

Pathological Evaluation of Phenobarbital and Atorvastatin Co-Administration on Kidney of Rat

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Article information	Abstract
<p>Article history: Received: 27 Aug 2011 Accepted: 29 Sep 2011 Available online: 7 Dec 2011</p>	<p>Background: Atorvastatin is a lipid-lowering drug used to treat hyperlipidemia. Phenobarbital is the inducer of cytochrome enzymes. This study examined the interfering effect of simultaneous consumption of these drugs on the biochemical and pathological changes in rat's kidney.</p> <p>Materials and Methods: Drugs were administered to 4 groups of Wistar rats (8 per group) for 15 days as follows: normal saline, atorvastatin, atorvastatin phenobarbital and phenobarbital alone. After anesthesia, blood was taken from the heart and serum was removed to measure myoglobin, creatinine, BUN, sodium, potassium and uric acid. After easy kill of rats, kidneys were removed and tissue sections were prepared through the conventional method of pathologic sections preparation and they were stained with Hematoxylin-Eosin, and pathological changes were examined by light microscopy.</p> <p>Results: The simultaneous use of atorvastatin with phenobarbital significantly increased serum myoglobin of rats compared with control group. Pathological changes in the group receiving atorvastatin and phenobarbital simultaneously was observed with a greater intensity.</p> <p>Conclusion: Phenobarbital can reduce renal toxicity of atorvastatin.</p>
<p>Keywords: Atorvastatin Phenobarbital Kidney Rat</p>	
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Introduction

Statins (including simvastatin, lovastatin and atorvastatin) or A inhibitors (3-hydroxy-3-methylglutaryl-coenzyme) and HMG Coenzyme A reductase may be the most common medical cause of rhabdomyolysis. There are many reports on muscle and renal toxicity after taking statins in patients who have received these drugs in combination with other drugs or have had other diseases at the same time. Simultaneous use of danazol, nicotinic acid, cyclosporine and itraconazole increases the risk of muscle disease resulting from these drugs. Simultaneous use of these drugs with gemfibrozil has a high risk of muscle toxicity. If the amount of creatine kinase is above three times as much the normal dose in patients taking these drugs, these drugs should be immediately discontinued [1-4].

Iron released from the damaged muscle tissue contributes to renal toxicity as a source of iron. As an oxidant, Iron causing damage to membrane oxidative of various cells, including renal tubes [5-7]. Several studies have shown that iron-induced oxidative stress can lead to acute renal failure and antioxidant drugs have had protective effects on this type of damages [6-8]. One of the enzymes involved in this toxicity, is the enzyme cytochrome P-450. This enzyme performs oxidation reaction and has the ability to be induced (increase of the amount of enzyme and its activity) and to be inhibited.

Various drugs can induce or inhibit this enzyme. For example, barbiturates, rifampin, phenytoin and phenylbutazone perform the enzyme induction while erythromycin, cimetidine, ketoconazole and nortriptyline are considered as inhibitors of the enzyme cytochrome P-450. Inhibition of cytochrome P-450 can possibly reduce the toxicity of myoglobinuric of kidney [2-4].

Phenobarbital is of barbiturates that are used to treat seizures, insomnia and anxiety. This drug can increase biotransformation of substances and drugs in the liver by enhancement of hepatic microsomal enzymes activity and cytochrome enzymes can be induced by phenobarbital. The purpose of this study is to investigate the interaction of phenobarbital and atorvastatin on renal toxicity in rats.

Materials and Methods

This basic experimental study was conducted in 2009 in Shahid Chamran University of Ahvaz. Four groups of apparently healthy male Wistar rats weighing about 200±10 grams with 8 in each group were randomly selected and were investigated for 15 days (daily) in following order: Group I (control) received only normal saline orally and was kept at the same nutritional and environmental conditions as the other groups. Second group: the rats that orally received atorvastatin with dose

of 20 mg/kg for 15 days. The third group: the rats that orally received atorvastatin with dose of 20 mg/kg for 15 days and then received phenobarbital with dose of 80 mg/kg intraperitoneally. Fourth group: the rats that received phenobarbital with dose of 80 mg/kg intraperitoneally for 15 days.

The rats used prepared pellets and clean and healthy water. At the end of tests, rats were anesthetized with injection of ketamine (100 mg/kg) and then blood samples were taken from their hearts, and the serum was removed. Rats were killed with ether according to ethics in research. Factors BUN, creatinine, sodium, potassium and uric acid (based on instructions of kits of Pars Azmoon Company) of serum were measured as serum indicators of renal function. In this study, the amount of myoglobin in serum was also measured by ELISA kits (Gentaur Europe BVBA). The kidneys were sampled. After fixation with buffered-formalin 10%, for microscopic studies on the intended samples, sections of 6-5 micron thickness were prepared using the technique to cut into microscopic slices via microtome and the slices were stained using the standard method of Hematoxylin-Eosin staining, and they were studied by light microscopy.

The average pathologic lesions were calculated in four counted fields in each slide and the statistical difference of means was quantitatively examined for the number of damaged cells. Also, the mean difference of biochemical factors was statistically analyzed. Software SPSS-11 and ANOVA test and then, posttest LSD were used for statistical analysis. The mean difference between groups was considered significant with ($p < 0.05$).

Results

Mean of serum myoglobin of rats in different groups is shown in figure 1. As can be seen, taking atorvastatin could increase the value of serum myoglobin from 122.7 to 297.7 ng/ml, and this increase is significant compared to the control group and is significantly different with ($p = 0.008$).

Taking phenobarbital alone had no significant effect on serum myoglobin levels compared to the control group. However, prescription of this drug along with atorvastatin reduced the amount of serum myoglobin. Although this decrease was not significant, it is significantly different with and more than the control group ($p = 0.02$). Measurement of serum creatinine levels in rats showed that the amount of creatinine in the group receiving phenobarbital alone, was less than all groups and this amount has been less than the third group, so that the average serum creatinine was significantly different between the control group and the group receiving phenobarbital ($p = 0.05$). Serum creatinine values in group receiving atorvastatin alone were not significantly different with control group. Serum creatinine values are shown in figure 2. Measurement of the values of serum BUN in rats showed that there is not much difference between the groups. Investigation of serum values of sodium showed that there is no significant difference

between control group and the group of atorvastatin alone. However, with the use of phenobarbital along with atorvastatin, serum sodium level decreased and showed a significant difference with the control group ($p = 0.018$). The mean of serum sodium in different groups is shown in figure 3

Investigation of serum potassium levels showed no significant difference between the groups. Measurement of serum uric acid levels in rats showed that the amount of uric acid in the group receiving phenobarbital alone was less than all groups and this amount was less than the group receiving atorvastatin+ phenobarbital, so that the mean of serum uric acid was significantly different ($p = 0.05$) between the control group and the group receiving phenobarbital. Uric acid value in the group receiving atorvastatin alone was less than the control group and this difference is statistically significant. Serum uric acid values are given in figure 4.

In microscopic examination, three slides from each rat in every group, and four fields from each slide were randomly examined, the cases investigated as the indicator of kidney tissue damage include: Presence of cast in urinary pipes, acute tubular necrosis, cell swelling, hyperemia, and ratio of the outer diameter to inner diameter of close urinary tubes (Fig. 5-7). The group which received two drugs of atorvastatin and phenobarbital at the same time, showed the highest frequency in all mentioned lesions.

In the evaluation of presence of cast in sections, the group receiving atorvastatin and phenobarbital showed the greatest amount of cast which increased considerably compared to the control group as well as the group receiving atorvastatin alone.

Acute tubular necrosis was determined in sections with damaged epithelia cells. The group receiving atorvastatin and phenobarbital had the highest value of acute tubular necrosis, in tissue examination and counting of kidney sections in 4 microscopic fields in each slide out of three slides belonging to each rat. This increase was also too high in the group receiving phenobarbital alone. Acute tubular necrosis level in other groups did not differ much from the control group.

Cell swelling was seen in all groups. The highest level of cell swelling was in the group receiving atorvastatin+ phenobarbital and phenobarbital alone. After that, the group receiving atorvastatin showed the highest level of cell swelling. The group receiving atorvastatin+ phenobarbital had the highest level of hyperemia. The group receiving phenobarbital alone showed less hyperemia than atorvastatin and phenobarbital. The group receiving atorvastatin alone also showed hyperemia.

The mean of the ratio of outer diameter to the inner diameter of the closed urinary tubes greatly increased in the group receiving phenobarbital alone and this increase was also observed in the group receiving phenobarbital and atorvastatin.

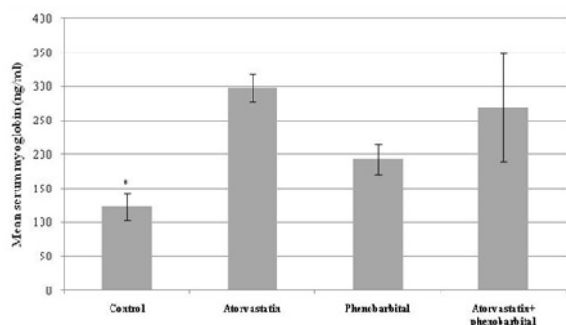


Figure 1. Mean of serum myoglobin in different groups of rats. *Indicating significant difference between control group and atorvastatin groups ($p < 0.05$)

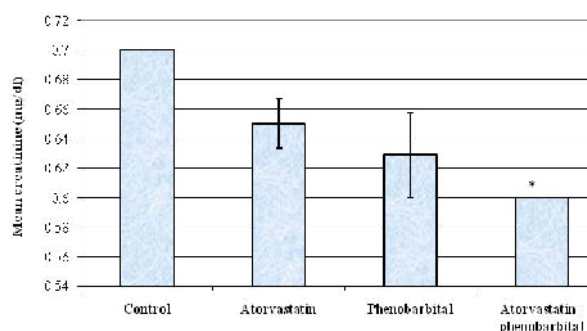


Figure 2. Mean (\pm standard error) of serum creatinine in rats. *Indicating a significant difference between phenobarbital alone group ($p < 0.05$)

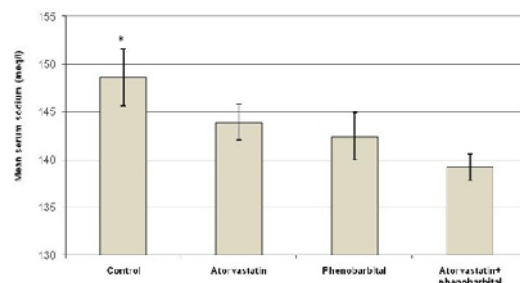


Figure 3. Mean (\pm standard error) of serum sodium in rats. *Indicating a significant difference between the control group and the groups receiving phenobarbital ($p < 0.05$)

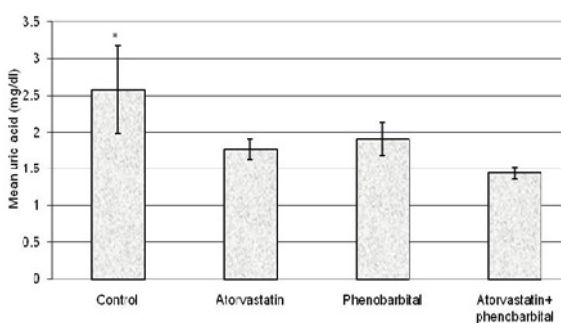


Figure 4. The mean \pm standard error of serum uric acid in rats. *Indicating a significant difference between control group and the groups of phenobarbital alone and atorvastatin alone ($p < 0.05$)

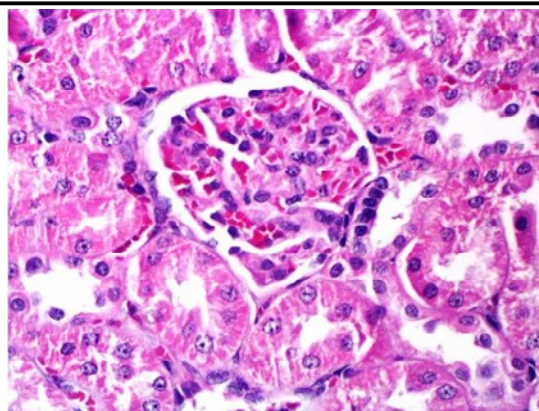


Figure 5. Microscopic view of normal kidney tissue in rats of the control group (H&E×40)

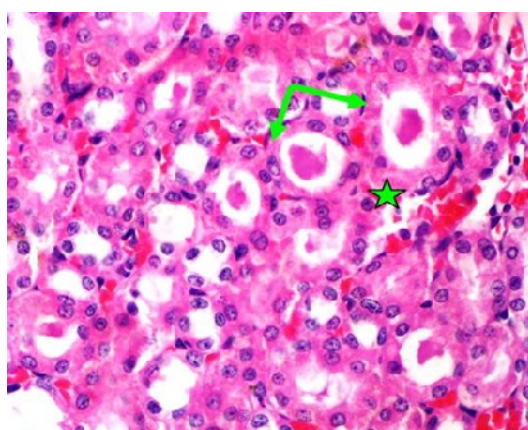


Figure 6. Microscopic view of kidney tissue in rats receiving atorvastatin. Pathologic lesions of casts (arrows) and hyperemia (stars) are observed in this figure (H&E×20)

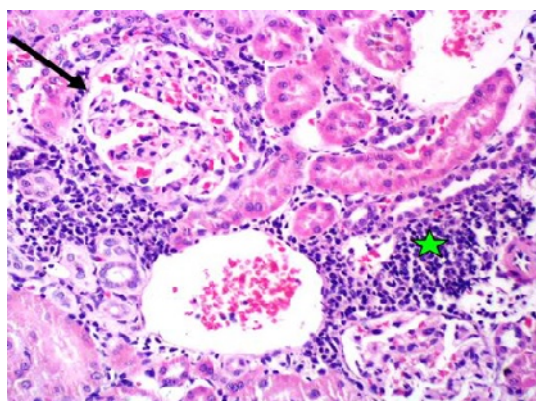


Figure 7. Microscopic view of kidney tissue in rats receiving atorvastatin and phenobarbital. In this figure, pathological lesions are observed as Bowman capsule's dilatation (arrows) and interstitial nephritis (stars) (H&E×20)

Discussion

Renal failure caused by drugs is considered a common cause of urinary tract infections. Different drugs with different mechanisms cause some damages to kidney cells

some of which cause the damage directly, such as aminoglycosides, and some others cause renal failure indirectly through releasing harmful elements such as iron in myoglobin and hemoglobin; statins, including atorvastatin, are of this class of drugs. In the present study, the effect of atorvastatin was studied on muscle damage and subsequently the possible renal failure and the effect of induction of the enzyme cytochrome P-450 was assessed by phenobarbital.

There are some reports on creation of rhabdomyolysis after taking statins, especially at the same time with other drugs or harmful elements of muscles some of which are mentioned below. It should be noted that no experimental study like the present study has been available on rhabdomyolysis caused by statins, particularly atorvastatin. In the present study, the use of atorvastatin with doses of 20 mg/kg in rats for 15 days caused muscle damage and rhabdomyolysis, so that the value of serum myoglobin in the group receiving atorvastatin alone was significantly more than control group.

Pierno et al. studied the effect of atorvastatin, fluvastatin and fenofibrate on muscle damage using biochemical, histological, and electrophysiological methods, and claimed that atorvastatin can lead to myopathy and muscle damage [9]. Jose et al reported rhabdomyolysis and nephrotic syndrome in a human patient after taking atorvastatin [10].

Mahoni et al. suggested that rhabdomyolysis induced by statin treatment is rare, but it can be fatal. They reported that in a 74-year-old patient who was treated with atorvastatin, rhabdomyolysis occurred after treatment with fusidic acid and flucloxaciline. They also assumed that pharmacokinetic interaction has caused such an incident [11].

Tufan et al. reported that after administration of atorvastatin in a 45-year-old man who received colchicine, severe rhabdomyolysis was observed. Also nephrotic syndrome with other clinical symptoms was observed after two weeks of receiving 10mg atorvastatin daily. Serum creatinine level increased, and acute renal failure was observed. They stated that atorvastatin and colchicine have undesirable effects on muscle [12] Burton et al. suggested that the simultaneous use of clopidogrel and atorvastatin increases concentrations of atorvastatin in plasma and leads to the onset of rhabdomyolysis [13]. Lewin et al. reported that simultaneous use of diltiazem and atorvastatin caused rhabdomyolysis [14].

There are also other reports on interactions of statin with other drugs that to create rhabdomyolysis, so that a study showed that simultaneous use of fusidic acid and simvastatin can lead to increase of simvastatin concentration in plasma and muscle damage [15]. Most side effects of statins are moderate and transient muscle symptoms, but severe symptoms such as myositis and rhabdomyolysis are rarely seen [16].

In a study, Thompson et al. investigated the effects of statins on myopathy, and claimed that statins decrease the production of small regulatory proteins which are necessary to protect muscle cells. Generally, the results of the present study are consistent with above reports.

However, more severe effects may be observed by changing the dose or duration of drug administration [17].

The iron in myoglobin can cause damage to the cell membrane, especially renal tubes, by creating oxidative stress. There are reports on renal failure following rhabdomyolysis, which are considered related to myoglobin iron and antioxidant drugs have had a protective effect against this complication. Oxidative reactions are involved in causing acute renal failure. Further, some studies related to myoglobin-induced renal failure will be pointed out.

Heyman et al. examined the effect of myoglobin in acute renal failure in rats and observed that the toxic effect of myoglobin on the kidney can be increased by acidosis [18]. Bosch et al. confirmed that rhabdomyolysis occurred after muscle damage, drugs, toxins or increased creatine can lead to acute renal failure [6]. In a study, Pelletier realized that after injection of rapamycin, potential myoglobin will be created and subsequently, acute renal failure will occur [19].

In this study, taking atorvastatin alone did not have much biochemical and pathological impact on kidney function and tissue, which is perhaps because the amount of released myoglobin is not high enough to cause serious damage or dose and duration of use of atorvastatin has not been enough. However, conflicting results have been reported regarding the effect of statins on the kidney tissue which some researchers have regarded to be toxic effect and some others considered beneficial and supportive effect.

Sabbatini et al. examined the effect of atorvastatin on ischemic acute renal failure in rats. They suggested that statins increase nitric oxide production and thereby, they may have protective effect on acute renal failure. These researchers administered atorvastatin with a dose of 12 mg/kg daily for 14 days to young rats (three months) and aged rats (eighteen months). Through renal artery ligation and ischemia in the kidney, they observed that preemptive administration of atorvastatin decreased renal vasoconstriction in old rats and revised glomerular filtration level in young rats. Nitrate secretion increased in young rats, which did not change by atorvastatin, while nitrate excretion did not increase in old rats, but it increased after treatment with atorvastatin. Atorvastatin had a protective effect on renal tubular cell damage in old rats, but it had no effect in young rats. Thus, low doses of atorvastatin have protective effect on tissue changes of the kidney pipes in acute ischemic failure [20].

In a study on 338 patients, Hedenmalm et al. observed that taking statins will cause muscle damage, so that potential myoglobin and 10-times increase in serum Creatine Kinase levels were observed. They also suggested that statins can cause muscle toxicity and rhabdomyolysis, which is exacerbated in cases where there is a renal disease or severe and unusual muscular activity [21].

Harterner et al examined the effect of statins in reducing glomerular inflammation and podocyte damage in rats with hypertension and claimed that statins (in this study fluvastatin) can reduce glomerular damage, podocyte

damage and macrophages and thereby, have beneficial effects [22]. In another study, Vidt investigated the effect of statins on proteinuria and suggested that when using, statins will cause transient proteinuria and this will be compensated when the drug is stopped and its clinical doses will not lead to nephrotoxicity or reduction of kidney function. The result of this study differs from previous studies [23]. In a study, Antoine et al. suggested that statins can avoid aminoglycoside-induced nephrotoxicity through the inhibition of mevalonate pathway [24]. In a study, the effects of statins on renal tubular cells were examined and it was suggested that HMG-CoA reductase inhibitors decrease proliferation, and increase apoptosis and fibrinolytic activity in renal tubular cells [25, 26].

One of the enzymes involved in iron caused renal failure, including myoglobinuric renal failure, is enzyme cytochrome P-450. Induction of this enzyme can cause more damage to the kidneys. In this study, in the group receiving atorvastatin plus phenobarbital, renal failure increased both in the biochemical assessment of renal function and pathological evaluation of kidney tissue and these changes were considerable and substantial compared with control group and the group receiving atorvastatin alone. Since phenobarbital induces liver enzymes metabolizing atorvastatin (CYP3A4), it reduces the effect of atorvastatin on plasma myoglobin.

In the study on toxicity of succinimide (herbal antifungal) in rats, Nyarko et al. observed that the use of phenobarbital along with induction of the enzyme cytochrome P-450 and increase of metabolism of this fungicide will produce nephrotoxic metabolites. Thus, they claimed that the enzyme cytochrome P-450 can be involved in renal toxicity [27]. Simultaneous use of statins and inhibitor drugs of cytochrome P-450 increases the risk of rhabdomyolysis in patients with liver and renal failure, which is probably because of pharmacokinetic interaction and inhibition of the metabolism of statins [28].

Toso et al. investigated the beneficial effects of atorvastatin with dose of 80 mg/kg in prevention from nephropathy in patients with chronic kidney disease and claimed that short-term administration of atorvastatin with dose of 80 mg/kg before or after the development of chronic kidney disease, had no effect in reducing the nephropathy level from this disease, and the results of this study are different from other studies [29].

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The present study showed that the use of atorvastatin causes muscle damage and significant increase in serum myoglobin in rats compared to the control group. Simultaneous use of atorvastatin and phenobarbital was still more than the control group, although it reduced serum myoglobin in rats. Pathological changes in kidney and biochemical factors were observed with greater intensity in the group receiving atorvastatin at the same time with phenobarbital. Thus, interaction of the effect of renal toxicity of atorvastatin with phenobarbital on renal toxicity is clinically important.

The results of this study revealed that the likelihood of damages caused by free radicals in active men is more than active women and considering insignificance of Cu/Zn SOD gene expression in both genders, both men and women are likely to respond to the increase of free radicals through enhanced activity of Cu/Zn SOD and gene expression of this enzyme does not significantly increase and accordingly, immune system of women and men somewhat responds to the increase in free radicals.

In the limited studies conducted on this issue in European and American races, significant gender differences have been also reported in terms of gene expression of this enzyme [4, 14] but in the Iranian population and active people, especially the impact of gender is not clearly determined and studied in which regard the results of this study can be used. In this study, other free radicals and other affective hormones that may affect the results of this study have not been measured, which is suggested to be reviewed in other studies.

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Authors' Contributions

All authors had equal role in design, work, statistical analysis and manuscript writing.

Conflict of Interest

No conflict.

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