International Journal of Research and Development in Pharmacy and Life Sciences
Available online at http//www.ijrdpl.com
February - March, 2014, Vol. 3, No.2, pp 910-915
ISSN: 2278-0238

Research Article

A CLINICAL STUDY OF DRUG-DRUG AND DRUG-FOOD STUDY INTERACTIONS ON THE MANAGEMENT OF HYPERLIPIDEMIC DISEASE: SIMVASTATIN, EZETIMIBE AND OMEGA-3-FATTY ACIDS

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(Received: November 01, 2013; **Accepted:** December 03, 2013**)**

ABSTRACT

This study was designed to investigate the effects of combination of ezetimibe, simvastatin and omega-3-fatty acids on lipoproteins in patients with mixed dyslipidemia. Among the 102 patients were screened 98 who met the inclusion and exclusion criteria after 6 weeks on a strict diet therapy were grouped into four treatment groups (2 patients left out in between). The inclusion criteria were mixed dyslipidemia with a high triglyceride level (200-499 mg per 100 ml) and a total cholesterol level more than 200 mg per 100 ml. Present study was conducted on dyslipidemic patients receiving ezetimibe (10 mg) alone, simvastatin (20 mg) alone, omega-3-fatty acids (4 g) alone and combination of simvastatin (20 mg) and ezetimibe (10 mg) and omega-3-fattyacids (4g) daily for 12weeks. After 12 weeks treatment (Tc, LDL)was found decreased, Tg level reduced significantly and HDL level increased in the combination therapy (Simvastatin, ezetimibe and omega-3-fattyacids) than monotherapy. From the result it is concluded that combination therapy of these three may be considered as an optimal treatment option for patients with mixed dyslipidemia.

Keywords: Simvastatin, Ezetimibe, Omega-3-fattyacids.

INTRODUCTION

Hyperlipidemia has been defined as plasma cholesterol and triglycerides levels exceed normal levels. Complications of atherosclerosis, such as myocardial infarction, stroke and peripheral vascular disease still account for half of the deaths in india. It is for the reason that so much attention is directed to toward understanding the etiology of hyperlipidemia and the development of effective therapeutic strategies. Less than 200, 130, 200 mg/dl of Total cholesterol (Tc), LDL cholesterol and triglycerides (Tg) and more than 60 mg/dl of HDL are considered to be the desired normal level.

Simvastatin is in a group of drugs called HMG CoA reductase inhibitors or statins. All statins act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme HMG-CoA reductase, the rate-limitingenzyme of the HMG-CoA reductase pathway, the metabolic pathway responsible for the endogenous production of cholesterol. Statins are more effective than other lipid-regulating lowering LDL cholesterol concentration, but they are less effective than the fibrates in reducing triglyceride concentration.

Ezetimibe is a drug that lowers plasma cholesterol levels. It acts by decreasing cholesterol absorption in the small intestine. Ezetimibe localises at the brush border of the small intestine. It appears to bind to a critical mediator of cholesterol absorption and the Niemann-pick C1 like protein on the gastrointestinal tract epithelial cells as well as

hepatocytes.

Omega-3 polyunsaturated fatty acids are found in oil from certain types of fish, vegetables, and other plant sources. These fatty acids are not made by the body and must be consumed in the diet. Omega-3 polyunsaturated fatty acids work by lowering the body's production of triglycerides. High levels of triglycerides can lead to coronary artery disease, heart disease, and stroke.

The mechanism of action of ezetimibe, a novel selective cholesterol absorption inhibitor, complements that of the statins and Omega 3 fatty acids. When these lipid-modifying agents are co-administered, both the exogenous and endogenous pathways of cholesterol metabolism are affected for dual activity and broader lipid control.

MATERIALS AND METHODS

The present study was a placebo controlled, randomized and parallel group, conducted at clinical research centre, Chennai to investigate the effect of ezetimibe, simvastatin and omega-3-fatty acids on dyslipidemic patients. The protocol was submitted to ethics committee and got approval. Male Subjects were selected based on inclusion and exclusion criteria. Informed consent was signed by the subjects.

Inclusion criteria of patients were mixed dyslipidemia with high triglyceride level 200-499 mg/dl and total cholesterol level more than 200 mg/dl. Exclusion criteria were hypersensitivity to drugs and liver toxicity. 182 patients were screened selected 126 patients were divided into 5 groups. (6 subjects left out in between).

Group 1 patients were received a placebo treatment. Group 2 received monotherapy with 10 mg ezetimibe (24 patients) orally, Group 3 was administered with 20 mg of simvastatin (n = 24) orally, Group 4 administered with omega-3-fattyacids 4g (n=24) and Group 5 received treatment with co administration of ezetimibe (10 mg), simvastatin (20 mg) and omega-3-fattyacids (4 g). All treatments were daily orally for 90 days.

Propose to collect blood and urine samples on 0 day (before dosing), 25thday, 50thday and 90th day for monitoring signs of muscle and liver injury. Vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature) are monitored during screening, before treatment administration and at 25thday, 50thday and 90thday. Subjects are continually observed and questioned for possible adverse events.

Pharmacodynamics

Propose to collect blood and urine samples on 0 day (before dosing), 25th day, 50th day and 90th day for lipid concentrations (LDL, TC, HDL and TG). Lipid concentrations are determined by direct quantitative assay methods (enzymatic colorimetric tests) using validated commercial assay kits.

Statistical analysis

Propose to calculate mean, standard deviation or standard error, and coefficient of variation, ANOVA for the lipid parameters LDL, TC, HDL and TG.

RESULTS AND DISCUSSION

In this study, the effect of ezetimibe 10 mg, 20 mg simvastatin plus omega-3-fatty acids combination therapy was evaluated in patients with mixed dyslipidemia. The percentage decrease from the baseline in LDL levels and triglycerides the primary outcome variable, was significantly greater with ezetimibe and simvastatin plus omega-3-fatty acids than with ezetimibe and simvastatin or omega-3 alone. Therefore significant reductions of total cholesterol levels observed after treatments. HDL cholesterol level was much increased after combination of ezetimibe, simvastatin and omega-3 fatty acids than ezetimibe, simvastatin or omega-3 fatty acids monotherapy.

Monotherapy of ezetimibe, Simvastatin and Omega 3 fatty acids

Ezetimibe has a rapid onset of action, with 8.52% of LDL, 7.64 % of TC and 9.15 % of TG reductions and 0.284% increase on HDL observed in 25th day of initiating mono therapy. On day 50, ezetimibe alone reduced 11.14% of LDL, 18.15 % of TC and 13.43 % of TG and also 1.28% HDL was increased. On day 90, ezetimibe reduced 24.85% of LDL, 20.52 % of TC and 21.74 % of TG and also 6.3 % HDL was increased.

Simvastatin has a rapid onset of action, with 7.72 % of LDL, 10.2-% of TC and 5.25 % of TG reductions and also 0.5893%increase in HDL observed in 25th day of initiating mono therapy. On day 50, Simvastatin alone reduced 9.87% of LDL, 17.13 % of TC and 12.19 % of TG reduction and also 2.545% HDL was increased. On day 90, Simvastatin reduced 22.86 % of LDL, 23% of TC and 18.21 % of TG reduction and also 5.799 % HDL was increased.

Table 01 Effect of Ezetimibe on Lipid Profiles

Lipoprotein mg /dl	Ezetimibe 10 mg			
	Base	**25thday**	**50thday**	**90thday**
T-c	231.4 + 1.292	213.7 + 0.7083	189.4+ 2.161	183.9 + 1.092*
T-G	189 + 1.387	171.7 + 1.076	163.6 + 1.182	147.9 + 0.931*
HDL-c	42. 17+ 0.5668	42.29 + 0.6355	42.71 + 0.5229	42.83 + 0.316
LDL-c	156.1±0.9926	142.8±0.6702	138.7 +0.8881	117.8+ 0.981*

T-c - Total cholesterol; T-g – Triglycerides; HDL-c - High density Lipoprotein; LDL-c - Low density Lipoprotein. Comparisons were made between base and 25th, 50th and 90th day. Statistical significance done by ANOVA. *P<0.05

Table 02 Effect of Simvastatin on Lipid Profiles

Lipoprotein mg /dl	Simvastatin 20mg			
	Base	**25thday**	**50thday**	**90thday**
T-c	233.4±1.049	209.5±0.8618	193.4±1.255	179.7 ± 1.834*
T-G	287.1.7± 1.132	272± 1.848	252.1± 1.676	234.8 ± 1.136*
HDL-c	42.42± 0.3943	42.67 ± 0.2056	43.50 ± 0.3185	44.88 ± 0.290
LDL-c	134.7 ± 0.9826	133.3 ± 0.5332	121.4 ± 1.010	103.9 ± 1.621*

T-c - Total cholesterol; T-g – Triglycerides; HDL-c - High density Lipoprotein; LDL-c - Low density Lipoprotein. Comparisons were made between base and 25th, 50th and 90th day. Statistical significance done by ANOVA. *P<0.05

Table 03 Effect of Omega-3-fattyacids on lipid profiles

Lipoprotein mg/dl	Omega-3-fattyacids			
	Base value	**Day 25**	**Day 50**	**Day 90**
T-c	222.2±0.4242	210.7±0.5160	209.5±0.8533	202.6±0.5275*
T-g	250.6±0.5547	231.2±0.4255	220.2±0.5516	179.8±0.8968*
HDL-c	43.08±0.1797	42.71±0.2290	44.38±0.2875	46.71±0.3155
LDL-c	155±0.3585	148.8±0.7279	143.5±0.8469	140.7±0.4112*

T-c - Total cholesterol; T-g – Triglycerides; HDL-c - High density Lipoprotein; LDL-c - Low density Lipoprotein. Comparisons were made between base and 25th, 50th and 90th day. Statistical significance done by ANOVA. *P<0.05

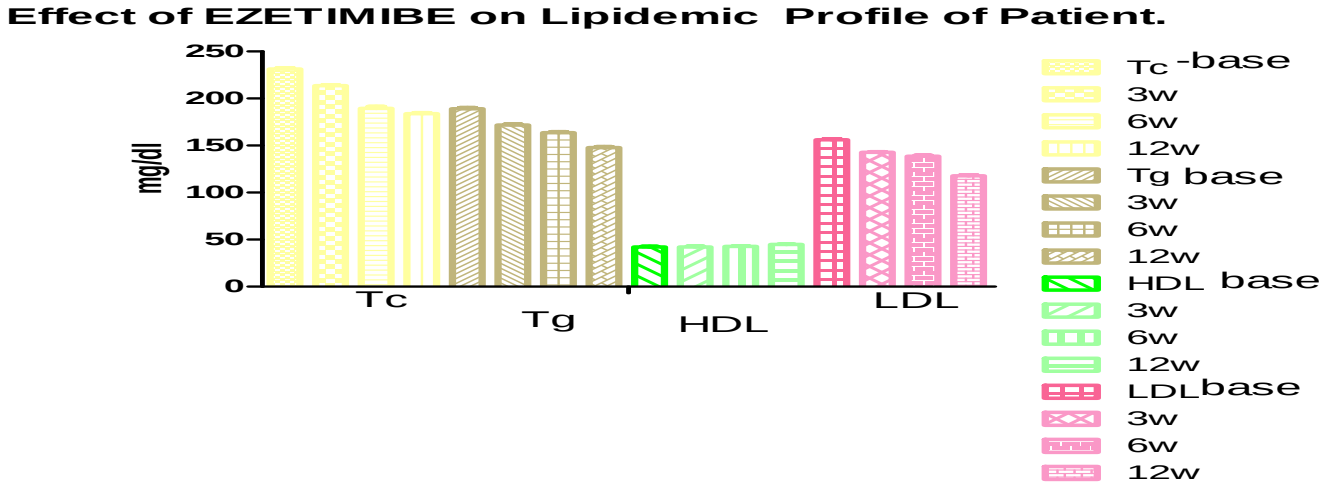

Figure 01: Effect of ezetimibe on lipidemic profile

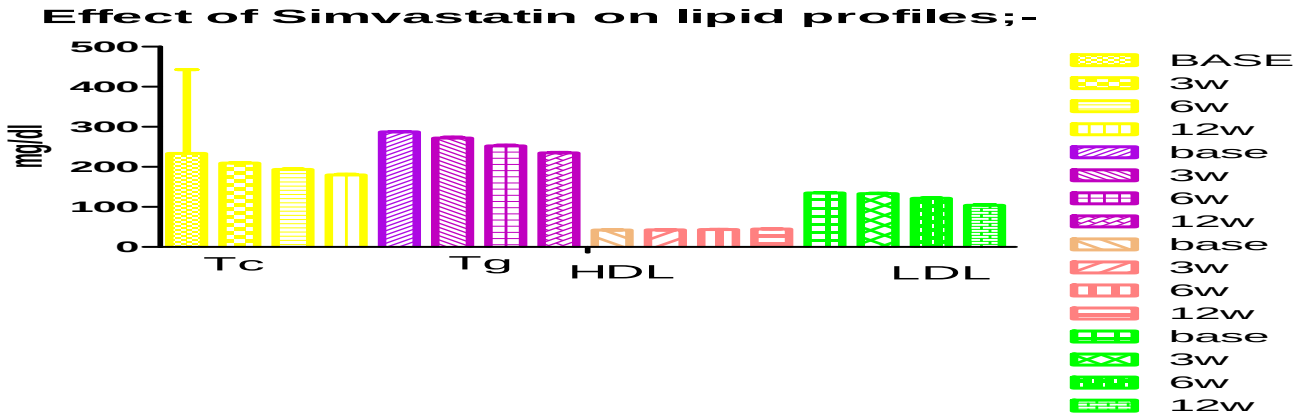

Figure 02: Effect of simvastatin on lipidemic profile

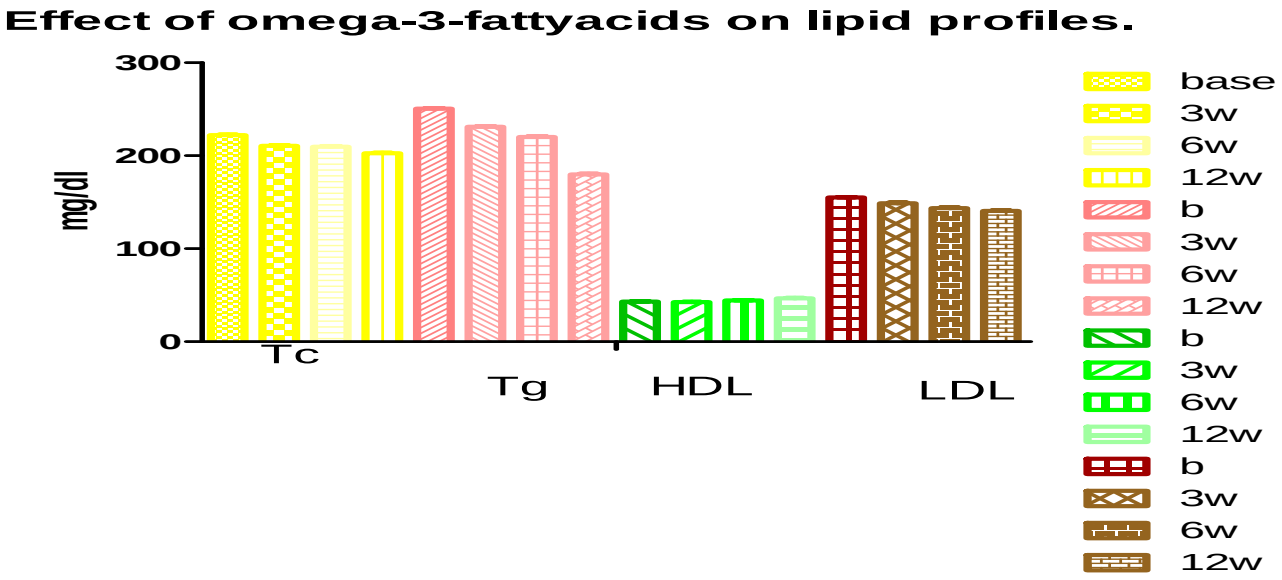

Figure 03. Effect of Omega-3-fattyacids on lipid profiles

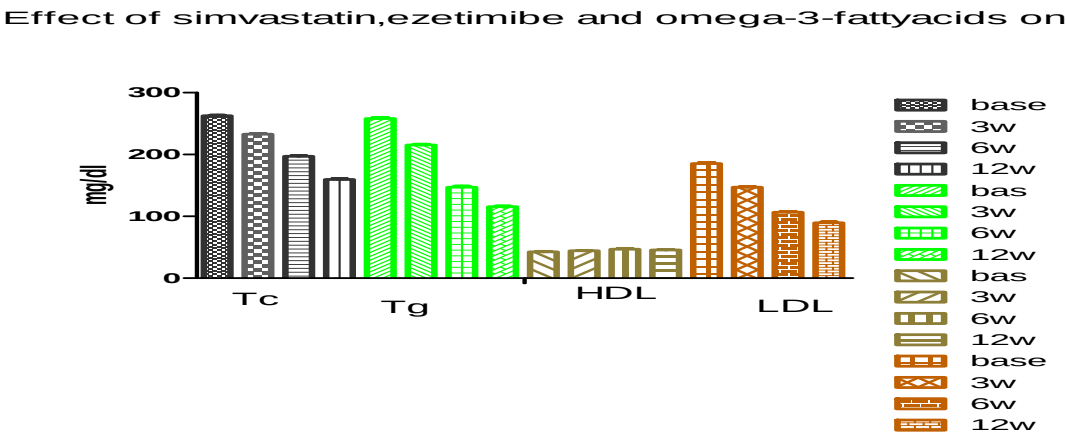

Figure 04 Effect of Simvastatin, ezetimibe and Omega-3-fattyacids on lipid profiles

Omega-3-fattyacids has a action, with 4% of LDL, 5.17% of TC and 7.74% of TG reductions and also 0.85% reduction in HDL observed in 25th day of initiating mono therapy On day 50, Omega 3 fatty acids alone reduced 7.41 % of LDL, 5.71 % of TC and 12.13 % of TG reduction and also 3.01% HDL was increased. On day 90, Omega 3 fatty acids reduced 9.22 % of LDL, 8.82 % of TC and 28.25 % of TG reduction and also 8.40 % HDL was increased.

Combined therapy with ezetimibe, Simvastatin and Omega -3-fattyacids

Simvastatin, ezetimibe and Omega-3-fattyacids co administration has a action, with 20.61% of LDL, 11.34% of TC and 16.51% of TG reductions and also 3.7% increase in HDL observed in 25th day of initiating mono therapy. On day 50, Omega 3 fatty acids alone reduced 42.41 % of LDL, 24.98 % of TC and 42.98 % of TG reduction and also 9.67% HDL was increased. On day 90, Omega 3 fatty acids reduced 51.67 % of LDL, 39.26 % of TC and 55.15 % of TG reduction and also 6.74 % HDL was increased.

The results of the combined therapy of simvastatin 20 mg, 10 ezetimibe and omega 3 fatty acids is presented in Table 04 and Figure 04. The results from present study shows that the combined therapy of ezetimibe, simvastatin and omega 3 fatty acids was well tolerated, with no evidence of increased incidence of adverse events or increases in clinical laboratory tests indicative of liver or skeletal muscle toxicity. The combination therapy caused significantly greater reductions in LDL and triglycerides than mono therapy with these drugs.

CONCLUSION

The reduction of elevated serum total cholesterol and low density lipoprotein (LDL) reduces the risk of coronary artery disease, resulting in a decrease in cardiovascular mortality. Combination of drugs that act by different mechanisms can provide additive effects in reduction of LDL and triglycerides, useful to meet target levels. In conclusion, combined therapy of ezetimibe 10 mg, simvastatin 20 mg and Omega 3 fatty acids to subjects with hypercholesterolaemia was well tolerated and significantly reduced serum LDL-c, T-g and T-c. Thus, combined therapy of ezetimibe 10 mg, simvastatin 20 mg and Omega 3 fatty acids is an alternative to titrating to higher doses of simvastatin. Since mono therapy may be ineffective in reaching the target by simvastatin, combination therapy would be the desirable option to meet the target in the management of hypercholesterolemia. Goals of future studies are to establish the efficacy and tolerability of combination therapy with large populations with primary hypercholesterolaemia.

Acknowledgement

I am grateful to Dr. M. Vasudevan for his guidance throughout the completion of this research work.

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