

Inositol Hexaniacinate: A Safer Alternative to Niacin

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Abstract

Niacin has long been prescribed for the treatment of various cardiovascular conditions, particularly the hyperlipidemias. It has been proven effective at lowering VLDL, LDL, total cholesterol and triglyceride levels while raising HDL levels. The side effects of niacin which may occur at the dosages often required for therapeutic efficacy, ranging from flushing and pruritus to hepatotoxicity and impaired glucose tolerance, often prove troubling for both patient and practitioner. The need for a safer approach to niacin supplementation has resulted in the investigation of niacin esters. One of the most widely studied of these is inositol hexaniacinate (IHN). In numerous trials it has been found to be virtually free of the side effects associated with conventional niacin therapy. Extensive research has found IHN to be effective in the treatment of hyperlipidemia, Raynaud's disease and intermittent claudication. A number of other conditions which respond favorably to niacin therapy such as hypertension, diabetes, dysmenorrhea and alcoholism bear further investigation.
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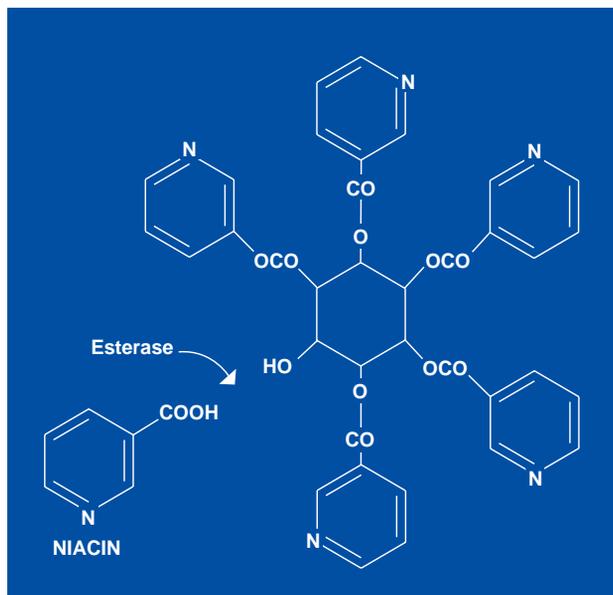
Importance of Niacin to Human Health:

Niacin (B3, nicotinic acid) is vital to cellular metabolism, principally through its role in the coenzymes, nicotine-adenine dinucleotide (NAD) and nicotine-adenine dinucleotide phosphatate (NADP), in oxidation-reduction reactions. Niacin is primarily metabolized in the liver to niacinamide (nicotinamide) and other derivatives. Niacinamide is, in turn, a precursor to NAD and NADP.¹ Due to its vasodilatory effects, niacin (but not niacinamide) has, for decades, been prescribed by orthodox and alternative practitioners alike for the treatment of cardiovascular disease, particularly the hyperlipidemias.¹⁻² In addition, the use of niacin for the treatment of peripheral vascular disorders including Raynaud's disease and intermittent claudication has been widely studied.³⁻⁶ Besides the use of niacin in therapeutic doses, there are certain fractions of the general population that may be deficient in niacin, requiring supplementation to prevent pellagra (the disease of niacin deficiency). These groups include alcoholics⁷ and the elderly.⁸

Adverse Effects of Niacin:

Although niacin has numerous therapeutic benefits, it may also result in a considerable number of side effects both acute and chronic, subjective and objective. The acute, subjective symptoms include flushing, particularly of the face and neck with pruritis and burning skin, GI complaints and weakness.⁹ These effects are due to histamine release from the mast cells, starting approximately 20 minutes after ingestion and lasting from one to one and a half hours.

FIGURE 1.



Side effects are often minimized by the addition of aspirin which may create further problems. Although there may also be a reduction of symptoms after several days by increasing the dose gradually and by taking the niacin with meals, many people discontinue its use before ever reaching optimal therapeutic

doses. Sustained-release niacin preparations may minimize flushing but result in more gastrointestinal complaints, according to at least one study.¹ Chronic conditions may also result from the use of niacin. These may include hepatotoxicity, hyperuricemia, glucose intolerance, ocular effects, exacerbation of peptic ulcer, postural hypotension, particularly in patients taking antihypertensive agents, and skin disorders including acanthosis nigricans.¹⁻² The ocular effects may include decreased vision, cystoid macular edema, periorbital edema, loss of eyebrows or eyelashes and superficial punctate keratitis. These may occur with the use of niacin in high doses and are reversible if it is discontinued.¹⁰ Niacin competes with uric acid for renal excretion with subsequent elevation of serum uric acid levels. On rare occasions, this may lead to the development of gout or uric acid kidney stones.¹¹

The hepatotoxic effects are perhaps of the most concern to those administering this therapy on a long-term basis. Abnormalities noted on liver function tests may include dose related increases in aspartate aminotransferase and alkaline phosphatase. Liver pathology may include cholestasis, hepatocellular disarray and nodular formation by fibrous tissue. Severe liver toxicity with regular niacin is quite

rare.¹ Coppola and Brady¹² reported on four cases of niacin-induced hepatotoxicity. All four were taking sustained-release niacin. Fulminant liver failure may occur with the use of high doses of sustained-release niacin as evidenced by the case of a 44-year-old male who developed liver failure after three days on 6

grams daily of timed-release niacin, reported by Mullin et al.¹³ He had previously consumed up to 6 grams daily of regular crystalline niacin. After 16 months on this regime his liver enzymes had remained normal. Gibbons et al.¹⁴ reported on the prevalence of side-effects of both sustained-release and regular niacin in a clinical setting. 110 patients in 133 separate trials were given nicotinic acid during a five year period. The results were that 43% of individuals given regular nicotinic acid and 42% of those receiving the sustained-release form were forced to discontinue treatment because of side-effects.¹⁴

Inositol Hexaniacinate: Biochemistry and Metabolism

Because of the therapeutic importance of this vitamin it is imperative that we explore safer and perhaps more effective forms of administration. One such form, and probably the most studied, is the hexanicotinic acid ester of meso-inositol, inositol hexaniacinate (IHN), also called inositol hexanicotinate or inositol nicotinate. The compound consists of six molecules of nicotinic acid and one molecule of inositol (See Figure 1).¹⁵ It is metabolized in the body into its component parts,

niacin and inositol (hexahydroxycyclohexane). In the United States it was first described by Badgett et al. in 1945.¹⁵ It appears that the compound is slowly metabolized, not reaching maximum serum levels for approximately 10 hours after ingestion.¹⁵ When IHN is administered orally to humans, the result is a sustained increase in the level of free nicotinic acid in blood and plasma.¹⁶ Pharmacokinetic studies have indicated that these esters are, at least in part, absorbed intact and hydrolyzed in the body with release of free niacin and inositol. The rise in niacin levels was more than could be explained by observation of the rate of hydrolysis of these esters in buffered solutions of various pHs, designed to simulate the gastric and intestinal juices. Therefore, it was assumed that another mechanism was involved. This was demonstrated by Harthon and Brattsand¹⁶ to be an active, enzymatic hydrolysis in the bloodstream.

Safety of Inositol Hexaniacinate

IHN appears to be safe and free of side effects at doses up to 4 grams. Welsh and Ede studied a group of 153 patients with a variety of conditions ranging from Raynaud's disease to psoriasis and reported not a single side effect, with doses ranging from 600 to 1800 mg daily. They compared this to patients with the same conditions receiving nicotinic acid. Approximately 1/3 of them reported one or more of the following symptoms: flushing, nausea, vomiting, giddiness and weakness. Furthermore, the IHN patients tolerated without side effects dosages 3 or 4 times larger than the nicotinic acid group.¹⁵ Numerous other investigators, studying the use of dosages of IHN in the range of 4 grams daily, reported not a single adverse reaction.^{3,17-19}

Therapeutic Applications of IHN

IHN has a fairly broad range of therapeutic applications. The most well researched conditions include the hyperlipidemias,

Raynaud's disease and intermittent claudication. Promising applications which bear further investigation include its use for stasis ulcers, dysmenorrhea, dermatitis herpetiformis, alcoholism, diabetes, cancer prevention and hypertension. These will each be addressed below.

Hyperlipidemia:

Numerous epidemiological studies, both prospective and retrospective, have demonstrated that hyperlipidemia is a major risk factor for the development of atherosclerosis. High levels of very low density lipoproteins (VLDL), low density lipoproteins (LDL), total cholesterol and triglycerides correlate positively with an increased risk for cardiovascular disease (CVD) while elevated levels of high density lipoproteins (HDL) convey cardioprotection.^{2,20}

Niacin, in doses up to 6 grams daily, has long been known to effectively reduce triglycerides, total cholesterol, and LDL cholesterol while at the same time elevating HDL levels^{1,2,21,22} Supplemental niacin will also reduce the risk of MI in patients with a previous history.²³ Niacin appears to effect blood lipids by a number of different mechanisms. It lowers LDL and triglyceride levels by decreasing VLDL synthesis in the liver. This decrease occurs as a chain reaction, beginning with the activation of the enzyme, phosphodiesterase and inhibition of adenylate cyclase activity by nicotinic acid. This in turn inhibits cAMP production in adipocytes.. There is a subsequent decrease in release of free fatty acids (FFA) from peripheral adipose tissue resulting in a decrease in FFA transport to the liver followed by a reduction of VLDL formation which results in a decrease in the LDL cholesterol fraction. The decrease in VLDL and LDL then leads to a decrease in serum triglycerides, phospholipids and cholesterol which generally combine with these lipoproteins.²⁴

Niacin also inhibits cholesterol synthesis from acetate in the liver and appears to

increase its degradation as well.²⁴ In addition, elevated blood levels of lipoprotein A have been studied as an independent risk factor for CVD.²⁵ Niacin appears to play a role by altering the function of lipoprotein A-I and reducing synthesis of lipoprotein A-II.² This is believed to result in an elevation of HDL levels.²

Another interesting effect of niacin is discussed by O'Keefe, Lavis and McCallister. The susceptibility of LDL to oxidative stress appears to be as or more important than actual levels of LDL cholesterol. It appears that LDL particles must be oxidized by free radicals before they become atherogenic. Relatively

small, dense LDL particles seem to be more easily oxidized than their larger, more buoyant counterparts. Niacin has been found to convert the smaller easily oxidized particles to the larger, oxidation-resistant LDL particles.²⁶

The wonders of niacin aside, the problem of side-effects in the doses often necessary to effect a change is significant. The prescription medications available for treatment of hyperlipidemia are also not without side effects. For a brief summary of these medications, mechanisms of action and potential side effects, see Table 1.

Table 1. Hypolipidemic Drugs: Mechanism of Action and Adverse Reactions

Category	Mechanism of Action	Adverse Reactions
Bile Acid sequestrants: (cholestyramine; colestipol)	decreases LDL by binding bile acids and increasing activity of LDL receptors	GI disturbances; may bind certain medications and fat soluble vitamins; decreased prothrombin
Nicotinic Acid	decreases FFA mobilization; decreases LDL and triglycerides by decreasing VLDL synthesis; increases HDL by decreased catabolism	flushing; pruritus; GI complaints; hepatotoxicity; hyperuricemia; impaired glucose tolerance
Inositol Hexaniacinate	assumed to be same mechanism as nicotinic acid with the addition of the lipotropic effects of inositol	No side effects reported
HMG-CoA reductase inhibitors: (fluvastatin; lovastatin; mevastatin; pravastatin; simvastatin)	decreases LDL by inhibition of HMC-CoA reductase; increases activity of LDL receptors	carcinogenicity; hepatotoxicity; elevation of creatine kinase; rhabdomyolysis; myositis; stomach ulcers
Fibric Acid derivatives: (bezafibrate; ciprofibrate; clofibrate; fenofibrate; gemfibrozil)	decreases triglycerides by increasing lipoprotein lipase activity; increases HDL	carcinogenicity; abdominal discomfort; gallstones; impaired glucose tolerance; hepatotoxicity; creatine kinase elevation
Probucol	decreases LDL by increasing non-receptor mediated LDL clearance	increase in QT interval; nonspecific GI complaints; reduced HDL; anemia

IHN appears to be a safer, effective alternative to many of the lipid lowering drugs currently in vogue. Dorner and Fischer¹⁷ reported statistically significant reductions of cholesterol without side effects in 16 hyperlipidemic patients treated with 400 mg IHN 3 times daily for one month followed by 400 mg 4 times daily for a total of 40 weeks. A study comparing IHN and nicotinic acid on blood lipid levels in hyperlipidemic Buscat rabbits demonstrated a marked reduction in total serum lipid levels at a daily dose of 30mg/kg body weight. The IHN treated group had a 62.2% reduction in total blood lipids while the niacin group demonstrated a 58.3% reduction. Total cholesterol decreased in the IHN treated group by 79.5%, in the niacin treated group by 74.9%. The greatest difference between the two groups occurred when triglyceride levels were compared, the IHN group exhibiting a 63.2 % decrease, the niacin group a 30.9% decrease.²⁴ These findings agree with Welsh and Ede who found IHN more effective than niacin in its antihypertensive, hypocholesterolemic and lipotropic effects.¹⁵

Peripheral Vascular Disorders:

IHN demonstrates particular effectiveness in the treatment of peripheral vascular disorders. Among the most thoroughly researched conditions are Raynaud's disease (syndrome; phenomenon) and intermittent claudication. Raynaud's disease is characterized by coldness and intermittent pallor or cyanosis of the distal portions of the digits, generally precipitated by exposure to cold or emotional stress. It is caused by vasospasm of the digital arteries and arterioles and may last from minutes to hours. It may occur as a primary disease or secondary to some other underlying pathology, usually a collagen vascular disease. A review of the literature over the last 35 years reveals numerous positive

studies on the use of IHN (often prescribed in Europe as a patented drug called Hexopal) in Raynaud's disease. As early as 1961, Welsh and Ede reported on the progress of one patient on a dose of 1800 mg. daily. "Large necrotic areas involving the finger tips healed normally, flexibility of fingers and hands increased, and it was assumed that the peripheral circulation had improved, inasmuch as the patient no longer complained of coldness and discomfort."¹⁵

Ring and Bacon,²⁷ in a preliminary 1977 pilot study, using quantitative thermographic assessment, a non-invasive procedure, to measure basal hand temperatures found IHN to be most effective at raising temperatures if used for several months. This precipitated speculation that the mechanism of action must be something other than transient vasodilation and prompted further study in which 15 patients were given IHN at a dosage of 4 grams daily for 36 weeks. The same means of assessment was used as in the preliminary trial. Objective improvement in the thermal gradient of the hand after cold challenge was observed. In addition, subjective improvement in patient reported symptoms of coldness, pain, numbness and burning was statistically significant.¹⁸

Holt further confirmed the necessity for a long build-up period with IHN.³ An assessment of a group of 30 patients, by evaluating total and nutrient digital blood flow as well as by recording the time required to induce Raynaud's phenomenon, yielded significant beneficial effects from IHN at dosages of 1 gram 4 times daily for 12 weeks. A study by Sunderland et al¹⁹ of 23 patients receiving 4 grams daily during cold weather yielded positive results, with patients reporting shorter and fewer attacks of vasospasm during the trial period. Mansel reported on a group of 20 females with primary Raynaud's disease who were prescribed 3 or 4 grams daily for 9 months. Statistically significant increases in

transcutaneous blood velocity were reported. In each study, the most significant results were achieved by long-term administration of the IHN.⁴

The earlier speculations that the mechanism of action must, in addition to transitory vasodilation, include something else have been borne out. Holti suggested that enhanced fibrinolysis and lowering of serum lipids may play a significant role.³ Mansel confirmed statistically significant reductions in cholesterol, triglycerides and plasma fibrinogen in his group during the first 3 months of the study, levels which were sustained throughout the remaining 6 months of the trial.⁴

Intermittent claudication, a deficiency of blood supply to an exercising muscle, results in pain, ache, cramping or fatigue, usually in the calf, after a short period of walking but not at rest. It may also involve hip, thigh, buttocks and foot. It is caused by arterial insufficiency, generally secondary to atherosclerosis. The use of niacin esters, IHN in particular, for this condition has been examined extensively. O'Hara,^{6,28} in a double-blind, placebo-controlled study, reported on a group of 100 patients who were given either 2 grams of IHN or placebo twice daily for 3 months. They were tested monthly on a special exercise machine that simulated box-stepping. The elapsed time and the number of steps taken to achieve claudication pain were recorded. There was a gradual increase in time to claudication pain in both groups over the 3-month period, but the changes were statistically significant only in the IHN group. Furthermore, after 3 months, the patients receiving IHN reported significantly greater subjective improvement than did the placebo group.

As with Raynaud's, discussion of the mechanisms involved has led to controversy. While arterial dilation may be involved, it has been postulated that reduction in fibrinogen, improvement in blood viscosity and resultant

improvement in oxygen transport is induced by IHN.²⁸ Kiff studied 80 patients with intermittent claudication over a 3 month period in a double-blind, placebo-controlled trial with IHN at a dosage of 2 grams twice daily. Symptoms, maximum treadmill distance and walking time were assessed. The most significant finding in this study was that reduction of cigarette smoking had a major influence on treadmill measurements. When smoking was factored out of the equation, the IHN group had significant improvement in treadmill distance.⁵ Tyson found improvement in walking time and number of paces, as measured by stop watch and pedometer, in a group of 86 patients, with statistical significance of IHN over placebo in the most severely effected group.²⁹ Intermittent claudication poses some difficulties in assessment as the exercise, in itself, will benefit both the placebo and the test group. The IHN, in all studies cited above, seemed to have been tolerated as well or better than placebo. Seckfort has reported that in chronic cases of vascular insufficiency, doses up to 1800 mg. daily were administered without noticeable side effect.³⁰

IHN appears to have application in the treatment of other conditions resulting from peripheral vascular insufficiency. A review of the literature uncovered a report of 8 patients with atherosclerosis for whom amputation was avoided, and 18 cases of manifested or threatened gangrene who responded remarkably well to IHN.¹⁵ This same report noted positive results in cases of restless leg syndrome, presumably if it is related to poor circulation.¹⁵ Welsh and Ede¹⁵ reported on 40 patients with stasis dermatitis with or without ulceration, secondary to peripheral circulatory failure. Patients with pruritis stasis experienced marked relief from itching while receiving inositol hexaniacinate. One of these patients also suffered from migraine headaches associated with atherosclerosis and had tried all

the usually prescribed medications for the previous 10 years. After 10 months of IHN at a dosage of 1200 mg daily, this patient experienced complete relief from the headaches.¹⁵ One patient in this group who had lesions of scleroderma improved markedly on 1200 mg daily.¹⁵ Also studied were patients with a variety of other dermatological problems, either those that had previously reported benefit from oral niacin or problems the researchers associated with defects in lipid metabolism. In the former group, patients with acne, dermatitis herpetiformis and exfoliative glossitis were evaluated. None reported side effects as they had with niacin and 4 out of 5 of the patients with dermatitis herpetiformis were helped considerably by the IHN. The bulk of the patients in the latter group had psoriasis. In a number of patients pruritis was relieved and skin lesions improved but a number of patients showed little or no response.¹⁵ It appears that the dermatological problems most dramatically effected by IHN are those related to vascular insufficiency. Welsh and Edes¹⁵ further reported on a study by Donatelli et al with a group of 64 hypertensive patients who had a 93% favorable response to IHN. A single dose of 200 mg IHN reduced blood pressure 10-45 mmHg (an average of 30 mmHg) for an average of 12 hours.

Other Conditions Which Respond Favorably to Niacin Therapy:

There are a number of other conditions which respond favorably to niacin therapy. It is this author's contention that they might respond as well or better to treatment with IHN. A brief review of some of these conditions follows. Elevated levels of acetaldehyde are postulated to contribute to addiction in alcoholics while a possible deficiency of NAD is believed to cause restlessness and irritability in this population. Niacin oxidizes alcohol to reduce acetaldehyde levels and also saturates NAD receptors in the brain to abolish a pos-

sible deficiency of NAD.³¹ A five year study of 507 alcoholics receiving 3 or more grams daily of niacin reported that 30-60% of alcoholics benefit from supplementation by reduced recidivism and symptom reduction.³² Most studies examined recommended a minimum of 500 mg daily for therapeutic efficacy. The obvious concern lies with the supplementation of high doses of niacin to a population with already compromised liver status. The use of IHN with its apparent lack of side effects coupled with the well-known lipotropic effects of inositol would seem a better choice.

The use of niacin in diabetics is somewhat controversial. Niacin is part of glucose tolerance factor (GTF). Therefore, a deficiency of niacin will interfere with GTF synthesis.³³ Furthermore, animal studies indicate that niacin may retard the development of diabetic nephropathy.³⁴ However, as previously mentioned, niacin, at least in large doses, may impair glucose tolerance. It is not known whether nicotinic acid increases blood glucose by decreasing insulin secretion or by promoting insulin resistance.¹ If it is the latter, then it would not be an issue for Type I diabetics since they have virtually no endogenous insulin secretion anyway. A 1977 study combining IHN at a dose of 250 mg 3 times daily with Mg-chlorophenoxyisobutyrate for the treatment of hyperlipidemia found no influence on glucose tolerance with this regime.³⁵ The inositol fraction of the IHN may be beneficial to diabetics as sorbitol accumulation, implicated in many of the long term effects of diabetes may be a result of inositol loss.³⁶ Positive studies of inositol for the treatment of diabetic neuropathy have been reported.³⁷⁻³⁸ It should be noted that the typical therapeutic dose for inositol for the treatment of diabetic neuropathy is in the range of 1 gram or more daily. A 600 mg dosage of IHN contains 90 mg inositol. Thus, addition inositol might be required to achieve optimal results.

There is evidence that niacin may be beneficial for the treatment of dysmenorrhea. Hudgins reported on a group of 80 women suffering from painful menstrual cramps who were supplemented with 100 mg niacin twice daily, beginning 7-10 days before the onset of menses and then every 2-3 hours during heavy cramps. Ninety percent of participants experienced significant relief.³⁹ The dosage required during heavy cramping is high enough to cause unpleasant side effects. It would seem that the use of IHN might be indicated. In addition, the inositol would provide lipotropic effects. Lipotropic agents help in the metabolism of hormones by the liver, important for the prevention of PMS.

Jacobson et al have initiated studies to evaluate the potential of niacin in the prevention of human carcinogenesis.⁴⁰ The known role of ADP-ribose polymer metabolism in limiting carcinogenesis and the dependence of this metabolic function on intracellular NAD levels leads to the prediction that niacin deficiency may enhance carcinogenesis.⁴⁰ With this in mind, it would seem imperative to consider broad scale supplementation of niacin in a safe, well-tolerated form.

Conclusion:

Inositol hexaniacinate as been shown to be a safer alternative than conventional niacin supplementation, free from the acute reactions and more harmful long term effects most often associated with moderate to high dose niacin therapy. The effectiveness of IHN for the treatment of hyperlipidemias and peripheral vascular disorders, including Raynaud's disease and intermittent claudication, has been demonstrated, in numerous studies, to be equal to or better than niacin. The use of IHN in other conditions which respond positively to niacin therapy such as hypertension, alcoholism, diabetes and dysmenorrhea merits further investigation.

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