Niacin: Nicotinic Acid, Nicotinamide, and Inositol Hexanicotinate

Introduction

Niacin is the vitamin B_3 and has fundamental roles as part of reduction/oxidation coenzymes involved in energy metabolism, amino acid metabolism, and detoxification reactions for drugs and other substances. Niacin comes from in several forms: (1) nicotinic acid (pyridine-3-carboxylic acid) (Burgeois et al. 2006), (2) nicotinamide (nicotinic acid amide), and (3) other derivatives (e.g., inositol hexanicotinate) "that exhibit the biological activity of nicotinamide" (Institute of Medicine [IOM] 1998). Other derivatives may be converted to nicotinic acid or may contain nicotinic acid, nicotinamide, or their releasable moieties; whether these compounds should be referred to as *niacin* depends on the biological effects that are attributed to them, the interpretation of the evidence for the rates of uptake and metabolism, and the release of the chemical components (apparent bioavailability) that produce biological effects similar to the primary forms of niacin.

Excess niacin is not stored in the body; therefore niacin must be ingested daily. It can come from nicotinic acid or nicotinamide. It can also come from the biological conversion of the amino acid tryptophan to nicotinic acid, but only if intake of protein is at a sufficiently high level. Thus, an individual's niacin level depends on the amount and quality of that person's dietary protein intake (Cervantes-Laurean et al. 1999).

Nicotinic acid at an intake of 1,000 mg or higher is an effective dyslipidemic agent with a broad spectrum of effects, including raising high-density lipoprotein (HDL) cholesterol, reducing low-density lipoprotein (LDL) cholesterol, reducing high lipoprotein(a), and reducing triglycerides (Witztum and Steinberg 1996; Carlson 2005). However, intakes of quantities of 1 g or more carry significant risk of adverse effects, ranging from nuisance effects to serious illness. For example, excessive intake of nicotinic acid can produce a vasodilative effect that results in an itching or burning sensation of the skin, especially on the face and neck. This "flushing reaction"

usually persists for only a few doses and may be reduced by splitting the daily dose into three parts, each increased gradually until the desired total dose is achieved. More serious side effects impacting the liver or intestines have occurred when gram quantities are taken for dyslipidemia. Because of these risks, liver function tests and tests for uric acid, fasting blood glucose, and lipid levels should be conducted as part of the medical treatment with nicotinic acid. Adverse reactions may require decreased dosage or discontinuation in favor of other agents. Clinicians should be aware that the flushing reaction may be substantially avoided through use of a "slow-release" preparation of nicotinic acid; however, such preparations carry greater risk of liver toxicity (Rader et al. 1992).

Nicotinamide, or niacinamide, performs all of the essential biochemical functions of niacin and prevents its deficiency. Large doses of nicotinamide do not cause vasodilatation or flushing and do not lower serum lipid concentrations.

Several forms of "niacin" are marketed in the United States as dietary supplements, including

- nicotinic acid (unmodified, immediate release)
- slow-release (extended release) forms that contain acid and an agent to slow the release (wax matrix, ion exchange gel, etc.)
- nicotinamide
- inositol hexanicotinate (IHN), described as "no flush niacin"

The bioavailability and safety considerations of each of these dietary supplements forms will be discussed and compared. One slow-release niacin product, Niaspan (nicotinic acid in an ion-exchange gel), is approved by the Food and Drug Administration (FDA) and marketed as a prescription drug for control of serum cholesterol and reduction of heart disease risk.

Bioavailability

Nicotinic Acid

Intestinal uptakes of free nicotinic acid are rapid and nearly total (IOM 1998); that is, single large doses of up to 3 to 4 g nicotinic acid are almost completely absorbed by adults (Bechgaard and Jespersen 1977). Once absorbed by the gut, up to 30 percent of the plasma nicotinic acid is bound to plasma protein. Nutritional functions related to niacin-dependent coenzymes occur at low intake levels (15 to 18 mg per day), whereas the flushing effect, which is a nuisance but is not dangerous, becomes noticeable when intakes exceed 50 mg per day (Spies et al. 1938). The beneficial effects reported on serum lipid profiles occur at much higher intake levels, such as 500 to 3,000 mg per day or more (Carlson 2005).

Extended-Release Nicotinic Acid

Extended-release nicotinic acid has been investigated for potential beneficial effects on serum lipids while minimizing or avoiding the flushing effect of crystalline nicotinic acid (Norris 2006). For extended-release nicotinic acid, the potential impacts on serum lipid concentrations are directly related to the release of the nicotinic acid from the matrix in which it is presented. Several product technologies may be used to extend the release of nicotinic acid, such as an ion exchange and a wax matrix selected to melt slowly at body temperature. Thus, the uptake of nicotinic acid from extended-release nicotinic acid formulations is dependent on the specific delivery matrix and is significantly slower than that of free nicotinic acid, but rapid enough to achieve effective plasma nicotinic acid concentrations (Aronov et al. 1996; Menon et al. 2007).

Nicotinamide

Escalating oral doses of 3, 4, 5, 6, and 10 g of nicotinamide showed a linear relationship between maximum recorded plasma concentrations and the dose in grams. Maximum plasma levels were observed by 30 minutes in most patients ingesting up to 6 g of nicotinamide. Doses up to 6 g were well tolerated and resulted in average maximum recorded plasma levels (mean ± 1 SEM) of

156.4 ± 33.6 µg per ml. Doses of 10 g were generally not well tolerated, but a high plasma level was maintained on average for at least 4 hour (Dragovic 1995).

Inositol Hexanicotinate (IHN)

In 2009, the European Food Safety Authority (EFSA) Scientific Panel on Food Additives and Nutrient Sources Added to Food concluded that nicotinate from IHN is a bioavailable source of niacin (EFSA 2009). IHN, like extended-release nicotinic acid, has been investigated for potential beneficial effects on serum lipids while minimizing the flushing effect (Norris 2006). The available data suggest that intestinal absorption of IHN varies widely, with an average of 70 percent of the administered dose being absorbed into the bloodstream (Harthorn and Lindqvist 1964). However, the majority of IHN that is absorbed appears to remain intact after absorption. Possible direct actions of IHN after absorption have not been demonstrated but seem plausible.

Metabolism of IHN to release free nicotinic acid can result in the physiological functions of nicotinic acid, depending on the dose, rate, and amount of release. Beneficial lipid-lowering effects of free nicotinic acid and extended-release nicotinic acid are well established, but the beneficial effects of IHN on serum lipids would be dependent on uptake of IHN and subsequent release of the nicotinic acid moieties from the IHN molecule. The available reports indicate that IHN does not produce plasma nicotinic acid levels sufficient to lower lipids. Humans given oral doses of IHN obtain peak, but very low, levels of plasma free nicotinic acid at 6 to 12 hours (Welsh and Ede 1961; Sommer 1965), whereas oral doses of nicotinic acid result in peak plasma levels of nicotinic acid at 0.5 to 1 hours (Carlson et al. 1968). The peak plasma levels of nicotinic acid after oral doses of IHN are dramatically lower compared with oral doses of nicotinic acid. For example, a single oral dose of 1,000 mg nicotinic acid resulted in a peak plasma level of 30 µg per mL nicotinic acid (Carlson et al. 1968), whereas 1,000 mg IHN (weight equivalent to approximately 910 mg nicotinic acid) resulted in a peak plasma level of 0.2 µg per mL nicotinic acid (Harthon and Brattsand 1979). Similarly, Kruse et al. (1979) gave 12 healthy young women 2,400 mg IHN orally over a 3-hour period and achieved a peak plasma nicotinic acid level of 0.1 µg per mL. Another experiment conducted in dogs compared the bioavailability of oral doses of 1 g of free nicotinic acid to the same amount of IHN and pentaerythritoltetranicotinate (INN).

The peak plasma level for nicotinic acid was 130 times greater (approximately 65 µg per mL) than the peak plasma level for IHN (approximately 0.5 µg per mL) and 80 times greater than that for INN (0.8 µg per mL) (Harthon and Brattsand 1979).

Some reports indicate that IHN produces a slight increase in plasma nicotinic acid but does not have any significant effects on plasma lipid profiles (Harthon and Brattsand 1979). If IHN is absorbed intact and hydrolyzed in the body with the release of free nicotinic acid and inositol, the extent of hydrolysis appears to be very low. The significant differences in plasma levels of free nicotinic acid that are achieved after similar oral doses of IHN and free nicotinic acid may account for the different effects observed in clinical studies. In fact, the observed effects for IHN may not be related to its total nicotinic acid content, but rather a direct effect of IHN itself. Overall, the evidence indicates that IHN produces only slight increases in plasma nicotinic acid, but these changes are not large enough to significantly alter plasma lipid profiles (Meyers et al. 2003).

Safety Considerations

Nicotinic Acid and Extended-Release Nicotinic Acid

Nicotinic acid can produce a variety of adverse effects, depending on the intake and health of the consumer. The skin flushing reaction produced by nicotinic acid has been recognized for more than 70 years (Bean 1978). When taken on an empty stomach, crystalline nicotinic acid in doses as small as 10 mg may produce a mild and transient, but noticeable, flushing reaction. While not desirable, such reactions produce no known adverse consequences, and they are almost never perceptible when small amounts of nicotinic acid are taken in tablet or capsule form or consumed as part of food.

Serious side effects on the liver or intestines from nicotinic acid have occasionally occurred when gram quantities were taken to lower serum lipids (Rader et al. 1992). Gastrointestinal side effects may include indigestion, nausea, vomiting, and diarrhea and, in some people, may necessitate discontinuation of nicotinic acid supplements. Liver toxicity clinically presents as increases in serum transaminase enzymes of liver origin released by damage to liver cells. Small

increases in serum concentrations of transaminases do not indicate significant liver damage and return to normal after cessation of nicotinic acid intake. More severe reactions may produce jaundice, fatigue, and, in at least one case, fulminant liver failure (Clementz and Holmes 1987).

There is a strong correspondence between the minimum adverse effect level identified through clinical trials and that suggested by published anecdotal case reports. Many severe reactions to nicotinic acid, especially liver toxicity, have involved ill-advised, uninformed, or inadvertent switching from unmodified nicotinic acid preparations to extended-release formulations (Rader et al. 1992; MacKay et al. 2012). Most reported adverse reactions to nicotinic acid have occurred with intakes of 2,000 to 6,000 mg of elemental nicotinic acid per day in both unmodified and extended release forms. There are two anecdotal cases reported in which intake levels were below 1,000 mg: one for extended-release nicotinic acid at 500 mg per day and one for unmodified nicotinic acid at 750 mg per day (Rader et al. 1992). The clinical trial of McKenney et al. (1994) used two groups of adult subjects, studying one for immediate-release nicotinic acid and one for slow-release nicotinic acid. These two groups were observed for 6 weeks at dosage levels of 500, 1,000, 1,500, 2,000, and 3,000 mg per day. The data showed no adverse reactions at 500 mg per day for either form of nicotinic acid, but did show statistically significant effects beginning at 1,000 mg per day for both forms (e.g., gastrointestinal effects for unmodified nicotinic acid, and mild liver toxicity for slow-release nicotinic acid).

More recently, Grundy et al. (2002) studied extended-release nicotinic acid (the FDA-approved product Niaspan) in an attempt to control dyslipidemia in patients with type II diabetes. In this well-designed but modestly sized clinical trial, groups with placebo (n = 49), 1,000 mg extended-release nicotinic acid (n = 45), or 1,500 mg extended-release nicotinic acid (n = 52) were assessed for clinical benefits and monitored for adverse effects. Rates of adverse events other than flushing were similar for the niacin and placebo groups. Four patients discontinued participation owing to flushing, but one of these was in the placebo group. No hepatotoxic effects or myopathy were observed. This trial involved persons with type II diabetes, so the application to the general population is not certain.

Gram quantities of nicotinic acid should not be self-administered as a dietary supplement but may be safely used under the care and monitoring of a physician. Such application, it should be noted, is a pharmaceutical use, not a dietary supplement use. It is especially important for individuals who want to achieve higher intakes of extended-release nicotinic acid to achieve these levels in a gradual step-wise manner.

Nicotinamide

Nicotinamide does not cause a flushing reaction. The 1998 study by the IOM's Food and Nutrition Board (FNB) study determined a LOAEL for vasodilatation and the flushing effect from nicotinic acid; but they then, unfortunately, applied that LOAEL to both nicotinic acid and nicotinamide. Later studies by EFSA and the EVM corrected this error.

IHN

IHN does not cause a flushing reaction. Clinical trials using IHN of up to 4,000 mg daily for 3 months do not demonstrate adverse effects (Sunderland et al. 1988). These clinical trials have not been designed to assess safety of IHN; however, no meaningful adverse effects have been noted in several well-designed clinical trials using IHN in amounts that range from 600 to 4,000 mg daily.

Official Reviews

IOM (1998). In 1998 the Food and Nutrition Board of the IOM, working in cooperation with scientists from Canada, published a comprehensive set of reference values for the B vitamins and choline for healthy U.S and Canadian populations. The panel members also reviewed data and applied risk assessment models to each B vitamin and choline to develop ULs. As noted above, the 1998 IOM report erroneously attributed the flushing effect from nicotinic acid to nicotinamide as well. In addition, it implicitly judged the flushing reaction to qualify as a "hazard" and therefore an appropriate basis for a UL, principally because of the undesirability of the effect rather than any evidence of actual harm. This nuisance caused by nicotinic acid was

clearly illustrated by the accidental addition of the substance to bagel dough, resulting in uncomfortable and unexpected effects that were experienced by several persons who consumed the bagels (Centers for Disease Control 1983). Clearly, this flushing effect is less acceptable in ordinary foods than in dietary supplements because the latter can carry label statements to inform the consumer of this likely effect.

The LOAEL identified by the IOM was 50 mg, based on the clinical studies by Sebrell and Butler (1938) and Spies et al. (1938). Because of the mild and transient nature of the flushing effect, the IOM justified a UF of 1.5 to apply to the LOAEL, leading to determination of a UL of 35 mg. The 35 mg dose, however, may trigger the flushing reaction in a few persons. It is noteworthy that the clinical studies from which the IOM derived the UL value involved bolus doses of nicotinic acid administered to subjects with empty stomachs and no previous regular exposure to dosed nicotinic acid, thus increasing the likelihood of this undesirable effect. The 1998 IOM report did not evaluate the UL for IHN.

European Commission, Scientific Committee on Food (EC SCF 2002). In 2002 the EC SCF published its report on nicotinic acid and nicotinamide, which is one in the series of opinions on the upper levels of vitamins and minerals. The SCF report recognized that the more severe forms of toxicity of nicotinic acid occur only at doses greater than 500 mg but identified a LOAEL of 30 mg, based on the skin flushing reaction in the same studies (i.e., Sebrell and Butler 1938; Spies et al. 1938) relied upon by the IOM. Regardless of the lower LOAEL identified by the EC SCF on the same studies used by the IOM, they selected a larger UF of 3 and therefore derived a UL of 10 mg for nicotinic acid. The EC SCF attempted to justify its identification of the vasodilatory (flushing) effects as the critical adverse effect endpoint (that is, as the *hazard* of concern in the UL risk assessment model) based not only on the nuisance of discomfort but also on the purely hypothetical possibility of exaggeration of positional hypotension and a possibly related increased risk of falls, which are a common cause of morbidity and mortality in the elderly. No evidence has emerged to support this supposition during the decade since this review was published.

For nicotinamide, the EC SCF identified a UL of 900 mg. This value has a substantial margin of safety built in to identify this UL as a value well below the clinical trial values that showed no adverse effects. The 2002 SCF report did not evaluate the UL for IHN.

Expert Group on Vitamins and Minerals (EVM 2003). The EVM's 2003 report concluded that "there are insufficient data from human or animal studies to establish a safe upper level for nicotinic acid." Nonetheless, the EVM set a guidance level for nicotinic acid based on UL methodology applied to animal data. In apparent disagreement with the IOM on a LOAEL of 50 mg (based on Sebrell and Butler 1938 and Spies et al. 1938) and with the EC SCF on a UF of 3, the EVM derived a unique guidance level of 17 mg for nicotinic acid.

Like the EC SCF, the EVM established a safe level for nicotinamide distinct from that for nicotinic acid. It identified no adverse effects for nicotinamide at intakes of 25 mg per kg (Pozzilli et al. 1995) and 42 mg per kg (Lampeter et al., 1998), but judged the database small enough to justify a UF of 3. The derived guidance level for a 60-kg person is 500 mg of supplemental nicotinamide per day. Assuming a food intake of not more than 57 mg from foods, the EVM identified 560 mg per day as the guidance level for total intake of nicotinamide from all sources. The EVM did not establish a guidance level for IHN.

CRN Recommendations

Nicotinic Acid

With its transient and nonpathological effects, the flushing reaction in response to supplemental nicotinic acid deserves to be characterized as a *nuisance*, but not as a *hazard.* When high intakes result from supplementation, appropriate product labeling can alert the consumer of the flushing effect. Thus, flushing does not qualify as a hazard for supplemental intakes of nicotinic acid. The CRN UL for excessive supplemental nicotinic acid is based on the hepatotoxic effects at much higher doses, effects that can be clearly hazardous.

There are only two anecdotal cases of reported hepatotoxic effects at intakes less than 1,000 mg per day, and many uncertainties exist in these cases regarding the amount consumed as well as the presence or absence of pre-existing or confounding conditions such as alcoholism or other compromises of liver function. The clinical trial data of McKenney et al. (1994) are appropriate to identify a NOAEL of 500 mg per day and a LOAEL of 1,000 mg per day for liver or gastrointestinal effects. It should be noted, however, that the adverse reactions to 1,000 mg of unmodified nicotinic acid were mainly gastrointestinal effects, which generally have less potential for serious outcomes, rather than the liver toxicity that results in some persons consuming 1,000 mg per day of slow-release nicotinic acid. With proper labeling, consumers can be aware of gastrointestinal effects and correct as needed. These differences warrant advising a lower limit for slow-release nicotinic acid than for the unmodified form, and the twofold decreases in the NOAEL and LOAEL for slow-release nicotinic acid seem ample, based on case reports (Rader et al. 1992) and clinical trial results (McKenney et al. 1994). Thus, the NOAEL is 250 mg and the LOAEL is 500 mg for slow-release nicotinic acid.

The reports by the IOM, the EC SCF, and the EVM did not set NOAEL or LOAEL values based on the hepatotoxic effects of nicotinic acid. Those reviews identified intakes of about 3 g as the levels at which such effects occur with substantial frequency. None of these reports addressed slow-release nicotinic acid preparations in any detail.

The results by Grundy et al. (2002) challenge the validity of the assumption that extended-release nicotinic acid is necessarily more toxic than crystalline nicotinic acid if used in an appropriate manner, with a gradual escalation of the dose and careful clinical monitoring. It may be very important in the clinical trial by Grundy et al. that the highest doses of extended-release nicotinic acid were achieved by weekly step-wise increases (e.g., 375 mg extended-release nicotinic acid at bedtime in week 1; 2,500 mg in week 2; 750 mg in week 3; and 1,000 mg in week 4). These results indicate that 1,000 mg extended-release nicotinic acid can be safely consumed with a step-wise escalation of intake and medical supervision.

Nicotinamide

There is much less information on nicotinamide than there is for nicotinic acid, but there also appears to be much less use at high levels of intake. Clinical trials on high-dose nicotinamide have been small. One study observed no adverse effects in 16 subjects who received 3,000 mg of nicotinamide per day (Vague et al. 1987), but the method of monitoring for such effects was not specified. Other studies that describe monitoring methods in more detail have found no adverse effects for nicotinamide intakes in the range of 1,000 to 2,900 mg per day (Mendola et al. 1989; Chase et al. 1990; Pozzili et al. 1995; Lampeter et al. 1998). Nicotinamide intakes of more than 3,000 mg per day have resulted in adverse gastrointestinal and liver effects (Rader et al. 1992).

The clinical trial results support a very confident NOAEL of 25 mg per kg per day. Because some of these trials were performed with subjects aged younger than 18 years who had lower than fully adult body weights, 60 kg was used to calculate a NOAEL of 1,500 mg per day. The absence of adverse effects in clinical trials that included nicotinamide dosages of up to 3,000 mg per day reduces the uncertainty in this value.

IHN

Several clinical studies have demonstrated that IHN may have a beneficial effect on endothelium-dependent vasodilatation. The clinical research literature includes several positive studies on the use of IHN for improving blood flow in conditions where blood flow is compromised (Ring and Bacon 1977; Head 1986; O'Hara et al. 1988). IHN is prescribed in Europe as a patented drug known as Hexopal, which is therapeutically indicated for the symptomatic relief of severe intermittent claudication and Raynaud's phenomenon. The usual adult dose of IHN for these conditions is 3 g per day and is increased to 4 g per day if necessary (Genus Pharmaceuticals 2008). Clinical trials using IHN range from 600 to 4,000 mg daily. No adverse effects have been identified in clinical trials even when 4,000 mg per day IHN was administered orally to humans for 3 months (Sunderland et al. 1988). Clinical trials on IHN have not been specifically designed to assess safety of IHN; however, no meaningful adverse effects have been noted in several well-designed clinical trials. These clinical trials support a NOAEL of

4,000 mg. The absence of observed adverse effects does not support the establishment of a LOAEL.

CRN identifies the following LOAEL and NOAEL values for niacin supplements:

Immediate-Release Nicotinic Acid Formulations	
LOAEL	1,000 mg/day
NOAEL	500 mg/day
Flushing label warning threshold	>35 mg/day
Slow-Release Nicotinic Acid Formulations	
LOAEL	500 mg/day
NOAEL	250 mg/day (without step-wise escalation); 500 mg/day (with step-wise escalation of intake over a few weeks)
Flush label warning threshold	Not needed
Nicotinamide	
LOAEL	3,000 mg/day
NOAEL	1,500 mg/day
Flush label warning threshold	Not needed
Inositol Hexanicotinate (IHN) Formulations	
LOAEL	Not established
NOAEL	4,000 mg/day
Flush label warning threshold	Not needed

Considering the infrequent occurrence at the LOAEL levels of intake and the reversible nature of mild, short-term hepatotoxicity, the NOAEL values are identified as the CRN UL values for supplements, provided that immediate-release formulations carry appropriate labeling.

Quantitative Summary for Nicotinic Acid

CRN UL, supplemental intake—immediate release	500 mg/day (based on liver effects)
CRN UL, supplemental intake—based on flushing effect	35 mg/day (no label statement needed)
CRN UL, supplemental intake—slow-release niacin	250 mg/day (step-wise increases)
IOM UL, total intake	35 mg/day (based on flushing effects)
EC SCF UL, total intake	10 mg/day (based on flushing effects)
EC supplement maximum	Not determined
EVM, guidance level, supplemental intake	17 mg/day (based on flushing effects)

Quantitative Summary for Nicotinamide

CRN UL, supplemental intake	1,500 mg/day
IOM UL, total intake	35 mg/day
EC SCF UL, total intake	900 mg/day
EC supplement maximum	Not determined
EVM, guidance level	500 mg/day supplemental intake; 560 mg/day total intake

Quantitative Summary for Inositol Hexanicotinate

CRN UL, supplemental intake	4,000 mg/day
IOM UL, total intake	Not determined
EC SCF UL, total intake	Not determined
EC supplement maximum	Not determined
EVM, guidance level	Not determined

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