Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 55 (2006) 1697–1703
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

Lipoprotein effects of combined ezetimibe and colesevelam hydrochloride versus ezetimibe alone in hypercholesterolemic subjects: a pilot study

Robert H. Knopp*, Christine Tsunehara, Barbara M. Retzlaff, Brian Fish, Hien Nguyen, Susan Anderson, Thuy Nguyen

Northwest Lipid Research Clinic, Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, University of Washington School of Medicine, Seattle, WA 98104, USA

Received 27 February 2006; accepted 14 August 2006

Abstract

Two drug classes act in the intestine to lower cholesterol. Ezetimibe inhibits cholesterol absorption, whereas bile acid–binding resins enhance cholesterol excretion via enhanced conversion to bile acids. Combining these 2 classes may be beneficial, but cholestyramine binds ezetimibe, and the combined effect of colesevelam hydrochloride and ezetimibe was little studied. The aim of the study was to determine if adding colesevelam HCl to ezetimibe provides additional lowering of low-density lipoprotein– and apolipoprotein B–containing lipoproteins or alters ezetimibe levels. Twenty subjects with low-density lipoprotein cholesterol (LDL-C) levels of 130 mg/dL or higher were enrolled and taught a National Cholesterol Education Program Step I diet. At a second baseline visit, lipoproteins were measured and subjects were randomly allocated to (1) ezetimibe 10 mg daily with placebo colesevelam HCl twice daily (E) or (2) ezetimibe 10 mg daily with 1.875 g colesevelam HCl twice daily (E + C). Lipoproteins were measured 6 and 12 weeks after initiating treatment. Baseline characteristics (mean ± SD) were statistically indistinguishable in E vs E + C: LDL-C (mg/dL), 167 ± 26 and 158 ± 27; triglyceride, 134 ± 75 and 140 ± 67; and BMI, 29.4 ± 4.9 and 27.8 ± 6.6 kg/m^2, respectively. Percent changes after 12 weeks in E vs E + C were as follows: LDL-C, −24 ± 12 vs −30 ± 11 (P = .102); triglyceride, −19 ± 34 vs 36 ± 85 (P = .054; at 6 weeks, P = .009); total cholesterol, −19 ± 9 vs −15 ± 8 (P = .50); non–high-density lipoprotein cholesterol, −25 ± 10 vs −21 ± 11 (P = .70); apolipoprotein B, −31 ± 14 vs −22 ± 14 (P = .41). Plasma ezetimibe levels at 12 weeks were 21% lower in E + C vs E, a nonsignificant difference (P = .54). In conclusion, in the short term, colesevelam HCl may not consistently add cholesterol-lowering benefit to ezetimibe. This observation requires confirmation.

1. Introduction

The intestine is an important organ in cholesterol regulation and is an important target for dietary and drug management of hypercholesterolemia. Two medication classes act in the intestine, the bile acid–binding resins and the cholesterol absorption inhibitors.

Bile acid–binding resins enhance cholesterol excretion by inhibiting bile acid reabsorption and increasing cholesterol conversion into bile acids [1]. The older bile acid–binding resins have limited use because of their bulk and nonspecific binding of other drugs. Nonetheless, cholestyramine diminished coronary artery disease incidence on the order of 20% in a high–cardiovascular disease risk, primary prevention setting [2,3]. The newer resin, colesevelam hydrochloride (WelChol, Sankyo Pharma Inc, Parsippany, NJ), has greater affinity for bile acids, requires only one tenth the dose of the older resins, yields better low-density lipoprotein lowering, and has less nonspecific binding of concomitant medications (Fig. 1).

Ezetimibe is the first of a new class of cholesterol absorption inhibitors (Fig. 1). Low-density lipoprotein levels are lowered an average of 18% [4-6]. Ezetimibe acts by inhibiting the intestinal cholesterol transporter, NPC1L1 [7]. This transporter resembles a lysosomal cholesterol transport protein defective in Niemann-Pick disease, a childhood disorder of lysosomal cholesterol storage [8].

Previous studies have shown that cholestyramine, the original bile acid–binding resin, binds ezetimibe and decreases its absorption [9,10]. As a result, ezetimibe is recommended to be taken at a different time than bile acid–binding resin [10]. However, binding of ezetimibe by colesevelam HCl has not been studied. The effect of

* Corresponding author. Tel.: +1 206 744 9116; fax: +1 206 744 9989.
E-mail address: rhknopp@u.washington.edu (R.H. Knopp).

0026-0495/$ – see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2006.08.013

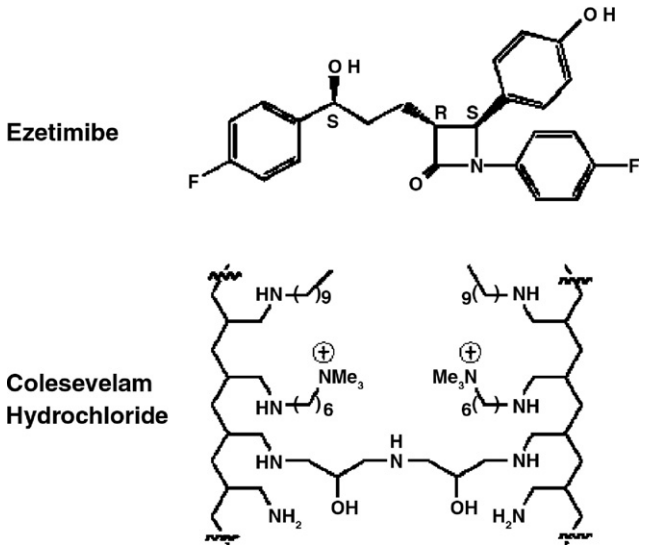

Fig. 1. Structural formulas for ezetimibe and colesevelam.

combined colesevelam HCl–ezetimibe administration has not been extensively studied, but a beneficial effect of combined drug has been observed in an open-label, crossover design study and in a retrospective lipid clinic chart review [11,12]. The present study addresses the questions: (*a*) does ezetimibe given with colesevelam HCl lower low-density lipoprotein cholesterol (LDL-C) more than ezetimibe given alone and (*b*) does colesevelam administration reduce plasma ezetimibe levels?

2. Methods

2.1. Study subjects

Study participants were recruited from public advertising and clinic records. The study protocol and advertising were reviewed and approved by the University of Washington Human Subjects Review Committee. Men and women aged 21 to 80 years were eligible with fasting LDL-C levels equal to or exceeding 130 mg/dL [13] at the initial screening visit. Eligible fasting plasma triglyceride levels were less than 350 mg/dL at the initial screening visit.

Subjects were ineligible if they had a clinical diagnosis of diabetes or had a fasting plasma glucose level of more than 125 mg/dL at the initial screening visit. Also ineligible were subjects who had coronary heart disease, congestive heart failure, blood pressure of more than 150/90, untreated hyper- or hypothyroidism, nephrotic syndrome or proteinuria on dipstick, taking lipid-altering drugs in the past 4 weeks, any concurrent illness that would prevent successful study participation, recent history of drug or alcohol abuse, swallowing or intestinal motility disorders, cancer diagnosis within 5 years except nonmelanoma skin cancer, unstable or cyclic hormone replacement therapy, pregnancy or lactation, or prior study participation within 30 days.

2.2. Study design

The study was double blind, randomized, and parallel in design consisting of 4 study visits over a 4-week screening period and a 12-week treatment interval. In addition, one subject was crossed over in a double-blind manner, receiving ezetimibe, colesevelam HCl placebo for 6 weeks, then ezetimibe, colesevelam HCl for 6 weeks. This subject is included in the table of characteristics of subjects studied, in the results of subjects at 6 weeks in the ezetimibe group, and separately in the narrative results.

Initial eligibility was established by a telephone contact with the study coordinator. If eligible, the subject was sent a consent form to review and given an appointment for a clinic visit after an overnight fast.

At visit 1, the consent form was explained to the subject and the questions were answered. After signing the consent form, vital signs were obtained including body weight, and a brief physical examination was also performed to rule out exclusionary disease states. Blood was drawn for a Cholestech (Cholestech, Haywood, CA) estimation of cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), calculated LDL-C, and glucose. A urinalysis was done to rule out urinary tract infection and clinically significant proteinuria. A baseline aspartate aminotransferase (AST) was also obtained. A diet history was obtained, and subjects were counseled on a National Cholesterol Education Program Step I diet [14] and instructed to maintain this level of intake throughout the study.

At visit 2 (baseline), subjects had a derived lipoprotein quantification, a medication and symptoms review, and vital signs were again obtained. Adherence to the National Cholesterol Education Program Step I diet was reviewed. Subjects were randomly assigned to their medication using a predetermined randomization code. Subjects were given a 6-week supply of ezetimibe 10 mg once daily at bedtime (Merck-Schering Plough, North Wales, PA) and colesevelam HCl placebo (3 capsules twice per day with meals) (Sankyo Pharma, Parsippany, NJ) or ezetimibe 10 mg once daily at bedtime and 0.625-g tablets of colesevelam HCl (3 tablets twice per day with meals).

At visit 3 (week 6), subjects returned for a repeat derived lipoprotein quantification, serum AST measurement, recording of vital signs and body weight, review of Step I diet, and medication use and symptom review. Returned medication was counted, and adherence to the assigned medication was calculated as a percentage of the medication dispensed. Then, the second 6-week supply of medication was provided.

At visit 4 (week 12), all of the procedures and measurements were repeated as at visit 3.

2.3. Measurements

Eligibility lipoprotein lipid and glucose measurements were performed at the first visit on the Cholestech LDX Lipid Analyzer using reagent-impregnated pads enclosed in