COMPARATIVE EFFECTS OF LOVASTATIN AND SIMVASTATIN ON LIVER FUNCTION TESTS IN HYPERLIPIDAEMIC PATIENTS

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ABSTRACT

Objective: to evaluate the effect of lovastatin and simvastatin on liver function tests in a number of hyperlipidaemic patients.

Design: case control study.

Setting: the study was conducted in Al-Salam Hospital in Mosul during the period from July 2003 to July 2004.

Participants: forty-two patients taking lovastatin and fifty-three patients taking simvastatin. Another fifty, apparently healthy subjects, were also involved as a control group.

Intervention: ALT, AST and ALP activities and bilirubin concentrations of patients on lovastatin, simvastatin and control group were compared.

Main outcome measures: measurement of serum of ALT, AST and ALP activities and serum bilirubin concentration in lovastatin, simvastatin and control groups.

Results: results of the study revealed a minor elevation of ALT, AST and ALP activities and bilirubin concentrations above the upper normal limit values in a number of participants taking lovastatin or simvastatin therapy. A significant elevation of ALT, AST and bilirubin in the lovastatin group compared with the control group and a significant elevation of ALT and bilirubin in the simvastatin group when also compared with the control group were found. Stratification of the patients according to age, duration of treatment and dose, revealed a good correlation between some of the hepatic parameters and the age, duration of treatment and dose, though some of these elevations were not statistically significant.

Conclusion: therapy with lovastatin or simvastatin is associated with a mild effect on the liver and the effect is related to the variables of age, duration of therapy and dose. Periodic monitoring of biochemical hepatic parameters during therapy with lovastatin and simvastatin may be of value to observe any serious elevation of these parameters.

INTRODUCTION

The importance of investigating hepatic adverse effects of drugs on the liver lies in the fact that drug-induced hepatotoxicity has become an important public health problem, contributing to more than 50% of acute liver failure cases[1]. Annually dozens of patients with drug induced hepatotoxicity were demonstrated, a fraction of whom requires immediate transplantation because of irreversible damages to their livers. Cases of severe drug-induced hepatotoxicity are defined as liver enzyme elevations five or more times above the normal limit. The attention of studying drug hepatotoxicity had increased when a number of fatal hepatic toxicity cases were demonstrated with 2 drugs of the thiazolidinedione antidiabetic agents *(troglitazone and rosiglitazone)* which caused acute hepatic failure and severe hepatocellular injury[2-4]. Among the drugs which are investigated to have hepatic toxicity potential are NSAIDs, and among the antihypertensive agents, methyldopa and angiotensin converting enzyme inhibitors[5], the antidiabetic agents, acarbose, gliclazide, metformin and human insulin have been implicated in causing liver injury. Among the anticonvulsant drugs, valproic acid hepatotixicity is well recognized. Other hepatotoxic agents include selective serotonin reuptake inhibitors, chlorpromazine, and phenytoin. The first clinical studies on HMG-CoA reductase inhibitors reported a low incidence of liver toxicity, but this is followed by observations of a large number of cases on statin therapy with hepatic toxicity[6]. Because of the absence of data concerning the hepatic toxicity of statins in Mosul population, the present study was performed to evaluate the hepatic adverse effects of statins by measuring the serum ALT, AST and ALP activities and serum total bilirubin concentration in a number of hyperlipidaemic patients who received lovastatin or simvastatin in Mosul population.

PATIENTS AND METHODS

This study was undertaken over a period of 12 months from July 2003 till July 2004 in Al-Salam Hospital in Mosul. Ethical approval was obtained from the regional ethics committee in Ninevah Health Administration.

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Patients

Patients on simvastatin therapy

Fifty-three known hyperlipidaemic patients who took simvastatin therapy (SIMVOR-RANBAXY-laboratories limited India) to lower their high blood lipid concentration participated in the study. Twenty-six were males and twenty-seven were females. Their ages ranged from 35 to 60 years (males and females). Simvastatin dose ranged from 10 to 20mg once a day at bedtime. Duration of treatment ranged from 1 month to 4 years.

Patients on lovastatin therapy

Forty-two known hyperlipidaemic patients who took lovastatin therapy (ROVACOR-RANBAXY- laboratories limited India) to lower their high blood lipid concentration participated in the study. Twenty were males and twenty-two were females. Their ages ranged from 38 to 60 years (males and females). Lovastatin dose ranged from 10 to 20mg once a day at bedtime. Duration of treatment ranged from 1 month to 3 years.

Criteria for patient selection

1. Hyperlipidaemic patients on simvastatin or lovastatin therapy.
2. Patients with any disease which may cause alteration of liver function tests were excluded from the study. This may be aided by taking history, and physical and clinical examination of the patients; e.g. diseases which may interfere with the study include: hepatitis, cirrhosis, obstructive jaundice, pancreatitis, heart attack, heart failure and gall stones.
3. Patients on continuous administration of other drugs were also excluded from the study.

Control subjects

Fifty apparently healthy subjects were also taken as controls. Twenty-five were males (age: 40 to 58 years) and Twenty-five were females (age: 35 to 55 years). Subjects with any disease or continuous administration of any drug were excluded from the study.

Methods

Determination of liver enzymes

Colorimetric methods were used for determination of ALP, ALT, AST activities and total bilirubin concentration in serum using kits supplied by (bioMerieux), (Randox), (Randox) and (Biocon), respectively.

Statistical methods

1. Statistical comparison between liver parameters of the patients and those of control groups was conducted using Z-test.
2. Comparison of the liver parameters according to the drug dosages was made by t-test, according to age groups (ANOVA-test) and according to duration of treatment (Duncan-test).
3. Some values were quoted as mean ± S.D. and some as mean ± S.E.
4. The level of significance is $P<0.05$.

RESULTS

Control group

The results of the investigation of the control individuals were presented in (Table-1). The majority of the values are within the normal ranges.

Table 1. ***ALT, AST, ALP activities and bilirubin concentrations of the control group***

Liver parameters	Range	Mean ±SD
ALT (U/L)	3.0-18.0	7.56 ± 3.61
AST (U/L)	3.0-18.0	6.86 ± 3.60
ALP (U/L)	31.5-107	63.07± 19.65
Bilirubin (μmol/L)	2.9-22.0	8.14 ± 3.91

Patients groups

Lovastatin group:

Table-2 shows the values of the measured liver parameters in lovastatin group. High abnormal values *(above the upper normal limit)* were found as follows:

ALT (8 patients-19 %)
AST (7 patients-16.6%)
ALP (3 patients-7.14%)
Bilirubin (5 patients-11.9%)

Table 2. ***ALT, AST, ALP activities and bilirubin concentrations of the lovastatin group***

Liver parameters	Range	Mean ± SD
ALT (U/L)	3-44	16.14 ± 10.18
AST (U/L)	5-46	13.07 ± 9.98
ALP (U/L)	39-112.7	70.39 ± 16.63
Bilirubin (μmol/L)	4-27.2	11.44 ± 5.71

Simvastatin group

Table-3 shows, the values of the measured liver parameters in simvastatin group. High abnormal values (above the upper normal limit) were found as follows:

ALT (8 patients-15.1%)
AST (8 patients-15.1%)
ALP (3 patients-5.6%)
Bilirubin (4 patients-7.5%)

Table 3. ***ALT, AST, ALP activities and bilirubin concentrations in the simvastatin group***

Liver parameters	Range	Mean ± SD
ALT (U/L)	3-39	15.42 ± 10.1
AST (U/L)	3-38	11.02± 10.51
ALP (U/L)	29.7-119.4	66.84± 19.72
Bilirubin (μmol/L)	3.5-29	11.82 ± 5.85

Table-4 shows, the results of comparison between liver parameters of lovastatin and control groups. Significant differences were found for ALT (P<0.001), AST (P<0.001) and bilirubin (P<0.01). A non-significant difference was found for ALP (P>0.05).

Table 4. ***Comparison between liver parameters of lovastatin and control groups***

Liver parameters	Controls (N=50) (Mean ± SD)	Lovastatin users (N=42) (Mean ± SD)
ALT (U/L)	7.56 ± 3.61	16.14 ± 10.18
AST (U/L)	6.86 ± 3.60	13.07 ± 9.98
ALP (U/L)	63.07± 19.65	70.39 ± 16.63
Bilirubin (μmol/L)	8.14 ± 3.91	11.44 ± 5.71

Table-5 shows, the results of comparison between liver parameters of simvastatin and control groups. Significant differences were found for ALT (P<0.001), and bilirubin (P<0.001) and a non-significant difference for AST and for ALP (P>0.05).

Table 5. ***Comparison between liver parameters of simvastatin and control groups***

Liver parameters	Controls (N=50) (Mean±SD)	Simvatatin users (N=53)
ALT (U/L)	7.56 ± 3.61	15.42 ± 10.10
AST (U/L)	6.86 ± 3.60	11.02 ± 10.51
ALP (U/L)	63.07 ± 19.65	66.84 ± 19.72
Bilirubin (μmol/L)	8.14 ± 3.91	11.82 ± 5.85

The distribution of serum ALT, AST, ALP activities and total bilirubin concentration according to age, dose and duration of treatment

Lovastatin group

Table-6 shows, liver parameters according to age of the patients. Non-significant elevations was found (P>0.05).

Table 6. ***Liver parameters of the lovastatin group according to age of the patients***

Age groups (year) / Parameters	Mean ± SE			Significant P-value
	31-40 (n=11)	41-50 (n=22)	>50 (n=9)	
ALT (U/L)	10.73±1.6	18.50±2.4	17.0±3.6	> 0.05
AST (U/L)	7.91±1.3	15.14±2.4	14.33±3.5	> 0.05
ALP (U/L)	63.96±5.7	71.76±3.5	74.92±4.5	> 0.05
Bilirubin (μmol/L)	9.14±0.8	11.96±1.3	12.99±2.3	> 0.05

Table-7 shows, liver parameters according to duration of using lovastatin. A statistically significant elevation was found as the duration of use increased.

Table 7. ***Liver parameters of the lovastatin group according to duration of using lovastatin***

Duration (month) / Parameters	Mean ± SE		
	<6 (n=18)	6-12(n=15)	>12(n=9)
ALT (U/L)	9.83±0.8 a	13.73±1.3 a	32.78±2.3 b
AST (U/L)	6.11±0.5 a	11.93±1.6 b	28.89±2.2 c
ALP (U/L)	64.28±4.1 a	72.94±3.6 ab	78.37±5.3 b
Bilirubin (μmol/L)	7.69±0.4 a	10.79±1.0 b	20.02±1.5 c

Different letters horizontally mean significant difference at (P≤ 0.05).

Table-8 shows, liver parameters according to doses of lovastatin. A statistically significant elevation was found among groups.

Table 8. ***Liver parameters of the lovastatin group according to doses of lovastatin***

Dose (mg) / Parameters	Mean ± SD	
	10mg (n=20)	20mg (n=22)
ALT (U/L)	10.50±3.8	21.27±11.4***
AST (U/L)	8.45±4.5	17.27±11.70**
ALP (U/L)	64.24±14.4	75.99±16.8*
Bilirubin (μmol/L)	8.55±2.9	14.07±6.4***

*Significant difference at (P<0.05)
**Significant difference at (P<0.01).
***Significant difference at (P<0.001).

Simvatatin group

Table 9 shows liver parameters according to age of the patients. Non-significant differences were found between the studied parameters.

Table 9. ***Liver parameters of the simvastatin group according to age of the patients***

Age groups (year) / Parameters	Mean ± SE			Significant P-value
	31-40(n=6)	41-50(n=26)	>50(n=21)	
ALT (U/L)	9.33±1.8	15.92±1.9	16.52±2.5	>0.05
AST (U/L)	5.00±1.06	10.04±1.9	13.95±2.6	>0.05
ALP (U/L)	70.25±9.8	63.62±3.1	69.85±5.0	>0.05
Bilirubin (μmol/L)	10.65±0.9	11.44±1.0	12.62±1.6	>0.05

Table-10 shows, liver parameters according to duration of using simvastatin. Statistically significant elevations were found among ALT, AST, and bilirubin groups.

Table 10. ***Liver parameters of the simvastatin group according to duration of using the drug.***

Duration (month) / Parameters	Mean ± SE		
	<6 (n=14)	6-12(n=22)	>12(n=17)
ALT (U/L)	10.41±1.3 **a**	12.47±1.3 **a**	26.86±2.9 **b**
AST (U/L)	4.41±0.4 **a**	9.41±1.3 **b**	23.36±3.4 **c**
ALP (U/L)	66.21±4.3 **a**	69.18±4.6 **a**	64.99±5.6 **a**
Bilirubin (μmol/L)	10.47±1.0 **a**	10.98±1.1 **a**	14.96±2.1 **b**

Different letters horizontally mean significant difference at (P≤0.05).

Table-11 shows, liver parameters according to doses of simvastatin. Statistically significant elevations were found among ALT and AST parameters.

Table 11. ***Liver parameters of the simvastatin group according to doses of the drug***

Dose (mg) / Parameters	Mean ± SD	
	10mg (n=17)	20mg(n=33)
ALT (U/L)	9.65±3.9	18.9±11.1***
AST (U/L)	6.3±3.8	13.88±12.2**
ALP (U/L)	69.99±17.3	64.93±21.1
Bilirubin (μmol/L)	10.47±5.0	12.64±6.2

** **Significant difference at (P<0.01).**
*** **Significant difference at (P<0.001).**

No statistically significant differences were found between liver parameters of lovastatin and simvastatin groups (Table-12).

Table 12. ***Comparison between liver parameters of simvastatin and lovastatin groups***

Parameters	Mean± SD	
	Lovastatin users (n=42)	Simvastatin users (n=53)
ALT (U/L)	16.14± 10.18	15.42±10.10
AST (U/L)	13.07± 9.98	11.02±10.51
ALP (U/L)	70.39± 16.63	66.84±19.72
Bilirubin (μmol/L)	11.44± 5.71	11.82±5.85

DISCUSSION

The present study revealed a mild but statistically significant effect of lovastatin on the liver parameters. The data from the present study can confirm results obtained from a study provided by Tolman[7], who declared that animal studies have given signals of hepatotoxicity of lovastatin, primarily minor elevations in serum ALT level and two cases in whom hepatotoxicity of lovastatin was demonstrated. A 48 years-old man treated with lovastatin at a dosage of 20 mg daily had developed cholestatic jaundice[8], another case was reported to have jaundice and increased aminotransferase and alkaline phosphatase activities[9]. The present study demonstrated a mild elevation of ALT and AST activities <3X the upper limit of normal values (UNL). These results are in contrast with data presented in other studies which reported values of ALT and AST activities >3X UNL[7,10,11]. In addition premarketing clinical trials revealed increases in ALT, <3X the upper limit of normal values in 21% of patients and >3X the upper limit of normal values in 1.9% of patients and appeared to be dose related. Elevations of all measured hepatic parameters in the current study were observed. This may indicate that the pattern of hepatotoxicity caused by lovastatin is hepatocellular damage (elevation of AST and ALT) and cholestasis (elevation of ALP and bilirubin). These results are in agreement with those obtained in many studies where elevations of all of the liver parameters have been noted[7,9,12]. The data obtained in the presesnt study also indicate a mild effect of simvastatin on the liver. Review of the literature demonstrated controversial effects of simvastatin on hepatic function. Some studies reported an elevations of liver parameters during simvastatin therapy[6,13-16], whereas others studies showed that simvastatin has no effect on liver parameters[17,18]. The present study demonstrated an age-dependent effect of both lovastatin and simvastatin on liver parameters indicating that statins may be more toxic in old patients; in addition the effect of lovastatin and simvastatin was higher during prolonged administration. Review of literature revealed varied periods of therapy at which the hepatic effect of statins was detected. These period range from 1 month to 3 years[8,9,11-13,19-

[21]. Data obtained in this study revealed that the effect of lovastatin and simvastatin groups was dose dependent. These results are in agreement with the results observed in other studies[11,20-22]. *The present study* showed non-significant differences between liver parameters of lovastatin and simvastatin groups which may indicate that the effect of both lovastatin and simvastatin on the liver may be similar. No studies could be found in the literature which involve comparison of the effect of these two drugs on liver parameters.

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