Mechanisms of Flushing Due to Niacin and Abolition of These Effects

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There are many factors that increase the risk of cardiovascular disease, and a prominent factor among these is dyslipidemia. The following literature review focuses on the use of niacin therapy in order to treat dyslipidemia and how to control the associated “niacin flush.” The associated studies gathered are reviews and randomized control trials. They were obtained by using electronic searches. Certain keywords took precedence, and articles focusing on niacin therapy were chosen. Recent research has found promising insight into more effective prevention of the niacin-mediated flush through a selective antagonist for the prostaglandin D2 receptor, laropiprant. Aspirin (or NSAIDs) also provide some prevention for flushing, although recent studies have shown that it is not as effective as laropiprant. There is a need for further research in order to come to a clear conclusion regarding combined therapies of aspirin and laropiprant pretreatment, as well as exact dosage requirements. J Clin Hypertens (Greenwich). 2009;11:685–689. ©2009 Wiley Periodicals, Inc.

Niacin, also known as nicotinic acid and vitamin B₃, is a colorless, water-soluble solid that has been known to have many pharmacologic uses. When niacin is taken in large doses, it blocks the breakdown of fats in adipose tissue, therefore altering the lipid levels of blood. Niacin may be used in treating hyperlipidemia because it lowers very-low-density lipoprotein cholesterol (VLDL-C), which is a precursor of low-density lipoprotein cholesterol (LDL-C), or “bad” cholesterol. Due to its inhibitory effects on breakdown of fats, niacin causes a decrease in free fatty acids in the blood, therefore decreasing secretion of VLDL-C and cholesterol by the liver.

Also, by lowering VLDL-C levels in the blood, niacin increases the level of high-density lipoprotein cholesterol (HDL-C), or “good” cholesterol. Therefore, niacin serves a purpose in helping patients with low HDL-C levels who are at high risk for myocardial infarction. Niacin was the first lipid drug shown to prevent cardiovascular disease and death in a large-scale placebo-controlled trial.¹ It has mainly been the HDL-C–elevating effects of nicotinic acid that recently led to a renewed interest in this drug.²–⁴

There are a variety of extended-release formulations of niacin in the market. Statins are the most potent cholesterol-reducing agents available, reducing LDL-C, or “bad” cholesterol by almost 30% to 50%. However, they have less of an effect than niacin and fibrates in reducing triglyceride levels and raising levels of HDL-C, or “good” cholesterol. When niacin therapy was used in combination with simvastatin (belonging to the class of statins), it reduced clinical cardiovascular events by as much as 80%.

PROBLEMS
One of the inherent problems with niacin therapy to prevent severe cardiovascular issues due to high cholesterol are the side effects that occur with the
pharmacologic doses of niacin administered. Facial flushing is the most common reported side effect in patients. This effect is essentially mediated by prostaglandin D2 and its effects on dilatation of small blood vessels. The “niacin flush” consists of skin reddening, itching, and/or burning starting 10 to 20 minutes after oral ingestion of the drugs and lasting about 60 to 90 minutes. This cutaneous vasodilation occurs in 70% to 100% of patients in clinical trials and cases, and many patients are forced to discontinue the medication due to the severe flushing of the face and upper body. It is important that these effects are controlled in order to allow treatment of such conditions as dyslipidemia.

There has been much advancement in the preventative methods of flushing with niacin intake. This research study will discuss how some of these mechanisms may be used to best control, eliminate, and/or prevent flushing. It is critical to recognize that flushing is a frequent event with niacin administration that can be managed with adequate physician and patient education.

EFFECT ON RATE OF NIACIN ADMINISTRATION AND ITS METABOLISM

In an experiment conducted in 12 healthy males, a dose-escalation study was performed with 2000 mg niacin administered at 3 different dosing rates: slow, intermediate, and fast. Plasma and urine were subsequently analyzed to determine the pharmacokinetics of niacin and its metabolites. It was found that the maximum plasma concentration and out-of-sample predictive ability for niacin and nicothnic acid (NUA) increased with the dosing rate, suggesting that the amount of niacin absorbed increased, or that clearance of niacin decreased, as the dosing rate increased. Niacin is used both in the immediate- and extended-release formulations for treatment of dyslipidemia. The rate of niacin administration is believed to affect the adverse event profile, most likely by influencing its metabolic profile. It can be interpreted that an increase in the niacin dosing rate (reflecting a more immediate release) may lead to an increase in total exposure to niacin and NUA, although total dose administered was the same. Immediate-release niacin has been associated with cutaneous flushing, whereas sustained-release formulations have been associated with hepatotoxicity.

In studies pertaining to niacin extended-release tablets, dated 1998, there was one reference to “prolonged-release” niacin acid reducing the incidence of flushing within the first 2 weeks of treatment by more than 50%, compared with immediate-release nicotinic acid. Also, the incidence of flushing was shown to decrease further with continued therapy. In a 96-week study using nicotinic acid, 1.9 episodes/patient/month during the first 4 weeks of treatment had decreased to 0.19 episodes/patient/month by the end of the study.

MEDIATION OF NICOTINIC ACID–INDUCED FLUSHING

As mentioned previously, nicotinic acid–induced cutaneous vasodilatation, or flushing, is one of the major problems with the therapeutic use of this drug, as it develops in virtually every patient taking nicotinic acid. In a few studies, it was determined that nicotinic acid–induced flushing is mediated by the GPR109 NA receptor and involves the formation of vasodilatory prostanoids, which mediate not only the short-term metabolic effects but also the flushing response. Studies have also pointed to epidermal langerhans cells as essential for the cutaneous flushing response by nicotinic acid; they respond to an increase in intracellular calcium concentration due to nicotinic acid, and they express prostanoid synthases required for the formation of vasodilatory prostanoids, including prostaglandin E2 (PGE2) and prostaglandin D2 (PGD2). The calcium increase is the major trigger for activation of phospholipase A2 and the subsequent formation of arachidonic acid, which is further metabolized by cyclooxygenase-1 and PGE2 and PGD2 synthases to create the vasodilatory prostanoids. It has been shown in experiments that depletion of these epidermal langerhans cells but not of macrophages of dendritic cells ablates nicotinic acid–induced flushing. Therefore, from the study mentioned, it would seem as though epidermal langerhans cells, besides their immunologic role, are essential mediators of nicotinic acid–induced flushing or local
regulation of blood flow. This is an important finding that shows potential for a generation of new strategies to suppress unwanted effects.

It has also been hypothesized that macrophages are the source of nicotinic acid–induced PGD2 secretions. The epidermal langerhans cells mentioned above are similar in morphology and function to macrophages and are also similarly derived from monocytes. Nicotinic acid (0.1–0.3 mmol/L) induced PGD2 secretion in cultured human macrophages but not in monocytes or endothelial cells. Preincubation of the cells with aspirin (100 mmol/L) entirely prevented the PGD2 side effects (see below for effects of acetylsalicylic acid [ASA]). This study provides some evidence that macrophages play a significant role in mediating the niacin flush and may also lead to better strategies to eliminate this limiting side effect.

Another study, conducted in 2006, screened a large set of human tissue and cells for the expression of GPR109A and characterized them by using immunocytochemistry with antibodies and specific cell markers, then assayed them for PGD2 release following nicotinic acid stimulation. The results maintained that langerhans cells specifically respond to nicotinic acid by releasing PGD2, which then activates vascular cells and causes cutaneous vasodilation. The GPR109A mRNA distribution in primary tissues was primarily expressed in a variety of immune cell types and epidermis, but it was not detected in endothelial cells, smooth muscle cells, dermal fibroblasts, or dermis.

In a more recent study, it was asked whether peroxisome proliferator-activated receptor α (PPARα) activation modulates epidermal langerhans cell function. The results showed that PPARα is expressed in immature langerhans cells and is down-regulated in mature langerhans cells, suggesting that an early decrease in PPARα expression in the cells may allow them to mature. It was also concluded that PPARα activation by endogenous ligands may provide a molecular signal that allows langerhans cells to remain in an immature state within the epidermis for extended periods of time despite minor environmental stimuli. Since PPARα activity can also be modulated by exogenous compounds, it is also a promising drug target in inflammatory skin diseases.

The most recent data on niacin’s mechanism of action indicate that it directly inhibits hepatic diacylglycerol acyltransferase 2, resulting in an inhibition of triglyceride synthesis and decreased apolipoprotein B–containing lipoproteins. By inhibiting the surface expression of hepatic ATP synthase β chain, niacin decreases hepatic holoparticle high-density lipoprotein catabolism and raises HDL-C levels. Niacin also increases redox potential in arterial endothelial cells, resulting in the inhibition of redox-sensitive genes. These recent findings may help to better explain the multiple actions of niacin.

EVIDENCE FOR USE OF ASA (ASPIRIN)

It was determined decades ago that the flushing response of nicotinic acid can be inhibited by pretreatment with cyclooxygenase inhibitors. It is known that flushing due to nicotinic acid is mediated by prostaglandins, and because ASA (aspirin) is an effective inhibitor of prostaglandin synthesis, it has been used and has been successful in preventing or reducing the severity of niacin-induced flushing, even currently. Although the recommendation to use ASA is supported by both pharmacologic evidence and experience from clinical studies, it is difficult to determine the relationship between ASA dose and efficacy in reducing the intensity/frequency of flushing.

Some studies suggest that a low dose (80 mg) of ASA would be ineffective, although most studies use a 325-mg dose and presume full effectiveness. According to Niaspan (Abbott Laboratories, Abbott Park, IL) prescribing information, administration guidelines for extended-release niacin indicate that flushing can be minimized by careful dose escalation, administration of extended-release niacin at bedtime with administration of ASA 30 minutes prior, and avoiding taking the drug on an empty stomach. The manufacturers of Niaspan have also stated that <6% of their patients discontinue use because of flushing. Daily use of ASA and/or other NSAIDs in doses of at least 325 mg 30 minutes before niacin administration is required, and due to this there may be a potential limit to long-term use. An example of a limiting effect would be the onset of gastrointestinal bleeding or generalized prolonged bleeding time.

SUPPRESSION OF FLUSHING WITH AN ANTAGONIST TO PGD2 RECEPTOR SUBTYPE 1

Laropiprant is a selective antagonist of the PGD2 receptor subtype 1 (DP1) that may be involved in the mediation of niacin-induced flushing. It has been shown that the coadministration of laropiprant at doses of 30, 100, or 300 mg with extended-release niacin significantly lowered flushing symptom scores (by approximately ≥50%) and also significantly decreased malar skin blood flow.
as measured by laser Doppler perfusion imaging.\textsuperscript{39} These experiments concluded that the DP1 receptor antagonist laropiprant was effective in suppressing both subjective and objective manifestations of niacin-induced vasodilation.\textsuperscript{39} The results also showed that laropiprant 300 mg and extended-release niacin 1500 mg resulted in less flushing and warmth compared with pretreatment with ASA 325 mg before administration of extended-release niacin 1500 mg. The laropiprant decreased by 75\% the peak increase in skin blood flow that was induced by extended-release niacin alone. The fact that pretreatment with ASA (at 325 mg 30 minutes before niacin administration) was less effective than coadministration with laropiprant (100 or 300 mg) provides great insight into where the future of niacin treatment may be headed.\textsuperscript{39}

The evaluation of safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple oral doses of laropiprant in healthy male volunteers was conducted in another study.\textsuperscript{40} It was found that single doses up to 900 mg and multiple doses up to 450 mg were generally well tolerated. The results exhibited dose-proportional pharmacokinetics and also were not affected by food. The oral absorption is rapid (2–8 hours), and the terminal half-life is approximately 12 to 18 hours.\textsuperscript{40} There were also no serious adverse effects associated with usage and no discontinuations due to adverse effects.\textsuperscript{40}

A more recent phase 2 dose-ranging study was designed to assess whether laropiprant would reduce extended-release niacin–induced flushing in dyslipidemic patients and support an accelerated extended-release niacin dosing paradigm: initiating extended-release niacin at 1 g and advancing rapidly to 2 g.\textsuperscript{41} In part A of the study, 154 dyslipidemic patients were randomized to laropiprant 150 mg/d or placebo in a 9-week 2-period crossover study. Patients who completed part A (n=122) entered part B (with a 2-week washout), together with additional patients who entered part B directly (n=290). Part B patients were randomized to placebo, extended-release niacin 1 g (no previous titration), or extended-release niacin 1 g coadministered with laropiprant 18.75, 37.5, 75, or 150 mg for 4 weeks, with doubling of the respective doses for the remaining 4 weeks. Patients treated with laropiprant and extended-release niacin experienced significantly less extended-release niacin–induced flushing than those treated with extended-release niacin alone during the initiation of treatment (extended-release niacin 1 g, week 1) and the maintenance treatment (extended-release niacin 1–2 g, weeks 2–8).\textsuperscript{41} It can be concluded that all doses of laropiprant were maximally effective in inhibiting niacin-induced flushing without altering the beneficial lipid effects of the extended-release niacin. Overall, the significant reduction in extended-release niacin–induced flushing provided by laropiprant plus extended-release niacin supports an accelerated extended-release niacin dose-advance paradigm to achieve rapidly a 2-g dose in dyslipidemic patients.\textsuperscript{41} A possible advantage of using laropiprant over ASA is that NSAIDs affect platelet aggregation and cause an increase in bleeding time compared with placebo, while laropiprant does not (following single doses up to 400 mg or multiple doses up to 450 mg).\textsuperscript{40}

CONCLUSIONS

Niacin lowers triglyceride and LDL-C levels and raises HDL-C levels. Current treatment for dyslipidemia via niacin therapy is restricted in a sense because the flushing response seen in most patients leads to discontinued use after a short period of time. While ASA pretreatment has allowed for the continuation of niacin treatment in many cases, there are potential long-term complications that may arise if used for long periods of time, including gastrointestinal bleeding and prolonged bleeding time. The selective antagonist of the PGD2 receptor subtype 1 (DP1), laropiprant, holds much promise in enhancing the tolerability of and compliance with niacin treatment for patients with cardiovascular disease or dyslipidemia. While substantial strides have been made in niacin therapy and its associations with dyslipidemia, there is a need for further research, especially in terms of event-based trials.

REFERENCES

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