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# Evaluation of the effect of Coadministration of Coenzyme Q10 and Rosuvastatin Calcium in Statin associated Myopathy in Guinea pigs

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## ABSTRACT

Rosuvastatin is a HMG CoA reductase inhibitor, and are used as antihyperlipidaemic drugs. Studies demonstrated a reduction of up to 54 % in plasma Coenzyme Q10 concentration after Statin therapy. Coenzyme Q10 (ubiquinone) is an important cofactor in the mitochondrial oxidative phosphorylation which generates ATP. The biosynthesis of this molecule requires isoprenoid chains generated in the *de novo* Cholesterol synthesis pathway, which is inhibited by Statin therapy. This is one of the mechanisms contributing to the Statin associated myopathy. The objective of the study is to evaluate the effectiveness of co administration of rosuvastatin calcium and coenzyme Q10, studied in guinea pigs. Histopathological examination of skeletal muscles of guinea pigs showed rosuvastatin treated group showed muscle fibres with mildly contracted, thin nuclei and longitudinal splits - suggestive of mild toxic changes. A reduction in fibre length in animals treated with rosuvastatin calcium was observed. There was a significant enhancement of serum creatine kinase value in rosuvastatin treated group. While the group with rosuvastatin coadministered with coenzyme Q10 showed a significant reduction in serum creatine kinase value. Co administration of coenzyme Q10 at a dose of 30mg and Rosuvastatin resulted in a significant decrease ($P<0.05$) in the incidence of muscle toxicity in guinea pigs as per the parameters studied.

## INTRODUCTION

Rosuvastatin is a hypolipidaemic drug in the class of HMGCoA reductase inhibitors [1]. IUPAC name of the compound is calcium;(E,3R,5S)-7-[4-(4-fluorophenyl)-2-[methyl(methylsulfonyl)amino]-6-propan-2-ylpyrimidin-5-yl]-3,5-dihydroxyhept-6-enoate. It reduces cholesterol biosynthesis in liver, thus preventing atherosclerotic and other cardiovascular complications. The main side effect which limits its use is statin induced myopathy found in about 0.1% of patients . Up to 25.4% of patients stop taking statins by 6 months after beginning of treatment. Treatment withdrawal or dose reduction or using a different statin is the next proceeding [2].

The risk factors of myopathy were reported as advanced age, female gender, low body mass index, patients with diabetes, hypertension, untreated hypothyroidism and renal-hepatic disease. Heavy alcohol use, cocaine use and increased exercise are also risk factors [3]. Studies have demonstrated reduction of up to 54% in the plasma coenzymeQ10 concentration following statin therapy [4].

CoenzymeQ10, also known as ubiquinone or ubidecarenone is a critical component of the mitochondrial electron transport pathway. The IUPAC name is 2-[(2*E*,6*E*, 10*E*, 14*E*, 18*E*, 22*E*, 26*E*, 30*E*, 34*E*) - 3,7,11,15,19,23,27,31,35,39 - decamethyltetraconta 2,6,10,14,18,22,26,30,34, 38-decaenyl] - 5,6-dimethoxy-3-methylcyclohexa-2,5-diene-1,4dione.It plays an important role in generation of ATP in all cells, which provides energy to carry out cellular metabolic functions at an optimal rate. The biosynthesis of CoenzymeQ10 (CoQ) requires isoprenoid chains generated in the *de novo* Cholesterol synthesis pathway, which is inhibited by a Statin therapy[5]. CoQ is not FDA-approved to treat any medical condition. It is available over-the-counter as a dietary supplement. The normal range of blood CoQ level varies from 0.4-1.9µg/ml[6].

CoQ supplementation ameliorated statin-associated muscle symptoms, implying that CoQ supplementation may be a

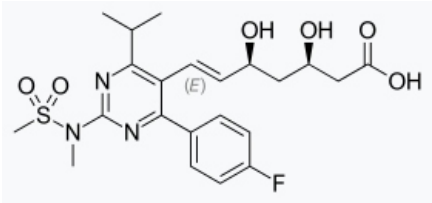


**Fig.1.** Rosuvastatin calcium

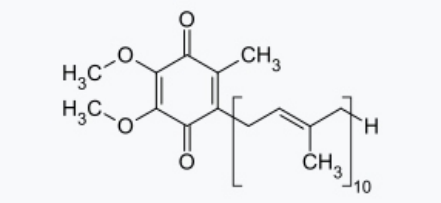


**Fig.2.** Coenzyme Q10

complementary approach to manage statin-induced myopathy [6].In the literatures reviewed the studies on effectiveness of coadministration was conducted on albino rats[7]. Guinea pigs are the only rodents possessing coenzyme Q10 as cofactor while others are having coenzyme Q9, which is having one isoprenoid unit less in its structure [8]. CoQ9 is a minor, rare form in humans while CoQ10 is the minor form in mice. The quinone head is the functional group, which undergoes reversible redox cycling, whereas the isoprenoid tail serves primarily to anchor ubiquinone in the membrane [9] .Hence a study of the effectiveness of CoQ10 in statin associated myopathy is more relevant in guinea pigs.

The objective of the study is to use guinea pig to evaluate the effectiveness of coadministration of rosuvastatin calcium and coenzymeQ10 .

Plasma level of creatine kinase (creatine phosphokinase) activity is the key biomarker for clinical diagnosis of myopathy. Creatine kinase is found primarily in skeletal muscle and myocardium. It generates ATP from ADP in the tissues. Muscle cell membrane damage and subsequent leakage into the systemic circulation causes elevation of CK level in circulation [10].

## MATERIALS

Rosuvastatin calcium was purchased from Relimark products and services, Hyderabad. CoQ10 was supplied as a gift sample by Universal Medicare Pvt. Ltd., Sarigam, Gujarat.

The Roche diagnostic cobas C311 automated chemistry analyzer was used for determination of serum creatine kinase.

### Experimental methods

The experimental protocol was approved by Institutional animal ethical committee as per the approval number: 01/03/IAEC/MCT dated 24/09/2017.

Hartely (250-450g) guinea pigs of both sexes were selected and were acclimatised for one week. Animals were given free access to food and water. Vitamin C supplementation was given throughout the experiment. They were maintained at room temperature, under hygienic condition with alternative 12 hours light and dark cycle.

The animals were weighed and were distributed evenly into three groups of three each. Animals were dosed by oral gavage using a 1ml syringe, once daily with drug dissolved in 0.5% carboxy methyl cellulose. The total volume of each dose was 0.5ml.

**Group I** was given Rosuvastatin calcium 6mg/kg/day/*p.o* (animal dose equivalent to the toxic dose of 80mg/kg in human).

**Group II** was given Rosuvastatin calcium 6mg/kg/day/*p.o*. along with Coenzyme Q10 2mg/kg/day/*p.o* (equivalent of 30mg of human dose)

**Group III** was kept as vehicle control.

Any weight loss in the animals was monitored. Study was conducted for 28 days. Animals were fasted overnight before the administration of final dose. One hour after administration of final dose animals were given anaesthesia with 2ml ketamine 50mg/ml injection intraperitonially and cervical dislocation was done. Blood samples were collected by cardiac puncture into clot activator vaccutainer tubes . About 2ml of blood sample was taken immediately for estimation of creatine kinase activity.

Skeletal muscle samples of quadriceps femoris, gastrocnemius and triceps brachii were taken for histopathology studies. The samples were collected in 10% neutral buffered formalin and kept for 24h and taken for histopathological analysis. Longitudinal sections of each sample were taken and examined microscopically.

For statistical analysis, each group of the drug treated animals were compared with the corresponding vehicle treated group using Student's t test.

## RESULTS

### Histopathological study:

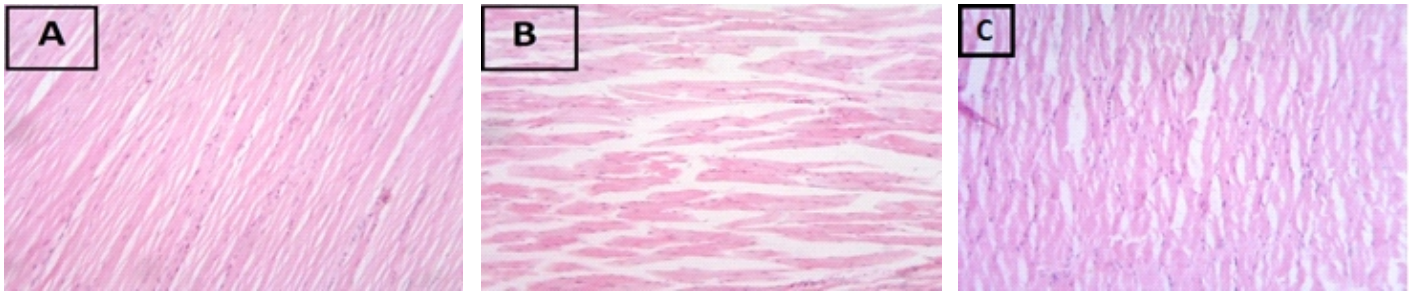


**Fig 3 :** Histopathology of gastrocnemius muscles taken at 100x.
A: Control, B: Rosuvastatin treated, C: Rosuvastatin with Coenzyme Q10 treated.

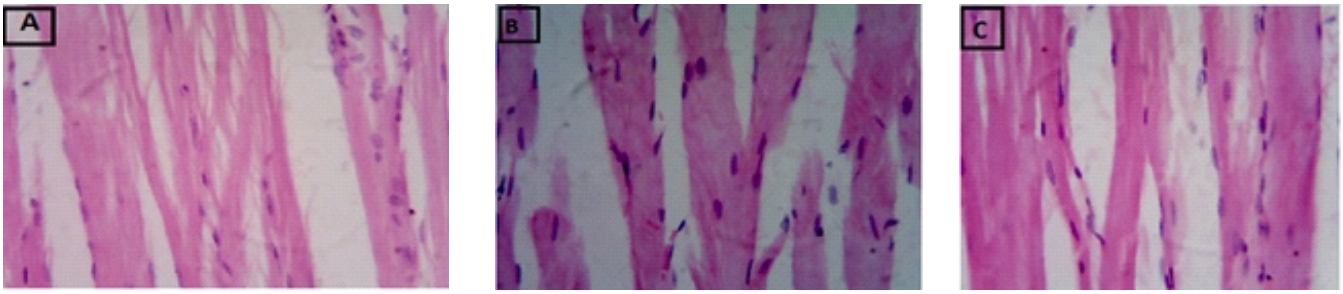


**Fig 4.** Histopathology of gastrocnemius muscles taken at 400x.
A:Muscle tissue of rosuvastatin administered animals. B: Muscle tissue of rosuvastatin and coenzyme Q10 coadministered animals, C:Control

Muscle histology of control animals revealed a normal profile. Cylindrical muscle fibres with elongated nuclei were seen peripherally. Rosuvastatin treated group showed muscle fibres with mildly contracted, thin nuclei and longitudinal splits - suggestive of mild toxic change. Histological studies showed reduction in fibre length in animals treated with Rosuvastatin calcium. There was no karyolysis or necrosis .Co administration of rosuvastatin calcium and coenzyme Q10 showed muscle regeneration in the form of hypercellularity with many nuclei and satellite cells.

### Serum creatine kinase

There was a significant enhancement of creatine kinase value in rosuvastatin treated group. While the group with rosuvastatin co administered with coenzymeQ10 showed a significant reduction in creatine kinase value.

Statistical analysis of results were carried out using student's t-test. The t-value for the coenzyme treated group was calculated in comparison with the rosuvastatin treated group. There was a significant decrease in creatine kinase,P value was $< 0.05$. While the t- value for rosuvastatin treated group was calculated in comparison with the control. There was a significant increase in creatine kinase, P value was $< 0.05$.

## DISCUSSION

The histological findings gave an indication of mild changes in the skeletal muscle fibres even from a brief period of exposure of 28 days. Serum creatine kinase levels gave a strong evidence of myopathy on the rosuvastatin treated group which was not observed in the coenzymeQ10 co administered group. The study can be correlated to human subjects as guinea pigs and humans possess the same coenzymeQ. The dose of coenzyme Q10 which produced effectiveness was 30mg per day.

In a reported study on adult male wistar rats histological changes of skeletal muscle was reported during the administration of rosuvastatin and clarified the possible protective effect of coenzymeQ10. The average mitochondrial diameter of the groups studied were also compared using electron microscopy [7]. CoQ supplementation was found to be beneficial in statin treatment according to the study and the dose of coenzymeQ10 reported to be effective for the human equivalent dose of 40mg of rosuvastatin was reported as 200mg.

Another study was conducted on efficacy of combined treatment of CoQ (30, 90 or 270mg) with Atorvastatin in 4- week-old Sprague Dawley male rats fed with normal or high fat diet for 6 week. The dose requirement for effective supplementation was 270 mg of coenzyme Q10 [12].

In the present study in guinea pigs a dose of only 30mg/ day showed effectiveness in countering myopathy when a toxic dose of 80 mg rosuvastatin was administered. The variation in the dose requirement may be due to the structure difference between the coenzyme in rat and guinea pig. Hence the study on effectiveness of CoQ10 in statin associated myopathy is found

**Table 1 :** Serum creatine kinase levels in U/L at 250C

| Animals | Group I | Mean± S.D | Group II | Mean± S.D | Group III | Mean± S.D |
|---|---|---|---|---|---|---|
| 1. | 862 | 857±259 | 250 | 213±37 | 247 | 358±152 |
| 2. | 1114 | *P < 0.05 *vs* group III | 176 | *P < 0.05vs group I | 532 | |
| 3. | 595 | | 215 | | 297 | |

more relevant in guinea pigs. The results of serum creatine kinase level substantiated the result obtained in histopatholoy. The limitation of the present study was the relatively small number of animals used per treatment group. But the study is justified by the use of 3 different muscles quadriceps femoris, gastrocnemius and triceps brachii from each animal. The dosage administration of 30 mg was selected as there was a marketed product of coenzymeQ10- 30mg in the international market (Wassen International Ltd. The Mole Business Park, Leatherhead, UK)

The relevance of supplementation with CoQ10 at a dose of 30mg in Rosuvastatin associated myopathy is explained by these findings.

## CONCLUSION

Coadministration of coenzyme Q10 in the dose of 30mg and Rosuvastatin calcium 80mg resulted in a significant decrease ($P<0.05$) in the incidence of muscle toxicity in guinea pig models as per the parameters studied.

## ACKNOWLEDGMENT

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## CONFLICT OF INTEREST

There are no conflicts of interest

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