Liv.52 DS Tablets

Evaluation of Liv.52 DS tablet as a hepatoprotective agent in prophylaxis with statin therapy

ABSTRACT
The present study was planned to evaluate Liv.52 DS tablet as a hepatoprotective agent in prophylaxis with statin therapy. HMG-CoA reductase inhibitors (statins) are the most commonly prescribed classes of medications for dyslipidemia, which is a risk factor for chronic heart disease. Statin can cause liver damage in the form of increasing transaminase levels.

The present study was an open clinical trial, conducted as per the ethical guidelines of Declaration of Helsinki. All patients on antihyperlipidemic therapy with statins were included in the study; patients having evidence of extensive disease that requires hospitalization, and pregnant women were excluded from the study.

A total of 50 patients were enrolled into the trial and all patients completed the study. Patients were divided into two equal groups of 25 each; one group received Liv.52 DS tablet + Atorvastatin tablet, while the second group received Atorvastatin tablet alone. Patients were advised to take Liv.52 DS tablet at a dose of 1 tablet twice a day and Atorvastatin 10 mg, 1 tablet twice a day for a period of three months.

A thorough history, symptomatic evaluation and clinical examination were done for all patients before treatment and during follow-up visits every week till the end of treatment after three months. Liver function tests, hemogram and other biochemical tests were done at the end of 1st, 2nd and 3rd month of treatment. The predefined primary endpoints were clinical and laboratory evidence of normal functioning of liver.

In the Atorvastatin alone group, there was a significant increase (p<0.01) in the mean values of SGPT from 45.87 ± 4.98 to 102.70 ± 12.05, SGOT from 42.70 ± 4.74 to 98.87 ± 12.35, and total bilirubin from 0.800 ± 0.026 to 1.022 ± 0.077 after 3 months, whereas no such increase in SGPT, SGOT and total bilirubin was observed in the group receiving Liv.52 DS tablet + Atorvastatin, after 3 months.

There were no significant differences between the groups in terms of physical examination and subjective signs after 3 months of treatment. Therefore, it may be concluded that Liv.52 DS tablet has hepatoprotective effect against statin-induced liver damage.

INTRODUCTION
Lipids are important biomolecules. Cholesterol, for example, is an essential component of the human cell membrane and a precursor for steroid hormones and bile acids. Triglycerides also play an important role in transferring energy from food into body cells. Elevation of different forms of lipids in the bloodstream, a condition generally termed hyperlipidemia, causes a constant health problem. Because lipids are carried in the bloodstream,
Hyperlipidemia is always a threat to coronary arteries and the most important risk factor for coronary heart disease (CHD).

However, to fight these problems, human wit has acquired several drugs, commonly known as lipid-lowering drugs. One group of drugs (statins) lowers cholesterol by interfering with the cholesterol biosynthetic pathway.\(^1,2\)

3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase is the key rate-limiting enzyme of the cholesterol biosynthetic pathway. Statins are structural analogues of HMG-CoA and thereby inhibit HMG-CoA reductase competitively with an affinity about 1000-10,000 times greater than that of the natural substrate. In addition to direct inhibition of cholesterol synthesis, statins have also been shown to lower plasma cholesterol levels indirectly due to up-regulation of the low-density lipoprotein (LDL) receptor.\(^3\)

There are currently seven statins available in pharmaceutical form - lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, and pitavastatin.\(^4,5\) Statins have become the mainstay of therapy for controlling lipid disorders. The future promises more patients to be taking these medications as goals for cholesterol therapy are dropped and new indications for statin therapy are introduced. While serious adverse events are rare with statin therapy, less serious side effects and minor laboratory abnormalities are relatively common.

Based on data from clinical trials and from review of primary care medical records, elevations in transaminases on liver function tests (LFTs) to clinically significant levels (usually defined as three times the upper limit of normal) are seen in about 0.5% to 2% of patients taking statins, and this abnormality is dose dependent.\(^6-8\) The majority of liver abnormalities, if they are to occur, appear within the first 3 months of therapy.\(^9\) Therefore, the challenge is to maintain cholesterol or lipid homeostasis in lipid-independent disorders after the use of lipid-lowering drugs in order to minimize side effects.

Liv.52 DS tablet is a polyherbal...
formulation that consists of powders of *Capparis spinosa*, *Cichorium intybus*, *Solanum nigrum*, *Cassia occidentalis*, *Terminalia arjuna*, *Achillea millefolium*, *Tamarix gallica*, and Mandura bhasma. It is a hepatotonic and has been used traditionally in the treatment of various liver disorders. This study was planned to evaluate Liv.52 DS tablet as a hepatoprotective agent in prophylaxis with statins.

**PATIENTS AND METHODS**

**Inclusion criteria**
All patients aged between 18 to 70 years, and on antihyperlipidemic therapy with statins were included in the study.

**Exclusion criteria**
Patients having evidence of extensive disease that requires hospitalization, and pregnant women were excluded from the study.

**Study procedure**
The study was an open, randomized, comparative and prospective clinical trial conducted at the Department of Medicine, Patna Medical College, Patna, India from January 2007 to February 2007 as per the ethical guidelines of Declaration of Helsinki. The study protocol, case report forms (CRFs), regulatory clearance documents, product-related information and informed consent forms (in English and Hindi) were submitted to the institutional ethics committee and were approved by the same.

The patients who attended the OPD general medical unit of Department of Medicine, Patna Medical College, Patna, India were informed about the study drug, its effects, duration of the trial, and overall plan of the study. The patients were included in the clinical study only after written informed consent was obtained from each of them.

The history was noted by interviewing the patient. Thorough clinical examination and symptomatic evaluation was carried out and the details were noted down in the CRF. The patients were randomly divided into two groups of 25 members each; Liv.52 DS tablet + Atorvastatin group and Atorvastatin alone group. Patients were advised to take Liv.52 DS tablet at a dose of 1 tablet twice a day and Atorvastatin 10 mg, 1 tablet twice a day for a period of three months.

All patients were reviewed every week till the end of treatment, and symptomatic evaluation and clinical examination was done for skin, general state, temperature, liver size, weight and for subjective signs like coating of the tongue, loss of appetite, nausea, vomiting, and pain and discomfort in the right hypochondrium.

Liver function tests, hemogram and other biochemical tests were done at the end of each month till the completion of the study after three months.

**Primary endpoints**
The predefined primary endpoints were clinical and laboratory evidence of normal functioning of liver.

**Statistical analysis**
Statistical analysis was done according to intention-to-treat principles. The changes in various parameters in the post-treatment values were carried out using Repeated Measures ANOVA test followed by Dunnett’s Multiple Comparison Posthoc test. The minimum level of significance was fixed at 95% confidence limit and a 2 sided *p* value of <0.05 was considered significant.

**RESULTS**
A total of 50 patients on antihyperlipidemic therapy with statins were included in the clinical trial and all patients completed the trial. The mean age of the patients was 56.84 ± 1.077 years and the population consisted of 40 males and 10 females.

In the Atorvstatin alone group, there was a significant increase (*p* < 0.01) in the mean values of SGPT from 45.87 ± 4.98 IU/L to 102.70 ± 12.05 IU/L (Table 1 and Figure 1), SGOT from 42.70 ± 4.74 IU/L to 98.87 ± 12.35 IU/L (Table 1 and Figure 2), and total bilirubin from 0.800 ± 0.026 g/dl to 1.022 ± 0.077 g/dl (Table 1 and Figure 3) after 3 months, whereas no such increase in SGPT, SGOT and total bilirubin was observed in the group receiving Liv.52 DS tablet + Atorvastatin, after 3 months.
hypochondrium. No significant differences were noticed in the other biochemical and hematological parameters between the groups.

**DISCUSSION**

Cardiovascular disease is the single largest killer of both men and women in the world. The World Health Organization estimates that more than 16 million adults/year die of cardiovascular disease. Furthermore, an estimated 32 million adults/year have a new or recurrent myocardial infarction.10

The major risk factors for CHD, in addition to old age, are hypertension, diabetes mellitus, tobacco use, elevated total and low-density lipoprotein cholesterol (LDL-C), and reduced high-density lipoprotein cholesterol (HDL-C).

Epidemiologic trials have established a direct relationship between LDL and cardiovascular events, and many clinical trials have confirmed that lipid-lowering therapy reduces the risk of cardiovascular events.11

To address the dyslipidemia aspect of CHD, lipid-lowering agents are typically used. The most potent lipid-lowering agents are HMG-CoA reductase inhibitors (statins). These medications are highly effective as monotherapy for dyslipidemia and may be combined with other agents, such as niacin or fibric acid derivatives (fibrates), when further reductions in triglycerides and/or elevations in HDL-C are required. HMG-CoA reductase inhibitors have become one of the most commonly prescribed classes of medications. The most common adverse events associated with statin therapy are gastrointestinal disturbances, fatigue, localized pain, and headache. Serious adverse events that have been reported in major statin trials include myopathy, elevated transaminase levels and rhabdomyolysis.

The term "transaminitis" represents liver enzyme leakage without hepatotoxic consequences in patients receiving drug therapy of any kind.8 Asymptomatic increases in transaminases to greater than 3 times normal occur in about 1 to 3% of patients and appear to be dose-dependent.8,12 These elevations are felt to be most common during the first 3 months of therapy but can happen at any time.3,14 Hepatic failure rarely occurs with statin therapy and is an idiopathic event.15

Due to concerns about liver toxicity, the Food and Drug Administration and drug manufacturers have recommended that LFTs be monitored before and 12 weeks after the start of therapy (or an increase in dosage) with statins, and periodically thereafter.

Reduction or withdrawal of statins is warranted if an increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level is greater than 3 times the upper limit of normal (ULN).16

Statin therapy requires ALT monitoring because animal studies and premarketing clinical trials showed signs of hepatotoxicity that were primarily minor elevations of ALT.

The present clinical study observed that in the Atorvastatin alone group, there was a significant increase in the mean values of SGPT, SGOT and total bilirubin after 3 months, whereas no such increase in SGPT, SGOT and total bilirubin was observed in the group receiving Liv.52 DS tablet + Atorvastatin, after 3 months of therapy. There were no significant differences between the groups in terms of physical examination like skin, general state, temperature, liver size, weight and subjective signs like coating of the tongue, loss of appetite, nausea, vomiting, and pain and discomfort in the right hypochondrium.

Hepatoprotective effect of Liv.52 DS tablet could be due to the synergistic actions of its individual ingredients.

The diuretic effect of *Terminalia arjuna* and anti-inflammatory and anti-immunotoxicity effect of *Cichorium intybus* have been shown in clinical and experimental studies.17-19

The anti-oxidative and anti-hepatotoxic property of esculetin and p-methoxybenzoic acid, the main constituents of *Cichorium intybus* and *Capparis spinosa*, respectively, have been reported in chemically-induced hepatotoxicity in experimental animals.20-22

*Achillea millefolium*, another component of Liv.52 DS tablet, contains several bioactive constituents including flavonoids and terpenoids with anti-oxidative and anti-inflammatory properties.23-25

The curative and hepatoprotective effect of Mandur bhasma and *Cassia occidentalis*, the other two components of Liv.52 DS tablet, were observed.

![Figure 2. Comparative increase in SGOT levels in Liv.52 DS + Atorvastatin and Atorvastatin alone treatment](image-url)
Figure 3. Comparative increase in total bilirubin levels in Liv.52 DS + Atorvastatin and Atorvastatin alone treatment

![Graph showing comparative increase in total bilirubin levels](image)

* *p<0.01 as compared with 1st month value

against chemically-induced liver damage in experimental animals.\textsuperscript{26,27} Furthermore, the anti-oxidative property of flavonoid content of \textit{Tamarix gallica} and inhibitory effect of \textit{Solanum nigrum} crude extracts on free radical-mediated DNA damage increase the hepatoprotective effect of Liv.52 DS tablet.\textsuperscript{26,29} In addition, the anti-oxidative and anti-lipoprotidative effects, and increase in glutathione content of liver cells was observed with arjunic acid and flavonoids present in \textit{Terminalia arjuna}.\textsuperscript{30,31}

**CONCLUSION**

There is a direct relationship between LDL and cardiovascular events, and many clinical trials have confirmed that lipid-lowering therapy reduces the risk of cardiovascular events. Statins have become one of the most commonly prescribed classes of lipid-lowering agents. However statin therapy is commonly associated with liver damage in terms of elevated transaminases. This study was conducted to evaluate Liv.52 DS tablet as a hepatoprotective agent in prophylaxis with statin. The present clinical study observed that in the Atorvastatin alone group, there was a significant increase in the mean values of SGPT, SGOT and total bilirubin after 3 months, whereas no such increase in SGPT, SGOT and total bilirubin was observed in the group receiving Liv.52 DS tablet + Atorvastatin, after 3 months of therapy. There were no significant differences between the groups in terms of physical examination and subjective signs at the end of the treatment period. Hence, it may be concluded that Liv.52 DS tablet has hepatoprotective effect against statin-induced liver damage.

**REFERENCES**

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