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Review Article

ASPIRIN AND NICOTINIC ACID AS TWO FACES OF SAME COIN IN THE TREATMENT OF DYSLIPIDEMIA

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ABSTRACT
Globally cardiovascular diseases are believed to be the no.1 cause of death. According to the current estimates of World Health Organisation, approximately one-third of all deaths (16.7 million people) around the globe resulted from cardiovascular diseases. Eighty percent of these deaths were reported from low and middle income countries. The main intention of writing this review article is that, India being the second most highly populated country characterized by a majority of low and middle income population, the need for an effective treatment for this devastating disease both cost and efficacy wise is most desired. Since a long time, antidislipidemic agent nicotinic acid has been continuously under consideration to tackle the cardiovascular diseases by treating dyslipidemia. But its use has been limited due to its notorious yet harmless side effect of flushing. Now the focus of attention would be to use nicotinic acid by cleverly handling the flush. At this adjuncture the entry of acetyl salicylic acid (Aspirin) has been taken to give the best result. No doubt the major intention to take aspirin (low dose) with the combination of major drug nicotinic acid is to reduce nicotinic acid -induced flushing, but its associated properties or remedies as you may tell are more equally supportive to the very treatment of cardiovascular diseases itself. Hence it may be construed that aspirin and nicotinic acid are nothing but the two sides of the same coin in the treatment of dyslipidemia. Hence the hypothesis "People with heart disease should be on aspirin anyway".
KEYWORDS: Antidislipidemic agent; acetyl salicylic acid; cardiovascular diseases, dyslipidemia, flushing and nicotinic acid.

INTRODUCTION

Dyslipidemia is a disorder of lipoprotein metabolism, which includes a number of abnormalities such as hypercholesterolemia and hypertriglyceridemia. Low density lipoprotein (LDL) cholesterol has long ago been recognized as an important risk factor for coronary heart disease (CHD). Lipoprotein(a) (Lp(a)) is an independent risk factor for all major forms of clinical atherosclerosis.[1] In the 1960s and 1970s the role of other components of dyslipidaemia, including raised levels of triglycerides[2,3] and low levels of High density lipoprotein (HDL) cholesterol[4] were shown by observational studies to be risk factors for CHD. Framingham later confirmed that both high triglycerides[5] and low HDL cholesterol[6] are risk factors for CHD. Studies suggest that CVDs will become the most important cause of disability in the future. Some of the major reasons attributed to CVDs are Commercialization, change in life style and eating habits, obesity, hypertension, diabetes, elevated cholesterol level, family history of CHD, and increasing stress levels. According to INTERHEART, a global case-control study of risk factors for acute myocardial infarction (MI), the most strongly predictive cardiovascular risk factor for MI was dyslipidemia.[7]

India being the second most highly populated country characterized by a majority of low and middle income population the need for an effective treatment for this devastating disease both cost and efficacy wise is most desired.[8]

Nicotinic acid (NA) is a potent lipid-modifying drug and has been shown to reduce total mortality, major coronary events, progression of atherosclerosis, coronary artery disease (CAD) mortality, need for revascularization, and incidence of stroke in high risk and CAD patients.

Today cholesterol-lowering medications are the 2nd most prescribed drug class; (behind only pain relievers).[9] Since a long time, NA has been continuously under consideration to tackle the CVDs by treating dyslipidemia. But its use has been limited due to its notorious yet harmless side effect of flushing. Now the

focus of attention would be to use NA by cleverly handling the flush. At this adjuncture the entry of acetyl salicylic acid (ASA) has been taken to give the best result. May it be recalled that "People with heart disease should be on ASA anyway" .

NA-induced flushing does not warrant the use of other drugs to solve the problem of flushing. Rather NA itself can handle the flush. That is to say the mere prolonging of the release mechanism of NA can if not eliminate but definitely reduce the severity of the flush effect to a large extent. The usual prescription for NA is always accompanied with ASA invariably so as to be taken half an hour before the administration of NA. This means there is a duplication of efforts of taking two concomitant drugs one following the other. Instead, the designing of a single dosage form that can give a combination of the two separate drugs (ASA and NA) with exclusivity of release mechanism is the theme of the present research.

Role of Acetyl salicylic acid (Aspirin) in cardiovascular events and NA-induced flushing

Acetylsalicylic acid (ASA) is also known as Aspirin. From times in memoriam ASA has been used as an analgesic, antipyretic and also as a panacea to many illness like pericarditis, acute myocardial infarction[10,11] heart attacks, strokes, blood clot[12] and migraine.[13] Nevertheless it is a highly effective inhibitor of prostaglandin synthesis, the best choice to prevent or reduce the severity of NA-related flushing.[14,15] Since ASA can inhibit and modify the COX-2 enzyme it can be used to permit the use of NA without flushing.[16] Aspirin sales revived considerably in the last decades of the twentieth century, and remain strong in the twenty-first century, because of its widespread use as a preventive treatment heart attacks and strokes. This paragraph may be magnified to the extent relevant for the present study in the forthcoming headings to give a short and to the point explanation.

Prevention of heart attacks and strokes

There are two distinct uses of ASA for prophylaxis of cardiovascular events: primary prevention and secondary prevention. Primary prevention is about decreasing strokes and heart attacks in the general population of those who have no diagnosed heart or vascular problems. Secondary prevention concerns patients with known cardiovascular disease. Low doses of ASA are recommended for the secondary prevention of strokes and heart attacks. For both males and females diagnosed with cardiovascular disease, ASA reduces the chance of a heart attack and ischaemic stroke by about a fifth. This translates to an absolute rate reduction from 8.2% to 6.7% of such events per year for people already with cardiovascular disease. Although ASA also raises the risk of hemorrhagic stroke and other major bleeds by about twofold, these events are rare, and the balance of ASA effect is positive. Thus, in secondary prevention trials, ASA reduced the overall mortality by about a tenth. For persons without cardiovascular problems the benefits of ASA are unclear. In the primary prevention trials ASA decreased the overall incidence of heart attacks and ischaemic strokes by about a tenth. However, since these events were rare, the absolute reduction of their rate was low: from 0.57% to 0.51% per year. In addition, the risks of hemorrhagic strokes and gastrointestinal bleeding almost completely offset the benefits of ASA. Thus, in the primary prevention trials ASA did not change the overall mortality rate.[17]

1) Treatment in post coronary artery bypass graft

The coronary arteries supply blood to the heart. ASA is recommended for 1 to 6 months after placement of stents in the coronary arteries and for years after a coronary artery bypass graft.

2) Treatment in post coronary artery stenosis

The carotid arteries supply blood to the brain. Patients with mild carotid artery stenosis benefit from ASA. ASA is recommended after a carotid endarterectomy or carotid artery stent. After vascular surgery of the lower legs using artificial grafts which are sutured to the arteries to improve blood supply, ASA is used to keep the grafts open.

3) Suppression of prostaglandins and thromboxanes

ASA's ability to suppress the production of prostaglandins and thromboxanes is due to its irreversible inactivation of the cyclooxygenase (PTGS) enzyme. Cyclooxygenase is required for prostaglandin and thromboxane synthesis. ASA acts as an acetylating agent where an acetyl group is covalently attached to a serine residue in the active site of the PTGS enzyme. This makes ASA different from other NSAIDs (such as diclofenac and ibuprofen), which are reversible inhibitors.

Low-dose, long-term ASA use irreversibly blocks the formation of thromboxane A_2 in platelets, producing an inhibitory effect on platelet aggregation. This anticoagulant property makes ASA useful for reducing the incidence of heart attacks.[18] 40 mg of ASA a day is able to inhibit a large proportion of maximum thromboxane A_2 release provoked acutely, with the prostaglandin I2 synthesis being little affected; however, higher doses of aspirin are required to attain further inhibition.[19]

Prostaglandins are local hormones produced in the body and have diverse effects in the body, including the transmission of pain information to the brain, modulation of the hypothalamic thermostat, and inflammation. Thromboxanes are responsible for the aggregation of platelets that form blood clots. Heart attacks are primarily caused by blood clots, and low doses of ASA are seen as an effective medical intervention for acute myocardial infarction.

Nicotinic Acid

Nicotinic acid (NA) was first reported to affect lipids in 1955,[20] is one of the oldest drugs used to treat Dyslipedemia and was most versatile in that favorably affect virtually all lipids parameters. NA was the best agent available for increasing HDL-C (increments of 30% to 40%); it also lowers Triglycerides 35% to 45% (as effectively as fibrates and the more potent statins) and reduces LDL-C levels by 20% to 30%.NA is also the only lipid-lowering drug that reduces Lp(a) levels significantly, by about 40%. The pharmacological doses of regular (crystalline) NA (>1 g per day) used to treat Dyslipedemia are almost completely absorbed, and peak plasma concentration (upto 0.24mM) are achieved within 30 to 60 minutes.[14] The National Pharmacy Cardiovascular Council (NPCC) recommends NA as first-line therapy for patients with hypertriglyceridemia (without diabetes) and for patients with isolated low HDL-C. Furthermore, the NPCC recognizes that NA's favorable effects on the overall lipid profile make it a valuable treatment option for patients with atherogenic or mixed dyslipidemia, a condition characterized by elevated LDL-C and triglycerides.[21]

NA has two faces. One is the vitamin potent in milligram doses; the other is the broad-spectrum lipid drug potent in gram doses. NA in gram doses lowers plasma cholesterol in normal as well as hypercholesterolaemic subjects. Of considerable interest is that nicotinamide (NAM) did not affect the plasma lipid levels. This is a remarkable observation as both NA and NAM, chemically quite alike, are nutritionally equivalent and known as vitamin B3. Both the acid and the amide are precursors to the coenzyme nicotinamide adenine dinucleotide which is a major electron acceptor in the oxidation of fuel metabolites. The unexpected difference between NA and NAM may be due to the fact that whilst NA is a powerful inhibitor of fat-mobilizing lipolysis in adipose tissue, this property is not shared by NAM.[22] The inhibition of lipolysis in adipose tissue resulting in a decrease in plasma free fatty acids (FFA) has been suggested to be a basic mechanism for the lipid effects of NA.[23] Hence NA is a potent lipid-modifying drug and has been named 'the broad-spectrum lipid drug.[24]

Effects of NA

1) NA and plasma lipids

From cholesterol to different types of hyperlipidemias: The 1960s witnessed a dramatic expansion in lipidology from dealing only with total blood cholesterol to comprise the six types of hyperlipidaemia of the Fredrickson/WHO classification system [25,26] presented in Table 1. An early study has also demonstrated that NA not only lowered cholesterol but also triglycerides, which percentage-wise were more lowered than cholesterol.

2) NA and plasma lipoproteins

a. VLDL and LDL: When the evaluations of the effects of NA were extended from plasma lipids to lipoprotein analyses, it was understood that, as expected, cholesterol lowering was, to a great extent, due to a lowering of LDL cholesterol and that the lowering of triglycerides was almost entirely caused by lowering of VLDL.

b. Small, dense LDL: The LDL fraction is heterogenous and comprises lipoprotein particles of different sizes. Small, dense LDL are considered to be the most atherogenic LDL particles,[27] carrying a high risk for clinical atherosclerosis.[28] Immediate-release as well as prolonged-release (PR) NA not only lower the total LDL cholesterol but also reduce the amount of small, dense LDL particles.[29]

c. Lipoprotein (a) [Lp(a)]: Lp(a) is an independent risk factor for all major forms of clinical atherosclerosis.[1] The usual lipid-lowering components such as diet, fibrates or statins do not affect elevated plasma concentrations of Lp(a).[30] However, NA has a pronounced lowering effect on elevated levels of Lp(a).[24]

d. Dyslipidaemia of diabetes: Diabetes is associated with a cardiovascular mortality which is about two to four times that of non diabetic subjects. Many risk factors contribute to clinical atherosclerosis in diabetic patients. However, dyslipidaemia and hypertension play a particularly important role. Diabetic dyslipidaemia is characterized by elevated plasma levels of triglycerides and low levels of HDL cholesterol but without major changes in LDL cholesterol. The lipid-modifying properties of NA makes this drug tailored for treatment of diabetic dyslipidaemia.[31-33]

e. HDL Cholesterol: In the 1950s Parsons and Flinn[34,35] had already shown that treatment with NA not only lowered total and LDL cholesterol but also

increased the concentration of cholesterol in the Alpha-lipoprotein fraction, i.e. HDL cholesterol. It is now generally accepted that NA is the most powerful drug for raising the concentration of HDL, in particular, the subspecies HDL_2.

3) NA and HDL

a. The pros for raising HDL for prevention of coronary heart disease (CHD): Low levels of HDL are firmly established as a major risk factor for CVD, and HDL is presently the focus of attention as a promising therapeutic target to reduce CVD.[36]

The two unique and pronounced lipid-modifying effects of NA, 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.[37] NA 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.[38] The protective role of HDL in 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.

Many observational studies have shown that low HDL cholesterol levels are present in high frequency in survivors of myocardial infarction. Two important prospective cardiovascular studies, The Framingham study in USA[6] and the PROCAM study in Europe,[39] clearly showed that low HDL is a risk factor for the occurrence of CHD.

b. Protective effects of HDL, particularly in reverse cholesterol transport (RCT): Raising HDL can be of benefit in the treatment and prevention of atherosclerosis by stimulating RCT and diminishing atheroma volume.

HDL has a number of effects contributing to its property as a protective factor for clinical atherosclerosis. The most important of these is the role of HDL in RCT. RCT starts with the cholesterol esters in the foam cells in the arteries (the hallmark of atherosclerosis) and ends up with the faecal steroids (elimination of cholesterol from the body). In addition to its major role in RCT, HDL stimulates other processes that may contribute to its protective actions such as protection against inflammation, protection against oxidation (especially of LDL), protection of endothelial function, protection of NO-production and protection against infections.[40] Moreover Parsons and Flinn have reported that subcutaneous cholesterol deposits (xanthoma tuberosum) were reduced during treatment with NA. This is the first report of a lipid modifying drug that reduces xanthomata, an effect that might reflect removal of cholesterol from tissues by means of HDL-mediated RCT.

NA in combination treatments

The increasing awareness of the risk for CVD associated with low HDL cholesterol and for the protective role of this lipoprotein for manifestations of clinical atherosclerosis has focused interest on the use of NA as an HDL-raising drug in combination with statins and other drugs primarily lowering LDL cholesterol.[41] The well-documented LDL cholesterol-lowering effects of statins and their beneficial effects on prevention of clinical atherosclerosis have made them drugs of first choice in the treatment of high LDL cholesterol. However, in the landmark studies with LDL lowering by statins in patients with high risk for CHD, such as 4S (Scandinavian Simvastatin Survival Study)[42] and HPS (Heart Protection Study),[43] the reduction in CHD events and mortality in high-risk subjects was never better than20–40%. Evidently, there is a need for improved treatment of the remaining 60–80% of the high risk population affected by CHD events, despite treatment with LDL-lowering statins. An option for the improvement of the lipid-modifying treatment with statins is to increase the levels of HDL cholesterol and decrease those of triglycerides as the statins only have moderate effects in this regard. For this purpose, nicotinic acid, with its striking HDL-raising and triglyceride lowering properties, is an ideal drug to combine with statins. Indeed, a dual component, single tablet containing a statin and an extended (PR) formulation of NA (Advicor, KOS pharmaceuticals) is registered for lipid modification in the USA.

Prolonged-release NA

NA as a lipid-modifying drug was, from the beginning, used as plain NA, i.e. in crystalline, IR form. But

unfortunately IR NA leads to a very disturbing side effect of flushing due to which its use has been limited. For this reason sustained-release (SR) formulations of NA were developed in the hope of diminishing the flush. Unfortunately, however, the SR preparations were associated with hepatotoxicity and have been abandoned in clinical use. A prolonged release (PR) preparation of NA, in USA called extended-release (ER), with absorption rates between IR and SR preparations was then developed.[44] It has been marketed in the USA as Niaspan and has just been registered in Europe. The typical NA side effects are not completely absent with the PR preparation. The flush, however, occurs much less frequently and intensely with PR NA than with IR NA. The PR NA is prescribed in doses of around 1–2 g once daily at bedtime to minimize the flushing effect during daytime.

NA and flushing

NA is highly effective in the management of dyslipidemia. Despite the versatility of NA in treating a range of lipid disorders and the compelling clinical evidence of mortality reduction, this medication has not become a first-line treatment. One reason for its underuse is the side effects. After administration of NA in doses as low as 100 mg, cutaneous symptoms, including redness, itching, burning, and paresthesias, occur.[45]This "NA flush" begins as soon as 10 to 15 minutes after ingestion and lasts 30 to 60 minutes. The flushing is thought to be most intense when levels of free NA are increasing in the serum.[46] Fortunately, both the frequency and severity of flushing episodes decrease with repeated doses of NA. Although many patients stop flushing within 1 week of initiating therapy, this side effect has contributed to discontinuance rates higher than 40% in some clinical series.[47] Flushing with NA is mediated by prostaglandins and as ASA is a highly effective inhibitor of prostaglandin synthesis, there is a rationale for its use to prevent or reduce the severity of NA-related flushing.

Findings from animal studies have subsequently suggested the involvement of prostaglandins.[48,49] A study by Morrow and colleagues identified cutaneous release of prostaglandin D_2 as the immediate cause of NA-induced flushing and established elevated levels of the prostaglandin D_2 metabolite 9α,11β-PGF_2.[50] *Ex vivo* data also showed significant elevations in prostaglandin E_2, thromboxane B_2 and leukotriene E_2 synthesis following NA administration (2.5g).[51] The involvement of G-protein-coupled receptor GPR109A in the flushing response to NA has recently been elegantly confirmed by studies in a variety of animal genetic models by Benyó and colleagues.[52] Knockout mice lacking COX-1 demonstrated no flushing response to NA, while those lacking endothelial nitric oxide synthase (eNOS) retained the wild-type response, indicating that NA-related flushing depends on prostanoid synthesis and is unconnected to the production of endothelial nitric oxide. Mice lacking PUMA-G (the murine form of GPR109A) showed no flushing response to NA, although the response could be elicited using prostaglandin D_2. Interestingly, the role of immune cells in NA-related flushing was also shown by Benyó and colleagues using bone marrow chimaeric mice.Transplantation into irradiated PUMA-G-deficient mice of bone marrow from wild-type mice, but not of that from PUMA-G-deficient donors, was able to restore NA-related flushing. The cell type responsible for NA-related prostanoid formation remains, however, to be identified. During clinical use of NA, flushing, together with other less-common cutaneous side effects, including rash, tingling and itching, has been reported in up to 100% of patients who were using older formulations of the agent.[53] Although tolerance to these side effects does develop with continued use, many patients discontinue NA treatment.

NA is rapidly and extensively absorbed after oral administration, with plasma concentrations reaching a maximum after 30-60 min with crystalline ('immediate-release') NA.[54] Metabolism of NA occurs by two different pathways: a high-capacity conjugative pathway involving glycine and leading to the metabolite nicotinuric acid responsible for flush and a low-capacity amidation pathway, leading to nicotinamide adenine dinucleotide and other nicotinamide derivatives responsible for hepatotoxicity.[55-58] The relative importance of these two elimination pathways, and thus the amounts of each metabolite group, depend on the pharmacokinetics of the NA formulation used. Much attention has been paid to optimizing NA delivery to achieve a balance between the two pathways and therefore to reduce flushing and avoid hepatotoxicity.

1) Reducing the severity of NA-induced flushing

Flushing after NA administration is an important limitation to the utility of an agent that has clinically important and beneficial effects on lipids and lipoproteins. Significant advances have been made in recent years with newer formulations of NA; for example, the 'prolonged-release' NA reduced the incidence of flushing within the first 2 weeks of treatment by more than 50% compared with 'immediate-release' NA.[59]

There is good supportive evidence for the value of ASA in reducing the severity of NA-related flushing, and the degree to which this is acknowledged is reflected not

only in long-standing NCEP recommendations [60] but also in the relatively large number of studies reporting the inclusion of ASA in the treatment regimen and in advice given to patients to take ASA 'as needed' to reduce flushing.

2) Dose of ASA for reducing flushing

While a recommendation to use ASA is supported by both pharmacological evidence and experience from clinical studies, it is more difficult to deduce a relationship between ASA dose and the efficacy in reducing the intensity and/or frequency of flushing. Findings from one small study suggested that a dose as low as 80 mg might be ineffective.[61] A subsequent study, however, found that a 160 mg dose was as effective as a 325 mg dose. Meanwhile, most studies using ASA in the protocol used a 325 mg dose (where specified). The two prospective studies using lower doses (100 and 150 mg) provided no evidence from discontinuation rates that these lower doses of ASA were less effective than the higher 325 mg dose.[62,63] Discontinuation rates due to flushing were probably higher in a cohort study using 160 mg ASA, but no details are provided in the report of the study.[64]

3) Lipid benefits without the flush

NA is the most effective enhancer of HDL and it also lowers problematic triglycerides and LDL. It would be the drug of choice to lower cardiovascular risk associated with serum lipids, because it is cheaper and more effective than the alternatives, such as statins. NA has not been used more extensively, because of flushing. ASA can inhibit and modify the COX-2 enzyme and can be used to permit the use of NA without flushing.

4) Other agents used to reduce NA induced flushing

In order to avoid or reduce the cutaneous flushing resulting from NA therapy, a number of agents have been suggested for administration with an effective antihyperlipidemic amount of NA, such as

a. Guar gum as reported (U.S. Pat. No. 4,965,252).

b. Mineral salts (U.S. Pat. No. 5,023,245).

c. Inorganic magnesium salts (U.S. Pat. No. 4,911,917),

d. Non-steroidal anti-inflammatories, such as aspirin (PCT Application No. 96/32942).

e. These agents have been reported to avoid or reduce the cutaneous flushing side effect commonly associated with NA dividend dose treatment.

f. Another method of avoiding or reducing the side effects associated with IR NA is the use of SR formulations. SR formulations are designed to slowly release the active ingredient from the tablet or capsule, which allows a reduction in dosing frequency as compared to the typical dosing frequency associated with conventional or immediate dosage forms. The sustained drug release reduces and prolongs blood levels of the drug, and thus minimizes or lessens the cutaneous flushing side effects that are associated with conventional or IR NA products. SR formulations of NA have been developed, such as Nicobid® capsules (Rhone-Poulenc Rorer), Endur-acin® (Innovite Corporation), and a SR NA formulation containing two different types of hydroxypropyl methylcelluloses and a hydrophobic component (U.S. Pat. Nos. 5,126,145 and 5,268,181). Niaspan® (MERCK)

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Table 1: The Fredrickson/WHO classification of hyperlipoproteinaemias

Type of hyperlipidaemia	Lipid increased	Lipoprotein increased
I	Triglycerides [a]	Chylomicrons
II A	Cholesterol	LDL
II B	Cholesterol [a] and triglycerides	LDL and VLDL
III	Cholesterol [a] and triglycerides	Beta-VLDL (IDL and chylomicron remnants)
IV	Triglycerides	VLDL
V	Triglycerides [a] and cholesterol	Chylomicrons and VLDL

LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein; IDL, intermediate-density lipoprotein. a Massive elevation.