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ROLE OF INTERNATIONAL PRODUCT OF SIMVASTATIN ON LIVER FUNCTION TEST IN PATIENTS WITH PRIMARY DYSLIPIDEMIA

Naveed Ali Siddiqui[1*], Shanila Feroz[2], Jai Kershan[3], Kiran[4], Rabyyan Junaid[5], Mohammad Yahya[6] and Saba Fatima[7]

[1]MBBS, MPhil. PhD, Associate Professor, Department of Biochemistry, United Medical and Dental College, Karachi, Pakistan.

[2]Assistant Professor, Department of ENT-Head & Neck Surgery, United Medical & Dental College, Karachi, Pakistan.

[3]Assistant Professor, Department of CHS, United Medical & Dental College, Karachi, Pakistan.

[4]Medical Officer, Basic Health Unit Larhi, Gambat, Khairpur.

[5]Lecturer, Department of Pathology, United Medical & Dental College, Karachi, Pakistan.

[6,7]Student, Final year MBBS United Medical & Dental College, Karachi, Pakistan.

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***Corresponding Author**
Naveed Ali Siddiqui
MBBS, MPhil. PhD,
Associate Professor,
Department of
Biochemistry, United
Medical and Dental College,
Karachi, Pakistan.

ABSTRACT

Objective: To observe the changes in liver function test in patients with primary dyslipidemia using international lipid lowering drug, Simvastatin. **Material and Methods:** This clinical trial was carried out at Surgeon Munawar Memorial Hospital, Karachi. The study was designed to assess the effects of HMG-CoA reductase inhibitor (Simvastatin) on LFT in patients with primary dysplipidemia. The study period consists of 8 weeks from 4th April 2016 to 29th May 2016. The exclusion included lactating/pregnant women's, renal, liver and established coronary artery disease. **Results:** Thirty patients with abnormal lipid profile were included in the study (age 30-60 years). Patients were orally administered with international product of Simvastatin (20mg/day) for 8 weeks. The total bilirubin, direct bilirubin, ALT, AST, alkaline phosphatase was estimated in the serum of primary dyslipidemic patients before and after treatment with international product of Simvastatin (20mg/day). After the treatment serum total bilirubin, direct bilirubin, ALT, AST, alkaline

phosphatase were increased. **Conclusion:** On the basis of this study it is concluded that Simvastatin increases the level of total bilirubin, direct bilirubin, ALT, AST and alkaline phosphatase.

KEY WORDS: LFT, Dysplipidemia, Simvastatin.

INTRODUCTION

Cardiovascular disease (CVD) is a primary reason of disability and premature transience throughout the world and contributes considerably to the escalating expenditure of health care.[1] Dyslipidemia is one of the major modifiable risk factors for the development and progression of coronary artery disease and atherosclerosis.[2,3] Primary hyperlipidemia is generally due to a single inherited gene defect or more commonly by combination of genetic and environmental factors. Primary hyperlipidemias divided into 5 classes.[4] In patients with risk of coronary heart disease or with high levels of total cholesterol or LDL cholesterol, drug therapy should be initiated at an early stage.[5] The frequency of coronary artery disease in Pakistan is soaring as in western part of world. Overall, raised cholesterol is estimated to cause 2.6 million deaths (4.5% of total) and 29.7 million disability adjusted life years (DALYS), or 2.0% of total DALYS.[6,7] The products used in primary dyslipidemia are internationally and locally manufactured.[8,9] The international and local products both contain simvastatin. It competitively inhibits HMG CoA reductase, the enzyme that catalyzes the rate limiting step in cholesterol biosynthesis.[10.11] Despite the well-known importance of statin therapy, the primary care physician faces daily challenges when prescribing statins because of development of adverse effects.[12] One common challenge is the elevations of serum liver enzyme levels. Liver function tests (LFT's), which include liver enzymes, are groups of clinical biochemistry laboratory blood assays designed to give information about the state of a patient's liver. These tests can be used to (1) detect the presence of liver disease, (2) distinguish among different types of liver disorders, (3) gauge the extent of known liver damage, and (4) follow the response to treatment. Use of statins is limited by a contraindication in concurrent active or chronic liver disease and during pregnancy.[13]

MATERIAL AND METHODS

Patients Selection

This clinical trial was carried out at Surgeon Munawar Memorial Hospital Bahadurabad, Karachi from 4th April 2016 to 29th May 2016. The study period consist of 8 weeks. The population under study was representative of Pakistani population with primary dyslipidemia.

Blood pressure, body weight and height of subjects were assessed. The patient answered the questionnaire on smoking, social role, health complaints, drug usage, family history and dietary pattern. Patients were asked to fill a consent form before starting the experiment. The initial inclusion criteria of the patient were 1) Age between 30 and 60 years old of either sex, 2) Patients with primary dyslipidemia. The exclusion criteria were 1) Patients with liver diseases, 2) Pregnancy or lactation, 3) Patients with renal diseases. Detailed medical history and physical examination of all patients were carried out.

Study Design

Thirty patients were selected for the study. Liver function test was done before and after the treatment. Patients were orally administered with international product of Simvastatin (20 mg/day) for 8 weeks. After 8 weeks, blood samples were collected again for the estimation of lipid profile.

Collection of Samples

The blood sample was drawn using 5ml syringe and centrifuged at 3000 rpm for 10 minutes. Serum was separated and collected in clean and dry Eppendorfs and was stored at -70 C till further analysis.

Biochemical Analysis

The serum levels of total bilirubin, direct bilirubin, ALT, AST, alkaline phosphatase were determined enzymatically on microlab using commercially available (Merck laboratories limited, USA) kits.

Statistical Analysis

The data was analyzed statistically using SPSS version-11.

RESULTS

In table 1 the total bilirubin, direct bilirubin, ALT, AST, alkaline phosphatase were estimated in the serum of primary dyslipidemic patients before and after treatment with international product of Simvastatin (20mg/day). Patients who have been given simvastatin at a dose of 20mg/day showed an increase in serum total bilirubin from baseline value of 0.82 to ± 0.02 mg/dl to 0.83 to ± 0.02 mg/dl, direct bilirubin from baseline value of 0.20 to ± 0.01 mg/dl to 0.28 to ± 0.01 mg/dl, ALT from baseline value of 37.63 to ± 0.44 U/L to 39.33 to ± 0.35 U/L, AST from baseline value of 36.16 to ± 0.49 U/L to 37.70 to ± 0.39 U/L and alkaline

phosphatase from baseline value of 181.56 to ± 3.53 U/L to 186.30 to ± 3.66 U/L at week 8. This increases was found to be statistically significant ($p < 0.05$) when compared from before and after treatment.

The Bilirubin total, Alanine aminotranferease (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase, were estimated in the serum of patients before and after 8 weeks treatment with international product of Simvastatin (20mg/day). The values are given as Mean ± S.E.M and the number of cases are given in paranthesis.

Table No.-1: Variation of Liver function test in Primary hyperlipidemia before & after treatment with international product of Simvastatin.

	Total Bilirubin mg/dl	Direct Bilirubin mg/dl	SGPT (ALT) U/L	SGOT (AST) U/L	Alkaline phosphatase U/L
Before treatment	0.82±0.02 (30)	0.20±0.01 (30)	37.63±0.44 (30)	36.16±0.49 (30)	181.56±3.53 (30)
After treatment	*0.83±0.02 (30)	*0.28±0.01 (30)	*39.33±0.35 (30)	*37.70±0.39 (30)	*186.30±3.66 (30)

*$p < 0.05$ statistically significant as compared to the before treatment with international product of Simvastatin (20mg/day).

DISCUSSION

Hyperlipidemia or hyperlipoproteinemia is the condition of abnormally elevated levels of lipids or lipoproteins in the blood. According to world health organization (WHO), most of the lipids in plasma are present as lipoproteins i.e. chylomicrons, very low density lipoproteins (VLDL), low density lipoproteins (LDL), and high density lipoproteins (HDL). Primary hyperlipidemia is generally due to a single inherited gene defect or more commonly by combination of genetic and environmental factors.[14] "Statins are among the best drugs for treating individuals who have elevated cholesterol, "said Robert Eckel, M.D president of the American Heart Association. Hyperlipidemia was reported to be about 12.6 percent of overall population and 24 percent of urban population were found to have high cholesterol levels.[15] Statins are considered as first-line therapy for the treatment of hyperlipidemia. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is rate-limiting step in the biosynthesis of cholesterol. Simvastatin, like all other statins, is an inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA reductase—a key enzyme in the cholesterol-synthesis pathway. The

effects of international product of Simvastatin were assessed on primary dyslipidemic patients in the present study.

In present study when patients were treated with international product of Simvastatin in primary dyslipidemic patients, their serum LFTs (Total bilirubin, Direct bilirubin, Alanine aminotranferease, Aspartate aminotransferase & Alkaline phosphatase) were significantly increased ($p < 0.05$) as compared to before treated patients (Table 1). Simvastatin experienced marked and persistent increases in serum transaminases (up to 3 times the maximum limit of normal). When the drug was discontinued or suspended, the levels of transaminases usually slowly returned to pre-treatment levels. Therefore it is prudent to evaluate liver function and measure serum transaminase levels periodically. These return to normal on suspension of the drug.[15] The present study matches with the study of Schmidt et al (2007) who observerd high levels of Alanine aminotranferease, Aspartate aminotransferase in patients who were using high dose of Simvastatin (80 mg) for 27 days. Aspartate aminotransferase, alanine aminotransferase & Alkaline phosphatase levels are used to (1) detect the presence of liver disease, (2) distinguish among different types of liver disorders, (3) gauge the extent of known liver damage, and (4) follow the response to treatment. Use of statins is limited by a contraindication in concurrent active or chronic liver disease.

CONCLUSION

It is concluded that international product of Simvastatin had side effects on liver function test (Total bilirubin, Direct bilirubin, Alanine aminotranferease (ALT), Aspartate aminotransferase (AST) & Alkaline phosphatase). Due to adverse effect and rising cost of international product of Simvastatin, the National Drug Policy should promote the usage of locally made products.

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