

Nicotinic acid, its mechanism of action and pharmacological effects

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ABSTRACT

Nicotinic acid has a great ability to change the plasma levels of various lipids and lipoproteins. Its ability to increase the plasma concentration of HDL lipoprotein cholesterol has created interest in researchers regarding pharmacological potent of nicotinic acid. Along with great pharmacological benefits, nicotinic also encounters some side effects that are not pleasant especially strong cutaneous vasodilation called flushing. Based on the insights in to the mechanism of action of nicotinic acid new strategies are currently being developed to maximize the potential of drug. In this paper pharmacokinetic, administration, contradictions, adverse effects, monitoring, toxicity are reviewed for nicotinic acid.

Keywords: *nicotinic acid, flushing, vitamin B, HDL lipoprotein, nicotinamide*

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1. Introduction

Nicotinic acid belongs to vitamin B complex. Nicotinic acid is also called as Niacin, by definition niacin means nicotinic acid (pyridine-3-carboxylic acid), nicotinamide (nicotinic acid amide and pyridine-3-carboxamide), and derivatives. These compounds takes an important role as they are precursors of the co-enzymes nicotinamideadenine dinucleotide and nicotinamide adenine dinucleotide phosphate. Vitamers of niacin are found in all foods from plant based and animals. Some foods which have balanced protein may have niacin in high amounts because of the contribution of tryptophan. So there will be deficiency of it seen in situations of malnutrition, poverty and chronic alcoholism. At the levels of pharmacological it is supplemented compounds of niacin can give more health benefits like fighting against cardiovascular disease, neurological problems, diabetes, and other skin disease.

Combination of nicotinamide and nicotinic acid is called Niacin- a B vitamin, and it is a pharmacotherapeutic agent which was being used since 1955, making it the oldest hyperlipidemic agent [1]. This vitamin plays an important role in protecting neural health and saving from neuronal death, which makes it more important in the functioning of central nervous system [2].

Use of niacin is extensive to reduce the total cholesterol, low density lipoprotein, triglycerides, and very low density lipoproteins (VLDL) whether it's being used alone or in combination with stain medication like hydroxymethyl glutaryl coenzyme. One of the important pharmacological agent to increase plasma high density lipoprotein HDL is niacin [3,4]. Patients who has mixed dyslipidemia or diabetes mellitus, many studies proved that niacin has the capability to counterbalance cardiovascular risk, and therefore is highly used to reduce cardiovascular mortality and morbidity, particularly when used with statin drugs [4].

The two unique and pronounced lipid-modifying effects of nicotinic acid, in addition to the lowering of cholesterol (LDL) and triglycerides (VLDL), are the raising of HDL cholesterol and the lowering of Lp(a). Both effects are of clinical significance as they lead to a diminished risk for atherosclerotic CVDs.

Turnover studies have indicated that the levels of HDL in blood, to a large extent, are regulated by the fractional catabolic rate (FCR) of apolipoprotein A-I (apo A-I), the major protein component of HDL [76]. Nicotinic acid has been shown to reduce FCR of apo A-I by decreasing hepatic removal of apo A-I without affecting the uptake of cholesterol esters from the HDL particles into the liver [77]. This mechanism may be one of the explanations for how nicotinic acid raises plasma levels of HDL. An additional mechanism that may raise the levels of HDL cholesterol is the stimulation of the expression of the membrane cholesterol transporter ABCA 1 protein induced by nicotinic acid.

The protective role of HDL in the development of clinical atherosclerosis comes from several pieces of evidence.

- Increasing HDL cholesterol levels are strongly associated with decreasing incidence of CHD.
- Low HDL cholesterol is common in CHD patients.
- HDL promotes RCT by transporting cholesterol from tissues to the liver.
- Trials increasing HDL cholesterol levels have decreased incidence of CHD.
- Infusion of 'synthetic HDL' stimulates RCT, increases cholesterol elimination from the body and reduces coronary artery atheroma volume.

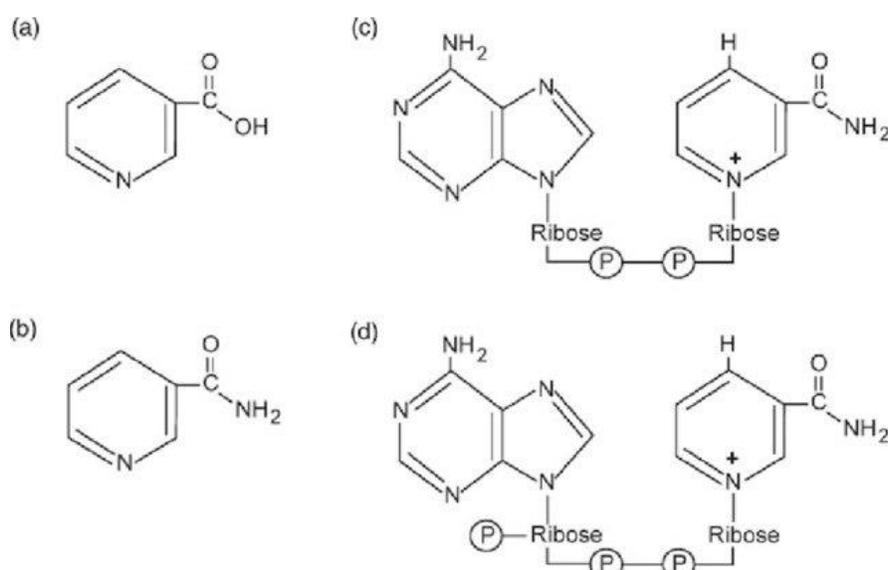


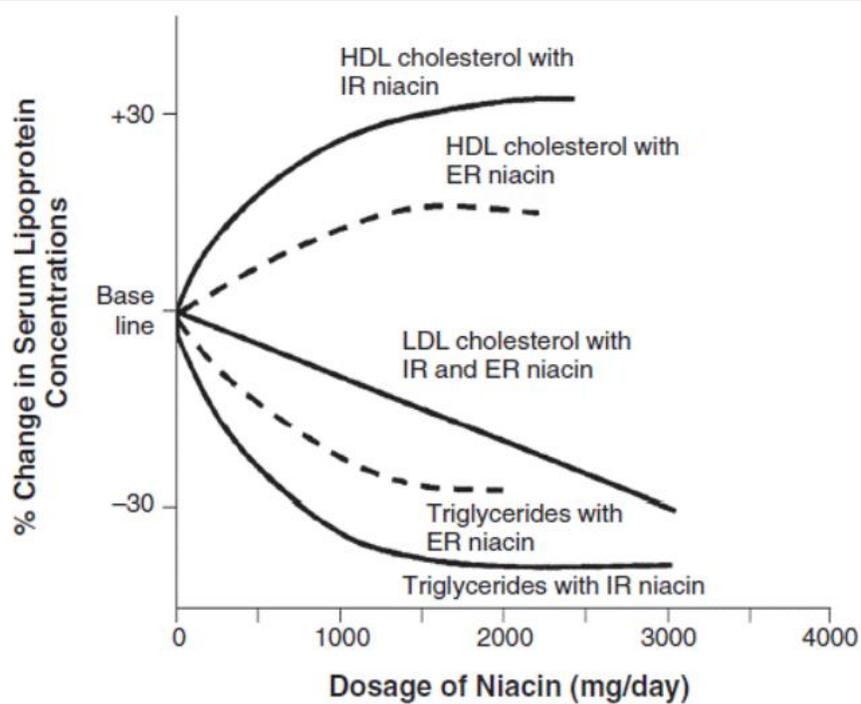
Fig. 1. niacin compounds: Chemical structures a. nicotinamide b. nicotinic acid c. nicotinamide adenine dinucleotide d. nicotinamide adenine dinucleotide phosphate.

Niacin still has some properties that are still not yet uncovered, some of the studies on the nicotinic acid are [5-14]. Use of niacin helps in premature aging, incidence of cardiovascular events, neurological disorders that are age related like:

1. Alzheimer disease
2. Huntington disease
3. Amyotrophic lateral sclerosis
4. Muscular atrophy
5. Parkinson disease
6. Squamous cell carcinoma
7. It is also used in treating diabetic encephalopathy, malignant glioma, schizophrenia, hyperphosphatemia in arthritis and kidney disease, neurodegenerative diseases.
8. Metabolism regulation and circadian rhythm through sirtuins
9. Regulation of Intracellular calcium

2. Pharmacological Properties:

Nicotinic acid blocks hepatic catabolic uptake of HDL particles which contains apolipoprotein A-I and by reverse augmenting cholesterol levels, increases the HDL- C levels. The proportion of HDL larger particles are increased which results in overall HDL particle size increase.



IR = immediate-release niacin

ER = prescription extended-release niacin

Figure 2: Effects of immediate-release niacin vs. prescription extended release niacin on lipids.

An improvement in endothelium-dependent vasodilation is seen in patients with coronary artery disease when there is an increase in HDL-C levels. From the peripheral adipose tissue to the liver, nicotinic acid reduces the mobilization of free fatty acids and thereby reducing the triglycerides and very low-density lipoprotein (VLDL) particles. Overall nicotinic acid increases the average number of LDL particle size and reduces the number of low density lipoprotein (LDL).

Differentiation between function of the liver and the damage of the liver should be made at the outset. The latter one manifests itself by showing changes structurally upon microscopic examination or gross, whereas the study of function of liver is usually carried out with battery of tests like BSP, cephalin flocculation, alkaline phosphatase level and serum protein concentration. There are six cases of liver damage cases that has happened with the use of nicotinic acid for therapy reported by [41]. but these studies lack the proof that nicotinic acid therapy is the one caused the liver involvement. In other studies where an extensive evaluation is done regarding liver when the nicotinic acid therapy is being done the studies have concluded that evidence of hepatic dysfunction was most frequently found in BSP test. This abnormality was accompanied by abnormalities in alkaline phosphate and serum transaminase levels. Also it seemed like in most cases the dysfunction represented disturbances in enzyme reactions without organic hepatocellular changes that can be demonstrated microscopically.

Niacin is available in two chemical forms. Nicotinic acid is only used for peripheral vascular disease and hyperlipoproteinemia. The other form nicotinic acid and nicotinamide also called as niacinamide is used for nutritional supplements. Oral extended niacin tablets are usually available in 250mg, 500mg, 750mg 1000 and 3000mg. To reduce LDL cholesterol a dose of 1 to 3 grams per day are used, and is the same for increasing serum HDL cholesterol. Niacin with modified release and crystalline immediate release showed same results in the research [5].

Immediate release tablets are available in the dosage forms starting from 50mg to 500mg. When taking the initial dose it should be as low as possible, so that adverse effects can be reversed, and its preferable to give no more than 500mg for the course of four weeks depending on response of patient and tolerance.

It is observed that insulin resistance induced is reversed and also plasma FFA rapid reduction is reduced with niacin's acute administration [18].

Patients who are taking niacin should not take alcohol as it might increase side effects like flushing and pruritus. As there is an increase in the risk of hepatotoxicity it is not recommended that patients who have severe alcohol history should not take niacin therapy. The biological half life of nicotinic acid is 1 to 3 hours. Author [15] has developed dissolution controlled system for nicotinic acid using natural phenolic antioxidant polymer. Using this approach, stability is achieved for drug levels in plasma with the help of

slow drug release over an extended period of time. Formulations F4 and F5 were calculated using this approach and a percentage of 97.7 is achieved for 11 hours and F5 has achieved a percentage of 97.2 for 12 hours. Through this approach it was observed that rather than conventional dosage forms controlled release tablets of NA has achieved better patient compliance.

Researcher [37] had demonstrated that administration of nicotinic acid for 2 to 3 weeks at a rate of 3gms daily caused a reduction in total amounts of serum lipids. Researcher [37] also demonstrated that there is reduction in total fatty acids is also seen and these are triglycerides. But other researcher also has found that phospholipids are not changed with therapy of nicotinic acid, that results in cholesterol phospholipid ratio.

Niacin type	Other names	FDA approval	Absorption	Effect on lipids	Clinical profile
Immediate-release	Crystalline, Plain	No	Less than 1 hour	Yes [16-21]	Highest rates of flushing
Prescription extended-release	Niaspan	Yes	6-8 hours	Yes [21-28]	Less flushing
Time-release	Wax-matrix	No	Similar to Niaspan [16]	Yes [29-33]	Less flushing
Time-release	Controlled-release, Long-acting, Sustained-release, Prolonged-release	No	Over 12 hours, but highly variable	Less effective than immediate-release or extended release niacin	Highest rates of hepatotoxicity
"No flush" or "flush free"	Zero-Flush	No	Unknown	No effect on lipids [34,35]	Contains no free/active niacin

Table 1: Niacin: the evidence, clinical use, and future directions [15]

3. Common reactions of Nicotinic acid are:

Flushing is the of the major side effects of niacin. Niacin also causes pruritus and sensation of burning usually limited to chest and face. It might last for about twenty to thirty minutes. The severity of this side effect reduces along with the time as well as frequency [5]. This side effect can be treated with having aspirin thirty minutes before taking niacin. Laropiprant which is a potent and antagonist of prostaglandin D2(PGD2)-receptor subtype-1 will help lower the side effects of nicotinic acid and also allow optimal pharmacological dosing if needed. Another reaction of taking niacin is its effect on patients who has dyslipidemia in controlling glycemia, regardless of their situation in terms of having diabetes mellitus and undergoing niacin therapy. This is the case whether niacin is being taken alone or together with stain medications.

In patients who has dyslipidemia and non-diabetic, when they are treated with niacin for a time period of five years with or without laropiprants, it was observed that 34% of the patients are associated with risk of developing diabetes. In patients with diabetes nicotinic acid proved to increase fasting glycemic levels. In patients with diabetes or metabolic syndrome it is recommended to avoid niacin therapy. Some other side effects also include dyspepsia, gastrointestinal disorders, hypotension hyperuricemia, paresthesia's elevation in AST and ALT, and vomiting.

4. Serious adverse reactions of nicotinic acid:

Peptic ulcer disease, arrhythmias, anaphylaxis, hepatotoxicity, hepatic necrosis, fulminant, macular edema. Laboratory monitoring is recommended in patients on niacin therapy due to its diverse side effects. In pre-diabetes or diabetic patients, frequent monitoring of blood glucose is necessary as niacin can increase fasting blood glucose.

Patients who are on diabetic medication like insulin, albiglutide, acarbose, and glipizide needs to have monitors for glucose levels in blood as niacin has antagonistic effect on blood glucose. Niacin causes antagonist effect on gout medications like allopurinolas it causes increase in uric acid.

With blood pressure medications, niacin exerts additive reaction and the pressure medications include amlodipine clozapine, diltiazem, bisoprolol. Niacin also exert additive reactions with opioids like morphine, tramadol, oxycodone and methadone and with antipsychotics (quetiapine, risperidone) phosphodiesterase type 5 inhibitor (tadalafil) and all this leads to hypotension. For this reason it is good to check blood pressure frequently. Niacin may decrease antihyperlipidemic efficacy when combined with beta blockers.

There is an increase in bleeding with the use of niacin. There is a reduction in the platelets count is also seen which is around 11% reduction with 2000mg of niacin, also there is an increase in prothrombin time which is approximately 4%, which leads to bleeding, particularly when combined with anticoagulants like alacizumab, apixaban and warfarin. So it is good to have blood coagulation test to be done on a routine basis.

Niacin when used in combination with diazoxide causes an additive effect which can lead to hyperglycemia. Patients also needs to monitor the phosphorous levels as use of niacin can cause decrease in the levels of phosphorus which is around 13% decrease with an average use of 2000mg, and so patients will be at risk of hypophosphatemia. This could potentially harm while nursing a baby, as niacin can pass into breast milk, and so patients who are breastfeeding should avoid the drug usage.

Acidity of nicotinic acid is another side effect of it, when given in larger doses. Researcher [38,39] demonstrated that the absorbability is improved in men when esterification of nicotinuric acid is done. This indicated esterase's in intestine are not enough active to hydrolyze ethyl nicotinurate prior to it being absorbed. Also it was demonstrated that prior to them being excreted in urine ethyl nicotinurtae was hydrolyzed by tissue or blood enzymes. Figure 3 shows that, during the first round of experiment 3gm of nicotinic acid in the form of ethyl nicotinate were administered daily and during the second round of 3gms of nicotinic acid was administered, and the studies pointed out that ethyl nicotinate is absorbed and metabolized to methylated products in a manner analogous to nicotinic acid. Ethyl nicotinate was effective in lowering serum cholesterol as nicotinic acid and in some patients flushing side effected seemed to have minimized, even though in other patients the side effects were seen similar to those observed with nicotinic acid therapy. Researcher [40] in their studies reported that hypo cholesteremic effect of nicotinic acid may be due to the increase in oxidation of cholesterol. This study contradicted the other studies that were carried out in man in which it was reported that the administration of nicotinic acid was without significant effect on the excretion of bile acids or sterols.

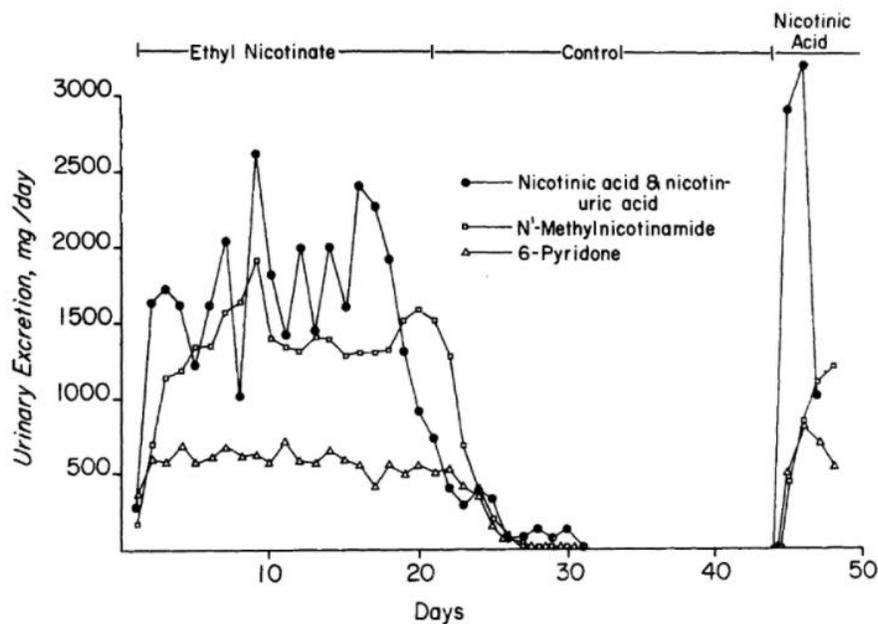


Figure 3: Urinary excretion of nicotinuric acid and nicotinic acid, N¹-methyl-nicotinamide and N¹- methylnicotinamide-6-pyridone are plotted against time in days.

5. Tolerability

Nicotinic acid is generally considered as tolerable as the adverse reactions caused by it are mild to moderate in intensity and transient in nature. The most common adverse effect is flushing and sometimes accompanied by gastrointestinal symptoms and other cutaneous reactions. Flushing associated with nicotinic acid decreases over time and was associated with low incidence of treatment discontinuation. The increase with IR nicotinic acid related flushing is relatively lower than PR nicotinic acid flushing.

PR nicotinic acid caused reversible and small elevation in liver transaminases, but there is no significant hepatotoxicity seen. In a similar way there is no instance of clinical gout is seen in the uric acid elevated levels that are associated with recommended PR nicotinic acid levels. There is a small but significant amount of increase in the levels of glycosylated hemoglobin are seen in patients with dyslipidemia and diabetes type 2 and are taking treatment with nicotinic acid. In the course of sixteen weeks in most of the patients fasting blood glucose levels are controlled.

With PR nicotinic acid the incidence of discontinuing the treatment and adverse events is higher than compared to lovastatin to rosuvastatin, due to the flushing adverse effect caused by PR nicotinic acid. The overall tolerability of PR nicotinic acid is similar to gemfibrozil. When PR nicotinic acid is combined with statins and administered to patients there is no new adverse effects of myopathy are seen.

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