. This was done when an effective niacin dose could no longer be tolerated and after it was determined that MER/29 alone (250 mg. for two months) was without effect. In both cases, successful reduction in cholesterol occurred.

E. Side Effects

1. *Nausea and Vomiting.* Three patients were unable to take more than a few doses of niacin because of this symptom. Nor could they tolerate the medication when aluminum nicotinate was substituted for niacin. Doses of 500 mg. were tolerated but were ineffective. In two men nausea and vomiting developed later, in one after three weeks and in the other after 84 weeks of therapy. Again the aluminum salt was not better tolerated.

2. *Flushing.* Flushing of mild to severe intensity occurred in all patients during the first week. Thereafter, the flushing was mild and intermittent and in no case was it a cause for discontinuing treatment. Aluminum nicotinate administration produced only slightly less flush than niacin. Taking the medication without food resulted in severe flushing from one to three hours later. If the evening meal was small, patients were occasionally awakened at night with flushing.

3. *Epigastric burning* occurred in three patients, two of whom had a history of duodenal ulcer and one of whom was an alcoholic. Distress was not controllable with antacids and in one case was severe enough to lead to discontinuing medication.

4. *Jaundice.* In one of the early patients in the series jaundice developed at 70 weeks. This was believed to be owing to drug-induced intrahepatic cholestasis and was reported upon in detail elsewhere.[15] Because of this experience, SGO-transaminase and alkaline phosphatase were measured every three to four months in all patients. No abnormalities were noted. Bronsulfonphthalein determinations were not done, nor was liver biopsy carried out.

5. *Typical hives* developed in one patient after two doses.

With two exceptions, diets were stable during the treatment period. Most of the patients were on standard, American, high-fat diets, and the medication was as effective in these patients as it was in patients on restricted diet. One patient changed from restricted saturated fat to regular diet during treatment without negating the niacin effect. Another, however, had a sharp rise in cholesterol upon liberalization of diet, with a rapid gain of 18 pounds in body weight.

Aluminum nicotinate had the same cholesteropenic effect as equivalent doses of niacin. Patients intolerant to niacin because of nausea, vomiting or epigastric burning were also intolerant of the aluminum salt. There appeared to be slightly less flushing with aluminum nicotinate. Although a 1.5 gm. dose was tolerated when a 3 gm. dose was not, this smaller amount was ineffective except in one in-

stance. When 1.5 gm. of niacin was combined with either a small dose of estrogen or MER/29 (neither of which alone was effective) a lipodiatic effect was achieved in five of six trials.

DISCUSSION

The decision as to the wisdom of using niacin therapy turns on the question of serious toxicity. Will important liver damage occur?

The case in which jaundice occurred in the present series, and the reports of other investigators regarding overt jaundice and abnormal liver function tests,[3,12,13] call for caution. While it is true that in each case the jaundice was reversible, and that in many cases enzymatic abnormalities of liver function appeared without histologic abnormality on liver biopsy, in at least one biopsy considerable parenchymal damage was seen.[4] We used only the alkaline phosphatase and SGO transaminase as screening procedures and detected no abnormalities in our other patients. These liver changes suggest, of course, that niacin is effective by virtue of some interference with liver synthesis of cholesterol. Such findings, plus the failure to observe reduced appetite or weight loss in patients, makes the Friedman suggestion[5] of anorexia as the mechanism of niacin-induced hypocholesterolemia, untenable for man.

Apparently clinically insignificant abnormalities in sugar tolerance and uric acid levels have been noted by other investigators.[3,7,13]

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REFERENCES

1. Altschul, R.: Niacin (nicotinic acid) and serum cholesterol, J.A.M.A., 166:822, Feb. 15, 1958.

2. Altschul, R., Hoffer, A., and Stephen, J. D.: Influence of nicotinic acid on serum cholesterol in man, Arch. Biochem., 54:558, 1955.

3. Berge, K. G., Achor, R. W. P., Christensen, N. A., Mason, H. L., and Barker, N. W.: Hypercholesterolemia and nicotinic acid, Am. J. Med., 31:24, July 1961.

4. Christensen, N. A., Achor, R. W. P., Berge, K. G., and Mason, H. L.: Nicotinic acid treatment of hypercholesterolemia, J.A.M.A., 177:546, Aug. 26, 1961.

5. Friedman, M., and Byers, S. O.: Evaluation of nicotinic acid as an hypocholesteremic and antiatherogenic substance, J. Clin. Invest., 38:1328, 1959.

6. Goldsmith, G. H., Hamilton, J. G., and Miller, O. N.: Investigation of mechanisms by which unsaturated fats, nicotinic acid and neomycin lower serum lipid concentrations: Excretion of sterols and bile acids, Trans. Assn. of Am. Physicians, 72:207, 1959.

7. Gurian, H., and Adlersberg, D.: The effect of large doses of nicotinic acid on circulating lipids and carbohydrate tolerance, Am. J. Med. Sci., 237:12, Jan. 1959.

8. Hardy, R. W. F., Gaylor, J. L., and Bauman, C. A.: Biosynthesis of sterols and fatty acids as affected by nicotinic acid and related compounds, J. of Nutrition, 71:159, 1960.

9. Jencks, W. P., and Durrum, E. L.: Paper electrophoresis as a quantitative method: The staining of serum lipoproteins, J. Clin. Invest., 34:1437, 1955.

10. Kingsley, G. R., and Schaffert, R. R.: Determination of free and total cholesterol by direct chloroform extraction, J. Biol. Chem., 180:315-328, Aug. 1949.

11. Merrill, J. M.: Effect of nicotinic acid on the incorporation of radiocarbon into cholesterol, Circulation Research, 6:482, 1958.

12. Pardue, W. O.: Severe liver dysfunction during nicotinic acid therapy, J.A.M.A., 175:137, 1961.

13. Parsons, W. B., Jr.: Treatment of hypercholesterolemia by nicotinic acid, Arch. Int. Med., 107:71, May 1961.

14. Parsons, W. B., Jr. and Flynn, J. H.: Alteration in serum cholesterol and lipoprotein cholesterol by nicotinic acid, Circulation, 28:765, Oct. 1958.

15. Rivin, A. U.: Jaundice occurring during nicotinic acid therapy for hypercholesteremia, J.A.M.A., 170:2088-2089, Aug. 22, 1959.

16. Rivin, A. U., and Wong, H.: Lipid measurements in coronary artery disease. Comparison with an age-matched normal control group, Am. J. of Cardiology, 5:784, 1960.

17. Rivin, A. U., Yoshino, J., Shickman, M., and Schjeide, O. A.: Serum cholesterol measurement—Hazards in clinical interpretation, J.A.M.A., 166:2108-2111, April 26, 1958.

18. Schade, H., and Saltman, P.: Influence of nicotinic acid on hepatic cholesterol synthesis in rabbits, Proc. Soc. Exper. Biol. and Med., 102:265, Nov. 1959.

19. Schon, H.: Effect of nicotinic acid on the cholesterol contents of rat livers, Nature, 182:534, 1958.