Toxicological effect of Rosuvastatin on renal and hepatic parameters in Wistar rats

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ABSTRACT

This study investigated the effect of high doses of Rosuvastatin on the kidney and liver of adult Wistar rats. Forty (40) adult Wistar rats were divided into four (4) groups: A, B, C and D with ten (10) rats per group. Group A, the positive control was placed on normal feed and water ad libitum. Rosuvastatin 20, 40 and 60 mg daily were administered orally to groups B, C and D, respectively for 14 and 21 days. A total of twenty (20) Wistar rats, five (5) from each group were sacrificed under chloroform anaesthesia on the 15th and 22nd day of the study. Blood was collected from each of the sacrificed rats through cardiac puncture for kidney and liver function tests. The results obtained showed statistically significant elevations in serum sodium ion, creatinine, conjugated bilirubin and alkaline phosphatase levels. This study therefore concludes that Rosuvastatin at high doses is hepatotoxic and nephrotoxic.

Keywords: Rosuvastatin, kidney, liver, Wistar rats.

INTRODUCTION

Statins were sequestered from mold, penicillium citrinum and recognized as inhibitors of cholesterol biosynthesis by Endo et al. (1976). Brown and Goldstein later discovered that statins act by inhibiting 3-Hydroxy-3-methylglutaryl coenzyme A reductase. Compactin, renamed mavastatin was the first statin studied in humans. The first statin to gain approval for application in humans wasLovastatin, the former mevinolin was produced by Albert (1978) at Merck Medical Laboratory. Other members of the statin group are Pravastatin and simvastatin which are chemically modified products of Lovastatin, atorvastatin, fluvastatin and rosuvastatin and are unique synthetic compounds (Robert and Thomas, 2006).

The use of statins as a clinical intervention for dyslipidemia lies in its ability to significantly reduce elevated low density lipoprotein (LDL) cholesterol levels. Therefore, a great reduction in coronary diseases and death rate from coronary heart disease has been recorded for statins. Statins inhibit the first enzymatic step of cholesterol biosynthesis and are the drug of choice and the most effective and best tolerated drugs for the management of dyslipidemia (Robert and Thomas, 2006; Richard et al., 2009).

CHEMISTRY OF STATINS

According to Davidson et al. (2002), Simvastatin, pravastatin and Lovastatin, are derived from fungi, while Rosuvastatin, pitavastatin, Fluvastatin, Cerivastatin and atorvastatin are chemically synthesized. The structures of statins based on function can be classified into three: (Gaw and Packard, 2000); (1) Analogue of HMG-CoA enzyme substrate, (2) Complex hydrophilic ring structure which is involved in binding to the reductase enzyme, and (3) Active side groups on the rings, which determines its solubility. The fungi derived statins are lipophilic compounds because of the hydroxyl group, while the synthetic statins are more hydrophilic as a result of the polar hydroxyl and methane sulphonamide groups (McTavish and Sorkin, 1991; McTaggart et al., 2001).

The fungal metabolite has a hexahydronaphthalene ring. The presence of a methyl group at carbon 3 differentiates Lovastatin from mevastatin. There are two major side chains in statins. One is a methylbutyrate ester found in Lovastatin and pravastatin or a dimethylbutyrate ester in simvastatin, while the other contains a hydroxy acid that forms a six-membered analogue of the intermediate.
compound in the HMG-CoA reductase reaction. Fluvastatin, atorvastatin and rosuvastatin are entirely synthetic compounds containing a heptanoic acid side chain that form a structural analogue of HMG-CoA intermediate (Robert and Thomas, 2006).

MECHANISM OF ACTION

Statins are structural analogue of 3-Hydroxy-3-methylglutaryl CoA, a substrate for the biosynthesis of cholesterol. Their strong affinity for HMG-CoA reductase enables them to compete efficiently to inhibit the enzyme, the rate limiting factor in the cholestrol biosynthesis. Through intervention with cholesterol synthesis, statins therefore reduce the intracellular delivery of cholesterol. More so, the diminution of intracellular cholesterol induces the cells to enhance the amount of specific cell surface LDL receptors that can bind the available cholesterol. Hence, the consequence is a decrease in plasmas cholesterol induced by limited cholesterol synthesis and unlimited catabolism of low density lipoprotein cholesterol (Richard et al., 2009).

METHODOLOGY

Determination of the effects of rosuvastatin on the kidney and liver of wistar rats

This research was performed using 40 adult male Wistar rats allocated to four (4) groups, A, B, C and D with 10 animals per group. Group A, positive control were placed on just normal feed and water throughout the treatment courses. Rosuvastatin 20, 40 and 60 mg daily was administered orally to groups B, C and D, respectively. A total of 20 Wistar rats, 5 from each group were sacrificed under chloroform anaesthesia on the 15th day of the study. One millilitre (1 ml) of blood was collected from each of the sacrificed rats through cardiac puncture. The blood samples were collected in herparinized bottle and sent to a Chemical Pathologist for kidney and liver function analysis. The same procedure was repeated on the 22nd day of the research.

Statistical analysis

This was done by application of SPSS version 20. Data from kidney and liver function test were analyzed with Tukey’s multiple comparison followed by post-hoc test to compare various treatment groups with the control group as well as, individual drug with respective combination therapy. P values less than or equal to 0.05 were considered significant.

RESULTS

The kidney function of Wistar rats after a two week of treatment with Rosuvastatin

The paired samples test for this study showed a significant increase in serum Na⁺ level at 20 and 60 mg/day oral Rosuvastatin (Figure 1) as compared to the positive control at P < 0.05. The elevation in serum K⁺ level was also significant at the doses of 40 and 60 mg of Rosuvastatin as compared to the control. In addition, significant changes in serum BCo₃ and creatinine were recorded at the three doses used in this study when compared to the control.

Kidney function test after a three week of treatment with Rosuvastatin

The result of the kidney function test after a three week treatment with Rosuvastatin showed significant elevation in serum Na⁺ level as compared to the positive control (P < 0.05). It also showed a statistically significant difference in the serum levels of bicarbonate ion and urea. However, changes in creatinine were insignificant (Figure 2).

Liver function test following a 14 day treatment with Rosuvastatin

The liver function test following a two week treatment with Rosuvastatin showed significant elevation in serum Na⁺ level at 20 and 60 mg of Rosuvastatin and in conjugated bilirubin (CB) at 40 mg of Rosuvastatin (P < 0.05) (Figure 4).

Liver function test following a 21 day treatment with Rosuvastatin

The result from the week three liver function test also recorded statistically significant changes in the serum levels alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline Phosphatase at the three doses of Rosuvastatin employed in this study (Figure 5). There were also significant alterations in serum conjugated bilirubin (CB) level (P < 0.05) (Figure 6).

DISCUSSION

It has been established that elevations in the plasma kidney parameters (creatinine, electrolytes and urea) are the biomarkers for acute nephritic damage (Bonventre, 2008). More so, increases in plasma hepatic enzymes (alanine aminotransferase (ALT), aspartate
aminotransferase (AST), alkaline phosphatase (ALP) and bilirubin (TB and CB) are indicators for acute hepatocellular impaired functions. Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. They are extensively used for plasma cholesterol level reduction in the prevention and management of cardiovascular diseases. Recently, a good number of researches have indicated a progressing interest towards the advantageous effects of statins irrelevant to their outstanding cholesterol reducing potentials.

Our study showed a time dependent significant change in the kidney function parameters and liver enzymes. These substances are built up in the serum following impaired liver and kidney functions resulting from acute hepatocytes and nephrotic injuries. Our findings is in agreement with the observation of Hardik et al. (2013) who studied adverse effects of Lisinopril and Rosuvastatin on Hematological and Biochemical Analytes in Wistar Rats; that rosuvastatin caused significant elevations in serum levels of AST, ALP and total bilirubin. Interestingly, the hypernatreamia and creatinine kinase (CK) reported in our study was nullified by lisinopril treatment in their research. Furthermore, this present research has also reaffirmed the hepatotoxic effects of statins formerly reported by Law et al. (2003).

According to Hamid et al. (2016), treatment with atorvastatin 150 mg/kg/day for 7 days was nephrotoxic for rats, while lower doses at 10 mg/kg/day or 50 mg/kg/day for 7 days was not accompanied by acute renal injury. Siddals et al. (2004) on the toxic effects of statins gave a report of statins-induced diabetes. This is attributed

**Figure 1:** Comparative changes in electrolytes, urea and creatinine at different doses (20, 40 and 60 mg) of Rosuvastatin, respectively on day 14 treatment. Na+: Sodium ion, K+: Potassium ion and BCO₃⁻: Bicarbonate ion.
Figure 2: Comparative changes in electrolytes, urea and creatinine at different (20, 40 and 60 mg) of Rosuvastatin, respectively on day 21 treatment.

Figure 3: Comparative changes in serum liver enzymes at different (20, 40 and 60 mg) of Rosuvastatin, respectively on day 14 treatment. **AST**: Aspartate, **ALT**: Alanine aminotransferase and **ALP**: Alkaline phosphatase.
Figure 4: Comparative changes in total bilirubin and conjugated bilirubin at different doses of Rosuvastatin on day 14 treatment.

Figure 5: Comparative changes in serum liver enzymes at different doses of Rosuvastatin subsequent to day 21 treatment.
to the impairment of insulin functions by statins. More so, a study showed that statins application is associated with a 46% elevation in the risk of type 2 diabetes. This rate is related to insufficient insulin secretion. In addition, there exists a strong correlation between rhabdomyolysis induced by statins and acute renal failure (Cederberg et al., 2015; Duane and Philip, 2006).

Rhabdomyolysis is a rare but most serious adverse effect of statins and is suggested to be caused by acute obstruction of renal tubular flow by myoglobin and muscle particles (Duane and Philip, 2006).

**Conclusion**

This study therefore concludes that Rosuvastatin at high doses is hepatotoxic and nephrotoxic.

**REFERENCES**


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