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Original Article

Evaluation of Adverse Effects of Lisinopril and Rosuvastatin on Hematological and Biochemical Analytes in Wistar Rats

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ABSTRACT

Objective: Combination therapy of lisinopril and rosuvastatin may be an important concept in developing more effective strategies to treat and prevent atherosclerosis, coronary heart disease, and co-morbid metabolic disorders. The present study was designed to evaluate toxic effects of lisinopril and rosuvastatin alone or its combination therapy on hematological and biochemical analytes in Wistar rats. **Materials and Methods:** Forty-two rats were divided into seven groups, with each group comprising six rats. Rats were administered with lisinopril, rosuvastatin alone, or in-combination at two different doses. The blood samples were collected from rats after 21 days of oral administration of the drug/s and analyzed for various hematological and biochemical analytes. **Results:** Lisinopril alone and its combination treatment with rosuvastatin at high doses decreased hemoglobin and hematocrit. Rosuvastatin alone at high dose and its concomitant administration with lisinopril at two different doses showed increase in total white blood cells and absolute lymphocyte count and neutrophil count. Serum levels of aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin were significantly increased in rosuvastatin alone and its combination with lisinopril at both the doses. Besides this, lisinopril treatment decreased serum levels of sodium and increased the levels of potassium. Serum creatine kinase (CK) levels were increased in the animals treated with rosuvastatin at both the doses. However, increased serum CK level because of rosuvastatin became normal with co-administration of lisinopril at low doses. **Conclusion:** Our results indicate that administration of lisinopril with rosuvastatin does not ameliorate hepatotoxicity caused by rosuvastatin. However, combination treatment reduces serum CK levels elevated due to rosuvastatin, implicating protective effect of combination treatment on myopathy at low doses.

Key words: Lisinopril, rosuvastatin, toxicity evaluation

INTRODUCTION

Cardiovascular disorder (CVD) is the largest cause of mortality in males (20.3%) as well as females (16.9%) and led to about 2 million deaths annually.[1] Urbanization, epidemiological transition, and demographic shifts are attributed to increase CVD risk factors such as smoking, sedentary lifestyle, obesity, hypertension, and hypercholesterolemia.[1] Hypertension and hypercholesterolemia are two common coexisting risk factors along with other risk factors such as "glucose intolerance," "type-II diabetes," and "obesity."[2,3] The mortality and morbidity rate along with risk of coronary heart disease (CHD) increases with an increasing number of metabolic risk factors. Common relationship among the hyperlipidemia, endothelial dysfunction, insulin resistance,

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and renin-angiotensin-aldosteron system (RAAS) may be responsible for causing atherosclerosis.[4] Statins and ACE inhibitors (ACEI) improve multiple risk factors associated with hypertension and hyperlipidemia and reduce cardiovascular morbidity and mortality.[5]

Drug therapies have better effects on minimizing the cardiovascular events by acting together to improve blood pressure, vascular endothelial dysfunction, and insulin resistance as compared to stand-alone antihypertensives or antihyperlipidemics.[4] Antioxidant activity and nitric oxide synthase (NOS) activity by statins contribute to enhanced nitric oxide bioactivity and reduction in the production of oxygen-derived free radicals.[6] Reduction in generation of oxygen-derived free radicals by RAAS blockade improves endothelial function.[7,8] Hence, statins and RAAS blocker combination therapy may have beneficial effects on endothelial function, insulin resistance, and atherosclerosis.[9,10] Previously, simvastatin and ramipril combination therapy had shown better effects in patients with type-2 diabetes mellitus.[11] Combination of a statin with ACEI also showed full renal protection in experimental diabetes.[12] Thus, there is a strong scientific rational for developing combination therapy of statins and ACEI in treating and preventing cardiovascular events. Lisinopril and rosuvastatin are used to treat hypertension and hyperlipidemia, respectively. Lisinopril showed adverse effects like proteinuria, rare liver toxicity, hyperkalemia, decreased hematocrit, and hemoglobin, whereas rosuvastatin showed skeletal muscle, renal, and liver toxicity.[13,14] Development of a combination drug therapy should primarily focus on safety and then efficacy. Efficacious but unsafe drug therapies or combination of drug therapies are not approved by drug regulatory authorities. There is no established toxicity profile of combination therapy of lisinopril and rosuvastatin in laboratory animals.

Considering the above, it was worth to assess toxic effect of lisinopril and rosuvastatin alone or in-combination in Wistar rats.

MATERIALS AND METHODS

Chemicals

Lisinopril and rosuvastatin were obtained from Cadila Healthcare Limited, Ahmedabad, Gujarat, India. All other chemicals used in this study were of the analytical grade.

Animals and housing

A 6-8-week-old female Wistar rats were obtained from animal research facility of Zydus Research Centre (Ahmedabad, Gujarat, India). Experiments comply with the Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA) guidelines. All animals were allowed free access to food (standard chakan pellet diet, Amrit Feeds, Sangli, Maharashtra, India) and water (clean water purified by Aqua Guard water system), except when urine was being collected. The animals were housed under 12 h light/dark in individually ventilated cage system. The temperature condition of animal housing was 22 ± 3°C.

Experimental design

The experimental design is shown in Table 1. All the animals were acclimatized for 5 days. Freshly prepared drug formulations were administered by oral gavage (5 mL/kg) daily for 21 days. Blood samples were collected from retro-orbital plexus of rats in microcentrifuge tubes with potassium-ethylene diamine tetra-acetic acid (K_3EDTA) for hematology and in plain microcentrifuge tubes for serum. Serum was collected by allowing blood samples to clot and then centrifugation at 4000 rpm for 5 min at an ambient temperature. Animals were fasted overnight before blood collection to avoid interference of variable feed consumption. Lisinopril 20 mg/kg has anti-hypertensive effect in previous pre-clinical studies, whereas lisinopril 50 mg/kg reduced urinary protein excretion, indicating therapeutic action of lisinopril against proteinuria.[15-17] Rosuvastatin 40 mg/kg showed anti-hyperlipidemic effect in previous studies, whereas higher dose (≥80 mg/kg) of rosuvastatin induced myopathy in rats.[18,19]

Clinical signs and gravimetric analysis

Animals were observed for mortality, general state, external appearance, behavior, and clinical signs, daily, during the treatment period. Animals were weighed on the first day of treatment (day 1) and weekly thereafter. Body weight was measured on day 1 and 21, and body weight gain (%) was calculated. Food consumption was measured weekly and daily average food consumption was calculated.

Hematological and biochemical analysis

At the end of treatment period, blood samples were collected for hematological and biochemical analysis. The hematological parameters examined, including total erythrocyte count (RBC), total leukocyte count (WBC),

Table 1: Experimental design: All the treatment were given p.o. for 21 days in the group of six animals each

Groups	Treatment groups	Dose (mg/kg)
I	0.5% CMC (control)	0
II	Lisinopril	20
III		50
IV	Rosuvastatin	40
V		100
VI	Lisinopril+rosuvastatin	20+40
VII		50+100

CMC = Carboxy methyl cellulose

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hemoglobin, hematocrit, platelets, and differential leukocyte count. The fresh samples were analyzed by automatic hematology analyzer (CELL-DYN®3700, Abbott Laboratories, CA, USA).

Biochemical analysis was done on serum samples. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total cholesterol, triglycerides, creatine kinase-N-acetylcysteine (CK-NAC), total bilirubin, chloride, potassium, and sodium were analyzed using automatic biochemical analyzer (Daytona, Randox Laboratories Crumlin, UK).

Urine analysis

Urine samples were analyzed for glucose, ketone, specific gravity, pH, urobillinogen, and nitrite. All the analytes were analyzed by automatic urine analyzer (Clinitek-status, Siemens Healthcare Diagnostics Inc., USA).

Statistical analysis

Statistical analysis was performed using GraphPad Prism (Version 4.00). Data were analyzed for dose-wise comparison. Analysis of variance (ANOVA) was used for comparison of different treatment groups with the control group. Tukey's multiple comparison test was used as post-hoc test to compare various treatment groups with the control group as well as individual drug with respective combination therapy. Significance was reported at 5% level.

RESULTS

Gravimetric analysis

Rosuvastatin alone and its combination with lisinopril at high dose showed statistically and clinically significant reduction in body weight gain [Table 2]. Feed consumption of animals treated with high dose of rosuvastatin was reduced, but was not statistically significant [Table 3]. The mortality and clinical signs are published elsewhere.[20]

Hematological analysis

High dose of rosuvastatin alone and its combination with lisinopril at both the doses showed significant increase in total WBCs, lymphocyte, and neutrophil count. However, lisinopril alone at both the doses and low dose of rosuvastatin alone did not cause significant change in these analytes. High dose of lisinopril alone and its combination with high dose of rosuvastatin caused significant reduction in hemoglobin and HCT [Table 4].

Biochemical analysis

Rosuvastatin alone and its combination with lisinopril at both the doses showed significant decrease in serum triglyceride and cholesterol levels. However, lisinopril alone at both the doses did not show any significant reduction in serum triglyceride and cholesterol. Rosuvastatin alone and its combination with lisinopril at both the doses caused significant increase in AST, ALP, and total bilirubin. Rosuvastatin and its combination with lisinopril at low dose showed significant increase in ALT. Reduction in serum sodium levels and increase in serum potassium were observed in lisinopril alone and its combination treatment with rosuvastatin at both the doses [Table 5]. Effects of this treatment on serum albumin, total protein, creatinine, and urea are published elsewhere.[20]

Rosuvastatin alone at both the doses showed significant increase in serum CK, whereas either dose of lisinopril did not alter the CK levels. However, this significant elevation of CK was not observed in combination therapy of lisinopril and rosuvastatin at low dose, but combination at high dose showed significant increase in serum CK levels [Figure 1].

Qualitative and semi-quantitative urine analysis

Rats treated with lisinopril and rosuvastatin alone or their combination at different doses did not show any significant

Table 2: Effects of repeated treatment with lisinopril and rosuvastatin alone and in combination on rat body weight

Treatment groups (mg/kg)	Body weight (Day 1, gram)	Body weight (Day 21, gram)	Body weight Gain %
0.5% CMC (0)	142.6±5.9	167.7±7.0	17.6±0.3
Lisinopril (20)	138.0±3.7	166.6±4.6	20.8±0.6
Lisinopril (50)	141.6±3.6	170.1±3.2	20.2±1.0
Rosuvastatin (40)	141.9±3.7	167.9±4.2	18.3±1.2
Rosuvastatin (100)	139.6±5.2	108.9±2.6**	–22.1±4.4**
L+R (20+40)	140.3±5.0	161.4±5.5	15.1±0.9
L+R (50+100)	140.0±3.9	110.8±10.5*	–21.7±5.8**

L+R = Lisinopril+rosuvastatin, CMC = Carboxy methyl cellulose. *n* = 6 in each group = Values in rows are expressed as Mean±SEM. *P<0.05 significant compared with control, **P<0.01 significant compared with control. Analysis of variance followed by appropriate *post-hoc* test

Table 3: Effects of repeated treatment with lisinopril and rosuvastatin alone and in combination on food consumption

Treatment groups (mg/kg)	Mean food consumption (g/day/rat)
0.5% CMC (0)	23.3±1.8
Lisinopril (20)	23.9±1.1
Lisinopril (50)	23.2±0.9
Rosuvastatin (40)	23.4±1.2
Rosuvastatin (100)	18.3±2.3
L+R (20+40)	22.6±0.9
L+R (50+100)	16.3±4.9

L+R = Lisinopril+rosuvastatin, CMC = Carboxy methyl cellulose. *n* = 6 in each group = Values in rows are expressed as Mean±SEM. *P<0.05 significant compared with control, **P<0.01 significant compared with control. Analysis of variance followed by appropriate *post-hoc* test

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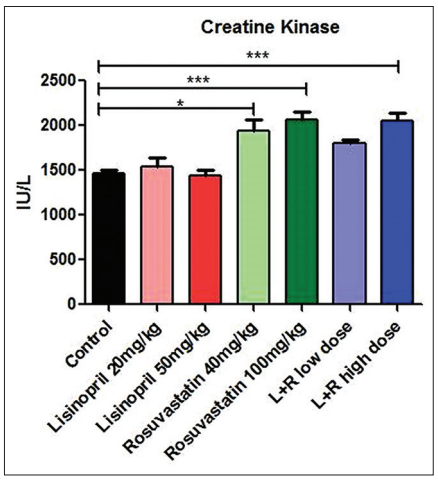


Figure 1: Effect of 21 days of repeated treatment lisinopril and rosuvastatin, alone and in combination, on serum creatinine kinase N-acetyl-L-cysteine levels in rats. L + R = Lisinopril + Rosuvastatin, CMC = Carboxy methyl cellulose. Each bar represents the Mean ± S.E.M. Statistical analysis by analysis of variance (ANOVA) followed by appropriate *post hoc* test. *$P < 0.05$ significant compared with control, ***$P < 0.0001$ significant compared with control

change in glucose, ketone, urobilinogen, and nitrite in urine samples. In addition, urine specific gravity and pH was unaltered with any treatment [Table 6]. Effect of this treatment on urinary protein excretion, urine output, and leucocytes and blood in urine is published elsewhere.[20]

DISCUSSION

In patients with CHD, it has been reported that cholesterol lowering effect of statins reduces morbidity and mortality.[21] The European trial on reduction of cardiac events with perindopril (an ACEI) in stable coronary artery disease (EUROPA) showed that perindopril significantly improves outcome in patients with CHD.[21] In the same study, authors further report that, in dyslipidemic CHD patients, the combinations of statins and ACEI reduces cardiovascular events more than in statin alone and substantially more than in ACEI alone.[21] In one of the study at two large hospitals in England, adverse drug reactions (ADRs) during treatment represented an

Table 4: Effects of repeated treatment with lisinopril and rosuvastatin alone and in combination on hematological analytes

Treatment groups (mg/kg)	HGB (g/dL)	HCT (%)	RBC count ($10^6/\mu L$)	WBC count ($10^3/\mu L$)	PLT count ($10^3/\mu L$)	LYMPH count ($10^3/\mu L$)	NEUT count ($10^3/\mu L$)
0.5% CMC (0)	13.8±0.18	44.4±0.70	7.05±0.17	4.18±0.38	882.8±20.8	3.12±0.25	0.63±0.06
Lisinopril (20)	12.6±0.17	40.3±0.69	6.53±0.11	4.84±0.31	913.1±45.4	4.09±0.24	0.51±0.06
Lisinopril (50)	12.2±0.27*	39.3±0.82*	6.41±0.14	4.64±0.50	934.6±33.2	3.83±0.48	0.51±0.06
Rosuvastatin (40)	13.8±0.06	44.2±0.34	7.38±0.08	6.35±0.20	944.0±82.2	5.40±0.62	0.74±0.12
Rosuvastatin (100)	14.1±0.18	45.6±0.33	7.55±0.09	10.65±1.01**	795.3±19.2	9.48±0.92**	0.98±0.09*
L+R (20+40)	13.0±0.57	41.4±1.82	6.95±0.32	6.93±0.43*	917.6±52.9	5.77±0.49*	0.94±0.09*
L+R (50+100)	11.4±1.25**	36.6±3.50**	6.16±0.60	9.37±3.33**	787.5±83.5	9.75±1.65**	0.95±0.09*

HGB = Hemoglobin, HCT = Hematocrit, RBC = Red blood cell, WBC = White blood cell, PLT = Platelet, LYMPH = Lymphocyte, NEUT = Neutrophil, L+R = Lisinopril+rosuvastatin, CMC = Carboxy methyl cellulose. *n* = 6 in each group = Values in rows are expressed as mean±SEM, *P<0.05 significant compared with control, **P<0.01 significant compared with control. Analysis of variance followed by appropriate *post-hoc* test

Table 5: Effects of repeated treatment with lisinopril and rosuvastatin alone and in combination on biochemical parameters in rat serum

Treatment groups	0.5% CMC (0 mg/kg)	Lisinopril (20 mg/kg)	Lisinopril (50 mg/kg)	Rosuvastatin (40 mg/kg)	Rosuvastatin (100 mg/kg)	L+R (20+40 mg/kg)	L+R (50+100 mg/kg)
TG (mg/dL)	57.1±1.93	51.3±1.32	56.3±2.51	38.7±2.02**	38.0±1.78**	44.9±1.77**	33.1±2.70**
Cholesterol (mg/dL)	44.8±0.98	44.2±1.65	43.6±0.99	35.4±1.40**	36.2±1.00**	36.1±1.72**	32.0±2.41**
TBIL (mg/dL)	0.1±0.03	0.1±0.02	0.1±0.01	0.2±0.03**	0.2±0.03**	0.2±0.01**	0.18±0.02*
AST (U/L)	150.9±2.35	139.3±4.79	132.3±3.78	275.5±12.24**	206.2±13.96*	237.4±22.3**	226.1±13.95*
ALT (U/L)	21.5±0.50	22.1±0.89	20.9±1.00	31.8±0.84**	21.2±2.36	27.4±0.94**	25.1±1.0
ALP (U/L)	111.7±4.05	127.9±3.63*	107.5±4.91	188.9±1.99**	198.5±3.80**	177.3±3.57**	192.7±2.58**
TP (g/dL)	6.35±0.10	6.08±0.10	6.07±0.09	5.82±0.22	5.43±0.36*	5.57±0.26*	5.08±0.25**
Albumin (g/dL)	4.03±0.07	3.85±0.06	3.80±0.04	3.73±0.07	3.53±0.17**	3.67±0.12*	3.43±0.17**
Globulin (g/dL)	2.32±0.04	2.23±0.05	2.27±0.07	1.85±0.13	1.90±0.19**	1.90±0.15*	1.65±0.10**
Urea (mg/dL)	47.5±1.44	50.5±3.73	63.4±1.93**	44.0±1.63	48.1±3.56	68.4±2.75**	31.40±1.40**
Creatinine (mg/dL)	0.64±0.01	0.70±0.02	0.68±0.03	0.60±0.03	0.57±0.01	0.73±0.02*	0.61±0.01
Na (mmol/L)	142.2±0.72	138.8±0.44*	139.0±0.76*	140.4±0.74	141.8±1.09	136.9±0.89**	139.0±2.55**
K (mmol/L)	3.87±0.06	4.35±0.06**	4.20±0.04*	3.57±0.08	3.62±0.21	4.5±0.07**	4.42±0.11**
Chloride (mmol/L)	104.4±0.39	103.1±0.31	103.2±0.63	102.8±1.04	104.8±0.77	102.2±1.07	104.2±1.34

TG = Triglyceride, TBIL = Total bilirubin, AST = Aspartate transaminase, ALT = Alanine transaminase, ALP = Alkaline phosphate, TP = Total protein, Na = Sodium, K = Potassium, Cl = Chloride, L+R = Lisinopril+rosuvastatin, CMC = Carboxy methyl cellulose. *n* = 6 in each group: Values in rows are expressed as mean±SEM. *P<0.05 significant compared with control, **P<0.01 significant compared with control. Analysis of variance followed by appropriate *post-hoc* test

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Table 6: Effects of repeated treatment with lisinopril and rosuvastatin alone and in combination on qualitative and quantitative urine analysis

Treatment groups (mg/kg)	Glucose (mg/dL)	Ketone (mg/dL)	Specific gravity	pH	Urobillinogen (Eh U/dL)	Nitrite (P/N)
0.5% CMC (0)	Nil	Nil	1.020±0.001	7.25±0.25	0.2±0.00	Nil
Lisinopril (20)	Nil	Nil	1.010±0.001	6.91±0.15	0.2±0.00	Nil
Lisinopril (50)	Nil	Nil	1.021±0.001	6.83±0.10	0.2±0.00	Nil
Rosuvastatin (40)	Nil	Nil	1.021±0.002	7.08±0.15	0.2±0.00	Nil
Rosuvastatin (100)	Nil	Nil	1.020±0.001	7.25±0.14	0.2±0.00	Nil
L+R (20+40)	Nil	Nil	1.021±0.002	6.91±0.08	0.2±0.00	Nil
L+R (50+100)	Nil	Nil	1.020±0.001	7.00±0.25	0.2±0.00	Nil

L+R=Lisinopril+Rosuvastatin, CMC=Carboxy methyl cellulose. *N*=6 in each group: Values in rows are expressed as mean±SEM

important cause of morbidity and mortality.[22] In view of this, we designed a systematic study to assess toxic effects of lisinopril (an ACEI) and rosuvastatin (a statin) alone or in combination on hematological and biochemical analytes in Wistar rats.

Clinical signs, histopathological observations in kidney, and changes in the key serum or urinary biomarkers of kidney injury observed in this study have been reported earlier.[20] Rats treated with rosuvastatin alone and in combination with lisinopril at high dose showed ≥50% mortality and decrease in motor activity, porphyria, and piloerection as prominent symptoms.[20] In addition to above, there were significant differences in body weight gain in animals treated with rosuvastatin alone and its combination with lisinopril at higher doses. Earlier toxicity studies of rosuvastatin reported clinical symptoms such as porphyria and decrease in motor activity, body weight reduction, and mortality, which may be due to systemic renal and liver failure and muscle toxicity.[18] Therefore, in the present study, it may be concluded that observed clinical symptoms, body weight loss, and mortality in rats treated with high dose of rosuvastatin alone and its combination with lisinopril is because of known individual toxic effects of rosuvastatin on liver, kidney, and skeletal muscles.

In the present study, lisinopril and its combination with rosuvastatin at high dose showed decrease in the hemoglobin and hematocrit. Decrease in hemoglobin, hematocrit, and RBCs in dogs after administration of more than 10 mg/kg of lisinopril have been reported earlier.[13] This effect may be due to decreased erythropoietin production with lisinopril administration. ACEI are known to decrease angiotensin II and inhibit differentiation of erythroid cells.[23] Hence, this effect on hemoglobin and hematocrit seen in the combination treatment may be attributed to lisinopril. Results indicate that rosuvastatin does not ameliorate this adverse effect of lisinopril. Furthermore, high dose of rosuvastatin alone and its combination with lisinopril at both doses increased WBCs, lymphocytes, and neutrophils. Rosuvastatin (40 mg/kg) showed increasing trend in these analytes, albeit non-significant, whereas rosuvastatin (100 mg/kg) showed significant changes in these analytes. These results indicate that changes in WBC, lymphocytes, and neutrophils in combination treatment may be due to the individual toxic effect of rosuvastatin. Lisinopril does not ameliorate or aggravate this effect. Earlier preclinical studies with rosuvastatin alone (40 and 80 mg/kg/day) also reported increase in WBC count in dogs.[24] Thus, it is possible that increase in the WBCs and decrease in hemoglobin and hematocrit could be due to individual toxic effect of rosuvastatin and lisinopril, respectively, and their combination does not ameliorate or aggravate these individual adverse effects.

In this study, rosuvastatin alone and in combination with lisinopril at both the doses increased AST, ALP, and total bilirubin levels. Therefore, it is evident from above findings that rosuvastatin has potential to cause liver damage. Co-administration of lisinopril does not ameliorate liver toxicity caused by rosuvastatin. Earlier toxicity study of rosuvastatin (40 and 80 mg/kg/day) also reported persistent elevations in hepatic transaminases.[18] Depletion of cholesterol synthesis by prolonged and extensive inhibition of hydroxyl methyl glutaryl-coenzyme A (HMG-CoA) reductase by rosuvastatin may be the cause of liver toxicity.[18,19] In our current study, lisinopril does not show indications of liver toxicity. However, some earlier studies report hepatocyte degeneration and serum liver enzyme elevation after lisinopril treatment.[25]

Renal toxicity due to drugs is characterized by increase in serum creatinine, serum urea, alteration in urine/serum electrolytes, and histopathological changes in the kidneys.[20] In our previous published study, we evaluated renal biochemical analytes and early renal toxicity biomarkers for lisinopril and rosuvastatin. We observed that lisinopril (50 mg/kg), rosuvastatin (100 mg/kg), lisinopril + rosuvastatin (20 + 40 mg/kg), and lisinopril + rosuvastatin (50 + 100 mg/kg) causes renal toxicity, especially in proximal tubules.[20] Here, we observed decrease in serum sodium and increase in potassium in lisinopril-treated rats at both the doses. A total of 17 case reports of hyponatremia related to the use of ACEI have been published.[26] The cause of hyponatremia and hyperkalemia was purported to be the

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result of dysregulated secretion of antidiuretic hormone and aldosterone.[27,28] The toxicology data in the product monograph of lisinopril also revealed reduction in the sodium and elevation of potassium in the serum.[13] No change in serum electrolytes was observed in either dose of rosuvastatin alone. However, co-administration of rosuvastatin did not ameliorate or worsen the effect of lisinopril on serum levels of sodium and potassium. In this study, rosuvastatin alone at the both doses caused elevation of CK. But, combination therapy of lisinopril (20 mg/kg) and rosuvastatin (40 mg/kg) decreased the elevated levels of CK due to rosuvastatin treatment (40 mg/kg). This effect was not observed at high dose combination treatment. These results indicate that 20 mg/kg lisinopril may ameliorate the toxic effect of 40 mg/kg rosuvastatin on muscles. Furthermore, lisinopril is ineffective to ameliorate the muscle toxicity caused by administration of 100 mg/kg rosuvastatin. Lisinopril did not reduce serum AST, which is another marker of muscle toxicity. However, these results need to be further confirmed by detailed studies. With our results, it is hard to differentiate whether elevation of CK is due to toxicity of skeletal or cardiac muscles, although it is well known that lipid lowering agents (statins and fibrates) are implicated in muscle damage.[29] The most common adverse reactions of statins are myalgia and myopathy. Statin-induced myalgia is characterized by a muscular symptomatology not accompanied with changes in levels of creatine kinase, whereas, in myopathy, an elevated level of creatine kinase (CK) is reported. Statins had more than 30 reports of musculoskeletal adverse drug reactions and ACEI had few reports (3 to 30 cases) of musculoskeletal adverse drug reactions.[30-33]

CONCLUSION

Our results suggest that rosuvastatin causes elevation in serum biochemical markers of liver toxicity and total WBCs, whereas lisinopril has adverse effect on hemoglobin, hematocrit, and serum electrolytes. Combination treatment does not ameliorate or worsen these effects. Increase in CK due to low dose of rosuvastatin treatment was normalized after co-treatment with 20 mg/kg lisinopril. This indicates that lisinopril may have protective effect on myopathy induced by rosuvastatin at low dose. However, these results need to be further confirmed by detailed studies including histopathological analysis.

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