INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

FENOFIBRATE ADVERSE EFFECTS VERSUS ATORVASTATIN

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ABSTRACT

The most frequently used lipid-lowering drugs in hyperlipidaemia are fibrates, statins (mainly atorvastatin),or combination of both.The present study was designed to assess the adverse effects of fenofibrate and atorvastatin monotherapy on liver biomarkers in patients with hyperlipidaemia.

Forty patients with hyperlipidaemia were included in this study. Of whom twenty patients received a dose of 200 mg/day fenofibrate and other twenty patients were on a dose of 20 mg/day atorvastatin for a period of one month .Lipid profile and liver biomarkers were analyzed and studied before and after treatment.

Liver function tests in hyperlipidaemic patients on atorvastatin (20 mg/day) showed high significant elevation ($P<0.005$) in mean serum total bilirubin and total alkaline phosphatase after one month of treatment. Whereas high significant elevation ($P<0.005$) appeared in mean serum alanine aminotransferase and aspartate aminotransferase in patients onfenofibrate (200mg/day) after one month of treatment.In conclusion,Atorvastatin (20 mg/day)treatment may inducecholestatic injury while fenofibrate (200mg/day) treatment mayinduce hepatocellular injury.

Keywords: Fenofibrate, Atorvastatin , liver function tests.

1. INTRODUCTION

Fenofibrate is one of the most commonly prescribed lipidlowering agents. It exerts its primary effects on lipid metabolism by the activation of Peroxisome proliferator-activated receptor alpha (PPAR-α) by fenofibric acid, the active moiety in plasma. Several target genes modulating lipid metabolism are encoded through the activation of these receptors[1].Moreover, fenofibrate exerts an antioxidant, anti-inflammatory, and anti-ischemic protective effect on the heart[2], intestine [3],brain [4], and kidney[5].

Atorvastatin, a member of statins, is used for lowering blood cholesterol. It is act as a competitive inhibitor of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase which catalyzes the reduction of HMG-CoA to mevalonate, which is the rate-limiting step in hepatic cholesterol biosynthesis[6].

Atorvastatin also have multiple non-lipid-lowering“pleiotropic” effects, it havevasoprotective, anti-inflammatory, antioxidant and immune modulating properties[7].

1.1 Patients and Methods

Forty patients, (22 females, 18 males) their ages ranging from (30-45) year, with hyperlipidaemia recruited from Al-yarmoukhospital. Of whom twenty patients received a dose of 200 mg/day fenofibrate and other twenty patients receiveda dose of 20 mg/day atorvastatin for a period of one month.

Diagnoses are made based on clinical symptoms and biochemical tests. Patients with liver disease, renal failure, and heart failure have been excluded .Blood samples are aspirated at the baseline (before treatment) and after one month of treatment with atorvastatin or fenofibrate to measure serum levels of liver function tests and lipid profile by Photometric Colorimetric Test. LDL-Cholesterol was calculated according to Friedewald's formula .

All blood samples were obtained after receiving patients' informed consent and followeda standardized protocol that approved by the institutional ethics committee.Results are shown as mean ± SD with 95% confidence interval (CI), and *P* values of 0 <0.05 were regarded to be statistical significant. Paired t-test was used for evaluating the effects of both drugs. All statistical analyses were performed using series SPSS version 16.

1.1.1 RESULT

The results of lipid assay showed high significant decreases (P< 0.001) in mean serum levels of total cholesterol ,triglyceride and low density lipoprotein cholesterol and insignificant change (P>0.05) in mean serum level of high density lipoprotein cholesterol after one month treatment with atorvastatin (20 mg/day) compared with the baseline value (before treatment).

Whereas treatment with fenofibrate (200 mg/day) after one month caused high significant decreases (P< 0.005) in mean serum levels of total cholesterol ,triglyceride and low density lipoprotein cholesterol and high significant increase (P< 0.005) in mean serum level of high density lipoprotein cholesterol compared with the baseline value (before treatment), Table -1 and Figure-1.

Analysis ofthe adverse effects of treatment on liver function revealed high significant increase (P< 0.001) in mean serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) with fenofibrate intake for one month compared with the baseline mean (before treatment) .On the contrary , high significant increase (P< 0.001) in mean serum levels of total bilirubin and total alkaline phosphatase (ALP) recited in patients with atorvastatin intake for one month compared with the baseline mean (before treatment),Table -1 and Figure-2.

1.1.2 DISCUSSION

Inhibition of the enzyme hydroxymethylglutaryl-coenzyme Areductase by atorvastatin decreases *de novo* cholesterol synthesis, increasing expression of low-density lipoprotein receptors (LDL receptors) on hepatocytes. This increases LDL uptake by the hepatocytes, decreasing the amount of LDL-cholesterol in the blood. Atorvastatin also reduces blood levels of triglycerides and slightly increases levels of HDL-cholesterol[8],this may explain the results of the present study showing that administration of atorvastatin 20 mg/day for one month highly significantly decreases (P<0.001) serum levels of total cholesterol, triglyceride and low density lipoprotein cholesterol (table-1and figure-1).

Fenofibrate is a fibric acid derivative, a prodrug comprising fenofibric acid linked to an isopropyl ester. It lowers lipid levels by activating Peroxisome proliferator-activated receptor alpha (PPARα)[12,13] PPARα activates lipoprotein lipase and reduces apoprotein CIII,

which increases lipolysis and elimination of triglyceride-rich particles from plasma. PPARα also increases apoproteins AI and AII, reduces very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) containing apoprotein B, and increases high-density lipoprotein (HDL) containing apoprotein AI and AII[9] .

In this respect, the results obtained in this study are consistent with those indicated previously, in which the intake of 200 mg/day fenofibrate for one month treatment produced high significant decreases (P< 0.005) in mean serum levels of total cholesterol, triglyceride and low density lipoprotein cholesterol and high significant increase (P< 0.005) in mean serum level of high density lipoprotein cholesterol (table -1 and figure-1).

Alanine aminotransaminase (ALT) is the enzyme that catalyses the reversible transfer of the α-amino group of alanine to the α-ketogroup of ketoglutaric acid to generate pyruvate and glutamate. ALT is an important enzyme for gluconeogenesis and amino acid metabolism. In humans, high ALT activity has been detected mostly in liver tissue [(10)].Therefore an increase in serum ALT level has been suggested to be an effective indicator of impaired liver parenchymal cells[16]. The mechanism by which intracellular ALT is transferred to the serum is may be due to leakage from damaged hepatocytes, even though blebbing of the plasma membrane[11].

Many reports , as ascertained in the results of this study , demonstrated that patients treated with fibrates produce transient elevations of aspartate aminotransferase (AST) and ALT in serum occur without any other signal of hepatotoxicity and is safe and well tolerated[14,15].

Fenofibrateprominently increases the expression of PPAR- α target gene in the liver[17].PPAR-α regulates hepatic neutrophil accumulation and hepato cellular injury. Furthermore, activation of PPAR- α in cultured hepatocytes is directly protective against oxidant-induced injury with significant impact on the hepatic inflammatory response[18]. Proliferation of peroxisomes in hepatocytes is induced by activation of the transcription factor PPAR-α[19] . Therefore it was found that PPAR-α agonist ,fenofibrate, prevent cell damage, oxidative stress, and inflammatory processes[20].

Calderon *et al.,* 2010 reported that atorvastatin is mostly associated with cholestatic liver injury than hepatocellular injury[21] and was proven by rapid improvement with cessation of the drug and recurrence of the injury with the re-initiation of atorvastatin[22]. The studies mentioned above are compatible with the results of the current study about the effects of atorvastatin treatment 20mg/day for one month on serum levels of ALP and total bilirubin in patients with hyperlipidemia .

1.1.3 CONCLUSION

Treatment with fenofibrate produced transient elevations of AST and ALT levels whereas treatment with atorvastatin produced transient elevations of ALP and Total bilirubin .Both drugs significantly reduced lipid biomarkers with significant increase in HDL-C level occurred on fenofibrate treatment more than atorvastatin treatment.

Table 1: Alterations of biochemical parameters (lipid and liver) after one month treatment with atorvastatin or fenofibrate

	Baseline (before treatment)	After atorvastatin treatment	After fenofibrate Treatment
Number(F,M)	40 (22 ,18)	20(10 ,10)	20(12 ,8)
Total Cholesterol (mg/dl)	290.144 ± 45.48	205.86 ± 32.84 ***	250.07 ± 30.5 **
Triglycerides (mg/dl)	385.43 ± 190.65	315.68 ±178.18 ***	335.46 ± 164.7 **
HDL-Cholesterol (mg/dl)	45.75±10.5	46.86 ± 11.72	52.66 ±12.35 **
LDL-Cholesterol (mg/dl)	167.2 ± 24.45	96.97 ± 18.16 ***	150.32 ± 20.42 **
ALT (U/L)	23 ± 8	24.5 ± 7.6	42.26 ± 15 ***
AST (U/L)	22 ± 4	23.5 ± 7	38.3 ± 19 ***
γGT (U/L)	18.4 ± 7	19.8 ± 10.5	18.3 ± 6.8
Total Bilirubin (mg/dl)	0.67 ± 0.2	1.12 ± 0.53 ***	0.68 ± 0.22
ALP (U/L)	63.34 ± 10	95.54 ± 15 ***	62.65 ± 9.5

P-values: * (0.05); ** (0.005); *** (0.001); (γGT)= gamma glutamyltransferase

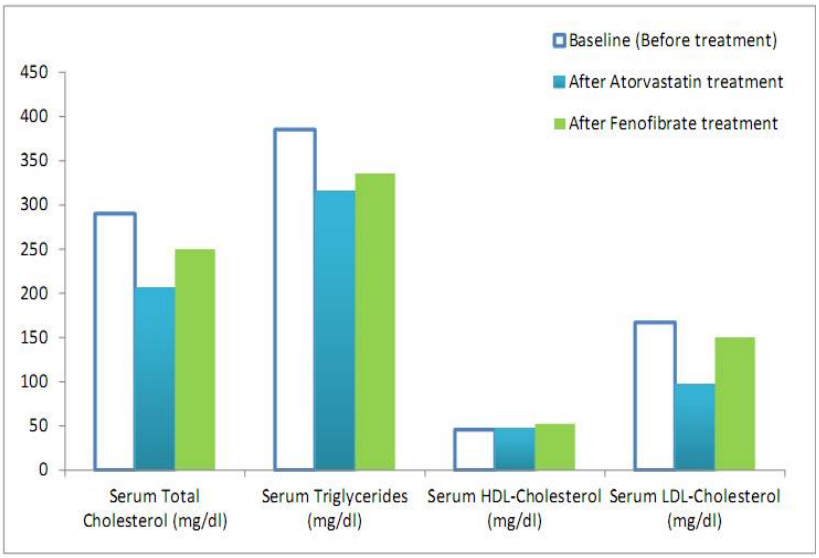

Fig. 1: The mean serum levels of total cholesterol ,triglycerides ,HDL-cholesterol and LDL-cholesterol at baseline (before treatment) and after one month treatments with Atorvastatin or Fenofibrate

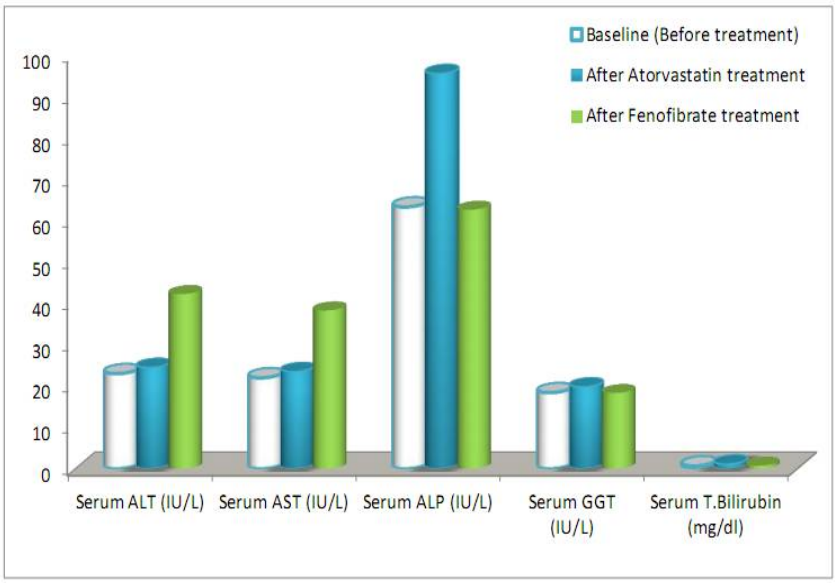

Fig. 2: The mean serum levels of ALT, AST, ALP, GGT and total bilirubin at baseline (before treatment) and after one month treatments with Atorvastatin or Fenofibrate

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