Paradoxical Effects of Atorvastatin on Renal Tubular Cells
An Experimental Investigation

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Introduction. Atorvastatin has antioxidant activity and has been reported to increase blood antioxidant capacity. This study aimed to evaluate the effect of different doses of atorvastatin on gentamicin-induced kidney injury.

Materials and Methods. In this experimental study, 30 male Wistar rats were designated into 6 equal groups for a 7-day period of intraperitoneal injections of gentamicin and atorvastatin. Group 1 received gentamicin, 80 mg/kg. Group 2 received phosphate buffer as the vehicle of atorvastatin. All rats in groups 3, 4, and 5 received gentamicin, 80 mg/kg/d, and then, after a 1-hour interval, atorvastatin was injected for 7 days as follow: group 3, 10 mg/kg/d; group 4, 50 mg/kg/d; and group 5, 150 mg/kg/d. Rats in group 6 received only 150 mg of atorvastatin. On the 8th day, blood samples were collected for evaluation of creatinine and blood urea nitrogen levels, and the animals' kidneys were dissected out for histopathological examinations.

Results. Morphological damages to the tubular cells in groups 3 and 4 were less than the those in groups 1 and 5. Injuries to the renal tubular cells in the rats of group 5 (gentamicin and atorvastatin, 150 mg/kg/d) and in group 6 (atorvastatin 150 mg/kg/d alone) were more extensive than those in group 1.

Conclusions. The none–dose-dependent effect of atorvastatin in inducing renal tubular cell protection and renal tubular toxicity of atorvastatin in higher dose suggest administration of low-dose atorvastatin in critical conditions associated with renal tubular cell protection.

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INTRODUCTION

Atorvastatin is one of the most frequently and extensively prescribed 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors which was first manufactured in 1985 for the treatment of hyperlipidemia.[1,2] Various studies have detected that atorvastatin has the capability to directly bind and metabolize reactive oxygen species resulting in reduction of intracellular reactive oxygen species levels.[2-4] Also, atorvastatin is able to act in the kidney as a potent free radical scavenger and inhibit mitogen-activated protein kinase and nuclear factor kappa B. It also inhibits signaling pathways activation by reactive oxygen species and hence prevents tubule cell apoptosis induced by gentamicin.[5-9]

In general, statins may exert lipid-independent benefits against kidney injury in experimental states of chronic or acute kidney function impairment.[10-14] Furthermore, statins influence various signaling pathways involving kidney inflammatory, proliferative, and cell-death responses. Thereby,

statins exert anti-inflammatory actions in kidney tissue.[13-18] Kidney antioxidant properties with consequent endothelial function regulation of kidney vasculature, following statin administration, may also account for pleiotropic protection against kidney injury. Whereas, some publications indicate that administration of statins in high doses may itself lead to direct kidney tubular cell toxicity.[14-18] However, data on this subject is scares. This study, therefore, was focused to evaluate the efficacy of different doses of atorvastatin on gentamicin-induced kidney injury.

MATERIAL AND METHODS

Animals

In this experimental study, 30 male Wistar rats weighing 200 g to 250 g were used and similarly handled in the animal house of Isfahan University of Medical Sciences, Isfahan, Iran. The animals were housed at a controlled environment with 50% to 60% humidity and temperature of 25 ± 3°C. Furthermore, the rats were kept with 12-hour dark-light cycles (lights on at 7.00 AM) and allowed free access to pelleted diet and tap water. They were also kept in animal lab at least 1 week prior to the experiment. During the experiment, the animal's general health status and activity were monitored closely. The project was confirmed by the Ethical Committee of Isfahan University of Medical Sciences and all animal experimentations were conducted in accordance with the National Institute of Health guidelines for the careful use of laboratory animals.

Drugs and Chemicals

Atorvastatin was purchased from Kharazmi Pharmaceutical Company (Tehran, Iran) and administered intraperitoneally. Gentamicin was purchased from Alborz Company (Tehran, Iran). The rats received 80 mg/kg body weight per day of gentamicin, based on previously reported protocols.[19,20] Administration of atorvastatin was according to a previous study.[21]

Experimental Design

In this experimental study, 30 male Wistar rats were designated into 6 equal groups and treated as follows (all injections were intraperitoneal): group 1 received gentamicin, 80 mg/kg/d, for 7 days. Group 2 received phosphate buffer as the vehicle of atorvastatin for 7 days. All rats in groups 3, 4, and 5 received gentamicin, 80 mg/kg/d, for 7 days, and then, after a 1-hour interval, atorvastatin was injected for 7 days as follow: group 3, 10 mg/kg/d; group 4, 50 mg/kg/d; and group 5, 150 mg/kg/d. Rats in group 6 received only 150 mg of atorvastatin for 7 days. Injections were done every day for 7 days, and then on the 8th day, all rats were anesthetized using ketamine and the blood samples were collected for evaluation of creatinine and blood urea nitrogen levels, and then all the rats were sacrificed.

Histopathological Examinations

At the end of the experiment, the animals' kidneys were dissected out and fixed in buffered formalin for 12 hours and processed for histopathological examinations. Three micrometer-thick paraffin sections were stained with hematoxylin and eosin for light microscopic examination using a conventional protocol.[22]

Histopathological studies were performed under a light microscope. Slides were coded and examined by a nephropathologist who was blinded to the treatment groups. All specimens were examined for morphologic parameters including epithelial cell degeneration, vacuolization, tubular dilatation, tubular cell flattening, and presence of hyaline cast and debris materials in the tubular lumen.[22]

Statistical Analysis

All numerical variables with a normal distribution were expressed as mean ± standard deviation and categorical variables were presented as absolute frequency and percentage. A new variable of score was generated by means of histopathology evaluations of degeneration, vacuolization, tubular dilatation, tubular cell flattening, and presence of hyaline cast and debris of injury to the renal tubular cells. According to normal data distribution, the 1-way analysis of variance and post hoc Bonferroni tests were used for the comparison of mean values between the groups. Data analysis was done using the Stata (version 12.0, StataCorp LP, College Station, TX, USA). *P* values less than .01 were assumed to be significant.

RESULTS

The mean of scores of injury to the renal tubular cells were 45.2 ± 8.8 in group 1 and 20.1 ± 3.2,

20.6 ± 3.9, and 21.6 ± 4.1 in groups 2, 3, and 4, respectively. The mean scores of injury to renal tubular cells in groups 5 and 6 were 25.8 ± 12.7 and 53.6 ± 14.9, respectively. The morphological damages to the tubular cells in groups 2 and 3 were less than those in groups 1 and 4 (Table 1). Injuries to the tubular cells in the rats which received 80 mg/kg of gentamicin and 150 mg/kg of atorvastatin were more extensive than those in group 1 (80 mg/kg of gentamicin alone; $P < .001$). There was no significant difference of mean scores of renal injury between groups 2 and 3 (Table 2). In addition, injuries to the tubular cells in the rats of group 6, which received only 150 mg of atorvastatin were more extensive than those in group 1 (80 mg/kg of gentamicin alone) and group 2 (the control group; $P < .001$).

The analysis of blood urea nitrogen and creatinine showed greater loos of function in group 4, in comparison with group 1 ($P < .001$; Table 3). These findings were in accordance with the morphologic findings of the tissue. The mean serum creatinine in group 1 was 1.01 ± 0.34 mg/dL, which reached to 0.29 ± 0.23 mg/dL and 0.18 ± 0.07 mg/dL after receiving atorvastatin with doses of 10 m/kg and 50 mg/kg, respectively. The serum values of creatinine in groups 5 and 6 were 0.55 ± 0.05 mg/dL and 1.45 ± 0.96 mg/dL, respectively, the latter of which was the highest value among all groups (Table 4).

DISCUSSION

Comparison of the administration effects of gentamicin (80 mg/kg) alone and co-administration of gentamicin and atorvastatin with various doses of 10 mg/kg and 50 mg/kg revealed that atorvastatin was able to effectively reduce the biochemical and histopathological alterations of gentamicin-induced

Table 1. Scores for Dilatation, Degeneration, Vacuolization, and Debris of Renal Tubular Cells

Score	Groups						F Statistic*	*P*
	I	II	III	IV	V	VI		
Vacuolization	76.0 ± 14.6	5.0 ± 7.0	20.6 ± 6.0	18.3 ± 7.5	55.0 ± 25.0	82.5 ± 9.3	35.41	< .001
Degeneration	81.0 ± 9.0	5.0 ± 7.7	31.6 ± 9.0	39.2 ± 10.0	50.0 ± 22.8	85.0 ± 7.0	30.62	< .001
Debris	40.0 ± 13.0	1.1 ± 2.0	30.8 ± 4.9	30.4 ± 7.4	22.5 ± 13.3	51.6 ± 23.8	10.51	< .001
Dilatation	45.0 ± 21.0	0.7 ± 1.0	14.2 ± 7.0	20.8 ± 10.0	9.5 ± 6.0	58.3 ± 14.0	20.25	< .001
Total score	45.2 ± 8.8	20.1 ± 3.2	20.6 ± 3.9	21.6 ± 4.1	25.8 ± 12.7	53.6 ± 14.9	24.69	< .001

*One-way analysis of variance for comparison groups

Table 2. Between-group Comparisons of Dilatation, Degeneration, Vacuolization, and Debris of Renal Tubular Cells

Score	Score Differences Between Groups							
	1 and 2	1 and 3	1 and 4	1 and 5	1 and 6	2 and 3	2 and 4	2 and 5
Vacuolization	71.0*	55.3*	57.6*	21.0	6.5	15.6	13.3	50.0*
Degeneration	76.0*	49.3*	41.8*	31.0*	4.0	26.6*	34.1*	45.0*
Debris	38.8*	9.1	9.6	17.5	11.6	29.6*	29.2*	21.3
Dilatation	44.3*	30.8*	24.1*	35.5*	13.3	13.5	20.1	8.8
Total score	43.1*	24.5*	23.6*	19.3*	8.4	18.5	19.5*	23.8*
	2 and 6	3 and 4	3 and 5	3 and 6	4 and 5	4 and 6	5 and 6	
Vacuolization	77.5*	2.3	34.3*	61.3*	36.6*	64.1*	27.5*	
Degeneration	80.0*	7.5	18.3	53.3*	10.8	45.8*	35.0*	
Debris	50.5*	0.4	8.3	20.8	7.9	21.2	29.1*	
Dilatation	57.6*	6.6	4.6	44.1*	11.3	37.5*	48.8*	
Total score	51.5*	1.0	5.2	33.0*	4.2	32.0*	27.7*	

*Significant ($P < .01$)

Table 3. Kidney Function Tests Results

Parameter	Groups						F Statistic*	*P*
	I	II	III	IV	V	VI		
Blood urea nitrogen, mg/dL	84.0 ± 52.0	49.3 ± 56.0	98.5 ±19.0	82.2 ± 8.3	60.8 ± 8.4	210.3 ± 64.0	11.33	< .001
Serum creatinine, mg/dL	1.01 ± 0.34	0.26 ± 0.29	0.29 ± 0.23	0.18 ± 0.07	0.55 ± 0.05	1.45 ± 0.96	7.54	< .001

*One-way analysis of variance for comparison groups

Table 4. Between-group Comparisons of Kidney Function Test Results

Parameter	Parameter Differences Between Groups							
	1 and 2	1 and 3	1 and 4	1 and 5	1 and 6	2 and 3	2 and 4	2 and 5
Blood urea nitrogen, mg/dL	34.6	14.5	1.7	23.1	126.3*	49.1	32.9	11.5
Serum creatinine, mg/dL	0.74	0.71	0.82	0.45	0.44	0.02	0.08	0.28
	2 and 6	3 and 4	3 and 5	3 and 6	4 and 5	4 and 6	5 and 6	
Blood urea nitrogen, mg/dL	161.0*	16.2	37.6	111.8*	21.4	128.1*	149.5*	
Serum creatinine, mg/dL	1.18*	0.11	0.25	1.15*	0.36	1.26*	0.90*	

*Significant ($P < .01$)

renal injury. In this study, there were no significant differences between 10 mg/kg and 50 mg/kg dosages for renal protective effect of atorvastatin. However, administration of 150 mg/kg of atorvastatin was not effective to improve the tubular cell damage of gentamicin, and even it aggravated tubular damage of gentamicin. Moreover, administration of 150 mg of atorvastatin alone was toxic for the renal tubular cells. This study showed that co-administration of gentamicin and high doses of atorvastatin might have additive renal toxic effects, and drug interaction may perturb kidney function and structure.

The pathogenesis of acute kidney injury is complex, and promoting factors may be completely different (ischemia or toxins are main factors that precipitate in the damage), however, similar pathways may be involved in subsequent damage responses.[23-26] For this reason, to investigate the acute kidney injury models, various methods have been described for each specific situation.[27,28] The none–dose-dependent effect of atorvastatin in inducing renal tubular cell protection in this study and renal tubular toxicity of atorvastatin in higher doses may suggest administration of low-dose atorvastatin in critical conditions associated with renal tubular cell protection. However, the effect of atorvastatin or other statins on other renal toxic agents needs more investigation. In this regard, a clinical investigation of the effects of atorvastatin in prevention of contrast media-induced acute kidney injury in patients with chronic kidney disease showed that a single high loading dose of atorvastatin (80 mg within 24 hours before contrast media) administered within 24 hours before contrast media exposure was able to reduce the rate of contrast media-induced acute kidney injury. However, this beneficial effect was observed only in patients at low to medium risk.[29]

Gentamicin has a potential for treating aerobic gram-negative bacteria.[30] Accumulation of gentamicin in the proximal renal tubular cells may cause renal toxicity, which results in brush border network injury.[30,31] The kidney toxicity involves renal free radical production and accumulation, consumption of antioxidant defense mechanisms, and acute renal tubular necrosis, leading to abolished creatinine clearance and kidney dysfunction.[30,31] The pathological mechanisms also involve an increase of endothelin-1, upregulation of transforming growth factor-β, significant increase in monocyte/macrophage infiltration into the kidney cortex and medulla, augmentation of oxidative stress, and finally apoptosis and consequently necrosis.[30,31] In this study, gentamicin in group 1 effectively perturbed kidney function and structure compared to the control group.

Statins have been shown to reduce lipoprotein oxidation and ameliorate free radical injury, and atorvastatin possesses significant antioxidant activity against hydroxyl free radical and peroxyl radicals.[1-5,16,18] Furthermore, metabolites of atorvastatin reduce lipoprotein oxidation in a number of oxidative systems. Additionally, it was detected that simvastatin diminished cisplatin-induced kidney injury by prevention of lipid peroxidation.[32] Previous investigations detected that statins diminished reactive oxygen species and superoxide anion kidney production either by downregulation of nicotinamide adenine dinucleotide phosphate oxidase activity or through a decrease in the kidney endothelial expression of inducible nitric oxide synthase.[1-5,16,18,32] Previous in vitro and in vivo results indicated that statins suppress the synthesis of inflammatory mediators, such as tumor necrosis factor-α. Likewise it was observed that simvastatin and pravastatin decreased tumor necrosis factor-α and myeloperoxidase through mevalonate-independent pathways.[16,18,32,33] Inhibition of increased myeloperoxidase activity may result in decreased inducible nitric oxide synthase overexpression and subsequently lesser generation of reactive oxygen and nitrogen

species.[16,18,32,33] In a similar preclinical study, the kidney function tests and histopathological and immunohistochemical pictures were improved in correlation with antioxidant capacity. Atorvastatin acts in the kidney as a potent scavenger of free radicals to prevent the toxic effects of gentamicin via the inhibition of mitogen-activated protein kinase and nuclear factor kappa B signaling pathways and inducible nitric oxide synthase expression.[16]

Atorvastatin decreases cholesterol level by inhibiting the enzyme 3-hydroxy-3-methyl-glutaryl-CoA reductase; however, it has been suggested that the clinical profits of statin therapy may be due to mechanisms independent of cholesterol lowering property.[2-5] These pleotropic impacts of statins include antioxidant activity, anti-inflammatory activity, ability to offer plaque stability and inhibit platelet aggregation, and also anti-proliferative and immunosuppressive possessions.[2-5,13,15] Moreover, some evidence denotes that dyslipidemia plays a role in introducing and sustaining chronic kidney failure. Furthermore, atorvastatin applies cellular antioxidant effects in cultured rat vascular smooth muscle cells.[34] In a comparative study to test the incidence of contrast-induced nephropathy between atorvastatin and rosuvastatin, the authors found that atorvastatin and rosuvastatin had similar effectiveness in preventing contrast-induced nephropathy in patients with ST-segment elevation myocardial infarction undergoing primary coronary angioplasty.[5] Accordingly it was found that atorvastatin was a protective adjuvant against doxorubicin toxicity, by antioxidant, antinitrosative, anti-inflammatory, and anti-apoptotic mechanisms.[18] In a nationwide retrospective cohort study, it was also reported that statins with high cholesterol-lowering efficacy might increase the risk for developing severe kidney failure.[35] It was suggested that the nephroprotection against the gentamicin nephrotoxicity offered by atorvastatin is mediated by scavenging gentamicin-generated free radicals through the inhibition of mitogen-activated protein kinase and nuclear factor kappa B signaling pathway, in addition to inducible nitric oxide synthase expression. Statins reduce morbidity and mortality from coronary heart disease, prevent strokes, and possibly reduce kidney disease as the result of improved endothelial function, cholesterol lowering, reduced inflammation, and reduced oxidative stress.[1-5]

Side effects such as myalgia and arthralgia are common with statins; however, frank rhabdomyolysis is infrequent.[17] Mechanisms of kidney toxicity potentially consist of interruption of a wide variety of metabolic functions comprising membrane glycoprotein composition and fluidity, chloride channel activation, and impaired mitochondrial function by reduced ubiquinone synthesis that may render lipoproteins more susceptible to oxidation injury.[17,36,36] Kidney injury associated with the use of statins is commonly due to associated rhabdomyolysis producing acute tubular necrosis.[17,35,36] To the best of our knowledge, direct renal tubular injury by statins is infrequent and is limited to few case reports and may be related to administration of very high doses of this drug.[17,35,36] In the present study, the administration of high dose of atorvastatin (150 mg/kg) not only was nephrotoxic when it was administrated alone, but also aggravated the tubular injury when it was co-administrated at a dose of 150 mg/kg with gentamicin.

CONCLUSIONS

The results of this study showed a none–dose-dependent effect for atorvastatin in inducing renal tubular cell protection. However, higher doses of atorvastatin (50 mg/kg and higher) imposed renal tubular toxicity when it was administered alone. This finding suggests administration of low-dose atorvastatin in critical conditions associated with renal tubular cell protection, otherwise applying higher doses alone or by interaction with other drugs may lead to aggravation of kidney function.

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CONFLICT OF INTEREST

None declared.

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