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Research Article

Study of Drug-interactions between Phenytoin and Rosuvastatin in Rats

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Abstract: Drug interactions between phenytoin and rosuvastatin may occur when used together in normal rats, so the present study was conducted to investigate the effects of the individual as well as combined drugs were studied in normal rats. Rats were divided into 4 groups namely: normal control, phenytoin (60 mg/kg i.p.), rosuvastatin (1.25 mg/kg i.p.) or combination of both phenytoin and rosuvastatin, respectively. Data of the present work revealed that, phenytoin increased serum total cholesterol. Rosuvastatin didn't affect serum total cholesterol or serum triglycerides. Combination increased serum total cholesterol but it didn't affect serum triglycerides. Phenytoin significantly increased serum LDL-C. Rosuvastatin had no effect on serum HDL-C, serum LDL-C and VLDL-C levels. Combination didn't change serum lipoproteins (HDL-C, LDL-C and VLDL-C). Individual drugs or their combination had no effect on risk factor and atherogenic index. Phenytoin significantly increased serum ALT level. Rosuvastatin had no effect on serum AST and serum ALT levels. Combination significantly increased serum AST level. Phenytoin significantly increased serum MDA level but it had no effects on serum NO level and blood SOD activity. Rosuvastatin significantly increased serum NO level. Combination significantly increased serum NO level, so Combination of phenytoin and rosuvastatin has a good effect on oxidative stress by increasing serum NO level. In conclusion, the results revealed that, there are drug interactions between phenytoin and rosuvastatin. The interactions improve liver functions and lipid peroxidation. A part from the action of the combination on total cholesterol, it improves lipid profile.

Keywords: Antiepileptic, drug interaction, lipid profile, liver functions, oxidative stress biomarkers, statins

INTRODUCTION

Phenytoin (PHT) is a classical antiepileptic drug. Clinically PHT is effective mainly against focal epileptic seizures and also against generalized tonic-clonic convulsions. The most important mechanisms of action of PHT are decrease of permeability of voltage-gated sodium channels and calcium channels (preferentially L-type). PHT blocks K-stimulated influx of Ca^{2+} into neurons and decreases synaptic release of glutamate in vitro (Pincus and Lee, 1973; Potter *et al*., 1991). It has been shown that PHT suppresses the spread of epileptic activity from the focus (Edmonds *et al*., 1974). PHT is most commonly used to reduce seizure frequency including seizure associated with acute brain lesions (Woodbury *et al*., 1982). It has a narrow therapeutic index and a change in bioavailability with other drugs or supplements administered concurrently may lead to toxic effects or therapeutic failure (Arnold *et al*., 1970).There is great interest to study the interactions of phenytoin with other drugs because of its enzyme inducing effects and special physiochemical and solubility properties (Potsalos *et al*., 2002; Lalonde and Botez, 1958).

Rosuvastatin is more effective than other statins in reducing LDL-C levels and produces significantly greater improvements in other elements of lipid profile (Blasetto *et al*., 2003). Rosuvastatin therapy also reduces risk of coronary heart disease, ischemic stroke, vascular mortality, because it lowers the level of C-reactive protein by approximately 30% (Takagi and Umemoto, 2012). It is a well-tolerated drug; most commonly reported side effects are nausea, dyspepsia and diarrhea. These symptoms are usually mild and transient (Jones *et al*., 2003; Cheng, 2004). The most serious adverse effects are related myopathy, liver toxicity and rhabdomyolysis (Blasetto *et al*., 2003; Jones *et al*., 2003).

The aim of the present study is to investigate the possible drug interactions between phenytoin and rosuvastatin when used together in normal rats.

MATERIALS AND METHODS

Animals: Male albino Wistar rats (120-150 g) obtained from the breeding unit of The Nuclear Research Centre, Atomic Energy Authority, Egypt. Animals were maintained on standard pellet chow diet, free access to

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water and kept under good ventilation conditions. The animals' treatment protocol has been approved by the animal care committee of the National Centre for Radiation Research and Technology, Cairo, Egypt.

Drugs and chemicals: Phenytoin was purchased from Sigma Company (Egypt), dissolved in saline and administrated in a dose of 60 mg/kg i.p. (Minaiyan *et al*., 2008). Rosuvastatin was purchased from AstraZeneca Company (Egypt), dissolved in saline and administrated in a dose of 1.25 mg/kg i.p. (Timothy *et al*., 2001). ALT, AST, Total cholesterol, Triglyceride and HDL-C kits were obtained from Bio diagnostic Company (Egypt).

Experimental design: Male albino Westar rats were divided into 4 groups each consisting of 8 rats. Group 1received saline (control), group 2 received phenytoin (60 mg/kg i.p.), group 3 received rosuvastatin (1.25 mg/kg i.p.) and group 4 received combination of phenytoin and rosuvastatin. Rats were sacrificed 3h after taking acute dose of phenytoin (60 mg/kg i.p.), rosuvastatin (1.25 mg/kg i.p.) and combination of both drugs. Blood samples were collected in non-heparinized and heparinized tubes by heart puncture for biochemical assay.

Biochemical estimations: Serum total cholesterol was determined using cholesterol kit (Richmond, 1973) and expressed as mg/dL, serum triglycerides were determined using triglycerides kit (Fossati and Prencipe, 1982) expressed as mg/dL and serum HDL-C level was determined using HDL-C kit (Lopes-virella *et al*., 1977) expressed as mg/dL. Serum LDL-C was calculated according to the Friedwald's formula [LDL-C (mg/dL) = Total cholesterol- (Triglyceride/5+HDL-C)] (Friedewald *et al*., 1972) expressed as mg/dL. VLDL-C concentrations were estimated by triglyceride/5 in Friedwald's formula (Friedewald *et al*., 1972) expressed as mg/dL. The atherogenic index (AI) (Total cholesterol-HDL-C/HDL-C) was calculated, as proposed by Liu *et al*. (2006). Risk factor was calculated by equation of Total cholesterol/HDL-C. Serum ALT and serum AST levels were estimated according to the method of Reitman and Frankel (1957) and expressed as u/L. Serum MDA level was determined according to Yoshioka *et al*. (1979) expressed as mmol/mL. Serum NO level was determined according to Geng *et al*. (1994) expressed as u/mL. Blood SOD activity was determined according to method of Minami and Yoshikawa (1979) expressed as u/mL.

Statistical analysis: Data are expressed as mean±S.E. of the mean. Statistical comparisons between different groups were done by using one way Analysis of Variance (ANOVA), followed by Tukey-Kramer for multiple comparisons test to judge the difference between different groups. Significance was accepted at $p<0.05$.

RESULTS

Lipid profile: Results are presented in (Fig. 1a, b) showed that serum total cholesterol and serum triglyceride levels of normal control rats were 61.97 mg/dL and 58.09 mg/dL, respectively. Phenytoin (60 mg/kg) significantly increased serum total cholesterol level to 152.30% of normal control, but didn't affect serum triglycerides. Rosuvastatin (1.25 mg/kg) didn't affect serum total cholesterol and triglyceride levels of normal control. Combination of phenytoin (60 mg/kg) and rosuvastatin (1.25 mg/kg) significantly increased serum total cholesterol level to 144.47% of normal control and significantly increased serum total cholesterol level to 89.53 mg/dL from rosuvastatin treated group, but that combination didn't significantly change serum triglycerides. Phenytoin antagonized the hypocholesterolaemic action of rosuvastatin.

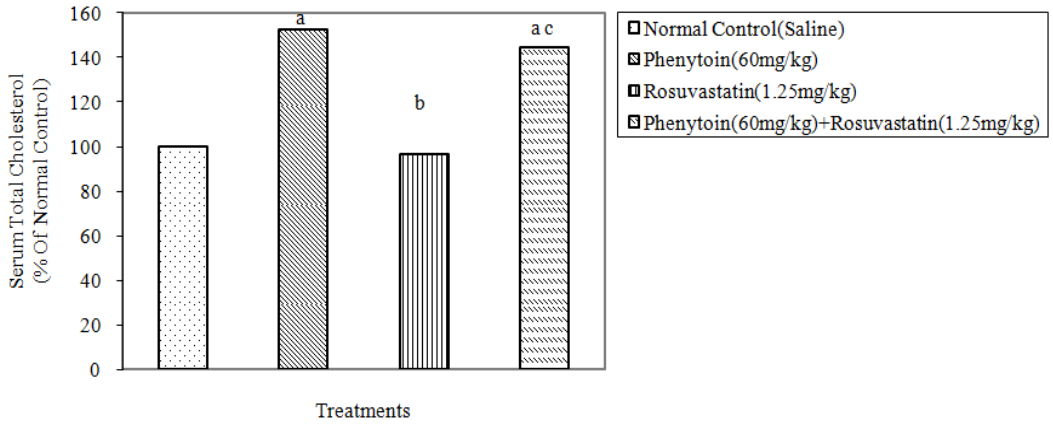

Fig. 1a: Effect of phenytoin, rosuvastatin and their combination on serum; Total cholesterol normal rat N = 8 rats per group; Each value represents the mean±S.E. of the mean; a: Significantly different from normal control at $p<0.05$; b: Significantly different from Phenytoin at $p<0.05$; c: Significantly different from Rosuvastatin at $p<0.05$; d: Significantly different from Phenytoin+ Rosuvastatin at $p<0.05$

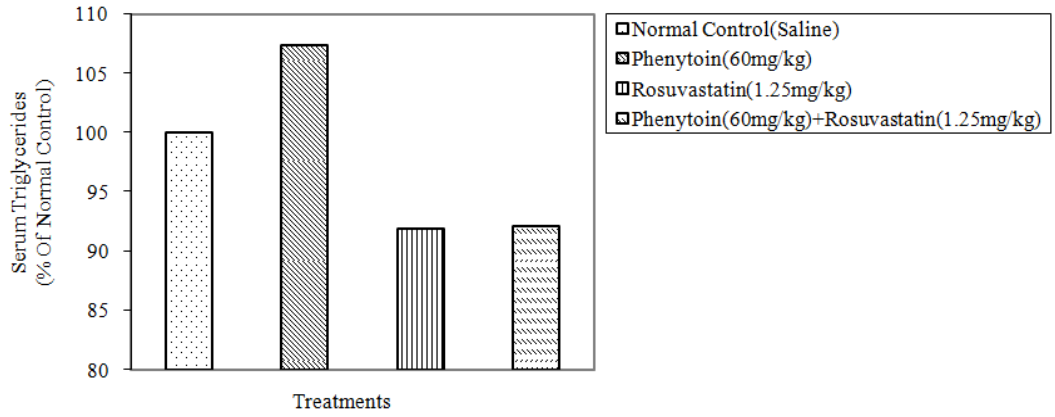

Fig. 1b: Effect of phenytoin, rosuvastatin and their combination on serum Triglycerides in normal rat; N = 8 rats per group. Each value represents the mean±S.E. of the mean; a: Significantly different from normal control at p<0.05; b: Significantly different from Phenytoin at p<0.05; c: Significantly different from Rosuvastatin at p<0.05; d: Significantly different from Phenytoin+Rosuvastatin at p<0.05

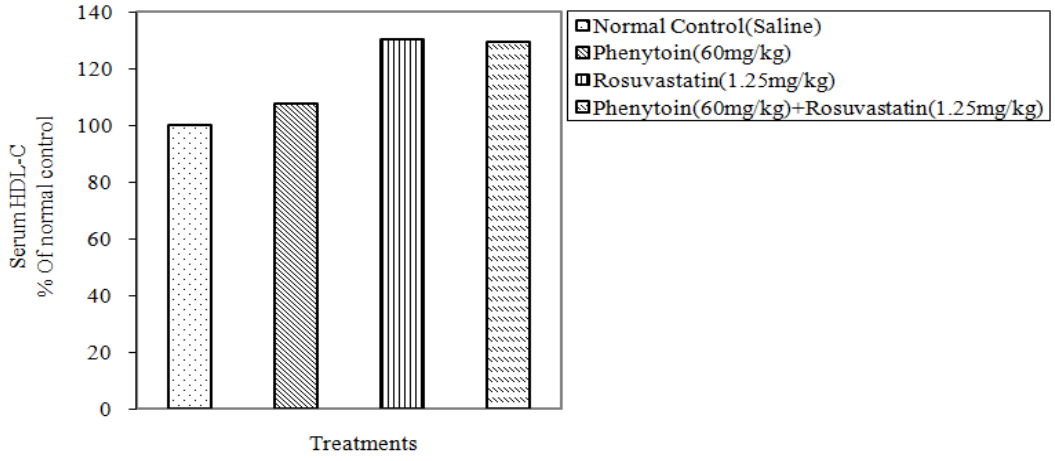

Fig. 2a: Effect of phenytoin, rosuvastatin and their combination on serum HDL-C level in normal rats; N = 8 rats per group; Each value represents the mean±S.E. of the mean; a: Significantly different from normal control at p<0.05; b: Significantly different from Phenytoin at p<0.05; c: Significantly different from Rosuvastatin at p<0.05; d: Significantly different from Phenytoin+Rosuvastatin at p<0.05

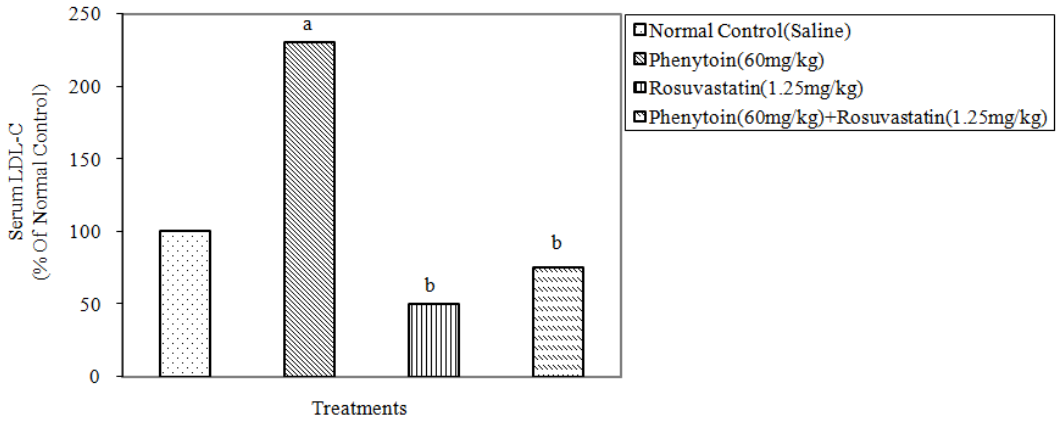

Fig. 2b: Effect of phenytoin, rosuvastatin and their combination on serum LDL-C in normal rat; N = 8 rats per group. Each value represents the mean ±S.E. of the mean; a: a: Significantly different from normal control at p<0.05. b: Significantly different from Phenytoin at p<0.05; c: Significantly different from Rosuvastatin at p<0.05; d: Significantly different from Phenytoin+Rosuvastatin at p<0.05

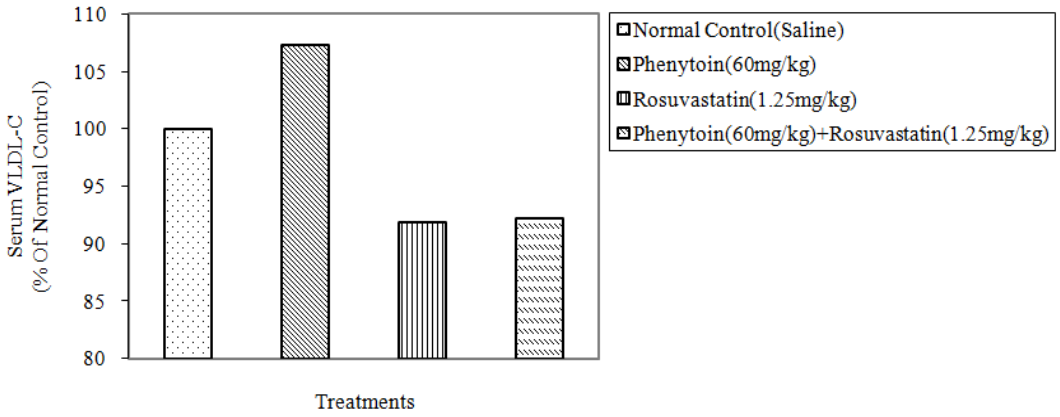

Fig. 2c: Effect of phenytoin, rosuvastatin and their combination on serum VLDL-C level in normal rats; N = 8 rats per group. Each value represents the mean±S.E. of the mean; a: Significantly different from normal control at p<0.05; b: Significantly different from Phenytoin at p<0.05; c: Significantly different from Rosuvastatin at p<0.05; d: Significantly different from Phenytoin+Rosuvastatin at p<0.05

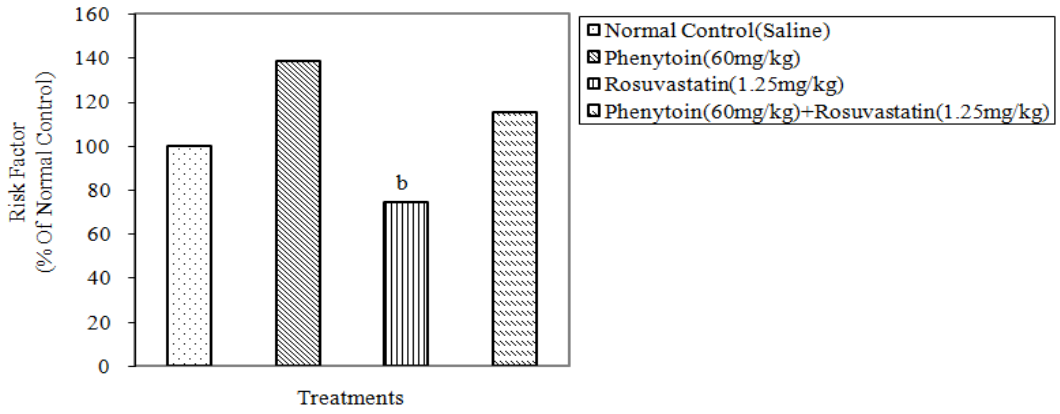

Fig. 3a: Effect of phenytoin, rosuvastatin and their combination on Risk factor in normal rats; N = 8 rats per group. Each value represents the mean ±S.E. of the mean; a: Significantly different from normal control at p<0.05; b: Significantly different from Phesnytoin at p<0.05; c: Significantly different from Rosuvastatin at p<0.05; d: Significantly different from Phenytoin+Rosuvastatin at p<0.05

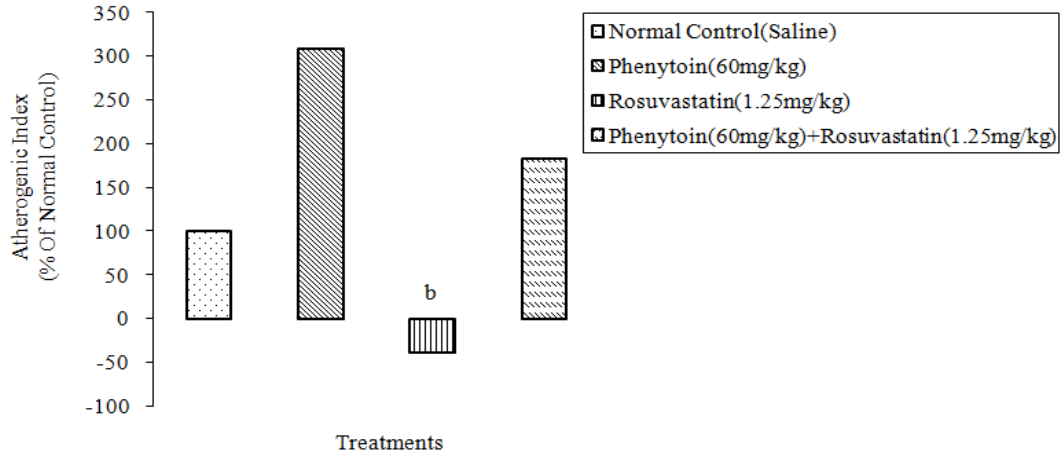

Fig. 3b: Effect of phenytoin, rosuvastatin and their combination on Atherogenic index in normal rats; N = 8 rats per group. Each value represents the mean ±S.E. of the mean; a: a: Significantly different from normal control at p<0.05; b: Significantly different from Phenytoin at p<0.05; c: Significantly different from Rosuvastatin at p<0.05; d: Significantly different from Phenytoin+Rosuvastatin at p<0.05

Serum HDL-C, serum LDL-C and serum VLDL-C levels of normal control rats were 50.59 mg/dL, 12.48 mg/dL and 11.62 mg/dL, respectively. Phenytoin (60 mg/kg) significantly increased serum LDL-C level to 230.16% of normal control, but didn't affect serum HDL-C and VLDL-C levels. Rosuvastatin (1.25 mg/kg) significantly decreased serum LDL-C level to 6.26 mg/dL from phenytoin treated group, but didn't significantly change serum HDL-C, serum LDL-C and serum VLDL-C levels from normal control. Rosuvastatin protects against hypercholesterolemia effect of phenytoin. Combination of phenytoin (60 mg/kg) and rosuvastatin (1.25 mg/kg) significantly decreased serum LDL-C level to 9.42 mg/dL from phenytoin treated group, but didn't significantly change serum HDL-C, serum LDL-C and serum VLDL-C levels from normal control values (Fig. 2a to c).

The recorded risk factor and atherogenic index of normal control rats were 1.23 and 0.23, respectively. Phenytoin (60 mg/kg) didn't significantly change risk factor and atherogenic index from normal control. Rosuvastatin (1.25 mg/kg) significantly decreased risk factor and atherogenic index to 0.91 and -0.09 from phenytoin treated group respectively, but didn't significantly change risk factor and atherogenic index from normal control. Combination of phenytoin (60 mg/kg) and rosuvastatin (1.25 mg/kg) didn't significantly change risk factor and atherogenic index from normal control (Fig. 3a, b).

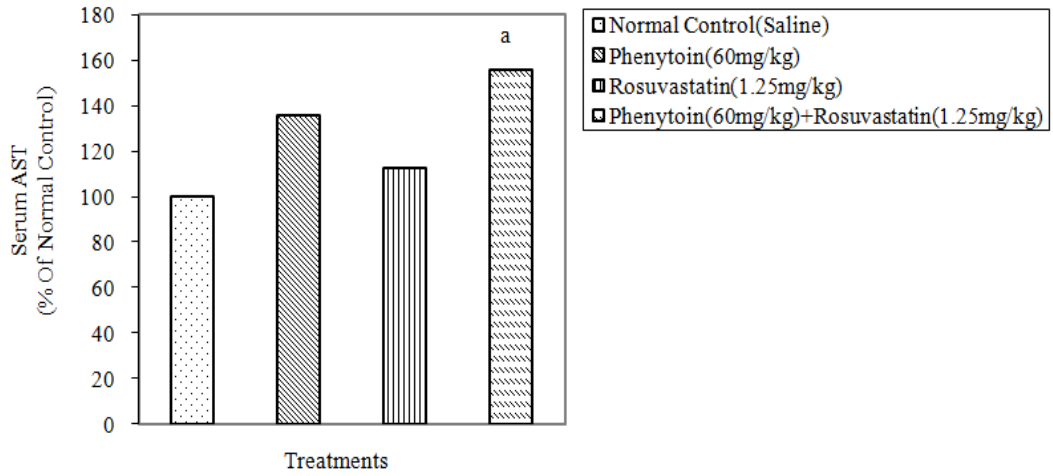

Fig. 4a: Effect of phenytoin, rosuvastatin and their combination on serum AST level in normal rats; N = 8 rats per group. Each value represents the mean ±S.E. of the mean; a: Significantly different from normal control at p<0.05; b: Significantly different from Phenytoin at p<0.05; c: Significantly different from Rosuvastatin at p<0.05; d: Significantly different from Phenytoin+Rosuvastatin at p<0.05

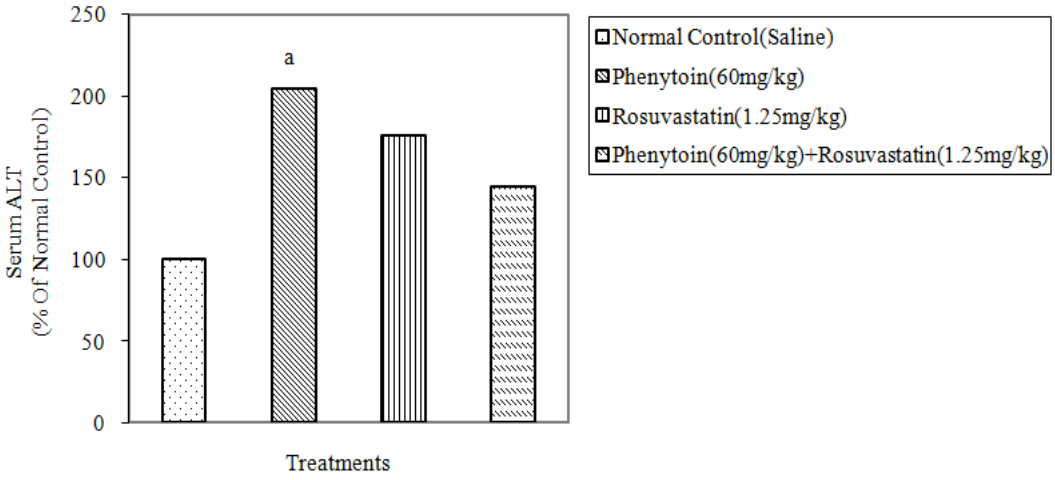

Fig. 4b: Effect of phenytoin, rosuvastatin and their combination on serum ALT level in normal rats; N = 8 rats per group. Each value represents the mean ±S.E. of the mean; a: a: Significantly different from normal control at p<0.05; b: Significantly different from Phenytoin at p<0.05; c: Significantly different from Rosuvastatin at p<0.05; d: Significantly different from Phenytoin+Rosuvastatin at p<0.05

Liver function tests: As shown in Fig. 4a and b, serum AST and serum ALT levels of normal control rats were 34.30 u/L and 15.80 u/L, respectively. Phenytoin (60 mg/kg) significantly increased serum ALT level to 204.43% of normal control, but didn't affect serum AST level. Rosuvastatin (1.25 mg/kg) didn't significantly change serum AST and serum ALT levels from normal control. Combination of phenytoin (60 mg/kg) and rosuvastatin (1.25 mg/kg) significantly increased serum AST level to 155.98% of normal control, but didn't affect serum ALT level from normal control.

Oxidative stress biomarkers: The results are presented in Fig. 5a to c showed that serum MDA, serum NO levels and blood SOD activity of normal control rats were 33.60 mmol/mL, 37.87 u/mL and 23.36 u/mL, respectively. Phenytoin (60 mg/kg) significantly increased serum MDA level to 168.13% of normal control, but didn't significantly change serum NO level and blood SOD activity from normal control. Rosuvastatin (1.25 mg/kg) significantly increased serum NO level to 155.40% of normal control, but significantly decreased serum MDA level to 32.37 nmole from phenytoin treated group and didn't affect blood SOD activity from normal control. Combination of phenytoin (60 mg/kg) and rosuvastatin(1.25 mg/kg) significantly increased serum NO level to 193.69% of normal control, but didn't affect serum MDA level and blood SOD

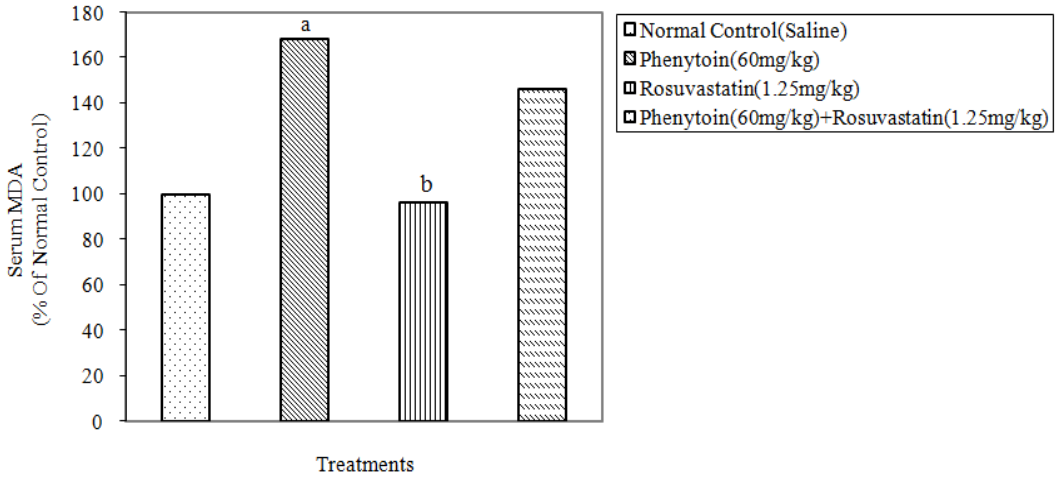

Fig. 5a: Effect of phenytoin, rosuvastatin and their combination on serum MDA level in normal rats; N = 8 rats per group. Each value represents the mean±S.E. of the mean; a: Significantly different from normal control at p<0.05; b: Significantly different from Phenytoin at p<0.05; c: Significantly different from Rosuvastatin at p<0.05; d: Significantly different from Phenytoin+Rosuvastatin at p<0.05

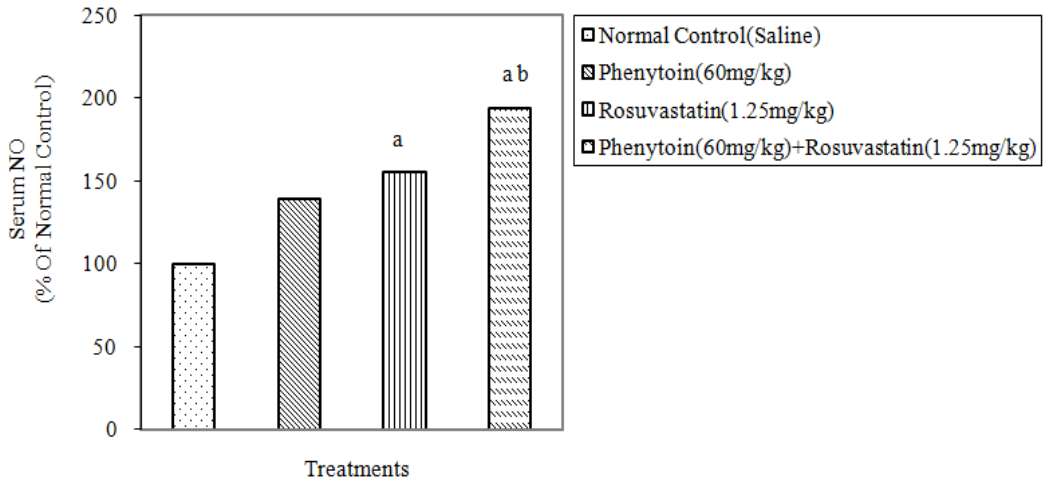

Fig. 5b: Effect of phenytoin, rosuvastatin and their combination on serum NO level in normal rats; N = 8 rats per group; Each value represents the mean±S.E. of the mean; a: Significantly different from normal control at p<0.05; b: Significantly different from Phenytoin at p<0.05; c: Significantly different from Rosuvastatin at p<0.05; d: Significantly different from Phenytoin+Rosuvastatin at p<0.05

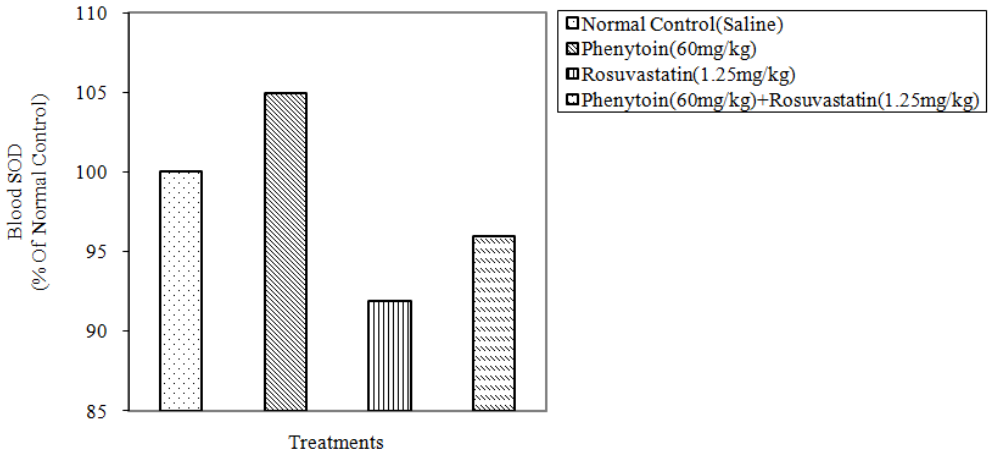

Fig. 5c: Effect of phenytoin, rosuvastatin and their combination on blood SOD activity in normal rats; N = 8 rats per group. Each value represents the mean ±S.E. of the mean; a: Significantly different from normal control at $p<0.05$; b: Significantly different from Phenytoin at $p<0.05$; c: Significantly different from Rosuvastatin at $p<0.05$; d: Significantly different from Phenytoin+Rosuvastatin at $p<0.05$

activity from normal control. That combination significantly increased serum NO level to73.35 u/mL from phenytoin treated group.

DISCUSSION

In the present study, administration of phenytoin caused significant increase in serum total cholesterol and serum LDL-C levels. These findings are in agreement with Itemobong *et al*. (2007) in rats. These results are in line with the data of Luoma *et al*. (1979) in healthy volunteers and epileptic patients treated with phenytoin.

In the current study results of lipid profile obtained from administration of rosuvastatin didn't significantly differ from the normal control. These results are in agreement with those of Ying *et al*. (2009), Preusch *et al*. (2010) and Ansari *et al*. (2012). The lack of significant effect by rosuvastatin could be due to that lipids are relatively low in normal rats and statins don't usually modify the lipid profile in rats (Endo *et al*., 1979).

Our results showed that administration of phenytoin together with rosuvastatin showed significant increase in serum total cholesterol in comparison with normal control. This result may be due to hepatotoxic effect of phenytoin, which antagonizes hypocholesterolaemic effect of rosuvastatin.

Administration of phenytoin showed significant increase in serum ALT level and slight increase in serum AST level. These findings are in accordance with the work of Rec. GSCC. (1972) and Itemobong *et al*. (2007). These results may be due to the effect of phenytoin on both mitochondrial and cytosolic enzyme activity (Itemobong *et al*., 2007).

Our study showed that, administration of rosuvastatin didn't significantly affect serum AST and serum ALT levels. These findings are in agreement with Rodrigo *et al*. (2013).These results may be due to that rosuvastatin-treated group had numerous mitochondria which is the main organelle responsible for beta-oxidation which is essential for prevention and/or reduction of hepatic damage in treated animals (Rodrigo *et al*., 2013).

On the other hand, the combined therapy of phenytoin with rosuvastatin caused significant increase in serum AST level while caused no significant change in serum ALT level. These results showed improvement in the liver function since ALT is a specific enzyme for the liver. The combination improves the effect on the liver and could be also on the heart. It's mainly on the liver because it is the organ which was exposed to dysfunction.

Free radicals are formed and degraded by all aerobic organisms, leading to either physiological concentrations required for normal cell function or excessive quantities, the state called oxidative stress. Free radicals threaten the integrity of various biomolecules including proteins (Stadtman and Levine, 2000), lipids, lipoproteins (Ylä-Herttuala, 1999) and DNA (Marnett, 2000). Oxidative stress is also proposed to be involved in the process of aging both by inducing damage to mitochondrial DNA and by other mechanisms (Cadenas and Davies, 2000; Finkel and Holbrook, 2000). MDA is an indicator of lipid peroxidation. It is the break-down product results from the oxidation of polyunsaturated fatty acids; it serves as a reliable marker of oxidative stress- mediated lipid peroxidation (Balci *et al*., 2009). SOD is a protective enzyme that can efficiently and specifically scavenge the superoxide radical by catalyzing its dismutation to hydrogen peroxide and oxygen. In the present study, we investigated the effect of the test drugs on oxidative stress biomarkers namely MDA, SOD and NO.

According to the results of this investigation, phenytoin significantly increased serum MDA level, which is consistent with the data obtained by Santosa *et al*. (2008) Who addressed that oxidative stress may be a potential mechanism responsible for AED-associated hepatotoxicity and evaluated the involvement of the oxidative stress in the toxic effect of phenytoin and other hepatotoxic antiepileptic drugs. These results may be due to a defective detoxification by the epoxide hydrolase leading to accumulation of arene oxides (Phenytoin metabolites) (Bavdekar *et al*., 2004).

Rosuvastatin caused significant increase in serum NO level, this result is in line with the data reported by Timothy *et al*. (2001). The mechanism of the effect of rosuvastatin on NO level could be produced via increase in the expression of endothelial nitric oxide synthase leading to enhanced release of NO (Laufs *et al*., 1998). Rosuvastatin didn't significantly affect serum MDA level. This effect is in agreement with (Olteau *et al.,* 2012). Rosuvastatin didn't significantly affect blood SOD activity as compared to normal control which is in accordance with the work of Ansari *et al*. (2012) and Olteanu *et al*. (2012). Rosuvastatin inhibits lipid peroxidation and acts as antioxidant drug.

Combination of phenytoin and rosuvastatin significantly increased serum NO level, but didn't significantly change serum MDA level and blood SOD activity. These results are positive indicator for improvement in lipid peroxidation state

CONCLUSION

In conclusion, the results revealed that, there are drug interactions between phenytoin and rosuvastatin. The interactions improve liver functions and lipid peroxidation. A part from the action of the combination on total cholesterol, it improves lipid profile.

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