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Immediate release niacin effect at stratified lipid levels☆,☆☆,☆☆☆

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ABSTRACT

Background: The Coronary Drug Project demonstrated a significant decrease in non-fatal myocardial infarction, and total mortality using immediate release niacin (IRN). However, AIM-HIGH and HPS-2-THRIVE showed no additional benefit from adding niacin to statin therapy.
Objective
To evaluate the efficacy and tolerability of IRN on low-density-lipoprotein-cholesterol (LDL-C), high-density-lipoprotein-cholesterol (HDL-C), triglycerides, and lipoprotein (a) (Lpa) at stratified lipid levels in a monotherapy IRN group (MTG) and a combined therapy group (CTG) statin + IRN.
Methods: We retrospectively studied 185 patients who were prescribed IRN for elevated LDL-C, triglycerides, lipoprotein a (Lpa), or low HDL-C. All patients used the same IRN products.
Results: 157 patients had complete records. (MTG = 74 patients, CTG = 83 patients with 68 combined with statins). Mean IRN dose = 2474 mg. Mean duration = 3.05 years.
If initial LDL-C was <130, LDL-C did not decrease significantly with IRN. If initial LDL-C > = 130, LDL-C decreased 35% in MTG vs. 32% decrease in CTG. If initial HDL-C < 40, there was a 40% increase in MTG vs. 61% increase in CTG. If initial triglycerides > 150, there was a 48% decrease in MTG vs. 54% decrease in CTG. Lpa decreased 49% for all patients with initially elevated Lpa. Data except for LDL-C < 130 were significant ($p < .001$).
Conclusion: Lowering LDL-C is the corner stone for decreasing cardiovascular events. IRN reduces LDL-C significantly when initial LDL-C > 130, but not significantly when LDL-C < 130. Patients in AIM-HIGH and HPS-2-THIRVE received statin therapy causing very low initial LDL-C. Our results may explain why adding niacin to statin therapy failed in AIM-HIGH and HPS-2-THRIVE since niacin did not further lower LDL-C.

1. Introduction

The first report regarding decreasing total serum cholesterol with immediate release niacin (IRN) was published in 1955 [1]. This initial report was followed by a number of studies demonstrating similar findings [2–5], but most of these studies regarded reduction of total serum cholesterol and triglycerides since high density lipoprotein-cholesterol (HDL-C) was not frequently analyzed at that time and low density lipoprotein-cholesterol (LDL-C) was not measured or calculated. The seminal study regarding niacin was the Coronary Drug Project begun in 1966 [6] and concluded in 1974. This double blind, randomized, placebo-controlled, male only, secondary prevention study demonstrated the efficacy of niacin for decreasing definite nonfatal recurrent myocardial infarction but failed to demonstrate a significant decrease in total mortality and cause specific mortality. However, a follow-up study with nearly complete ascertainment of the original niacin and placebo groups at 15 years demonstrated a significant 11% decrease in mortality for the niacin group compared to placebo group even though the niacin group was no longer treated after conclusion of the original study [7].

Niacin has been demonstrated over the course of other studies to increase HDL-C, and decrease LDL-C, LDL particles, apoprotein B, triglycerides, and lipoprotein (a) [8,9]. Epidemiologic studies suggest that these changes in lipids would be beneficial [10]. In this regard, studies more recent than the Coronary Drug Project using longer acting niacins have demonstrated positive results in clinical trials for reductions in plaque and cardiovascular events [11,12]. Despite these salutary results, niacin has not been widely used because of side effects, which include cutaneous issues such as flushing, itching, and occasional rash. Other reported side effects include increasing fasting glucose [2], uric acid [3], increased atrial fibrillation, and gastrointestinal effects such as abdominal pain, diarrhea, and decreased appetite [6]. These side effects

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CTG, combined therapy group; HDL-C, high density lipoprotein cholesterol; IRN, immediate release niacin; LDL-C, low density lipoprotein cholesterol; Lpa, lipoprotein (a); MTG, monotherapy IRN group.

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led to the development and utilization of niacin preparations that were more slowly released to reduce the side effects, particularly flushing. Many of these products are nonprescription preparations sold as food additives. Approximately a decade ago an extended release form became a prescription medication that has gained favor with many physicians because of its once daily dosage and presumed decrease in flushing [13]. Further, studies using longer acting niacins with or without a statin have demonstrated positive results in clinical trials [11,12]. The IRN form is currently seldom used today. The extended release prescription product in conjunction with intensive statin and other therapy was recently used in a clinical trial, AIM-HIGH [9], which failed to demonstrate that adding this niacin preparation provided an additional benefit beyond that of statins combined with other lipid treatments. Further, the HPS-2-THRIVE [14] study demonstrated a higher incidence of adverse drug reactions in the simvastatin-extended release niacin–laropiprant (with or without ezetimibe) group than in the control statin arm without significant additional reduction in cardiovascular events. Thus, results for use of longer acting niacin forms have given inconsistent results. The major purpose of adding niacin in most studies has been to increase HDL-C and niacin products have been used in conjunction with statins and ezetimibe to lower LDL-C. Whether raising HDL-C pharmacologically is useful remains an unresolved issue [15], but lowering LDL-C has been demonstrated in many studies to reduce cardiovascular events [16,17]. Niacin also reduces LDL-C and the immediate release form may reduce LDL-C more that the extended release form.

Immediate release niacin is very inexpensive compared to a prescription extended release form and the immediate release form has been used in our lipid clinic for many years. The purpose of the current study was 1) to determine at what lipid levels IRN causes the greatest changes in LDL-C, HDL-C, lipoprotein a, and triglycerides 2) to determine the side effects of a more modern immediate release preparation than that used in the Coronary Drug Project and 3) and to evaluate the lipid results of immediate release niacin as monotherapy and as an addition to prior statin therapy.

2. Methods

This was a retrospective study of all patients recommended to take immediate release niacin (IRN) in a lipid clinic between 1980 and 2013. Study data were retrieved from paper charts or electronic records. The study was approved by the Institutional Review Boards of the University of Arizona and informed consent was deemed unnecessary since data were kept in an anonymous manner.

2.1. Patients

Treatment with IRN was recommended for patients >18 years. Patients were prescribed niacin due to several common etiologies: statin and other LDL-C lowering medication intolerance with elevated LDL-C, considerably elevated triglyceride, very low HDL, elevated Lpa, and as an adjunct for those with familial hyperlipidemia whose LDL-C remained substantially elevated after statin therapy.

2.2. Niacin protocol

All patients used the same preparations of immediate release niacin (Rugby Pharmaceutical Company 100 mg with the product # 0536–4076-01-2 and 500 mg with the product numbers of 0-0536-4078-10-8). All patients were started on the same niacin protocol with the initial dose of 50 mg taken following meals 3 times per day. The dose was doubled every 2 weeks. Chewable 81 mg aspirin was used on alternate weeks or as necessary to prevent flushing. To stop a severe flush patients were instructed to chew three 81 mg aspirins and drink a large glass of water. Aspirin was discontinued as soon as patients no longer experienced flushing. The maximal daily dose of IRN was decided by correction of the lipid abnormality or 3000 mg daily, whichever came first.

2.3. Data collection

The reason for initiation of niacin therapy, initial pre-niacin data and last niacin data were recorded. The following parameters were identified: birthdate, date for first and most recent evaluation, comorbidities, LDL-C, HDL-C, triglyceride, lipoprotein (a) (Lpa), fasting glucose, alanine transaminase (ALT) and aspartate transaminase (AST). Patients were specifically asked about adverse reactions to niacin at each clinic visit and results were recorded except for initial, occasional, mild flushes at low doses of niacin. Co-administered lipid medications and reason for discontinuing niacin, if applicable, were also recorded.

2.3.1. Laboratory data

All blood samples were collected in the fasting condition. LDL-C was computed from the Friedewald equation if triglycerides were <400 mg/dl. If triglycerides >400 mg/dl, LDL-C was obtained via direct measurement. If a patient had normal Lpa on the initial sample, no further Lpa measurements were obtained. If Lpa was abnormal, and the patient had no recent infection, Lpa was re-measured at full niacin dosage.

2.4. Statistical analysis

To evaluate changes in different lipid panel parameters paired 2 tail T-tests were used to compare initial and final data within each group (MTG, CTG). Values of $p < 0.05$ were considered significant. Changes between MTG and CTG and at stratified lipid levels were tested by unpaired T-test.

3. Results

3.1. Study cohort

Of the 185 eligible patients, 23 patients had missing records leaving 162 patients with available records. Most of those with missing records were initially evaluated between 1980 and 1995 as some of these records were purged by the hospital. Of the 162 patients who had records, 5 never started IRN or never returned for a second visit leaving 157 patients for analysis, all of whom had initial and on treatment data. However, not all data for Lpa, fasting glucose, ALT, and AST were available on the last evaluation. In that instance we included analyses for the prior to final visit.

Of the 157 patients with available records, 74 were treated with MTG and 83 were on the CTG and other lipid lowering medications such as statin, gembrozil, fenofibrate, or omega 3 fatty acids. 68 of the 83 patients were treated only with the combination of IRN + statins. These 68 patients will be called the CTG. The mean age for these 157 patients was 55.8 years; mean duration of niacin therapy was 3.05 years. 47% of patients were classified as secondary prevention and the remainder as primary prevention. Secondary prevention was defined as patients having had a documented stroke, myocardial infarction, coronary bypass surgery, coronary interventional procedures at catheterization, coronary calcium score > 400, significant carotid atherosclerosis or significant peripheral vascular disease.

Data for lipid changes and number of patients for the following parameters are included in Tables 1-3.

3.1.1. LDL-C change

(Data are reported in mg/dl).