



Prolonged-release nicotinic acid

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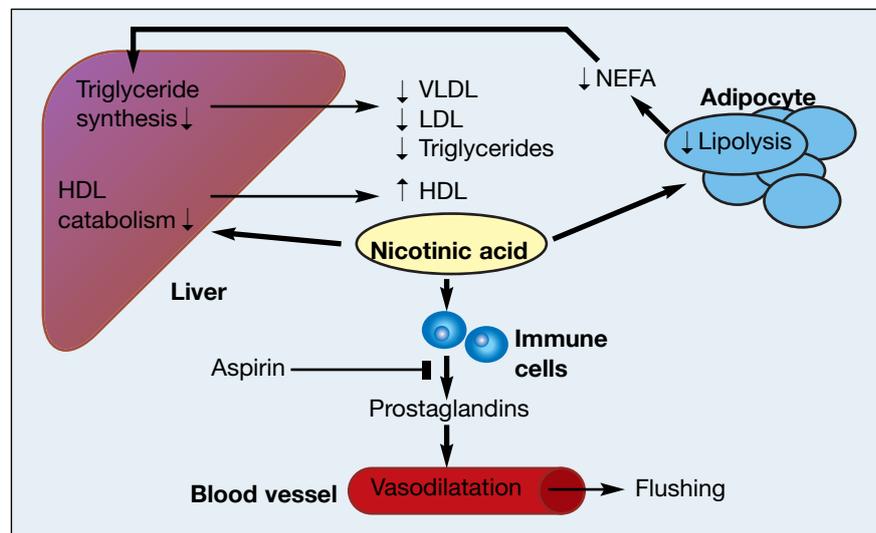
Introduction

Dyslipidaemia frequently encountered in patients with type 2 diabetes is characterised by increased total cholesterol, triglycerides, free fatty acids, low-density lipoprotein cholesterol (LDL) particles, and low levels of high-density lipoprotein cholesterol (HDL) in plasma. Current management strategies in the treatment of dyslipidaemia in diabetes emphasise total cholesterol and LDL reduction by statin therapy, whereas other lipid-modifying agents are generally recommended as second-line options. Nicotinic acid favourably affects all traditional classes of lipoproteins and has been used to treat dyslipidaemia since the 1950s.

Pharmacology

The pharmacological action of nicotinic acid is outlined in Figure 1. Nicotinic acid, also known as niacin, is a water-soluble vitamin essential for the synthesis of co-enzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). Adequate daily intake of 12–18mg nicotinic acid is required in adults to prevent pellagra and most multivitamin tablets contain small amounts (up to 50mg) of nicotinic acid or its derivative nicotinamide. Immediate-release (IR) or crystalline nicotinic acid, the original form of the lipid-regulating drug, causes immediate cutaneous flushing in many recipients. In comparison, sustained-release (SR) – also known as timed-release, controlled-release or long-acting – preparations cause less flushing but are less effective in altering lipid profiles and are associated with an increased risk of hepatotoxicity. Prolonged-release nicotinic acid (PRNA, Niaspan), also referred to as

Figure 1. Pharmacological action of nicotinic acid on liver, adipocyte and blood vessel



extended-release (ER) niacin in the USA, has an absorption rate intermediate between IR and SR preparations.

The liver is the major target organ for nicotinic acid, which decreases synthesis of triglycerides and their subsequent availability for very low-density lipoprotein (VLDL) assembly.¹ Without altering apolipoprotein A (apoA) synthesis, nicotinic acid also inhibits HDL-apoA catabolism, resulting in net increases in HDL available for reverse cholesterol transport. In adipose tissue, activation of a G-protein-coupled receptor identified in 2003, the nicotinic acid receptor, which is also known as GPR109A or HM74A, decreases lipolysis and thus release of non-esterified fatty acids (NEFA) into the circulation. Nicotinic acid is also believed to increase production of prostaglandins D₂ and E₂ by immune cells resulting in vasodilatation. It is by this mechanism that you get the adverse cutaneous flushing reaction commonly experienced by recipients.

Trials of safety and efficacy

Multiple randomised, controlled clinical trials have examined the efficacy of PRNA in the treatment of dyslipidaemia, including both PRNA as monotherapy and comparisons between PRNA monotherapy and PRNA/statin combinations.^{1,2} In brief, single-drug comparison studies demonstrate that treatment with PRNA 1000–2000mg daily for four to 12 weeks significantly reduced total cholesterol (-4% to -12%), LDL (-6% to -17%), and triglycerides (-11% to -35%), and increased HDL levels (15% to 26%). PRNA is the most potent lipid-regulating agent currently available to increase HDL levels.

Five published randomised clinical trials compared potential effects of PRNA/statin combinations on lipid profiles with statin alone at the same dosage. In these studies, PRNA 1000mg further improved levels of HDL, triglycerides and apolipoprotein B in patients receiving simvastatin 20mg but not in those treated

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by a high dose of rosuvastatin (40mg). Lipoprotein(a) was the only lipid parameter significantly altered (-18%) by PRNA 1000mg/rosuvastatin 40mg combination compared with rosuvastatin monotherapy.

The Coronary Drug Project was the only published large-scale study evaluating the effects of nicotinic acid on long-term clinical outcome in patients with coronary heart disease (CHD).³ After six years, nicotinic acid (at an average dose of 2000mg daily) reduced recurrent non-fatal CHD, stroke or transient ischaemic attack, and cardiovascular surgery ($p < 0.05$), but did not affect total mortality in patients receiving nicotinic acid ($n = 1119$) compared with the placebo group ($n = 2789$). Mortality data at 15 years, more than nine years after the study ended, showed that both total and CHD mortality rates among patients originally randomised to nicotinic acid were approximately 11% less than in those originally randomised to receive placebo. Median survival time was 13.0 and 11.4 years in the nicotinic acid and placebo groups, respectively ($p = 0.0012$).

PRNA is well tolerated in all clinical trials and most adverse effects were transient and mild to moderate. Adverse events observed in patients receiving a combination of PRNA with a statin were essentially the same as those expected of the individual statins. Marked elevations in liver transaminases are mostly associated with the slow-release formulations of nicotinic acid. Severe hepatotoxicity occurs rarely with PRNA and there is little evidence to support any increased risk of hepatotoxicity attributed to the addition of PRNA to statin therapy. Although myopathy has been reported in patients receiving PRNA/statin combinations, addition of PRNA does not appear to increase the risk of myopathy or myalgia compared with statin monotherapy.

Cutaneous flushing due to nicotinic acid-induced, prostaglandin-mediated vasodilatation is the most commonly encountered side effect in up to 80% of patients.¹ To reduce potential side effects, PRNA can be commenced at low dose and titrated up depending on tolerability. The recommended daily maintenance dose is 1000–2000mg. Aspirin administered

30 minutes before or concomitantly with PRNA can reduce the incidence, intensity and duration of flushing. Other strategies for improving compliance include consistent dosing with meals or at bedtime, and avoidance of alcohol, hot beverages and spicy food-stuff close to or after dosing.

Specific evidence for use in diabetes

The potential of nicotinic acid to adversely affect glycaemic control has limited the use of PRNA in diabetes patients. ADVENT is the only published randomised, placebo-controlled, double-blind study looking at the efficacy and safety of once-daily PRNA in type 2 diabetes patients.⁴ A total of 146 adult patients with HbA_{1c} no greater than 9% on two separate occasions were assigned to one of the following three groups: placebo ($n = 49$), PRNA 1000mg ($n = 45$) or PRNA 1500mg ($n = 52$) daily for 16 weeks. Concomitant medications included metformin, sulphonylureas, insulin and statins, but not thiazolidinediones. After eight weeks, dose-dependent increases in HDL were evident in both PRNA treatment groups compared with the placebo group. At week 16, HDL increased by 0.04mmol/L, 0.20mmol/L (19%, $p < 0.05$) and 0.28mmol/L (24%, $p < 0.05$) in the placebo, 1000mg and 1500mg groups, respectively. Triglyceride levels were reduced only in patients receiving PRNA 1500mg (-28% to -36%, $p < 0.05$), whereas changes in LDL in all three groups were $< 10\%$. A small but statistically significant increase in HbA_{1c} from 7.21% to 7.50% ($p = 0.048$) was observed after 16 weeks in those receiving PRNA 1500mg.⁴

Discussion

Despite the widespread use of statins in people with diabetes, cardiovascular mortality and morbidity remain a challenge. Mounting evidence supports targeting low HDL and hypertriglyceridaemia in addition to LDL reduction in the prevention of cardiovascular complications. PRNA should be considered an option to improve diabetic dyslipidaemia characterised by low HDL and high triglycerides or in patients who cannot tolerate statins. Ongoing studies

Key points

- Nicotinic acid reduces triglyceride synthesis and HDL catabolism in the liver, and inhibits lipolysis in adipose tissue
- Nicotinic acid favourably affects all major classes of lipoproteins and is the most potent lipid-regulating agent currently available to increase HDL levels in plasma
- Limited long-term data suggest beneficial effects of nicotinic acid on the prevention of cardiovascular disease

such as AIM-HIGH will shed light on the effects of statin/PRNA combination therapy on cardiovascular disease prevention. Laropiprant, a selective antagonist of the prostaglandin D₂ receptor subtype 1 (DP₁), is being tested in clinical trials to inhibit prostaglandin-mediated cutaneous flushing, with a view to improving the tolerability and compliance of PRNA.

Conflict of interest statement

Clement Ho has no conflict of interest to declare. Mark Strachan has received consultancy fees, fees for speaking and reimbursement for attending a symposium from GlaxoSmithKline, and sits on a GSK Independent Data Monitoring Committee; he has also received funds to support staff members from Takeda, Pfizer and sanofi-aventis. Simon Walker has received honoraria related to advisory activities from Merck Pharmaceuticals.

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