Original Article

Comparative Study of Simvastatin and Rosuvastatin

Analyzing Hepatotoxicity: A Comparative Study of Simvastatin and Rosuvastatin, and Their Reversal Using Montelukast and Coenzyme Q10

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ABSTRACT

Objective: The study aims to compare the hepatotoxic potential simvastatin and rosuvastatin owing to the lack in knowledge regarding the comparative hepatotoxic potential of the two very commonly prescribed statins. In addition, the study also aims to assess the hepatoprotective efficacy of two other compounds, montelukast and coenzyme Q10.

Study Design: Experimental study.

Place and Duration of Study: This study was conducted at Pharmacology Dept, Animal house Northwest School of Medicine Hayatabad from 15th Jan 2023 to 10th July 2023.

Methods: An experimental study was carried out in northwest school of medicine from 15th Jan 2023 to 10th July 2023 on 35 mice, randomly divided into 7 groups of 5 mice each. Group 1 served as a control group. Simvastatin 50mg/kg/day was administered intraperitoneally (I/P) to Group 2. Rosuvastatin I/P 50mg/kg/day was given to group 3. Simvastatin 50 mg/kg/day I/P and 3 mg/kg of montelukast were given to group 4. Rosuvastatin 50 mg/kg/day plus 3 mg/kg of Montelukast were given to group 5. Simvastatin 50 mg/kg/day and 10 mg/kg coenzyme Q10 were given to group 6. Group 7 received rosuvastatin 50 mg/kg/day plus 10 mg/kg I/P of coenzyme Q10.

Results: Both statins demonstrated liver damage, although Rosuvastatin had more abnormalities in liver function. In the simvastatin group, montelukast did attenuate hepatotoxicity and induce regenerative changes. Instead of substantial liver function abnormalities, coenzyme Q10 did not demonstrate any protection against statins.

Conclusion: Rosuvastatin had a higher hepatotoxic potential compared to simvastatin, as evidenced by the elevated liver enzymes and histological changes in the liver tissue. However, the study also found that montelukast showed a better hepatoprotective effect compared to coenzyme Q10, as it was able to effectively reverse the liver damage caused by both simvastatin and rosuvastatin.

Key Words: Hepatotoxicity, Statins, Coenzyme Q10, Montelukast

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INTRODUCTION

Statins can cause cirrhosis, fulminant hepatitis, autoimmune hepatitis, and cholestatic hepatotoxicity. They can raise AST and ALT levels. The hepatotoxicity brought on by statins has been attributed to a variety of processes. Statins inhibit HMG-CoA (3-hydroxy-3 methylglutaryl coenzyme A) competitively, preventing it from converting to mevalonate, which is a precursor to Coenzyme Q10 (CoQ10). CoQ10 possesses antioxidant properties in addition to its ability to stabilise membranes. Statins decrease the body's Coenzyme Q10 levels, which may contribute to hepatotoxicity. The focus of our study is to compare the hepatotoxic potential of simvastatin and rosuvastatin. It is known that chronic simvastatin therapy is associated with hepatotoxicity, however, little evidence exists regarding rosuvastatin[1,2].

The ubiquinone coenzyme, also known as Coenzyme Q, participates significantly in oxidative phosphorylation inside the mitochondria. Coenzyme Q undergoes reduction/oxidation cycles during oxidative phosphorylation, and it transfers protons across the mitochondrial membrane to form a proton gradient. Coenzyme Q is also involved in the stimulation of cell growth and the inhibition of apoptosis, or programmed cell death and control of the formation of hydrogen

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peroxide and regulate membrane channels, which are important for the transport of molecules in and out of the cell. Coenzyme Q can donate electrons to neutralize free radicals, thereby preventing them from damaging cellular components such as proteins, lipids, and DNA. Statins can also reduce the levels of coenzyme Q in the liver, leading to oxidative stress and damage to liver cells. Overall, the various roles of coenzyme Q in cellular processes and its anti-oxidative potential make it an important molecule for maintaining cellular health and function[3].

Montelukast (MNK) is used to prevent and treat allergic rhinitis and chronic bronchial asthma. MNK has powerful antioxidant and anti-inflammatory activity in a range of tissues and cells in addition to its bronchodilator capabilities. It has been shown to reduce oxidative stress and inflammation by reducing the production of reactive oxygen species (ROS) and pro-inflammatory cytokines such interleukin-1 beta (IL-1), tumor necrosis factor-alpha (TNF-), and interleukin-6 (IL-6). MNK has been postulated to protect the liver by lowering oxidative stress, inflammation, and liver damage in various hepatotoxic animal models induced by alcohol and carbon tetrachloride. Overall, the antioxidant and anti-inflammatory properties of MNK make it a useful medication for the treatment of asthma and allergic rhinitis. Its ability to protect the liver against toxic substances further expands its potential therapeutic applications[4].

METHODS

Experimental Design: In the normal control group (*n=5* mice), 5 mice were administered 1 ml of saline daily intraperitoneally. In the simvastatin group (n=5 mice) 50mg/kg of simvastatin was administered intraperitoneally (I/P) in saline daily. In the rosuvastatin group (n=5 mice) 50mg/kg of rosuvastatin was administered I/P in saline daily. In group 4 (n=5 mice) 50mg/kg of simvastatin+3mg/kg of Montelukast was administered I/P in saline daily. Group 5 (n=5 mice) received 50mg/kg of rosuvastatin+3mg/kg of Montelukast I/P in saline daily. In group 6 (n=5 mice) 50mg/kg of simvastatin+10mg/kg of coenzyme Q10 was administered I/P in saline daily. Group 7 (n=5 mice) received 50mg/kg of rosuvastatin+10mg/kg of coenzyme Q10 I/P was administered in saline daily.

Data Collection Procedure: Assessment of liver enzymes was performed from the blood samples collected after animals were sacrificed. The liver was removed, and consistency, color and weight were noted. It was dipped in 10% formalin and sliced into sections. Staining was done with eosin and Hematoxylin. The histopathology division at the Northwest School of Medicine used light microscopy to search for changes in the architecture.

Data Analysis: Data was analyzed through social sciences (SPSS) version 23. Continuous variables were chosen. The arithmetic means and standard deviation of the observed values were calculated. One way ANOVA was used to compare biochemical markers at the beginning and end of the study in the same group, and then the Post Hoc Tukey Test was used. A value of $p < 0.05$ was taken as significant.

RESULTS

In control group, LFTs stayed within acceptable ranges. The average serum ALT level was 24.6 + 1.14, the average AST level was 80.4 + 1.51, and the average bilirubin level was 0.13 + 0.01. The histology of the liver was normal. (Fig 1 – Fig 5)

Mice receiving simvastatin were less energetic and fatigued than mice in the control group. By the end of two weeks, the mice in group 2 had lost an average of 21g of their initial 30g weight. The mean result of 186.8 + 3.42U/L represents a considerable increase in mean serum ALT levels. While the rise in bilirubin levels was within normal bounds with a mean value of 0.12 + 0.01mg/dl, the levels of AST showed an elevated mean value of 306 + 13.43. The liver's histology revealed fatty alterations and localized necrosis. (Fig 1 – Fig 5)

Mice receiving Rosuvastatin demonstrated lethargy and weight loss from an initial average of 30g to an average of 26g. The average weight of the mice in group 2 reduced from 30g initially to 21g by the end of 2 weeks. The mean result of 301.4 + 32.72 represents a considerable increase in mean serum ALT levels. While the rise in bilirubin levels was within normal bounds with a mean value of 0.12 + 0.01mg/dl, the levels of ast showed an elevated mean value of 421.4 + 45.85U/L. Liver histopathology showed focal moderate chronic inflammatory cells infiltrate. (Fig 1 – Fig 5)

In Group 4 mice were noted to have decreased physical activity and the weight reduced from initial 30g average to 26g average. The liver function test parameters of ALT and AST were elevated; however, the increase was less as compared to the group that received only simvastatin. Mean serum ALT was 88.6 + 3.36; AST registered a mean value of 97.2 + 2.5/L and Bilirubin was 0.12 + 0.01mg/dl. Regenerative changes were observed on histopathology. (Fig 1 – Fig 5)

Group 5 mice were noticed to be lethargic, and the weight reduced from initial 30g average to 25g average. The liver function test parameters of ALT and AST were elevated; however, the increase was less as compared to the group that received only Rosuvastatin. Mean serum ALT was 91.4 + 5.45U/L; AST had a mean value of 104.8 + 4.2/L and Bilirubin was 0.10 + 0.02. Histopathology revealed fewer inflammatory cell infiltrates, however no significant regenerative changes. (Fig 1 – Fig 5)

Group 6 mice were noted to be extremely lethargic, and the weight reduced from initial 30g average to 19g average. The liver function test parameters of ALT and AST were elevated higher as compared to the group

that received only Simvastatin. Mean serum ALT was 100.2 + 8.25/L; AST had a mean value of 136.2 + 6.37/L and Bilirubin was 0.15 + 0.00 mg/dl. Inflammatory cells infiltrate surrounding central veins C and extending upto the portal tracts were seen in histopathological analysis. (Fig 1 – Fig 5)

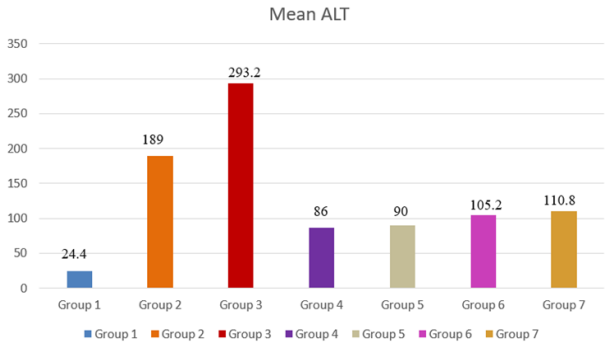

Figure No.1: Group 3 receiving Rosuvastatin showed the highest ALT level while the control via Montelukast was better as compared to Coenzyme Q10 with a significant difference of 0.000.

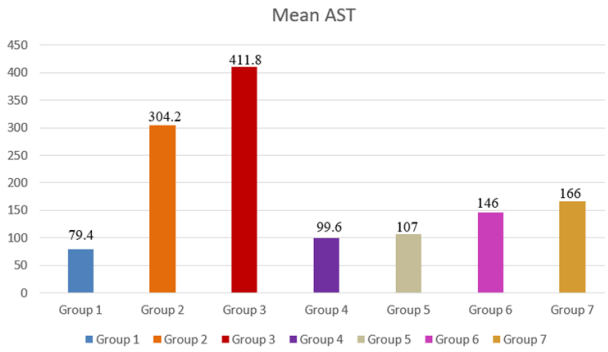

Figure No. 2: Group 3 receiving Rosuvastatin showed the highest AST level while the control via Montelukast was better as compared to Coezyme Q10 with a significant difference of 0.000.

Tukey results denoted better control of montelukast as compared to coenzyme Q10.

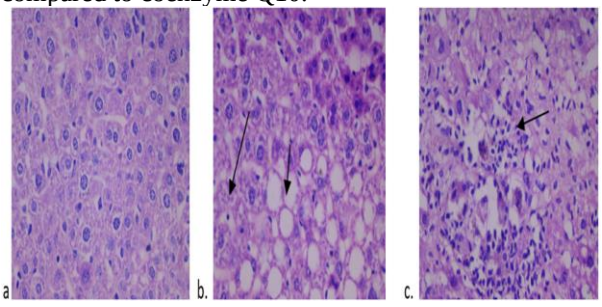

Figure No.3: Hematoxylin- and eosin-stained sections, a. Normal liver parenchyma (40x). b. Effects of Simvastatin on liver parenchyma (Large arrow: focal necrosis, small arrow: Fatty change (40x).c Effects of Rosuvastatin focal moderate chronic inflammatory cells infiltrate (arrow 40x)

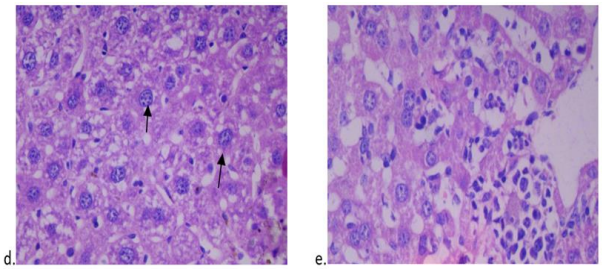

Figure No.4: Hematoxylin- and eosin-stained sections showing.d.Effects of Simvastatin + Montelukast showing regenerative changes (arrow40x) on liver parenchyma e. Effects of Rosuvastatin +Montelukast fewer inflammatory cells infiltration (arrow 40x)

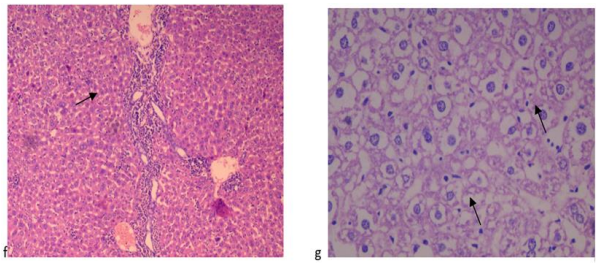

Figure No. 5: Hematoxylin- and eosin-stained sections showing f. Effects of Simvastatin + Co enzyme Q10 showing inflammatory cells infiltrate surrounding central veins C and extending upto the portal tracts (arrow 10x) g. Effects of Rosuvastatin +Co enzyme Q10 wide focus of necrosis (arrow 40x)

Group 7 mice were noted to be extremely lethargic, and the weight reduced from initial 30g average to 18g average. The liver function test parameters of ALT and AST were elevated higher as compared to the group that received only Simvastatin. Mean serum ALT was 110.8+ 4.96/L; AST had a mean value of 174.8+ 7.39/L and Bilirubin was 0.12 + 0.01 mg/dl. Histopathology revealed wide focus of necrosis. (Fig 1 – Fig 5). Tukey results denoted better control of montelukast as compared to coenzyme Q10.

DISCUSSION

In the current study one of the objectives was to compare the hepatotoxic potential of simvastatin with rosuvastatin. One group of the BALB/C mice received simvastatin, while the other received rosuvastatin. The liver function parameters of both the groups including serum ALT, AST and bilirubin were compared with each other as well as the negative control group that received normal food and water. Simvastatin raised the liver parameters significantly. In addition, the experimental animals were weak and less active by the end of the study. Numerous studies have suggested that simvastatin has hepatotoxic potential[5,6]. The biopsy of the statin-induced livers revealed hepatic fibrosis and persistent inflammation of the tracts in the portal

system[10]. The major pathophysiology of the simvastatin-induced liver toxicity is the immuno-allergic idiosyncrasy[7].

The group of mice given rosuvastatin also displayed weight loss, a decline in activity levels, and noticeably elevated ALT, AST, and bilirubin levels. The information from the literature supports the findings of our investigation[8,9]. There have been cases of clinically severe liver damage brought on by rosuvastatin, despite pre-marketing studies of statin hepatotoxicity showing a 20- to 30-fold lower incidence of rosuvastatin hepatotoxicity as compared to the other statins[10]. Therefore, the toxic potential of rosuvastatin and the pathophysiology involved in the hepatic damage still remains unclear. The comparison of the levels of rise of ALT, AST and bilirubin among the group of mice receiving simvastatin with the one receiving rosuvastatin, indicated a higher rise among the rosuvastatin receiving group. Based on the finding, two hypotheses can be drawn, firstly rosuvastatin possess a hepatotoxic potential at higher doses and secondly, the hepatotoxic potential of simvastatin is lower as compared to simvastatin.

The current study did show a hepatoprotective effect of coenzyme Q10 but it was not strong enough. Although it was comparatively better in simvastatin group but was weaker as compared to the hepatoprotective effect by Montelukast. Several animal studies have shown that CoQ10 supplementation can attenuate the hepatotoxicity induced by statins[11,12]. Another study by Mabuchi showed that CoQ10 supplementation could prevent liver injury induced by atorvastatin[13]. A showed that CoQ10 supplementation improved liver function in patients with nonalcoholic fatty liver disease who were also taking statins. However, our study has reported conflicting results. Although the available evidence suggests that CoQ10 supplementation may have a hepatoprotective effect in statin-induced hepatotoxicity, particularly in animal studies.

A limited number of studies have investigated the potential hepatoprotective effects of Montelukast in statin-induced hepatotoxicity. One study by MS Hardeey et al. evaluated the effect of Montelukast on liver enzymes in patients receiving simvastatin[14]. The study found that Montelukast supplementation significantly reduced levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), indicating improved liver function. Some studies have investigated the hepatoprotective effect of Montelukast against agents other than statins and found that Montelukast treatment significantly reduced liver injury, improved liver histology, and reduced oxidative stress markers[15,16]. In conclusion, the available evidence suggests that Montelukast may have potential hepatoprotective effects in statin-induced hepatotoxicity. However, more research is needed to confirm these potential benefits in humans and to determine the optimal dose and duration of Montelukast supplementation in this setting.

CONCLUSION

Rosuvastatin had a higher hepatotoxic potential compared to simvastatin, as evidenced by the elevated liver enzymes and histological changes in the liver tissue. However, the study also found that montelukast showed a better hepatoprotective effect compared to coenzyme Q10, as it was able to effectively reverse the liver damage caused by both simvastatin and rosuvastatin. The exact mechanism of montelukast's hepatoprotective effect is still unclear, but it may be due to its anti-inflammatory and antioxidant properties. Overall, the findings suggest that clinicians should be aware of the potential hepatotoxicity of rosuvastatin and consider using montelukast as a hepatoprotective agent when prescribing statins, particularly in patients with pre-existing liver disease or elevated liver enzymes.

Author's Contribution:

Concept & Design of Study:	Sarwat Jahan
Drafting:	Manzoor Khan, Maaz Khan
Data Analysis:	Salman Zahir, Rabia Syed, Amber Ashraf
Revisiting Critically:	Sarwat Jahan, Manzoor Khan
Final Approval of version:	Sarwat Jahan

Conflict of Interest: The study has no conflict of interest to declare by any author.

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