A Comparative Study between Rosuvastatin and Pitavastatin Toxicity on Liver and Kidney in Albino Rats

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Abstract

Statins are group of drugs utilized to large degree as therapy of hypercholesterolemia, that is a substantial hazard in evolving cardiovascular diseases, like myocardial infarction, this achieved by competitive inhibition of three-hydroxy-three-methyl glutaryl coenzyme A reductase (HMGCR), three-Hydroxy-three-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors. Statins are applied widely to control serum cholesterol in an attempt to lower mortality and morbidity related to atherosclerosis.

Method: This study was conducted on 18 Sprague dawley male rats. They were separated into three groups each group consist of six animals each as the following:

- **Control group:** Drenched normal saline for 30 days.
- **Rosuvastatin group:** Drenched 15 mg/kg/day of rosuvastatin, for 30 days.
- **Pitavastatin group:** Drenched 0.8 mg/kg/day of pitavastatin for 30 days.

Objective: To determine the hepatic and renal toxicity, and safety of rosuvastatin compared with pitavastatin in rats.

Results: Results has revealed considerable rise in serum and ALP in rosuvastatin group, while for pitavastatin group the results revealed significant difference in serum ALP and no significant increase in serum ALT and AST.

Also there is significant difference in the serum level of creatinine in pitavastatin group and rosuvastatin group when compared between the three groups. and no significant increase in serum TSB and urea in both rosuvastatin and pitavastatin groups.

Conclusions: The study concluded that the pitavastatin is more safely used in patients with liver and kidney diseases and the pitavastatin is safer than rosuvastatin.

Keywords: *Rosuvastatin, Pitavastatin toxicity, liver, kidney.*

Introduction

Anti hyperlipidemic drugs (Statins)Statins have excessively utilized in treating hypercholesterolaemia through competitive inhibition of three-hydroxy-three-methyl glutaryl-coenzyme A reductase (HMGCR) that is cholesterol rate limiting enzyme in cholesterol synthesis, intracellular cholesterol shortage is caused by statins, there by prompting activating element bounding proteins by activating photolytic sterol, low density protein receptor expression causing plasma concentration of LDL cholesterol reduction caused by hepatocellular uptake increment[1].

Statins are recognized to decrease atherosclerosis catastrophes and minimize morbidity and mortality[2]. Also statins evince different biological impacts that are designated pleiotropic actions including anti-

inflammatory[3] and antioxidant effects[4], suppression of Platelet derived growth factor, stimulate propagation and up regulation of Tumor Growth Factor-B messaging in cardiac cells cultures and renal mesangial cells[5-6].

Pitavastatin: The construction of Pitavastatin reserves upgraded pharmacokinetics, comprising typical action as inhibition of HMG-CoA reductase and superior medicine imbibition. Pitavastatin is effectively superior to other statins in LDL receptor expression and minimize serum LDL cholesterol level through boosting liver uptake from circulation [7].

Pharmacokinetics of pitavastatin: Pitavastatin has been pretended to have elevated bioavailability reaching of 80% at a dose of 1 mg/kg[8] where it is selectively dispersed and metabolized by liver cytochrome P450 [9].

Adverse Effect of Pitavastatin: Muscle, back and joint pain, diarrhea, constipation, skin rash, headache, flu symptoms[10].

Toxicity of Pitavastatin: Temporary and little increase in serum aminotransferase without symptoms in about 1% of patients is seen in pitavastatin treatment, although results exceeding three times upper normal values are rare and absence of case reporting of obvious clinical hepatitis [11] although manufacturers has extradited records of hepatic failure, hepatitis and jaundice compromising lethal conditions[12], otherwise obvious acute hepatic insult appear after using other statins for one to six months with rise of serum liver enzymes in hepatocellular or cholestatic manner[13]. Allergic signs that have not confirmed yet in pitavastatin like eosinophilia, rash and fever are rare, hence autoimmune picture appear in few conditions comprising chronic hepatitis and production of autoantibodies proved in hepatic histopathology and clinical improvement after treatment with corticosteroids [14].

Rosuvastatin: Rosuvastatin is another drug of statins having antilipidemic and active antineoplastic effects. Rosuvastatin is blocked and bound to liver hydroxymethyl-glutaryl coenzyme A reductase in as selective and competitive manner causing distribution of LDL cholesterol into liver after decreased liver cholesterol values. Moreover, rosuvastatin, similar to else statins, shows variated actions on neoplasms as growth inhibition, pro_apoptotic, and pro_differentiation bounce[15].

Rosuvastatin presented lipid mitigation impacts in both in vivo and in vitro researches via rise the number of liver cell surface of LDL receptors promoting raise in uptake and catabolism of LDL [16].

Pharmacokinetic of Rosuvastatin: In man clinical researches peak serum, summit plasma concentrates of rosuvastatin were extended to three to five hours pursuing parenteral dosing. The ultimate rosuvastatin bioavailability is nearly twenty percent [16].

Rosuvastatin is mainly bound to plasma albumin reaching eighty-eight percent that is not permanent and unconditional to its plasma level [16].

Metabolism: The metabolism of rosuvastatin is restricted as nearly ten percent of dose is get metabolite. N-desmethyl rosuvastatin is the main metabolite that is emerged chiefly via cytochrome P450 2C9 that is about one sixth to half the blocking effect of HMG CoA reductase of founder component, meaning more than ninety percent of efficacious plasma HMG CoA reductase inhibitory activity is expounded by original compound [16].

Rosuvastatin and related metabolites are taken out mainly in feces about ninety percent after oral dosing at a nineteen hours half life, next to parenteral potion about twenty eight percent of whole body clearance through kidney and seventy tow percent via liver expel[16].

Materials and Method

This study was conducted on 18 Sprague dawley rats of male sex weighting between 270-370 g. They were separated into three groups each group consist of six animals maintained in the animal house of pharmacy college of Karbala university with open assess to water and food ad libitum, as the following:

- Control group: drenched normal saline for thirty days.
- Rosuvastatin group: drenched fifteen mg per kg per day of rosuvastatin for thirty days.
- Pitavastatin group: drenched 0.8 mg per kg per day of pitavastatin for thirty days.

The study was conducted after obtaining approval from the ethics committee of college of pharmacy / University of Karbala.

Rosuvastatin is used orally at a dose of fifteen mg per kg per day, and pitavastatin is used orally at a dose

of 0.8 mg per kg per day. Monitoring of the animals in their cages was achieved to elucidate clinical signs each day. Termination of the work time is done by analyzing serum enzymes aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphates (ALP), total serum bilirubin (TSB), serum creatinine and blood urea, and liver and kidney histopathological slides were prepared.

Statistical Analysis: SPSS version twenty in one-way analysis of variances; ANOVA was used to experiment and check difference between drugs groups and control group and results were demonstrated as mean ± SE. (ANOVA). Differences were dealt to the level $P < 0.05$.

Results

Impact of the antihyperlipidemic drugs on the blood level of liver enzymes in rats:

The output values reveal significantly raise ($p<0.05$) in serum level of ALP and ALT (except AST) in rosuvastatin group when compared with control groups, while for pitavastatin group the results revealed no significantly raise ($p>0.05$) in serum values of AST and ALT (except ALP) when matched with control group, also serum level pf ALP in pitavastatin group is significantly different ($p <0.05$) when matched with control group as in table (1).

Table (1): Shoo the impact of rosuvastatin and pitavastatin on the serum values of ALT, AST and ALP in comparison with control group

Parameters / Groups	ALT (U/L) Mean ±SD	AST (U/L) Mean ±SD	ALP (U/L) Mean ±SD
Control	61.20± 4.597[a]	101.80 ± 17.707[a]	210.40 ± 20.144[a]
Rosuvastatin mg/kg	81.40 ± 7.846[b]	116.20 ± 6.272[a]	555.60 ±90.147[b]
Pitavastatin mg/kg	70.20 ± 1.959[a]	101.20± 2.437[a]	421.20 ±49.396[b]

*The mean difference is significant at the 0.05 level. SD: standard deviation, ALT: Alanine amino transferase, AST: Aspartate amino transferase, ALP: Alkaline phosphates.

Results with superscripts (a, b) between study groups were considered significantly different. ($P < 0.05$)

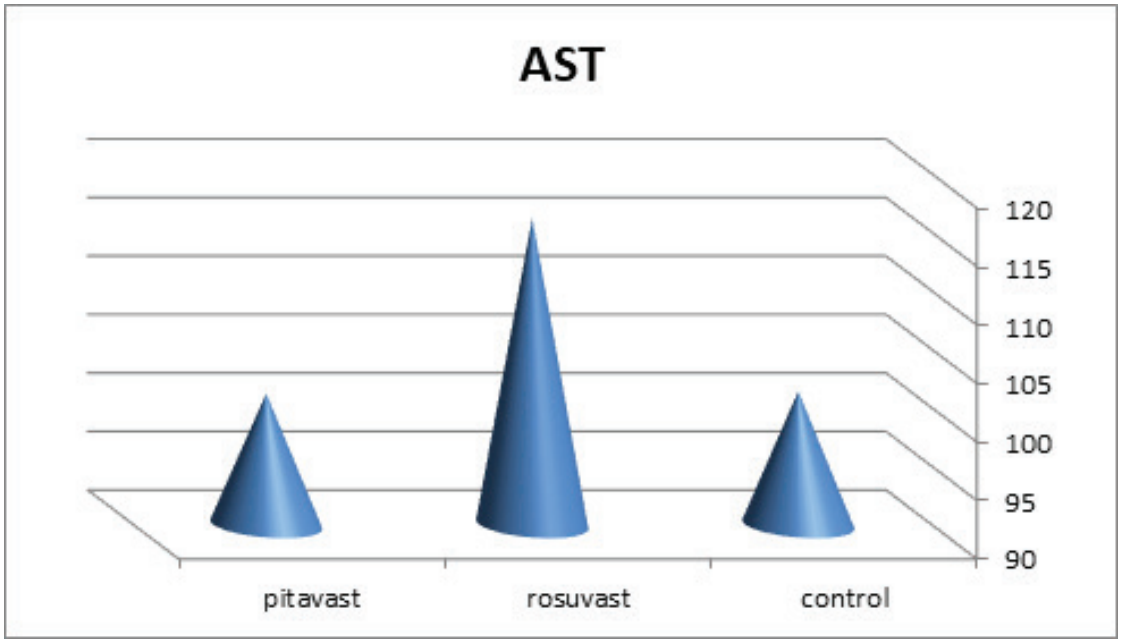

Figure (1): Serum level of Alanine amino transferase in control, rosuvastatin & pitavastatin in rats.

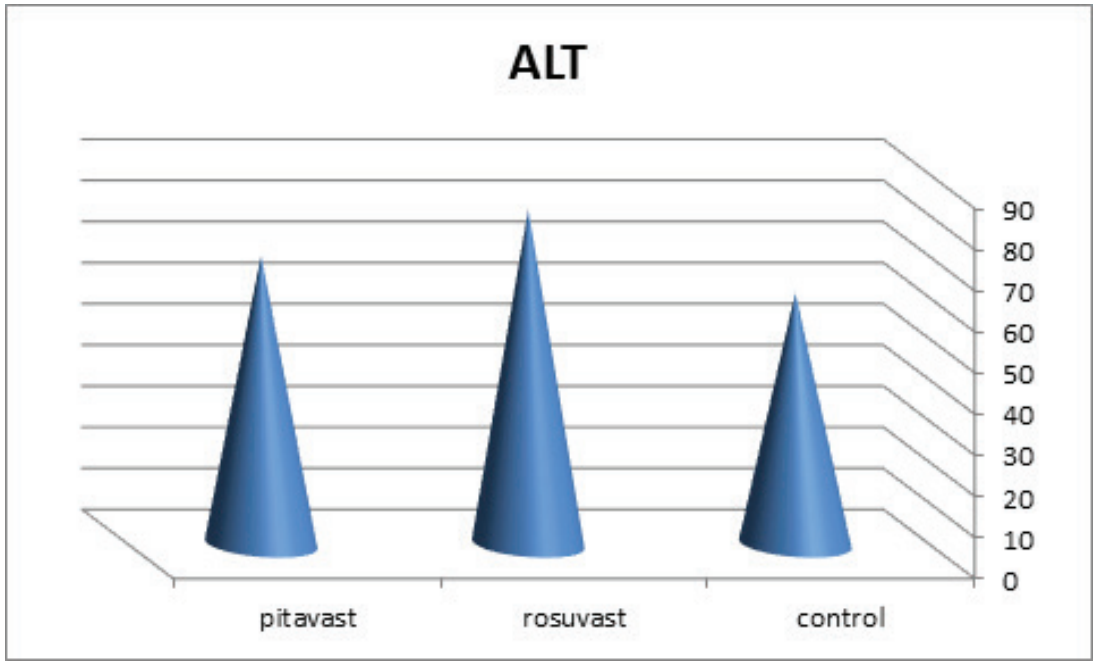

Figure (2): Serum level of Aspartate amino transferase in control, rosuvastatin & pitavastatin in rats.

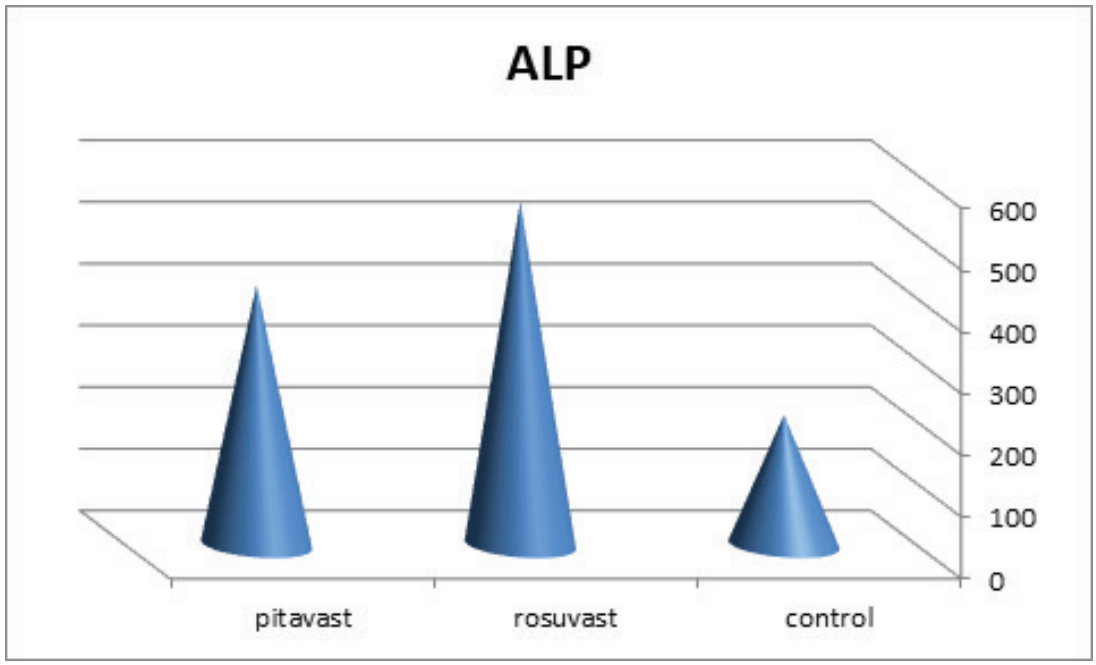

Figure (3): Serum level of Alkaline phosphates in control, rosuvastatin & pitavastatin in rats.

Effect of the antihyperlipidemic drugs on the serum level of kidney enzymes in rats: The results showed no significant increase ($p>0.05$) in serum level of TSB and urea (except creatinine) in rosuvastatin group when compared with both control groups and pitavastatin group, also there is no significant difference ($p>0.05$) in the serum level of TSB and urea in pitavastatin group when compared with both control groups and rosuvastatin group between the three groups, also there is significant difference ($p<0.05$) in the serum level of creatinine in pitavastatin group and rosuvastatin group when compared between the three groups, as in table (1).

Table (2): Show the impact of rosuvastatin and pitavastatin on the serum levels of urea, creatinine and TSB in comparison with control group.

Parameters / Groups	TSB (mg/dl) Mean ± SD	Urea (mg/dl) Mean ± SD	Creatinine (mg/dl) Mean ± SD
Control	0.40±.054[a]	35±.707[a]	0.38±0.033[a]
Rosuvastatin mg/kg	0.50±.031[a]	36.20±.979[a]	0.58±0.058[b]
Pitavastatin mg/kg	0.52±.037[a]	36.60±1.392[a]	0.38±0.038[ac]

The mean difference is significant at the 0.05 level. SD: standard deviation, TSB: Total serum bilirubin

Results with superscripts (a, b, c) between research groups that they were conceived significantly different ($p < 0.05$)

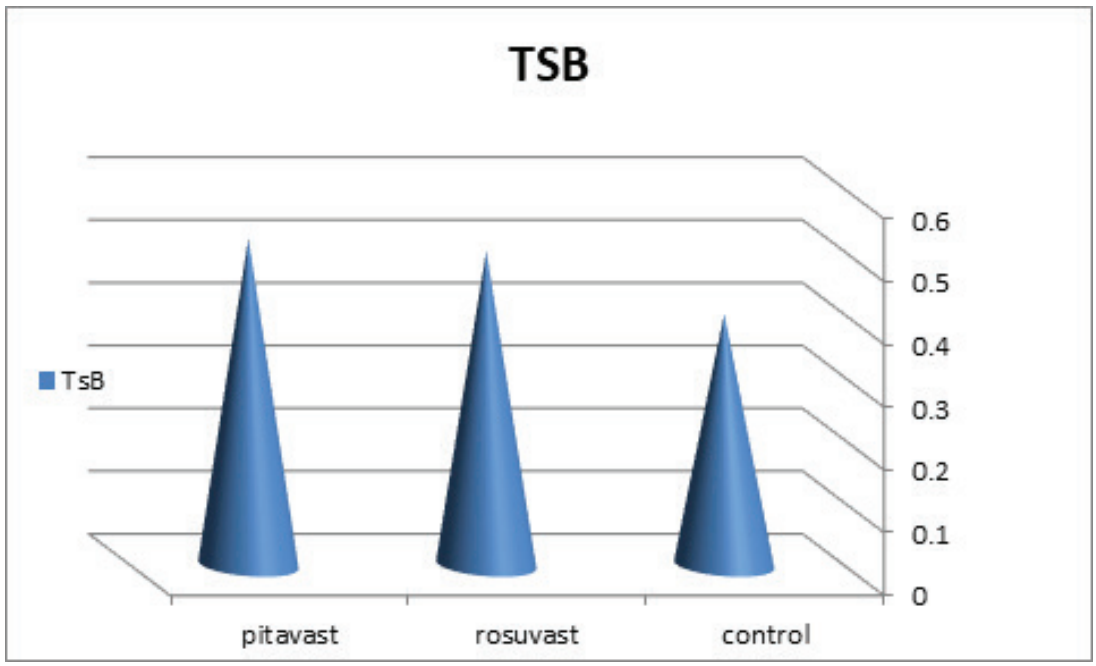

Figure (4): Serum level of total serum bilirubin in control, rosuvastatin & pitavastatin in rats.

Discussion

Statins are sort of medicine utilized to lower levels of lipid in circulation including whole cholesterol and especially [22]. HMG Co A reductase enzyme inhibition is controlling factor for cholesterol product and the prime function of statins. Hence decreasing the availability of cholesterol and in addition they rise the synthesis of the harmful LDL cholesterol receptors that facilitate to refine circulation from LDL cholesterol and assist hepatic cells to comprehend from circulation further LDL cholesterol as it cross in[23]. The evolving output is a decreasing whole cholesterol LDL cholesterol and triglycerides. On the other hand, the advantageous high density lipoprotein C, HDL C, is raised[24]. Serum levels of ALT and ALP except AST reveal significant increment that $p < 0.05$ in rosuvastatin group when they were compared with control group, furthermore ALT is significantly raised in rosuvastatin group when they were compared with pitavastatin group. these are due to rosuvastatin that is taken up by hepatocyte more selectively and more efficiently than other statin therefore it is considered a prime variable associated with the hepatotoxic potential of rosuvastatin[24].

Functional and structural modulations in liver are assessed by efficacy of ALP, ALT and AST in the circulation. The values of mentioned aminotransferases in blood are realized to raise in every hepatic illnesses and it is conspicuous that an extremely elevated level exceeding one thousand units could be detected in acute hepatitis[25]. We identified a clear temporal relationship

between initiation of rosuvastatin therapy and the elevation of liver enzymes.

While for pitavastatin group the results revealed no significantly increased $p < 0.05$ in serum levels of ALT and AST except ALP when they were compared with the group. So from all these consequences, pitavastatin is related to suave, non-symptomatic and temporal serum transaminase raises through management though it is comparatively recent evolved statin where it still has restricted use that could be related to the clear acute hepatic damage[26].

Conclusion

People are vastly using statins for hypercholesterolaemia, that is a distinctive part of growing risk of clusters of diseased related to cardiovascular system, so that the chronic use of these drugs made the patients exposed to adverse and toxic effects of it, and by making comparison of both rosuvastatin and pitavastatin to evaluate their toxic effects by measuring biochemical and histological alterations which showed significant findings for liver and kidney.

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Conflict of Interest: None to declare.

Ethical Clearance: All experimental protocols were approved under the College of Pharmacy and all experiments were carried out in accordance with approved guidelines.

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