In: Human Biology & Medicine. Vitamins. MH Briggs (ed.) CRC Press Inc, Florida 1981; 81-94.

Chapter 4

EFFECTS ON PLASMA CHOLESTEROL OF NICOTINIC ACID AND ITS ANALOGUES

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I. INTRODUCTION

The plasma cholesterol lowering properties of nicotinic acid or niacin were first recognized by Altschul and colleagues in 1955.[1,2] The pharmacological dosages of 3 to 9 g/day required are well in excess of the daily allowances of about 20 mg/day for niacin as a vitamin. Although low plasma and arterial wall levels of pyridine compounds have been observed in hypercholesterolemic animals,[3] overt niacin deficiency has not been recognized nor advanced as a basis for nicotinic acid therapy. The cholesterol lowering properties of nicotinic acid at megadosage appear distinct properties. They are not evident with nicotinamide[4,5] and do not appear dependent on nicotinic acid metabolites.[6-9]

II. RATIONALE FOR LIPID LOWERING

The ultimate rationale for the pharmacological use of nicotinic acid must be a reduction in total mortality through a decrease in cardiovascular events attributable to atherosclerotic vascular disease.[10] There is ample experimental and epidemiological evidence that the severity of atherosclerotic vascular disease is dependent, in part, on plasma cholesterol concentration,[11,12] plasma triglyceride concentration,[11,13] and inversely, on high density lipoprotein concentration.[14-17] There is increasing evidence that reduction of plasma cholesterol by diet[18-20] or drugs[21-23] will reduce coronary events, although not necessarily fatal events or total mortality.[21-23]

III. MECHANISM OF ACTION OF NICOTINIC ACID

An agent which reduces plasma cholesterol or triglycerides will do so through decreased synthesis and/or increased removal. It is likely, too, that the nature of the underlying defect in lipid metabolism will influence the effectiveness of the agent.

An impressive metabolic action of nicotinic acid in megadosage is antilipolysis.[24-26] The reduced flux of free fatty acids (FFA) to the liver ought to decrease very low density lipoprotein triglyceride (VLDL TG) production, and with it, cholesterol production.[27-29] In any case, VLDL is a precursor of low density lipoprotein (LDL), the major cholesterol-bearing lipoprotein.[30] Nicotinic acid does decrease the rate of synthesis of LDL.[31] In addition, there is evidence that nicotinic acid directly inhibits cholesterogenesis. Not all studies, however, support the view that cholesterogenesis is inhibited and some actually suggest it is enhanced,[32-40] but where assessment was 14 hr after the last dose of nicotinic acid, rebound effects might have been operative.[40]

Enhanced cholesterol oxidation has been reported.[41] Negative neutral steroid balance has been observed with nicotinic acid.[42,43] Although bile acid excretion does not appear enhanced,[42] the biliary cholic acid to chenodeoxycholic acid ratio is increased by nicotinic acid[44] which may suggest a differential effect of nicotinic acid on the alternative pathways for bile acid formation, 7 α-hydroxylation and 26-hydroxy cholesterol generation.[45] The interpretation of sterol balance studies in this context is complicated by, potentially, the mobilization of cholesterol from tissue deposits, and, therefore, nonsteady-state conditions. Triglyceride removal may also be enhanced[46] as lipoprotein lipase activity is stimulated by nicotinic acid.[47,48] The mechanism for antilipolysis with nicotinic acid remains incompletely understood. There does appear to be a combined effect on re-esterification and lipolysis.[49] Nicotinic acid does inhibit adenyl cyclase activity and cyclic AMP formation in adipose tissue, and this may relate to its antilipolytic effect.[51] Little or no effect on cyclic AMP is likely through phosphodiesterase inhibition.[50] Prostaglandin synthesis might be involved.[52-54]

The determination of nicotinic acid in blood[55-58] allows an examination of the rela-

tionship between pharmacokinetics[6,7,9] and action.[29,50] Plasma concentrations of nicotinic acid of greater than 2 μg/mℓ lower free fatty acids.[29] Often, plasma free fatty acids are used as an index of the duration of action of a nicotinic acid preparation.

When lipoprotein lipase activity is increased and triglyceride clearance enhanced, as it appears to be with nicotinic acid, HDL cholesterol concentration increases. On this basis, HDL elevation with nicotinic acid might be a secondary phenomenon. However, nicotinic acid does lead to an enrichment of apoproteins $apoA_I$ in the HDL_2 subfraction and $apoA_{II}$ in the HDL_3 subfraction.[60] The plasma $apoA_I$ to $apoA_{II}$ ratio is increased[61,62] as also is the HDL_2 to HDL_3 ratio.[60,63] These features appear to result from reciprocal changes in the synthetic rates of $apoA_I$ which is increased, and of $apoA_{II}$, which is decreased, as well as a redistribution of $apoA_I$ and $apoA_{II}$ between HDL_2 and HDL_3.[62] The HDL subfraction changes with nicotinic acid will undoubtedly assume more importance as their relationship to atherosclerotic vascular disease is defined.

IV. EFFECTIVENESS OF NICOTINIC ACID

A. Plasma Lipids

Modification of dietary fat intake in its own right will reduce plasma lipid concentrations[18,19,64,65] and, generally, this is done prior to the introduction of lipid-lowering drugs. Several clinical trials attest to the plasma cholesterol and triglyceride lowering properties of nicotinic acid.[1,2,21,27-29,66-72] Reductions of cholesterol concentration by 10 to 25% and triglyceride concentration by 23 to 46% have been observed and these effects are at least comparable to those of the other principal lipid-lowering drugs, clofibrate (Atromid-S), and the resin cholestyramine (Questran) (Table 1). With resins, only cholesterol is lowered while triglyceride is often elevated.[68,73] The only hypertriglyceridemia in which nicotinic acid appears not to be effective is the hyperchylomicronemia seen in Type I hyperlipoproteinemia.[74,75]

Of considerable potential importance is the consistent increase in high density lipoprotein (HDL) cholesterol seen with nicotinic acid therapy.[27] HDL has the capacity to decrease arterial cholesterol deposition by interference with LDL cholesterol uptake[76] and through an increase in the removal of free cholesterol.[77]

B. Xanthomata

There are reports of tuberous and tendinous Xanthomata softening, reducing in size, and even disappearing on nicotinic acid therapy.[27]

C. Atherosclerotic Vascular Disease

An early report of Öst and Stenson[78] of serial arteriography indicated that atherosclerosis might regress during nicotinic acid therapy. With computerized femoral angiography,[79] the extent of risk factor correction has been related to regression of preclinical atherosclerotic vascular disease. In rabbits[80,81] and mini-pigs[82] nicotinic acid or its derivatives, niceritrol and β-pyridyl carbinol, limit the development of atherosclerotic lesions. It has been suggested that nicotinic acid might directly and favorably affect arterial cholesterol deposition, independent of its effect on blood lipids.[82] This would be consistent with the recognized metabolic activity of atherosclerotic lesions.[83-85]

D. Angina Pectoris

Nicotinic acid markedly alters myocardial fuel supply in favor of carbohydrate and away from FFA.[86-90] Since glucose is the only fuel from which ATP can be obtained anaerobically and since the oxygen cost for ATP generation is less with glucose than

Table 1
DRUG THERAPY OF HYPERLIPOPROTEINEMIA

	Nicotinic acid and derivatives			Other agents			Combined therapy		
	Nicotinic acid	Aluminum nicotinate	Niceritrol	β Pyridyl carbinol	Clofibrate	Cholestyramine	Niceritrol & clofibrate	Nicotinic acid & cholestyramine	Ref.
Total cholesterol	−25%	−25%[a]							104
	−13%		−21%[a]						69
				−10%					135
				−18%[b]					136
	−10%				−7%				21
	−11%		−16%		−14%		−28%		66
			−12%		−17%	−23%	−23%		133
	−21%					−26%			68
	(1)					0%		−46%	43
	(2) −36%[c]							−28%	
Total triglyceride	−46%		−11%						69
				−15%					135
				−18%[b]					136
	−26%				−22%				21
			−26%		−21%		−38%		133
	−23%					−28%			68
High density lipoprotein cholesterol			+28%[c]						69
							0[c]		133

Note: Standard dosages were used alone or in combination unless otherwise indicated (nicotinic acid 3 g/day, niceritrol 3 g/day, β pyridyl carbinol 1.2 or 1.8 g/day, clofibrate 1.5 or 2 g/day, cholestyramine 16 g/day). Percentage changes from untreated values are shown.

[a] Dosage of nicotinic acid individualized rather than 3 g/day.
[b] In this study, comparison with placebo indicated that the fall in cholesterol was highly significant whereas that in triglyceride was not.
[c] Data for types IIa and IIb hyperlipoproteinemia combined.
[d] Two cases studied are shown separately.

for FFA, nicotinic acid could protect the ischemic myocardium. Angina pectoris occurs less often when sufferers have their hearts paced during an infusion of nicotinic acid.[91] In addition to its metabolic effects, nicotinic acid has a favorable effect on distribution of coronary blood flow during experimental coronary oclusion in dogs.[92]

E. Myocardial Infarction

Electrocardiographic evidence of myocardial infarction, by way of ST segment elevation, is less when a nicotinic acid analogue, 5-fluoronicotinate, is administered.[93] A 3-year prospective study of secondary prevention of myocardial infarction with a combination of nicotinic acid and clofibrate, produced a significant 50% reduction in nonfatal reinfarction.[94] Greater lipid lowering was seen in this study than in the Coronary Drug Project, also a secondary prevention study.[21,22] In the Coronary Drug Project a reduction in nonfatal coronary events with nicotinic acid was also found.

V. USE IN SPECIAL SITUATIONS

A. Children

Clofibrate is relatively ineffective in children with familial hypercholesterolemia, and cholestyramine is generally used.[95] There is probably a place for nicotinic acid in resistant cases. Effective lipid lowering in a child at risk from premature ischemic heart disease is likely to outweigh the disadvantage of prolonged therapy. It may also allow a reduction in resin therapy with its risk of interference with fat soluble vitamin availability.

B. Renal Disease

The management of hyperlipidemia in renal failure, renal transplant patients, and in the nephrotic syndrome is difficult. Dietary therapy alone is probably the least difficult management, but not always sufficiently effective.[96,97] In patients on chronic hemodialysis, nicotinic acid therapy achieves a 20% reduction in plasma cholesterol and a 35% reduction in plasma triglycerides.[97] A limiting factor to nicotinic acid use in renal disease is the presence of hyperuricemia which may be exacerbated.

C. Alcohol Abuse

Nicotinic acid is effective in alcohol-sensitive hyperlipidemia.[98] In rats it potentiates ethanol fatty liver.[99] Species differences may be important, however, since in the rat, plasma triglyceride, but not cholesterol, is lowered by nicotinic acid.

VI. SIDE EFFECTS

A. Flushing

Cutaneous vasodilation occurs within about 1 hr of ingestion of plain nicotinic acid during introduction of therapy. To minimize flushing, niacin is taken with meals and dosage is increased progressively. It is usually convenient to begin with 250 mg thrice daily with increments of 250 mg thrice daily every 1 to 3 days until a daily dose of 3 g is reached. Flushing only occurs while plasma nicotinic acid concentrations increase.[9,100] With constant i.v. infusion of nicotinic acid, the flush disappears when steady-state plasma concentrations have been achieved.[9] Cutaneous and muscle blood flows increase and total peripheral resistance falls.[9]

When an aluminum nicotinate (Nicalex®) is used, the occurrence of the flush is much less predictable and it may occur hours away from the time of injection.[138] This presumably represents altered and variable absorption of nicotinic acid with this

preparation. Pentaerythritoltetranicotinate (niceritrol or Pericyt®) produces less flushing,[101] probably because of prolonged action and more constant blood nicotinic acid concentrations[9]

There is evidence that, at least in part, the vasodilation is induced by prostaglandin and that it can be prevented by indomethacin.[102]

B. Gastrointestinal

Nausea, vomiting, abdominal pain, and diarrhea are occasionally reported during nicotinic acid therapy.[103] In the Coronary Drug Project, only abdominal pain occurrence was significantly increased over placebo.[21] Activation of peptic ulcer has also been reported,[104] but it would be of interest to reexamine this question now that endoscopic facilities are more acceptable and available. Whether or not nicotinic acid can be used in conjunction with cimetidine, now commonly used in the management of peptic ulcer, needs to be studied. If it could, this may allow treatment of a patient group otherwise denied this form of lipid lowering therapy.

C. Cutaneous

Cutaneous side effects include pruritus, dryness of the skin, pigmentation in flexural creases, and scars which may resemble acanthosis nigricans.[21, 105] These effects are rarely a problem and are reversible on cessation of therapy.

D. Hyperuricemia

Serum uric acid increases significantly on treatment with megadosage nicotinic acid[21] and acute gouty arthritis can occur.[21] Nicotinic acid is probably antiuricosuric by a renal tubular mechanism.[106]

E. Glucose Tolerance

Impairment of glucose tolerance is found in a proportion of healthy and diabetic subjects given nicotinic acid.[21,106-109] In the Coronary Drug Project, fasting blood glucose did not change significantly over a period of 5 years, although the 1 hr blood glucose rose significantly from 168 to 186 mg/100 m*l*.

There are diabetics, however, whose carbohydrate status improves on nicotinic acid.[110,111] In vitro, nicotinic acid stimulates insulin release from isolated islets of mouse pancreas.[112] It has been suggested that in diabetics whose carbohydrate status improves on nicotinic acid, a decrease in FFA, according to Randle's glucose-fatty acid cycle hypothesis, is responsible.[111] As far as the human heart is concerned, at lower FFA concentrations more glucose, lactate, and pyruvate are extracted.[86-89] One of the potential problems when thrice daily plain nicotinic acid therapy is used that a rebound rise in plasma FFA occurs as the evening dose wears off.[46] However, most studies have been unable to relate whole body glucose handling, as assessed by a glucose tolerance test, with FFA concentrations during nicotinic acid therapy.[46,110] The observation that there is often a lag in the development of impaired carbohydrate tolerance[69,113] has suggested that the impairment might relate to hepatic dysfunction.[114]

In acute studies with nicotinic acid infusion, nicotinic acid has been shown to reduce hepatic ketone production in relation to a decrease in splanchnic FFA flux.[115] It might be expected that, conversely, during the rebound rise in FFA flux after withdrawal of nicotinic acid, ketone production would rise. An interesting aspect of nicotinic acid and glucose tolerance, is that as a complex with chromium, the glucose tolerance factor (GTF), it facilitates insulin action.[116,117]

F. Hepatic Dysfunction

Hepatic enzyme activities in serum are often raised with nicotinic acid

therapy.[21,118,119] Jaundice has been seen.[8,9,120,121] In the Coronary Drug Project, however, less nicotinic acid treated individuals had serum bilirubin outside specified limits than did those on placebo.[21] The enzyme changes are reversible on withdrawal of therapy. Ultrastructural changes of mitochondria and endoplasmic reticulum are seen in liver biopsies from persons treated with nicotinic acid.[122] A case of hepatic fibrosis has been reported.[123] Where liver disease is present, nicotinic acid therapy should be avoided.

G. Arrhythmia

There was an excess of atrial fibrillation and other arrythmias in the nicotinic acid treated group in the Coronary Drug Project.[21] It is possible this could relate to the rebound rise in FFA and be a case for a longer acting nicotinic acid derivative or analogue.[93,124] Another possibility is that lower levels of serum potassium, seen with nicotinic acid, were responsible.[21]

H. White Cell Count

Nicotinic acid lowered total white cell count (WCC) and absolute neutrophil count (NC) from means of 7470 to 6610/cmm, and 4580 to 3970/cmm over 5 years, respectively, in the Coronary Drug Project.[21] There was an excess over placebo, for total WCC, of 7% below 3500/cmm and for NC, of 2% below 1800/cmm.

I. Maculopaphy

An atypical form of cystoid macular edema and loss of central vision has been reported with high dose nicotinic acid.[125] There is no capillary leakage evident on fluorescein angiography. It is reversible on cessation of nicotinic acid therapy.

J. Other

Whereas with clofibrate in the Coronary Drug Project, cholelithiasis, including cholecystectomy, was significantly increased by comparison with placebo. This was not the case for nicotinic acid.[21] Also in the Coronary Drug Project, unexpected loss of appetite, loss of weight, and excessive sweating were seen more commonly with nicotinic acid than with placebo or clofibrate.[21] Serum CPK was significantly increased with nicotinic acid in the Coronary Drug Project.[21]

VII. DERIVATIVES AND ANALOGUES

Derivatives and analogues have been sought with two objects in mind:

1. Reduction in side effects, particularly cutaneous flushing and gastrointestinal symptoms
2. A more prolonged action so as to reduce tablet frequency and to overcome the rebound rise in plasma FFA

In general, it can be said that those pharmaceutical preparations which have been designed to release nicotinic acid slowly into the gut for more prolonged absorption and sustained plasma concentrations, have met with little success. This appears to be because nicotinic acid is a weak acid, and is, therefore, poorly absorbed from the more distal gastrointestinal tract.[59] Aluminum nicotinate (Nicalex®) was developed to reduce gastrointestinal side effects.[126,127]

Various esters have been prepared,[128,129] but of them, niceritrol (Pericyt®) or pentaerythritol tetranicotinate has been used longest and most extensively.[59,66,81,82,101,130-134] It does not lead to hyperuricemia. Nicotinyl alcohol (Ronicol®)

or β-pyridyl carbinol has also been used to lower plasma cholesterol and appears about three or fourfold more potent than nicotinic acid on a weight for weight basis.[135,136] It is not significantly effective in hypertriglyceridemia.[36] The relative effectiveness of these derivatives and analogues is shown in Table 1.

VIII. COMBINED DRUG THERAPY

As in antihypertensive and antitumor therapy, it seems rational to combine antihyperlipidemic agents.[137] In this way, additive effects or possibly synergism can be sought. For instance, a drug which reduces cholesterol synthesis could be combined with a drug which increases its removal. Smaller dosages of each drug should be possible with combined therapy and this would lessen side effects. In this regard, the combination of nicotinic acid and a resin such as cholestyramine, colestipol, or DEAE Sephadex (Secholex®) is one of the most attractive regimens. Available studies of combined therapy are shown in Table 1.

IX. CONCLUSIONS

Nicotinic acid is an agent which can contribute to the management of hypertriglyceridemia (except pure hyperchylomicronemia), hypercholesterolemia, and combinations of these. Although a number of side effects may be seen, they are usually reversible and not of a serious kind. There is experimental evidence that less atherosclerotic vascular disease may be seen with nicotinic acid therapy. Secondary prevention of ischemic heart disease with less nonfatal mycardial infarctions has occurred with its use. It has yet to be shown whether total mortality is favorably influenced. Data available should provide a stimulus for the development of derivatives and analogues and for an examination of niacin therapy in combination with other agents to improve efficacy. In this way, nicotinic acid might contribute to the management of hyperlipoproteinemia which is presently unsatisfactory.

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