Niacin (Nicotinic Acid)

DESCRIPTION

The term niacin is used in two different ways. As a collective term, it refers to both nicotinic acid and niacinamide. It is also used synonymously with nicotinic acid. In this monograph, the biochemistry and pharmacology of niacin—nicotinic acid and niacinamide—will be discussed, as well as the actions and indications for niacin. The actions of and indications for niacinamide will be discussed in a separate monograph (see Nicotinamide). Nicotinic acid and niacinamide have identical vitamin activities, but have very different pharmacological activities.

Niacin is a member of the B-vitamin family. It is sometimes referred to as vitamin B3. Nicotinic acid was first discovered as an oxidation product of nicotine and thus, the origin of its name. In fact, much of the confusion caused by the use of the term niacin for both nicotinic acid and niacinamide, as well as for nicotinic acid alone, was created by the attempt to dissociate nicotinic acid from its nicotine origins. Niacin, via its metabolites, is involved in a wide range of biological processes, including the production of energy, the synthesis of fatty acids, cholesterol and steroids, signal transduction, the regulation of gene expression and the maintenance of genomic integrity. Nicotinic acid, in pharmacological doses, is used as an antihyperlipidemic agent.

Niacin and substances that are convertible to niacin are found naturally in meat (especially red meat), poultry, fish, legumes and yeast. In addition to preformed niacin, some L-tryptophan found in the proteins of these foods is metabolized to niacin. Niacin is also present in cereal grains, such as corn and wheat. However, consumption of corn-rich diets has resulted in niacin deficiency in certain populations. The reason for this is that niacin exists in cereal grains in bound forms, such as the glycoside niacytin, which exhibit little or no nutritional availability. Interestingly, niacin deficiency is not common in Mexico and Central America even though the diets of those in these countries are based on corn. Alkaline treatment, such as soaking corn in a lime solution, the process used by the populations of Mexico and Central America in the production of corn tortillas, yields release of bound niacin and increased availability of the vitamin.

The well-known disorder of niacin deficiency is pellagra. The term pellagra is derived from the Italian words pelle agra meaning rough or smarting skin. Pellagra is characterized by the triad of dermatitis, diarrhea and dementia. A fourth d, death, is the final outcome of the disease, if not treated. The skin lesions are primarily located on sun-exposed areas of the face, hands, arms and feet. The dermatitis progresses from an erythematous, often pruritic rash, to vesicles and blisters with scales and fissures, and finally, to thickened, lichenified, hyperpigmented skin. Casal’s necklace refers to characteristic advanced skin lesions of pellagra. Casal’s necklace is named for Gaspar Casal, the physician to King Ferdinand of Spain, who first reported on the symptoms and signs of pellagra in modern times. He called the disease mal de la rosa (disease of the rose), because of the red and glossy color of the skin lesions. Casal attributed the disorder to the diets of the poor laborers; diets which were mainly comprised of corn. Although pellagra was commonly found in the United States through the 1930s, the disorder is rare today in industrialized countries. This is due, in large part, to the enrichment of refined flours with niacin.

Niacin deficiency, however, can and does occur under certain conditions. These conditions include alcoholism, malabsorption syndromes, cirrhosis and in those receiving total parenteral nutrition (TPN) with inadequate niacin. It may also occur in Hartnup’s syndrome, an autosomal recessive disorder in which there is defective conversion of tryptophan to niacin; carcinoid syndrome, in which tryptophan metabolism is diverted to form 5-hydroxytryptamine, also known as serotonin; and in those receiving isoniazid for the treatment of tuberculosis.

The biochemical effects of niacin are principally mediated by its metabolite nicotinamide adenine dinucleotide or NAD+. NAD+ serves both coenzyme and substrate functions. NAD+ was originally called cozymase and was also known as coenzyme I and DPN or diphosphopyridine nucleotide. The positive sign in NAD+ refers to the fact that the nitrogen in the pyridine ring of niacin is positively charged in the NAD+ structure. NAD+ and its reduced form NADH (reduced nicotinamide dinucleotide) are the major hydrogen acceptor and donor, respectively, in many biological redox reactions. NAD+ is used in metabolic reactions to transfer the potential free energy stored in carbohydrates, lipids and
proteins to NADH, which is used to form ATP (adenosine triphosphate).

NADP+ or nicotinamide adenine dinucleotide phosphate is formed from NAD+ via a kinase-catalyzed phosphorylation. NADP+ participates as a coenzyme in the oxidation of glucose 6-phosphate via the enzyme glucose 6-phosphate dehydrogenase. This is the oxidative reaction in the pentose phosphate pathway which produces, among other things, ribose 5-phosphate. During the oxidation of glucose 6-phosphate, NADP+ is reduced to NADPH or reduced nicotinamide adenine dinucleotide phosphate. NADPH serves as the reducing agent in fatty acid and steroid biosyntheses and serves to maintain glutathione in its reduced form.

In addition to its coenzyme role in many metabolic reactions, NAD+ also serves as a substrate in a number of biochemical reactions. The beta-N-glycosylic bond of NAD+ can be cleaved by three types of enzymes. In the process, nicotinamide and ADP (adenosine diphosphate)-ribose are formed. One type of enzyme catalyzes mono(ADP-ribosyl)ation of proteins—a posttranslational modification—by transferring ADP-ribose from NAD+ to target proteins. The enzymes are known as mono(ADP-ribosyl)transferases (mADPRTs). Mono(ADP-ribosyl)ation of endogenous proteins by bacterial toxins, such as diphtheria toxin and cholera toxin, accounts, in large part, for the pathogenic effects of these toxins. The physiological functions of endogenous mono(ADP-ribosyl)transferases are not clear. Another type of enzyme catalyzes poly(ADP-ribosyl)ation of target proteins. This enzyme is known as poly(ADP-ribose)polymerase or PARP. PARP is also known as poly(ADP-ribose) synthetase (PARS), poly(ADP-ribose)transferase (pADPRT), and PARP1. PARP is believed to be involved in DNA repair, among other things.

NAD+ is also involved in the biosynthesis of signaling molecules. A third type of beta-N-glycosyl bond-cleaving enzymes catalyzes the formation of cyclic ADP-ribose (cADPR). Cyclic ADP-ribose is an intracellular calcium mobilizing agent. The enzyme that catalyzes the synthesis of cyclic ADP-ribose is called ADP-ribosyl cyclase. NADP+ is also involved in the biosynthesis of signaling molecules. NADP+ leads to the formation of NAADP+ (nicotinic acid adenine dinucleotide phosphate) and cADPRP (2’-phospho cyclic ADP-ribose). NAADP+ and cADPRP are also intracellular calcium mobilizing agents.

The enzyme poly(ADP-ribose) polymerase (PARP) is a highly abundant nuclear protein, the physiological role of which is not yet clear. PARP poly(ADP-ribosyl)ates various nuclear proteins as well as itself. PARP is thought to be involved in a number of biological processes, including DNA repair and replication, cell differentiation and cellular apoptosis. DNA damage appears to enhance the activity of PARP. In damaged cells, PARP binds to DNA and becomes enzymatically activated. Once activated, PARP automodifies itself through poly(ADP-ribosylation). This results in its inactivation and its dissociation from DNA breaks. This dissociation is necessary for DNA repair.

Recently, it has been found that NAD+ plays a key role in life-span extension by calorie restriction in the yeast Saccharomyces cerevisiae. It does so by serving as the cofactor for an NAD+-dependent histone deacetylase, an enzyme that removes acetyl groups from the lysine residues of histone proteins, thus promoting genomic silencing. Maintenance of genomic silencing may be critical to longevity either by repressing genomic instability or by preventing inappropriate gene expression. A similar mechanism may operate in metazoans, including humans.

As mentioned above, niacin is used either to refer to both nicotinic acid and niacinamide or to nicotinic acid itself. Nicotinic acid, in addition to being known as niacin, is also known as pyridine-3-carboxylic acid, vitamin B3, 3-pyridine-carboxylic acid, pyridine-beta-carboxylic acid, antipellagra vitamin and pellagra preventive factor. The molecular formula of nicotinic acid is C6H5NO2. The molecular weight of nicotinic acid is 123.11 daltons and the structural formula is:

![Nicotinic Acid](attachment:image.png)

Nicotinamide is also known as pyridine-3-carboxamide, niacinamide and nicotinic acid amide. Its molecular formula is C6H6N2O and its molecular weight is 122.13 daltons.

**ACTIONS AND PHARMACOLOGY**

**ACTIONS**

Nicotinic acid has antihyperlipidemic activity and may have anti-atherogenic activity.

**MECHANISM OF ACTION**

Nicotinic acid in gram doses, but not nicotinamide, lowers serum levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein (VLDL) and triglycerides. High-dose nicotinic acid also increases serum levels of high-density lipoprotein cholesterol (HDL-C) and decreases serum levels of lipoprotein (a) [Lp(a)] and apolipoprotein B-100 (Apo B). The mechanism of the antihyperlipidemic action of nicotinic acid is not well understood. It is thought that this effect is mediated, in part,
via decreases in the release of free fatty acids from adipose tissue, thereby decreasing the influx of free fatty acids into the liver, the hepatic reesterification of free fatty acids and the rate of production of hepatic very low-density lipoprotein (VLDL). A decrease in the hepatic production of VLDL reduces the level of circulating VLDL available for conversion to LDL. Another hypothesis holds that nicotinic acid directly inhibits hepatic synthesis or secretion of apolipoprotein B-containing lipoproteins. Still another hypothesis holds that nicotinic acid has the potential to cause a generalized inhibition of synthetic function in the liver. This mechanism may be considered a manifestation of nicotinic acid hepatotoxicity resulting in decreased LDL-cholesterol. However, this liver-damaging hypothesis would not explain the HDL-elevating effect of nicotinic acid. The mechanism by which nicotinic acid elevates HDL is unclear. A recent study suggested that the mechanism may have something to do with nicotinic acid’s inhibition of the cell surface expression of the ATP synthase beta chain, leading to a reduced hepatic removal of HDL proteins, and thus implicating a potential cellular target for nicotinic action to raise HDL. This possibility is certainly worthwhile to pursue.

High dose nicotinic acid has been found to significantly decrease cardiovascular and cerebrovascular events in those with coronary heart disease. It is thought that this effect is due, in part, to nicotinic acid’s antihyperlipidemic activity.

**PHARMACOKINETICS**

Both nicotinic acid and nicotinamide are efficiently absorbed from the stomach and small intestine. At low amounts, absorption is mediated by sodium-dependent facilitated diffusion. Passive diffusion is the principal mechanism of absorption at higher doses. Doses of up to three to four grams of nicotinic acid and niacinamide are almost completely absorbed. Nicotinic acid and nicotinamide are transported via the portal circulation to the liver and via the systemic circulation to the various tissues of the body. Nicotinic acid and nicotinamide enter most cells by passive diffusion and enter erythrocytes by facilitated transport.

Nicotinic acid and nicotinamide are metabolized through different pathways. Nicotinic acid is not directly metabolized to nicotinamide. It undergoes a number of metabolic steps to yield NAD+ which in turn can be converted to nicotinamide. Nicotinamide can be directly converted to nicotinic acid. Nicotinic acid is metabolized to nicotinic acid mononucleotide (NicMN, nicotinic acid ribonucleotide). NicMN is also the first niacin metabolite to which dietary L-tryptophan is converted. NicMN is converted to nicotinic acid adenine dinucleotide (NicAD, desamido-NAD+). NicAD is converted in turn to NAD+, NAD+ has a number of metabolic opportunities. These include, the formation of nicotinamide, NADP+, nicotinamide 5'-mononucleotide (NMN), cyclic ADP-ribose and nicotinic acid dinucleotide phosphate (NAADP). NAD+ also serves as the substrate for mono(ADP-ribosyl)ation and poly(ADP-ribosyl)ation reactions. Nicotinamide is converted to nicotinic acid via the enzyme nicotinamidase. Nicotinamide is also metabolized to NMN which in turn is converted to NAD+.

In the liver, the principal catabolic product of high doses of nicotinic acid is the glycine conjugate of nicotinic acid called nicotinuric acid. The principal catabolic products of nicotinamide are N'-methylnicotinamide, N'-methyl-5-carboxamide-2-pyridone, N'-methyl-5-carboxamide-4-pyridone and nicotinamide-N-oxide.

High doses of nicotinic acid are excreted in the urine as unchanged nicotinic acid and the glycine conjugate of nicotinic acid nicotinuric acid. High doses of nicotinamide are excreted in the urine as unchanged nicotinamide, N'-methylhydrosorcinol, N'-methyl-5-carboxamide-2-pyridone, N'-methyl-5-carboxamide-4-pyridone and nicotinamide-N-oxide.

The pharmacokinetics of the various forms of nicotinic acid (immediate-release, intermediate-release, extended-release) differs in certain particulars. The time to reach peak serum concentrations of the immediate-release or crystalline form of nicotinic acid is approximately 45 minutes following ingestion. The time to reach peak serum concentrations of the extended-release form of nicotinic acid is from 4-5 hours following ingestion. Administration of nicotinic acid with food maximizes its availability. Nicotinic acid-induced flushing, which is due to vasodilation, occurs within 20 minutes following ingestion of immediate-release nicotinic acid and may last for up to one hour.

**INDICATIONS AND USAGE**

Nicotinic acid has demonstrated an ability to lower LDL-cholesterol and triglycerides and to protect against atherosclerosis. Recently, researchers have begun focusing on its abilities to boost the “good” HDL-cholesterol and on ways to diminish the so-called “niacin flush” that has prevented some from using this helpful agent.

**RESEARCH SUMMARY**

Nicotinic acid has been tested for its effects on cardiovascular-disease risk factors in a number of major trials. In the largest of these, the effect of nicotinic acid monotherapy on cardiovascular endpoints was investigated. The study included 8,341 men who had suffered myocardial infarction. In this randomized, six-year study, nicotinic acid, given in 1 gram doses three times a day, decreased cholesterol levels by 10% and triglyceride levels by 26%. There was a decrease of 27% in recurrent non-fatal heart attacks among the nicotinic-acid treated subjects. They also experienced 26% fewer cerebrovascular events.
In a five-year randomized, placebo-controlled study of 555 survivors of myocardial infarction, nicotinic acid, in combination with clofibrate, was found to significantly decrease total and cardiac mortality. Total mortality declined by 26%. Nicotinic acid was given in 1 gram doses three times daily. Clofibrate was given in 1 gram doses twice daily.

In another well-controlled study of men aged 40 to 59 who had undergone coronary artery bypass, nicotinic acid used in combination with colestipol significantly decreased disease progression in some and significantly increased disease regression in some others, compared with placebo.

Various studies have shown that nicotinic acid can significantly lower total cholesterol, LDL-cholesterol, triglycerides and lipoprotein (a) levels. It can also increase HDL-cholesterol levels.

Nicotinic acid may be an effective and safe lipid-modifying agent even among those with diabetes. A recent report of the analysis of data from the Arterial Disease Multiple Intervention Trial (ADMIT), showed that those with and without diabetes who received crystalline nicotinic acid (3,000 milligrams/day) had significantly increased levels of HDL-cholesterol and decreased levels of LDL-cholesterol and triglycerides after 18 weeks of treatment. Glucose levels were only modestly increased among subjects with and without diabetes. Among those with diabetes, HbA1c levels were unchanged in the nicotinic acid group, but decreased in the placebo group. No significant differences in nicotinic acid discontinuation or hypoglycemic therapy were noted in those with diabetes assigned to nicotinic acid vs. placebo.

A newer extended-release nicotinic acid, used once daily, either as monotherapy or in combination with lipid-lowering drugs, has demonstrated the same favorable effects on lipids in clinical trials. This form may be less hepatotoxic than slow-release nicotinic acid.

More-recent studies continue to produce positive results for nicotinic acid. In one of these, it was shown to inhibit vascular oxidative stress, redox-sensitive genes and monocyte adhesion to human aortic endothelial cells. All of this provides evidence that niacin inhibits vascular inflammation and has antiatherosclerotic properties independent of, and in addition to, its lipid-modulating effects. In a recent double-blind, placebo-controlled study, niacin, either alone or in combination with statins, was found to reduce coronary heart disease morbidity and mortality in patients with confirmed coronary heart disease and low levels of HDL-cholesterol.

Studies have shown that the cutaneous vasodilation niacin induces—resulting in the so-called "niacin flush" that is harmless but causes some people discomfort and prevents them from continuing to use niacin—can be blocked to some extent by pretreatment with aspirin. Some further research has identified prostaglandin receptors involved in this flushing process and has raised hopes that even more effective and safe antagonists of these receptors may be found. Other strategies for minimizing the flush have lately been proposed, including regular consistent dosing; the use of extended-release formulations as discussed above; patient education; dosing with meals or at bedtime; and avoidance of alcohol, hot beverages, spicy foods and hot baths or showers near the time of dosing or soon after.

A number of other new discoveries have further revived interest in niacin as a unique agent for the promotion of heart health. Findings related to its influence on HDL-cholesterol, in particular, have excited much recent interest. Niacin is now recognized, as one group of researchers recently stated, as "the most potent available lipid-regulating agent to increase HDL levels." HDL particles have antiatherogenic properties owing to their ability to take up cholesterol and remove it from blood vessels; additionally, it has been shown to have antiinflammatory and anticoagulatory properties. And as important as reducing plasma concentrations of harmful LDL-cholesterol is (through use of statins, for example), researchers note that this is insufficient in itself for purposes of substantially reducing cardiovascular disease. Low HDL is an established independent risk factor; thus increasing attention is being focused on strategies to increase HDL. One reviewer recently observed that "though there are several novel strategies being pursued, the oldest lipid-modifying drug, nicotinic acid, has recently enjoyed a renaissance owing to its strong HDL-cholesterol elevating effect, which is unique among the drugs currently approved for clinical use." Another reviewer, similarly hailing the re-emergence of niacin as an important therapy in cardiovascular disease, added that concerns about niacin's safety have been largely assuaged by results seen over the long course of its use: "Evidence is also accumulating that hyperglycemic responses are minor and manageable, that liver toxicity is very infrequent when appropriately dosed, and that myopathic potential is absent or minimal in combination with statins."

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS
Niacin is contraindicated in those who are hypersensitive to any component of a niacin-containing product. High-dose nicotinic acid is contraindicated in those with hepatic dysfunction, unexplained elevations of serum aminotransferases (transaminases), active peptic ulcer disease and arterial bleeding.

PRECAUTIONS
Pregnant women and nursing mothers should avoid supplement doses of niacin greater than U.S. RDA amounts (20
milligrams daily) unless higher doses are prescribed by their physicians.

The use of nicotinic acid as an antihyperlipidemic agent should only be undertaken under medical supervision.

Those with a past history of hepatobiliary disease, jaundice, peptic ulcer disease or gastritis should exercise caution in the use of high-dose nicotinic acid. Those with a history of diabetes, renal dysfunction, cardiovascular disease (especially acute myocardial infarction and unstable angina) and gout should exercise caution in the use of high-dose nicotinic acid. Those who consume substantial amounts of alcohol should also exercise caution in the use of high-dose nicotinic acid.

Those who take high-dose nicotinic acid should have their serum aminotransferase levels monitored. Aspartate aminotransferase (AST, also known as SGOT or serum glutamate oxaloacetate transaminase) and alanine aminotransferase (ALT, also known as SGPT or serum glutamate pyruvate transaminase) levels should be determined prior to starting high-dose nicotinic acid therapy, then every 6-12 weeks for one year and after one year, periodically. High-dose nicotinic acid should be discontinued if the aminotransferase levels are equal to greater than three times the upper limit of normal.

Intermediate-release (extended-release) and slow-release forms of nicotinic acid should not be substituted for equivalent doses of immediate-release (crystalline) nicotinic acid. Cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in subjects who have substituted sustained-release nicotinic acid products for immediate-release nicotinic acid at equivalent doses. Those who switch from immediate-release nicotinic acid to sustained-release forms of nicotinic acid, should start off with low doses of sustained-release nicotinic acid and the dose should then be slowly increased in order to obtain the desired therapeutic response.

High-dose nicotinic acid may negatively affect glucose tolerance. Diabetics who take nicotinic acid for lipid-lowering, should have their serum glucose levels carefully monitored and the dose of their antidiabetic medications adjusted as necessary.

ADVERSE REACTIONS

Nicotinic acid can cause vasodilation of cutaneous blood vessels, resulting in increased blood flow, principally in the face, neck and chest. This produces the niacin- or nicotinic acid-flush. The niacin-flush is thought to be mediated via the vasodilatory eicosanoids, particularly prostaglandin D2 (PGD2). It is thought that an antagonist to the PGD2 receptor subtype might significantly reduce the flush, and at least one pharmaceutical company is developing such a drug. Histamine may also play some role in the niacin-flush. Flushing is the adverse reaction first observed after intake of a large dose of nicotinic acid, and the most bothersome one. It is the principal reason for compliance issues with the use of high-dose nicotinic acid for the treatment of hyperlipidemia. Nicotinamide does not appear to be associated with flushing. However, high-dose nicotinamide does not possess antihyperlipidemic activity. The symptoms of flushing include a burning, tingling and itching sensation. A reddened flush occurs primarily on the face, arms and chest. Flushing is often accompanied by pruritus and headaches. In one study, 5% of subjects ingesting 50 milligrams of nicotinic acid experienced flushing, 50% experienced flushing after ingesting 100 milligrams of nicotinic acid and 100% of subjects ingesting 500 milligrams of nicotinic acid experienced flushing. In another study, 66% of subjects experienced a flushing sensation after ingestion of 50 milligrams of nicotinic acid. Based on these studies, the Food and Nutrition Board of the Institute of Medicine has established a LOAEL (lowest-observed-adverse-effect level) for niacin of 50 mg/day. Based on this LOAEL, the Tolerable Upper Intake Level (UL) for niacin, for adults, is set at 35 mg/day. To obtain this UL, the LOAEL of 50 mg/day was divided by an uncertainty factor (UF) of 1.5 and rounded off.

The flushing effect of nicotinic acid is transient and tolerance to this effect occurs with continued administration of the vitamin. The flushing effect, as mentioned above, is prostaglandin mediated, and tolerance results from reduction in prostaglandin levels with continued administration.

Other adverse reactions of nicotinic acid include dizziness, palpitations, tachycardia, shortness of breath, sweating, chills, skin rashes, insomnia, nausea, vomiting, abdominal pain and myalgia. Nicotinic acid can cause hepatotoxicity. In the most severe cases, subjects develop liver dysfunction and fulminant hepatitis and may progress to stage 3 and 4 encephalopathy requiring liver transplantation. The most frequently observed manifestations of nicotinic acid-induced hepatitis are increased levels of serum aminotransferases (transaminases) and jaundice. Many, if not most of the subjects who developed hepatotoxicity from nicotinic acid appeared to be taking the slow-release form. A recent double-blind comparison suggested that the slow-release form is more hepatotoxic than the immediate-release form. However, not all studies find this to be the case. Another recent study reported that both the slow release and immediate-release forms of nicotinic acid are hepatotoxic.

High-dose nicotinic acid (approximately 3 grams daily) has caused impaired glucose tolerance in otherwise healthy individuals. Further, glucose tolerance in some diabetics may be worsened by nicotinic acid therapy. High doses of
nicotinic acid (1.5 to 5 grams/day) have also caused ocular effects, including blurred vision, macular edema, toxic amblyopia and cystic maculopathy. Nicotinic acid-induced ocular effects do not appear to be common and appear to be reversible. Elevated uric acid levels have also occurred with nicotinic acid therapy.

**INTERACTIONS**

**DRUGS**

*Alpha<sub>1</sub>-blockers (doxazosin, prazosin, tamsulosin, terazosin)*: Concomitant use of high-dose nicotinic acid and an alpha<sub>1</sub>-blocker may potentiate the hypotensive effect of the alpha<sub>1</sub>-blocker and may cause postural hypotension.

*Alpha-glucosidase inhibitors (acarbose, miglitol)*: High-dose nicotinic acid may antagonize the antidiabetic action of alpha-glucosidase inhibitors, requiring adjustment of their dosage.

*Biguanides (metformin)*: High-dose nicotinic acid may antagonize the antidiabetic activity of metformin, requiring adjustment of its dosage.

*Calcium channel blockers*: Concomitant use of high-dose nicotinic acid and a calcium channel blocker may potentiate the hypotensive effect of the calcium channel blocker.

*Cholestyramine*: Concomitant use of high-dose nicotinic acid and cholestyramine may reduce the absorption of nicotinic acid. It is recommended that a 4 to 6 hour interval elapse between the ingestion of cholestyramine and the administration of nicotinic acid. Administration of high-dose nicotinic acid and cholestyramine may produce complementary antihyperlipidemic effects.

*Colestipol*: Concomitant use of high-dose nicotinic acid and colestipol may reduce the absorption of nicotinic acid. It is recommended that a 4 to 6 hour interval elapse between the ingestion of colestipol and the administration of nicotinic acid. Administration of high-dose nicotinic acid and colestipol may produce complementary antihyperlipidemic effects.

*Ganglionic blocking agents (mecamylamine HCL, trimethaphan)*: Nicotinic acid may potentiate the effects of ganglionic blocking agents resulting in postural hypotension.

*Gemfibrozil*: Administration of high-dose nicotinic acid and gemfibrozil may produce complementary antihyperlipidemic effects.

*HMG-CoA reductase inhibitors or “statins” (atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, simvastatin)*: Concomitant administration of high-dose nicotinic acid and HMG-CoA reductase inhibitors have resulted in rare cases of rhabdomyolysis. Those receiving concomitant high-dose nicotinic acid and an HMG-CoA reductase inhibitor should be carefully monitored for any signs or symptoms of muscle pain, tenderness or weakness. Administration of high-dose nicotinic acid and a statin may produce complementary antihyperlipidemic effects.

*Meglitinides (repaglinide)*: High-dose nicotinic acid may antagonize the antidiabetic action of repaglinide, a meglitinide analogue, requiring adjustment of its dosage.

*Nicotine patch*: Concomitant use of a transdermal nicotine patch and nicotinic acid may enhance the flushing reaction.

*Nitrates*: Concomitant use of high-dose nicotinic acid and a nitrate may potentiate the hypotensive effect of the nitrate.

*NSAIDs (ibuprofen, etc.) and aspirin*: The use of aspirin (80 to 325 milligrams), ibuprofen (200 to 400 milligrams) or other NSAIDs, taken 30 minutes to one hour before a dose of nicotinic acid, may blunt the flushing effect of high-dose nicotinic acid. Nicotinic acid induces the release of vasodilatory eicosanoids, particularly prostaglandin D<sub>2</sub> (PGD<sub>2</sub>). Prostaglandin D<sub>2</sub> (PGD<sub>2</sub>) is thought to account for, in large part, nicotinic acid-induced flushing. Aspirin may help to antagonize the effect of PGD<sub>2</sub> and also may decrease the metabolic clearance of nicotinic acid.

*Sulfonylureas (chlorpropamide, glimepiride, glyburide)*: High-dose nicotinic acid may antagonize the antidiabetic action of sulfonylureas, requiring adjustment of their dosage.

*Thiazolidinediones (pioglitazone, rosiglitazone)*: High-dose nicotinic acid may antagonize the antidiabetic action of thiazolidinediones, requiring adjustment of their dosage.

*Warfarin*: Extended-release (intermediate-release) forms of nicotinic acid have been associated with small but statistically significant increases in prothrombin time. Concomitant use of extended-release forms of nicotinic acid, as well as other forms of nicotinic acid, may enhance the anticoagulant activity of warfarin. INRs should be closely monitored in those taking high-dose nicotinic acid concomitantly with warfarin.

**NUTRITIONAL SUPPLEMENTS**

*Red yeast rice*: The nutritional supplement red yeast rice contains HMG-CoA reductase inhibitors, including lovastatin. Concomitant administration of high-dose nicotinic acid and HMG-CoA reductase inhibitors, including lovastatin, has resulted in rare cases of rhabdomyolysis. Otherwise, high-dose nicotinic acid and red yeast rice may produce complementary antihyperlipidemic effects.

*Luteolin*: Animal studies suggest that the flavonoid luteolin may help to ameliorate the niacin-induced flush.
**FOODS**

*Ethanol-containing beverages:* Concomitant intake of nicotinic acid and ethanol-containing beverages may cause an increase in nicotinic acid-induced flushing.

*Hot beverages and hot foods:* Concomitant intake of hot beverages or hot foods and nicotinic acid may cause an increase in nicotinic acid-induced flushing.

**OVERDOSAGE**

There are no reports of niacin overdosage in the literature.

**DOSAGE AND ADMINISTRATION**

Niacin, as nicotinamide (niacinamide) is the principal form used for nutritional supplementation. It is available as a single ingredient product (see Nicotinamide) and in multivitamin and multivitamin/multimineral products. Typical supplemental dosage, ranges from 20 to 100 milligrams daily. Nicotinamide is also the form of niacin used in food fortification.

The Food and Nutrition Board of the Institute of Medicine of the National Academy of Sciences has recommended the following dietary reference intakes (DRIs) for niacin:

- **Infants**
  - **Adequate Intake (AI)**: 2 mg/day of niacin equivalents
  - **0-6 months**: 2 mg/day of niacin equivalents
  - **7-12 months**: 4 mg/day of niacin equivalents

- **Children**
  - **Recommended Dietary Allowances (RDA)**
  - **1-3 years**: 6 mg/day of niacin equivalents
  - **4-8 years**: 8 mg/day of niacin equivalents

- **Boys**
  - **9-13 years**: 12 mg/day of niacin equivalents
  - **14-18 years**: 16 mg/day of niacin equivalents

- **Girls**
  - **9-13 years**: 12 mg/day of niacin equivalents
  - **14-18 years**: 14 mg/day of niacin equivalents

- **Men**
  - **≥19 years**: 16 mg/day of niacin equivalents

- **Women**
  - **≥19 years**: 14 mg/day of niacin equivalents

- **Pregnancy**
  - **14-18 years**: 18 mg/day of niacin equivalents
  - **19-50 years**: 18 mg/day of niacin equivalents

- **Lactation**
  - **14-18 years**: 17 mg/day of niacin equivalents
  - **19-50 years**: 17 mg/day of niacin equivalents

**ND** = Not determinable

The DV (Daily Value) for niacin (nicotinamide and nicotinic acid), which is used for determining percentage of nutrient daily values on nutritional supplement and food labels, is 20 milligrams. This is based on the U.S. RDA for niacin.

Nicotinic acid is available as a single ingredient product. It is available both as an OTC product and as a prescription product. The use of nicotinic acid as an antihyperlipidemic agent should only be undertaken under medical supervision. Three different formulations are available for antihyperlipidemic use: immediate-release (crystalline) nicotinic acid, extended-release (intermediate-release) nicotinic acid and slow-release nicotinic acid. Recommended adult doses are up to 3 grams daily of the immediate-release form or 1 to 2 grams of the extended-release forms. It is recommended that nicotinic acid be started at low doses and slowly titrated to the desired therapeutic dose. Administration on an empty stomach is not recommended. The use of an NSAID taken 1/2 hour before nicotinic acid may blunt the flushing reaction. The flushing is less severe with extended-release and slow-release forms than it is with immediate-release forms. However, the slow-release form may lead to an increased incidence of gastrointestinal problems and hepatotoxicity. The intermediate-release form may be less hepatotoxic than the slow-release form.
LITERATURE


Nickel

DESCRIPTION

Nickel is a hard, malleable and ductile metal with atomic number 28 and symbol Ni. It occurs in igneous rock and as a free metal and, together with iron, it is a component of the earth’s core. Nickel also occurs in living organisms, mainly in plants.

Nickel is not currently considered an essential nutrient for humans. Nickel deficiency states have been reported in some animals. Rats and goats fed nickel-deficient diets have depressed growth, reproductive performance and plasma glucose, as well as abnormalities in mineral status. Nickel is conjectured to play a role in processes related to the vitamin B12- and folic acid-dependent pathway in methione metabolism.

The major dietary source of nickel is plant foods. Nickel-rich food items include nuts, beans, peas, grains and chocolate. Animal foods are low in nickel. Total daily dietary intakes of nickel vary depending on the amount of plant and animal foods consumed. Diets high in plant foods, such as the ones listed above, supply about 900 micrograms daily of nickel. Nickel intake in the United States ranges from 69 to 162 micrograms daily. A daily dietary requirement of 25 to 35 micrograms has been suggested.

Nickel allergies are not uncommon and usually manifested as hand eczema. The results of one open, prospective trial suggested that low-nickel diets may benefit some nickel-sensitive individuals.

ACTIONS AND PHARMACOLOGY

ACTIONS

The actions of dietary nickel are not known.

PHARMACOKINETICS

Little is known about the pharmacokinetics of dietary nickel in humans. Apparently nickel is poorly absorbed when ingested in typical diets. The mechanism of absorption is unclear. Following absorption, nickel is transported in blood bound to serum albumin. Nickel is not significantly accumulated by any tissue in the body, although the thyroid and adrenal glands have relatively high nickel concentrations compared with other tissues. Most of the absorbed nickel is excreted by the kidney as low-molecular weight complexes. Nickel is also lost in sweat and bile.

INDICATIONS AND USAGE

There is no indication for the use of supplemental nickel.

RESEARCH SUMMARY

Though decreased levels of nickel have been reported in some conditions, there is no evidence that supplemental nickel is of any benefit in any of these conditions.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Known hypersensitivity to a nickel-containing product.

PRECAUTIONS

Those with nickel-sensitivity should avoid nickel supplementation.

ADVERSE REACTIONS

None known.

Dosage and Administration

No recommendation.