Sys Rev Pharm 2020;11(10):1224-1227
A multifaceted review journal in the field of pharmacy

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

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ABSTRACT

Background: therapy of hypercholesterolemia used mainly statin group , which considered as the main disorder in human metabolism and may be led later to suffer from cardiovascular disease in future like myocardial infraction. By "competitive inhibition" of "3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), the main function of statins to decrease serum levels of cholesterol and then limited the severity of "atherosclerotic cardiovascular" disease. **Method:** This study was conducted on 18 albino rats weighting between (200-300) g. They were separated into three groups each group consist of six animals maintained in "animal house" of "university of Karbala/ college of pharmacy" with free access to food and water ad libitum. As the following: **Control group**: drenched normal saline for 60 days. **Atorvastatin group**: drenched 0.6 mg/kg/day of atorvastatin, for 60 days. **Pitavastatin group**: drenched 1mg/kg/day of pitavastatin for 60 days. **Objective:** To determine the toxicity, and safety of atorvastatin compared with pitavastatin in rats, and the effect of high doses on kidney and liver functions**. Results:** The results showed elevated significantly "($p<0.05$)" in concentration of "ALT , AST and ALP" of "atorvastatin group" when compared with control group, while for "pitavastatin group" the results reveal no significant elevation "($p>0.05$)" in concentration of "ALP and AST" when compared with control group, also the difference is significantly in concentration of "AST" in pitavastatin group when compared with healthy group ,for the more the deficiency is significant in" (ALP and AST)" of "pitavastatin" group when compared with "atorvastatin" group. Also, the elevation in the concentration of "urea and Creatinin" of" atorvastatin" group is not significantly when compared with healthy group at($p>0.05$) , and in "pitavastatin" group when compared with healthy group and "atorvastatin" group , while there is significant difference ($p<0.05$) in the concentration of urea in pitavastatin group when compared between the three groups. **Conclusions**: The study conclude that the pitavastatin safer than "atorvastatin ", especially in hepatitis patients ,while in patients with renal failure disease "atorvastatin" is more safe .

Keywords: Atorvastatin, pitavastatin toxicity, liver, kidney, albino rats

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INTRODUCTION

Statin

Therapy of hypercholesterolemia used mainly statin group, which considered as the main disorder in human metabolism and may be led later to suffer from cardiovascular disease in future like myocardial infraction. By "competitive inhibition" of "3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR)",which is the rate-limiting enzyme in "cholesterol synthesis", which lead to depletion intracellular of cholesterol, by stimulating the activity of photolytic of "sterol response element-binding proteins", then triggers the expression of bad cholesterol "low-density lipoprotein (LDL) receptor". As results so, the plasma concentration of "LDL cholesterol" is decreased when hepatocellular uptake elevated [1].

1.1.1. "Renal failure" means there is disorder in kidney functions. There are many causes of renal failure. The main cause is deficiency in supplement of blood to kidney.

1.1.2. Liver impairment can be due to a variety of factors including infections, autoimmune conditions, drugs, toxins. Liver impairment can be acute or occur as a chronic process involving a progressive destruction and regeneration of the liver parenchyma leading to fibrosis and cirrhosis.

Indication

Hydroxymethylglutaryl "coenzyme A reductase (HMG-CoA)" inhibitors. This group of drugs very famous and common in markets from the last twenty years. The main types of drugs as known in markets are "pitavastatin, atorvastatin, rosuvastatin, pravastatin, simvastatin and fluvastatin". The basic function of drugs group to inhibit the mechanism of biosynthesis process of cholesterol [2].

The treatment by statin group was very successful in decreasing "low density lipoprotein cholesterol (LDL-C)" concentration 20-50%, also, decreasing triglyceride concentration 10-20% which leading to slight elevation in "high density lipoprotein cholesterol (HDL-C)" Good cholesterol levels. The treatment of statin has been combined by the raising of liver enzymes in up to 1-3% of patients. Statin therapy has many side effects like Myalgia, with rates from 1-10%.the long term of statin therapy causes many effects like" Rhabdomyolysis" with low percent (less than 0.1%). also " hypothyroidism, polypharmacy and alcohol abuse " considered as triggers for "statin-related" muscle disorder. also, the disorder in hepatic activity, with percent up to 1% of cases. These drugs lead to increase the appearance of Diabetes Mellitus in patients due to their"diabrtogenic "feature .there aren't sufficient studies about the relation of "statins" with " acute nephritis ,mood disorder ". there are many drug interactions of statins like those with "cytochrome p450" enzyme group [3]

Pitavastatin

Mechanism of actions

The main mechanism of "Pitavastatin" to discourage the process of " adipocyte differentiation" of "3T3-L1 preadipocytes" by" adipogenic inducers". The presence of "Oil Red positive droplets, a few amounts triglyceride and decreased expression of adipocyte-specific genes, including fatty acid binding protein (aP2), CD36, adipsin and glucose transporter 4 (GLUT4)" is a good proof for mechanism of this drug. The effects of this drug on

"adipocyte differentiation of 3T3-L1 preadipocytes" on "time and concentration". the inhibition of "PPARγ expression" occurs by the effect of "pitavastatin", with no effect on "C/EBPα expression or DNA binding activity of PPARγ". As well as the stimulatory effect of this drug on "pref-1 expression in preadipocytes" with continuance the affecting of "pref-1" with elevated concentration in "differentiated cells". Also stimulated the "expression" of the "LDL receptor more efficiently than the other statins" and facilitated the entrance of "LDL" from the blood to the liver to decrease the levels "LDL" in serum [6].

pharmacokinetics: pitavastatin has "a bioavailability" reaches to 60%, greater than that of any other "statin" and the majority of the bioavailable fraction of an oral dose is excreted unchanged in the bile. Also, the "entero-hepatic" circulation of unchanged drug contributes to the prolonged duration of action and allows "once-daily, any-time dosing" [7]

Adverse effects: Muscle pain, back pain, joint pain, pain in your arms and legs, diarrhea, skin rash, headache, flu symptoms [8].

Toxicity : Many studies proved that long term therapy of "Pitavastatin" may be led to "mild "without signs, with raising in the concentration of "ALT, AST". There are many cases of diseases associated with the using of "Pitavastatin" although with poor proof like "Jaundice, hepatitis" and liver failure with "fatal cases". While, the use of other drugs of "statin" lead to many lethal cases. As well as many studies reported hepatic disorder was the main result of long-term using this drug. Which the main indicator is raising in the concentration of "ALT, AST, Alp". Also, the clinical symptoms like "autoimmune feature, chronic hepatitis, chronic hepatitis on liver biopsy and a clinical response to corticosteroid therapy" [9]. Much research shows the medium effect of Pitavastatin on liver functions and tissues [10]

Drug interaction: There are many drugs interaction associated with this drug like erythromycin-triggered the "inhibition" of "organic anionic transport polypeptide (OATP) –mediated" which released by the accumulation of "pitavastatin" when used with "erythromycin", also there is the "cyclosporine-pitavastatin" which led to many cases at the same mechanism of "erythromycin". As well as when using with" Niacin, Gemfibrozil" which increases the risk of muscle disorder. [11]

Atorvastatin

Mechanism

The main action of this drug illustered by the inhibition of "3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase" and this occurs by stop the "conversion" of "HMG-CoA" to "mevalonate", as well as the drugs of "statin" generally leads to lowering the production of cholesterol in liver. This drug usage led to elevation in number of "LDL receptors" on the hepatocytes surface in many cases with "families hypercholesterolemia", so at end many studies showed that the lowering the value of total cholesterol, hypercholesterolemia, mixed dyslipidemia, isolated hypertriglyceridemia" associated with "atorvastatin" uptake [12].

Pharmacokinetics : This drug has many features like the fast absorption after oral uptake with highest concentration up to "2 hours" . in other way this drug combined with plasma protein in ratio up to 98% with maximum volume as (380 liters) and metabolized by "CYP3A4" to active picture as "ortho-and Para hydroxylated". Then ejected with "metabolites" in bile. Its "half-life" reached to 14 hours [13].

Adverse Effects : Many side effects occur when long-term taking this drug like muscle disorders which have many cases like "muscle aches, muscle tenderness, or muscle weakness" and the indicator is the elevation of "creatine phosphokinase". As well as the other effects include"arthrslgia, dyspepsia ,diarrhea, nausea ,urinary tract infections" .also the destruction of striated muscle cells occurred in patient using "atorvastatin" .this case may be developed from the long term of impaired kidney disorder. Also, hepatic function disorder may be occurred by using "atorvastatin" and then elevation the concentration of liver enzymes. [14].

Toxicity : The toxic effects of this drug always combined with hepatic disorder when raised the levels of "AST, ALT" after "12 h" from taking the medicine. The liver has certain feature to return healthy after "11 h" when stopped the treatment. Many factors such as "advanced age, chronic and systemic disease". "Hepatotoxicity" known by rising "bilirubin, AST, ALT, alkaline phosphate". [15].

Drug Interactions: Many drugs have interaction with "atorvastatin "like " CYP3A4" inhibitors and then accumulated in plasma which led to many disorders' "myopathy". also, the interaction of "Atorvastatin" with " OATP1B1 inhibitors" elevated the "bioavailability"". Many drugs may lead to accumulated of "atorvastatin" in plasma when taken together with this drug such as "digoxin, ethinyl estradiol". [16]

Aim of the study.

To evaluate the effect of pitavastatin and atorvastatin on liver and kidney regarding toxicity and function in rats.

MATERIALS AND METHODS

Experimental animals

This study was conducted on 18 albino rats of female sex weighting between 200-300 g. They were separated into three groups each group consist of six animals maintained in "animal house of university of Karbala/ college of pharmacy" with free access to food and water ad libitum. As the following:

Control group: Drenched normal saline for 60days.

Atorvastatin group: drenched 1 mg/kg/day of atorvastatin, for 60 days.

Pitavastatin group: drenched 0.6g/kg/day of pitavastatin for 60 days.

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

Experimental technique

Drugs used to include atorvastatin tablet (20 mg), at dose of 1 mg/kg/day, and pitavastatin tablet (2 mg), at dose "0.6 mg/kg/day". The doses prepared by "dissolved in distilled water before administration by dose to each animal in the groups orally using a stomach cannula for 60 days". When the experiment the animal was killed using chloroform and "blood samples" collected for "biochemical analysis".

"Biochemical parameters"

Samples collected after at the end of experiment for biochemical assay. "Serum enzymes alanine amino transferase (ALT), aspartate amino transferase (AST), alkaline phosphates (ALP), total serum bilirubin (TSB)", serum Creatinin and blood urea.

Biochemical assay methods

Measurement of serum ALT, AST, TSB,ALP, Creatinin, Urea [17].

Statistical analysis

The results were represented as mean ± SEM. statistical significance using SPSS version (20) one- way analysis of variances (ANOVA). "At ($p \leq 0.05$)".

RESULTS

Effect of the antihyperlipidemic drugs "on" the level of liver enzymes in rats:

Table 3.1: The effect of atorvastatin and pitavastatin on liver enzymes in different study groups.

Groups / Parameter	Control	Atorvastatin	Pitavastatin
ALT mean ±SEM	38.2 ±1.93[a]	50.8±0.74[b]	53.2 ±1.65[b]
AST mean ±SEM	78 ±4.3[a]	116.5 ± 4.2[b]	88.1 ±2.3[a]
ALP mean ±SEM	356.75 ± 52.79[a]	816.16 ±106.06[b]	593.16 ±38[a]

Different letters mean significant differences at the 0.05 level. SEM: standard error mean, ALT: Alanine amino transferase, AST: Aspartate amino transferase, ALP:Alkaline phosphates.

Results were expressed as mean ±SEM "with superscripts" (a, b) between study groups were "considered significantly different ($p \leq 0.05$)".

Effect of the antihyperlipidemic drugs on the serum level of urea and Creatinin in rats:

Table 3.2: The effect of "atorvastatin and pitavastatin" on levels of urea and Creatinin in different study groups.

Groups / Parameters	Control	Atorvastatin	Pitavastatin
B.urea mean ±SEM	38 ±2.5[a]	40.8±1.9[a]	50.5 ±4.1[b]
S.cr mean ±SEM	0.175±0.025[a]	0.216 ± 0.06[a]	0.225 ±0.025[a]

Different letters mean difference is significant at the 0.05 level. SEM: standard error mean. Results were expressed as mean ±SEM, "with superscripts (a, b)" between study groups were considered significantly different ($p \leq 0.05$).

DISCUSSION

The results show a reduction of "total cholesterol, LDL cholesterol and triglyceride" fats. A little elevation in "(HDL-C)", the "good" cholesterol, is also produced[20]. The results showed significant elevation ($p<0.05$) in concentration of "ALT , AST and ALP" in "atorvastatin" group when compared with control group, while for pitavastatin group the results reveal no significant increase in the level of "ALP and AST" when compared with control group .This is due to atorvastatin is taken up by hepatocyte more selectively and more efficiently than other statin and this may represent an important variable associated with the hepatotoxic potential of atorvastatin's[21] ,The values of "AST, ALT and ALP" "are routine biochemical indicators of liver functions". The disorders in the liver lead to elevation in "levels of these enzymes in circulation". The concentration of these enzymes (ALT and AST) increased in in hepatic disorders. There are highly elevation in the concentration "of more than 1000 units" can be seen in "acute hepatitis" [22]. There is "a clear temporal relationship between initiation" of atorvastatin therapy and "the elevation of liver enzymes".

While for pitavastatin group the results revealed that pitavastatin group reveal no significant elevation ($p>0.05$) in concentrations of "ALP and AST "when compared with healthy group, also "there is significant difference ($p<0.05$) in the serum level" of AST in pitavastatin group when compared with control group, for the more (ALP and AST) significantly lowered in "pitavastatin" group when compared with "atorvastatin" group. pitavastatin is a little developed "cholesterol lowering agent" (statin) that is related with "mild, without symptoms and "self-limited" increasing in liver enzymes during therapy, but has combined with acute liver injury[23] , also there are many drugs overdose led to elevated (ALT and AST) as a single of liver injury [24].Because pitavastatin is a relatively new agent, less information is available on its potential hepatotoxicity [25].The result of renal function test show no significant difference ($p>0.05$) in concentrations of Creatinin in pitavastatin group when compared with both control group and atorvastatin group , while "there is significant difference ($p<0.05$) in the concentration of urea" in pitavastatin group against other groups , this is due to "Creatinin is filtered by glomerulus and thus, serum Creatinin level is considered as an indirect measure of glomerular filtration. Diminishing of glomerular filtration rate results in rise of plasma concentrations of serum Creatinin and urea. This rise indicates progression of kidney disease and thus serum Creatinin has greater prognostic ability compared with urea for predicting the adverse outcomes"[26],and this result was disagree with (Vidt et al.,) state that long-term administration of atorvastatin and other statins have been shown not to be associated with any decline in renal function, but instead have been shown to produce modest but clear improvement in glomerular filtration rate [27] .Therefore, it is clear that atorvastatin, and other statins, are not very safe agents and carry significant risks to hepatic or renal function.

CONCLUSION

Statins are widely used in the treatment of hypercholesterolemia, which is a key feature of the metabolic syndrome in humans and an important risk factor for the development of cardiovascular diseases, such as myocardial infarction, 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 atorvastatin and pitavastatin to evaluate their toxic effects by measuring biochemical and histological alterations which showed significant findings for liver and kidney.

RECOMMENDATION

1- All statins should be used with caution and in the lowest effective doses to avoid their adverse effects.
2- We recommend avoiding the indication of atorvastatin and pitavastatin as antihyperlipidemic in patients with liver disease and myopathy, also pitavastatin should be avoided in patients with renal disease because of its effect on urea level.

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