

NICOTINIC ACID — THE BROAD SPECTRUM LIPID DRUG



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The Lipid Drug with the Best HDL-Raising Effect

Some fifty years ago the Canadian pathologist Rudolf Altschul discovered that nicotinic acid in gram doses lowered plasma cholesterol in man, an effect surprisingly not shared by nicotinamide [1]. Altschul had also shown that nicotinic acid lowered plasma cholesterol and reduced aortic atherosclerosis in the cholesterol-fed rabbit. At that time, 5 years before bile acid sequestrants and 6-8 years before clofibrate were available as lipid lowering drugs nicotinic acid was used by several groups for the treatment of dyslipidemia. Its clinical use is, however, limited by the flush which occurs as a regular unpleasant but harmless side effect once treatment with nicotinic acid is started. I have used nicotinic acid in clinical practice as well as in experimental medicine since the 1960s and I will briefly discuss past, present, and future aspects of nicotinic acid in clinical lipidology.

Effects on Plasma Lipids and Lipoproteins

In the late 1950s it had already been shown that nicotinic acid not only lowered plasma levels of the cholesterol-rich LDL (low density lipoproteins) but also raised the concentration of HDL (high density lipoproteins). The lowering of LDL was well accepted as beneficial for the prevention of atherosclerosis but the importance of the HDL-raising effect was not understood at that time. In the early 1970s we reported results on treatment of dyslipidemic subjects with a standard dose of 1 gram of immediate release (IR) nicotinic acid three times daily. In both women and men we obtained good reductions of cholesterol and triglycerides, particularly of triglycerides, in Fredrickson-WHO hyperlipidemia types IIA, IIB, III, IV, and V. In a study done in the 1980s we analyzed the effect of 4 grams of IR nicotinic acid on the lipoprotein pattern. The results, summarized in Figure 1, show that the cholesterol content of VLDL (very low density lipoproteins), LDL, and Lp(a) were lowered substantially while the cholesterol content of HDL was increased by around 40%. However, the most striking effect was on the HDL subfraction HDL₂, the cholesterol content of which increased by about 100%. In addition to these effects nicotinic acid also lowers the concentration of chylomicrones present in fasting blood in type V hyperlipidemia. The effects of nicotinic acid on plasma lipoproteins are

summarized in Table 1. Taking together the remarkable, multiple effects on lipoproteins, all indeed beneficial for the prevention of CVD (cardiovascular diseases), we have called nicotinic acid the broad spectrum lipid drug [2].

Effects on High-Density Lipoproteins

In the 1950s Parsons and Flinn at the Mayo Clinic showed that nicotinic acid lowered LDL and raised HDL (determined by the then novel technique of lipoprotein electrophoresis as α -lipoproteins) [3]. The HDL-raising action of nicotinic acid did not obtain much attention at that time as the protective properties of HDL for CVD had not yet been recognized and the “lipid hypothesis” was dominated by the role of high LDL levels. It should be some 15 years until the protective role of HDL became clear through the landmark Lancet paper by the Miller brothers [4]. They proposed that “a reduction of plasma HDL concentration may accelerate the development of atherosclerosis...by impairing the clearance of cholesterol from the arterial wall.” This is the first statement on the process presently called “reverse cholesterol transport” (RCT) by means of which cholesterol of peripheral tissues, including arteries, is transported by HDL to the liver for excretion via feces.

Several Mechanisms Have Been Proposed for the HDL Raising Effect of Nicotinic Acid

Several mechanisms have been proposed for the HDL raising effect of nicotinic acid:

- 1) Plasma triglyceride lowering by inhibition of fat mobilizing lipolysis in adipose tissue,
- 2) Plasma triglyceride lowering by inhibition of diacylglycerol acyltransferase 2 in the liver,
- 3) Decreased hepatic removal of HDL-apolipoprotein (apo) A-I.

There is a strong negative correlation between plasma triglyceride levels and the concentration of HDL, in part related to the cholesteryl ester exchange between VLDL and HDL mediated by CETP (cholesteryl ester transfer protein). Reduction of triglycerides in general increases HDL. Nicotinic acid may lower triglycerides by the inhibition of lipolysis in adipose tissue which will decrease the flux of FFA (plasma free fatty acids) to the liver where FFA are important precursors for the hepatic synthesis of triglycerides, the major component for the formation of VLDL in the liver. Nicotinic acid may also directly decrease hepatic triglyceride synthesis by its inhibition of diacylglycerol acyltransferase, an enzyme involved in triglyceride synthesis in the liver.

Results of *in vivo* turnover studies and *in vitro* experiments with Hep G2 (human hepatoblastoma) cells have indicated that nicotinic acid reduces the removal of HDL-apo A-I, thereby raising the plasma level of HDL. Studies from Kashyap's group with the Hep G2 cell model have shown that while nicotinic acid causes a decreased uptake of HDL, apo A-I nicotinic acid does not reduce the uptake of HDL-cholesteryl esters.

Effects on Clinical Atherosclerosis

In clinical trials nicotinic acid in monotherapy or in combination with bile acid resins, fibrates or statins has been shown to arrest the progression of coronary as well as carotid atherosclerosis and even induce regression of such lesions reduce the incidence of major CVD events in secondary prevention reduce mortality in secondary prevention of CHD.

For a review of the effects of nicotinic acid on clinical outcomes, coronary angiograms and effects on carotid-intima thickness, see [5,6]. Of particular importance are the beneficial effects obtained with extended release (ER) nicotinic acid in the secondary prevention ARBITER 2 and 3 studies [7,8]. Patients with low HDL who were on regular treatment with statins were on top of this treatment given either ER nicotinic acid or placebo. In the placebo plus statin group carotid atherosclerosis, measured as CIMT (carotid-intima-media thickness), progressed while in the ER nicotinic acid plus statin group CIMT either did not change [7] or regressed [8].

My personal experience over the years with long-term treatment of dyslipidemias with IR nicotinic acid (3-4 grams daily, or more) in motivated patients who have attained tachyphylaxis for the flush is that they have been doing very well, the only complications being the rise in uric acid (easily controlled by allopurinol) and acanthosis nigrans (in less than approximately 0.1% of treated patients).

The IR preparation of nicotinic acid which I have used since the 1960s, usually in doses of 1-2 grams tid or qid, is no longer available in Sweden. I have therefore prescribed Niaspan in doses of 1-2 grams a day at bed-time to those of my patients who still want to continue their long-term treatment with nicotinic acid. The effect on the plasma lipids, especially on HDL, has been excellent and there have been no adverse affects, particularly no or very little disturbing flush.

A large trial, AIM-HIGH, sponsored by the National Institutes of Health, USA, comparing the effect of ER nicotinic acid plus simvastatin with simvastatin alone on CVD and other clinical outcomes has just started. The results are expected to be available within 5 years.

The Special Case of Type V Hyperlipidemia and Pancreatitis

The rare type V hyperlipidemia, characterized by very high triglyceride levels (10-100 mmol/L) and the presence of chylomicrones in fasting plasma (revealed by the simple "standing test:" plasma standing overnight in the test tube gets a creamy top layer) is often associated with recurrent attacks of pancreatitis. The 10 cases with this condition that I have seen have all responded to very high doses of IR nicotinic acid (8-16 gram per day) with immediate disappearance of the often monthly occurring attacks of acute pancreatitis and reduction of triglycerides to below 5 mmol/L (and increases of HDL-C from ~ 0.2 to ~ 1 mmol/L) without any adverse effects during treatment for many years. No doubt nicotinic acid has been a life saver in these cases.

The mechanism behind the harmless but annoying flush is presently subject to intensive research with focus on two receptors, one for nicotinic acid and one for prostaglandin D2. Nicotinic acid, but not nicotinamide, always induces flush, an intensive cutaneous vasodilation starting in the face, spreading to the upper body, sometimes even down to the feet, when taken for the first time. This unpleasant effect has greatly limited the use of nicotinic acid in the treatment of dyslipidemia in spite of its excellent broad spectrum effect with raising HDL and lowering all atherogenic lipoproteins. The flush appears to be due to prostaglandin release, particularly PGD2 [9,10] and can be inhibited by cyclooxygenase inhibitors such as aspirin and indomethacin. However, the high doses required for preventing the flush makes this approach for inhibiting the flush impractical for long-term treatment with nicotinic acid. The new extended release preparation of nicotinic acid [11,12] gives rise to much less flush than IR nicotinic acid [11,12] and has the same broad spectrum lipid effects as IR nicotinic acid. It is noteworthy that

there is ongoing an intensive research on the mechanisms behind the flush with focus on the newly discovered nicotinic acid receptor as well as the prostaglandin D2 receptor [9,10].

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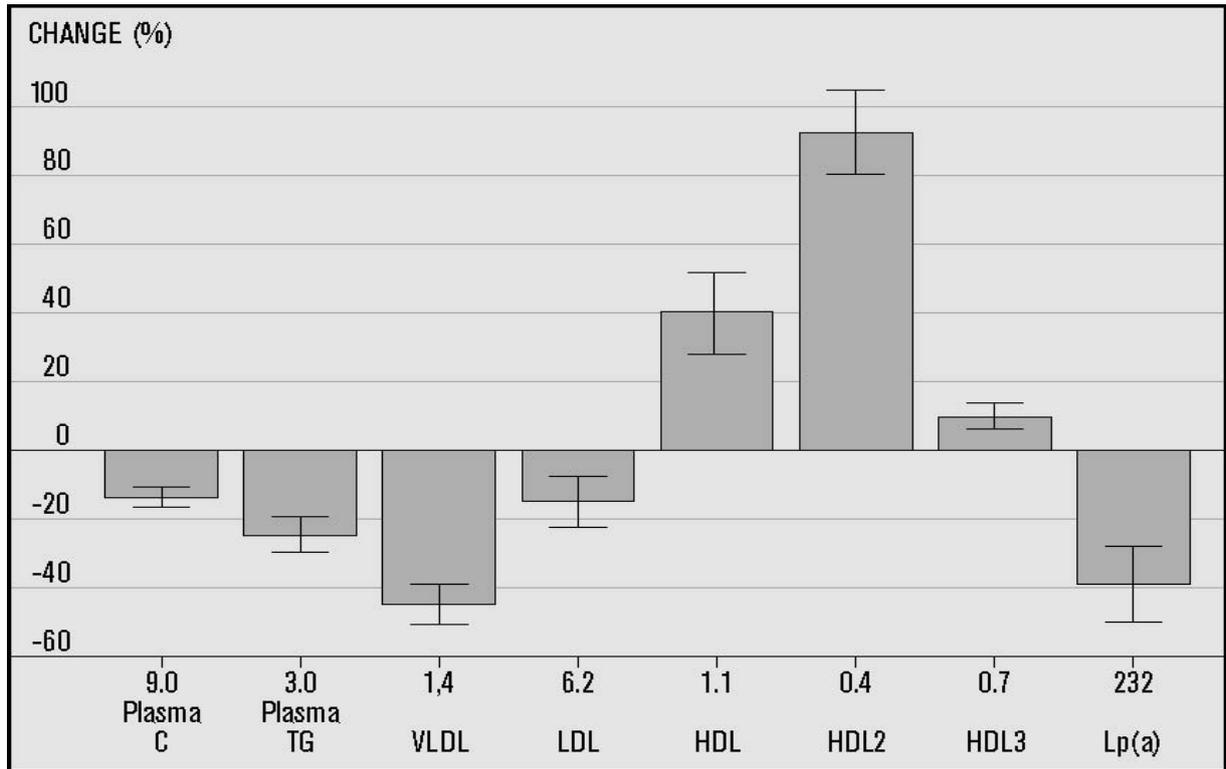


Figure 1. Effect of nicotinic acid (4 grams daily for 6 weeks) on plasma lipids, lipoprotein cholesterol and Lp(a) (mg protein/L) in dyslipidemic patients. Mean \pm SEM. Data from Carls LA et al. Pronounced lowering of Lp(a) in hyperlipidemic subjects treated with nicotinic acid. *J Intern Med* 1989;226:271-6.