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Research Article

CLINICAL STUDY OF PHARMACODYNAMIC DRUG INTERACTION ON THE MANAGEMENT OF HYPERLIPIDEMIC DISEASE

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Abstract: This study was designed to investigate the pharmacodynamic interaction of co-administration of ezetimibe and omega-3-fatty acids on lipoproteins of mixed dyslipidemia in human subjects. Human male subjects were induced hyperlipidemia and they were divided into 4groups of 24 subjects in each group. The inclusion criteria were mixed dyslipidemia with a high triglyceride level (200-499mgper100ml) and a total cholesterol level more than 200mg per 100ml. Present study was conducted on dyslipidemic subjects receiving ezetimibe (10mg) alone, omega-3-fatty acids(4g) alone and combination of ezetimibe (10mg) and omega-3-fattyacids (4g) daily for 90days. After 90days treatment, (Tc, LDL) was found decreased, Tg level reduced significantly and HDL level increased in the combination therapy (ezetimibe and omega-3-fattyacids) than their mono therapies. From the result it was concluded that combination therapy of these two may be considered as an optimal treatment option for mixed dyslipidemia.

Keywords: Ezetimibe, omega-3-fattyacids, combination therapy, Hypolipidemic therapy.

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 this reason that so much attention is directed to toward understanding the etiology of hyperlipidemia and the development of effective therapeutic strategies. Normally the level should be less than 200,130 and 200mg/dl of Total cholesterol (Tc), LDL cholesterol and triglycerides (Tg) respectively and more than 60mg/dl of HDL are considered to be the desired normal level.

Ezetimibe is a drug that lowers plasma cholesterol levels. It act 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, 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 fattyacids 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[1-2].

MATERIALS AND METHODS

The present study was a placebo controlled study, conducted at clinical research centre. Human ethical clearance obtained from local independent committee to investigate the effect of ezetimibe, and omega-3-fatty acids on dyslipidemic subjects. Male subjects were selected based on inclusion and exclusion criteria. Inclusion criteria were mixed dyslipidemia with high triglyceride level 200-499 mg/dl and total cholesterol level more than 200 mg/dl. Written permission obtained from individuals to participate in the study.

Group 1 received placebo, Group2 received monotherapy with 10 mg ezetimibe (24subjects) orally, Group3 administered with omega-3-fattyacids 4g (n=24) and group 4 received treatment with co-administration of ezetimibe (10mg), and omega-3-fattyacids (4g). All treatments were daily orally for 90 days.

Propose to collect blood and urine samples on 0 day (before dosing), 25th day, 50th day and 90th day for monitoring signs of muscle and liver injury. Vital signs

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(blood pressure, heart rate, respiratory rate, and oral body temperature) are monitored during screening, before treatment administration and at 25th day, 50th day and 90th day. Subjects are continually observed and observed 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 measurement (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, and used one way ANOVA (followed by Dunnet's t test) for the lipid parameters LDL, TC, HDL, and TG. P value less than 0.05 was considered as significant.

RESULT AND DISCUSSION

In this study, the effect of ezetimibe 10mg, omega3 fatty acids, ezetimibe plus omega-3-fatty acids combination therapy was evaluated in subjects with mixed dyslipidemia. The percentage decrease from the baseline in LDL levels and triglycerides the primary outcome variable, was significantly greater with ezetimibe plus omega-3-fatty acids than with ezetimibe or omega-3 alone. There were significant reductions of Total cholesterol levels observed after treatments. HDL cholesterol level was much increased after combination of ezetimibe, and omega-3 than ezetimibe, or omega-3 mono therapies.

Table 1: Placebo treatment (group I)

	Placebo treatment			
	Base	25thday	50thday	90thday
T-c	233.4±1.049	232.7±0.234	232.4±0.255	233.7±1.834
T-G	287.12± 1.132	287.34± 1.848	286.1± 1.676	286.8±1.136
HDL-c	42.42± 0.3943	42.67 ± 0.2056	42.50 ± 0.3185	42.88 ± 0.2906
LDL-c	134.7 ± 0.9826	133.3 ± 0.5332	133.4 ± 1.010	133.9± 1.621

There were no changes in lipid parameters during placebo treatment.

Table 2: 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 + 0.9312.
HDL-c	42. 17+ 0.5668	42.29 + 0.6355	42.71 + 0.5229	44.83 + 0.3166
LDL-c	156.1±0.9926	142.8±0.6702	138.7 +0.8881	117.8+ 0.9811

T-c-Total cholesterol, T-g-Triglycerides, HDL-c – High density Lipoprotein, LDL- c, Low density Lipo protein. Comparisons were made between, base and 25th, 50th and 90th. Symbol represents the statistical significance done by ANOVA.

*P<0.05,

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.

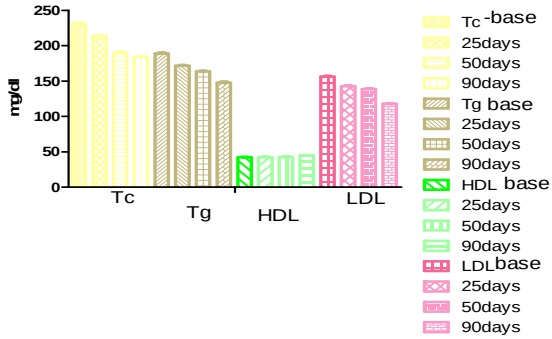

Fig1: Effect of lipid ezetimibe on lipid profiles.

Table.3: Effect of omega-3-fattyacids on lipoproteins

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

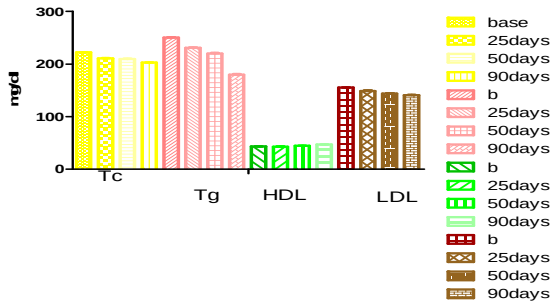

Fig.2: Effect of omega-3-fattyacids on lipoproteins

Omega-3-fattyacids reduced 4% % of LDL, 5.17%-% of TC and 7.74% of TG and also 0.85% increase 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.

Table 4: Effect of ezetimibe and omega-3-fattyacids on lipoproteins

mg/dl	Base value	Day 25	Day 50	Day 90
LDL	185.3±1.70	147.1±0.92	106.7±1.174	89.54±1.562
TC	262.6±0.9797	232.8±0.9743	197±1.222	159.5±1.290
TG	258±1.965	215.4±1.343	147.1±1.733	115.7±1.012
HDL	42.71±0.5433	44.29±0.4564	46.83±0.9492	45.58±0.7516

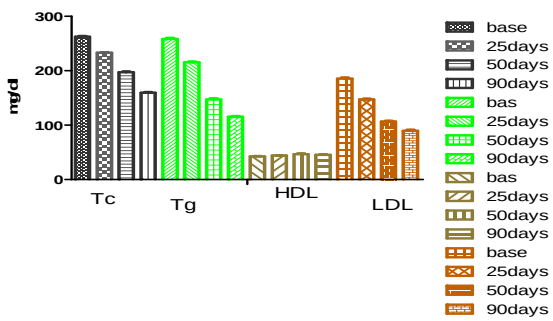

Fig 3: Effect of ezetimibe and omega-3-fattyacids on lipoproteins

Ezetimibe and Omega-3-fattyacids co-administration had reduced 20.61% of LDL, 11.34% of TC and 16.51% of TG and also 3.7% increase in HDL observed in 25th day of initiating mono therapy. On day 50, Omega 3 fatty acids and ezetimibe 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 and ezetimibe reduced 51.67 % of LDL, 39.26 % of TC and 55.15 % of TG reduction and also 6.74 % HDL

The results from present study shows that the combined therapy of ezetimibe, 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 cholesterol (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 LDL reduction and triglycerides, useful to meet target levels.

In conclusion, combined therapy of ezetimibe 10 mg, and Omega 3 fatty acids to subjects with hypercholesterolaemia was well tolerated and significantly reduced the serum LDL-C, TG and TC. Thus, combined therapy of ezetimibe 10 mg, and Omega 3 fatty acids is an alternative to titrating to higher doses of ezetimibe mono therapy in reaching the target. 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.

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