IS CO Q10 REALLY VALUABLE IN SHIELDING STATIN INDUCED MYOPATHY-AN EXPLORATION

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ABSTRACT

Objective: This study was designed to scrutinize the shielding effects of Co enzyme Q10 (Co Q10) supplementation in statin associated muscular adverse effects in rabbits.

Study Design: Randomized controlled trial.

Place and Duration of Study: Pharmacology dept Army Medical College Rawalpindi from Jan 2012 to Jun 2012.

Material and Methods: Twenty two healthy rabbits were taken and divided into four equal groups randomly with six in each batch. The two groups (G1 & G2) were given toxic doses of simvastatin (60mg/kg/day) with and without Co Q10 (5mg/kg/day) orally for 14 days and rest of two groups (G3 & G4) were kept on therapeutic doses (1mg/kg/day) of simvastatin with and without Co Q10 (5mg/kg/day) orally for 90 days. Blood samples were drawn and serum creatinine kinase (CK) and lactate dehydrogenase (LDH) were assessed before and after the drug therapy. Histopathological examination was done to observe the inflammatory changes under light microscope. The results were analyzed by applying paired "t' test, independent "t" test and ANOVA test for biochemical markers and 'Chi-Square test' for histopathologcal findings. The *p*-value < 0.05 was considered significant.

Results: The biochemical markers went up sharply (G1. CK=28899.5 ± 874.09 IU/L & LDH = 4694.33 ± 352 IU/L) & (G2. CK = 29191.33 ± 3019.79 IU/L & LDH = 4334.83 ± 143.44 IU/L) as compared to baseline values. They were given toxic doses of simvastatin with and without Co Q10. Histopathological examination of muscular tissue also revealed gross inflammatory changes in these groups. However histopathological examination of groups who were given therapeutic doses of simvastatin with and without Co Q10 for 90 days showed mild to moderate inflammatory changes but serum CK and LDH remained in the normal ranges in these groups.

Conclusion: Our results suggest that Co Q10 supplementation could not produce any beneficial effects on the statin induced muscular adverse effects.

Keywords: Co Q10, Muscle pain, Statin myopathy.

INTRODUCTION

Statins also known as HMG Co A (3-hydroxy-3-methyl glutaryl coenzyme A) reductase inhibitors are the most efficacious drugs for the treatment of hypercholesterolemia. It has been established in various clinical trials that statins efficiently avert acute cardiovascular events and diminish mortality by primary and secondary prevention of ischemic heart disease[1]. Although they are usually very well tolerated by majority of patients, adverse muscular symptoms are the most frequent complaints resulting in withdrawal or reduction of dose of these valuable drugs[2]. These undesirable muscular effects may occur with & without raised CK & LDH levels[3]. Statins block the rate limiting step of cholesterol biosynthesis by inhibiting HMG Co A reductase enzyme. By doing so they not only reduce the cholesterol production but also trim down the serum Co Q10 levels[4]. It has been publicized in various studies that serum Co Q10 concentration decreases (from 16% to 49%) in patients receiving HMG Co A reductase inhibitors[5-6]. This diminished Co Q10 is proposed to be responsible for muscular adverse effects of statins[7]. Co Q10

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also known as Ubiquinone was first discovered in the mitochondrial respiratory chain[8]. It is an essential cofactor which takes part in the mitochondrial energy making process and its depletion may impair oxidative phosphorylation and ATP (Adenosine Triphosphate) synthesis, providing the basis for its association in the development of muscular symptoms[9]. Our literature search revealed three small trials, they tried to explore the beneficial effects of this essential cofactor in statin related myopathic symptoms but they all have yielded inconsistent results and warranted further studies to clearly expose the favorable role of Co Q10 in muscular adverse effects related to statins[5,9,10].

MATERIAL AND METHODS

This randomized control trial was designed and conducted on 24 healthy rabbits of local breed, which were randomly divided into 4 equal groups (G1, G2, G3, and G4) and were kept under standard conditions. This 6 months duration study was carried out in pharmacology department of Army Medical College in accordance with guidelines for animal experimentation, Centre for Research in Experimental and Applied Medicine (CREAM) Army Medical College, Rawalpindi. It was an animal based study so we did not included any inclusion and exclusion criteria.

Two groups (G1 & G2) were given toxic doses (60mg / kg / day) of simvastatin for 14 days[11] and the rest of two groups (G3 & G4) were placed on therapeutic doses (1mg / kg / day)[12] for 90 days. In addition to simvastatin, Co Q10 5mg / kg / day[9] was also given to G2 & G4 for 14 & 90 days respectively. Both the drugs were given orally via feeding tube.

Serum CK and LDH were taken as the marker of muscular toxicity. About 5 ml of blood for enzyme analysis was taken on day 0 and day 15 in G1 & G2 and on day 0 and day 91 in G3 & G4 from the marginal ear vein of rabbits[13]. Enzyme levels were measured by using automated chemistry analyzer SELECTRA E (Netherland). The base line values of all animals were assessed by ANOVA, the final results within groups were analyzed by paired "t" test and between the groups were assessed by independent "t" test and expressed as mean ± S.E.M. A *p*-value of <0.05 was considered statistically significant.

The results were analyzed by applying paired "t' test, independent "t" test and ANOVA test for biochemical markers and 'Chi-Square test' for histopathologcal findings. The *p*-value < 0.05 was considered significant.

All animals were sacrificed at the end of dosing schedule and muscle specimens were taken from both legs. The muscle sections were stained with hematoxylin and eosin (H & E) and examined under light microscope for inflammatory changes and assessed according to following criteria.

Grade 0 = Normal

Grade 1 = Mild changes: when edema & infiltrates are present.

Grade 2 = Moderate changes: when cellular degenerative changes are also present along with edema & infiltrates.

Grade 3 = Severe changes: when fibrosis or nuclear degenerative changes are also present along with Grade II changes. (14)

The results of histopathology were analyzed by using 'Chi-Square test'. The differences between the observations were considered significant if the *p*-value was < 0.05.

RESULTS

All the animals survived the duration of study and the base line values of CK and LDH taken on day 0 were in normal range in all the rabbits. All the four groups found comparable with respect to baseline CK (*p*=.06) & LDH (*p*=.744) as assessed by ANOVA. The statistically significant increase was observed in serum CK (28899.5 ± 874.09 IU / L) & LDH levels (4694.33 ± 352 IU / L) (table-1) on day 15 of G1 when compared with base line readings by paired "t" test (*p* = <.001). This group was treated with toxic doses (60mg / kg / day) of simvastatin alone for 14

days. The histopathologic examination revealed grade 3 toxicity with extensive edema, degenerative changes and heavy infiltration with different inflammatory cells in 4 (66.7%) slides where as rest of 2 (33.3%) had grade 2 inflammatory changes.

In G2, which was given Co Q10 (5mg/kg/day) in addition to toxic doses of simvastatin for 14 days, similar pattern of raise in both biochemical markers (CK 29191.33 ± 3019.79 IU/L) (LDH 4334.83 ± 143.44 IU/L) was evident (table-1) (*p*-value=.001). The microscopic findings in G2 were also almost identical to G1 with grade 3 necrotic changes in 4 (66.7%) of the slides. The moderate inflammatory changes in 4 (66.7%) of G3 and 5 (83%) slides of G4 which were contrary to biochemical results, indicating the trivial damage to muscles in therapeutic doses of simvastatin. The *p*-value was > 0.05 (table-2) when the two groups were compared by Independent sample "t" test.

DISCUSSION

This study was designed to investigate the potential valuable role of Co Q10 in statin associated adverse muscular effects, both in toxic and therapeutic doses. Our results clearly indicate that CoQ10 supplementation could not halt the development of muscular effects related

Table-1: Comparison of serum markers within groups from base line (Day 0) to final day (n=24).

		G1 (n=6)		G2 (n=6)		G3 (n=6)		G4 (n=6)	
		CK	LDH	CK	LDH	CK	LDH	CK	LDH
Baseline Day 0	Mean ± SEM	2550.5 ± 268.07	1106.8 ± 55.14	1742.66 ± 201.29	1179.33 ± 88.39	1852.33 ± 87.36	1178.83 ± 78.29	1865.50 ± 113.05	1226.83 ± 81.24
Final Day		28899.5 ± 874.09	4694.33 ± 352.00	29191.33 ± 3019.78	4334.83 ± 143.43	1902.83 ± 49.29	1227.16 ± 99.37	1897.0 ± 122.78	1266.0 ± 73.18
	p-value	<.001	<.001	<.001	<.001	.554	.522	.468	.650

Unit of CK and LDH = IU/L, *paired t-test.

Table-2: Group wise comparison of serum parameters on final day (n=24).

		G 1	G 2	*p*-value	G 3	G 4	*p*-value
CK (Day 0)	Mean ± SEM	28899.50 ± 874.09	29191.33 ± 3019.78	.928	1902.83 ± 49.29	1897.00 ± 122.78	.966
LDH (Final Day)		4694.33 ± 352.00	4334.83 ± 143.43	.367	1227.16 ± 99.37	1266.00 ± 73.18	.759

Unit of CK and LDH = IU/L , * independent t-test.

comparison of the two groups was statistically insignificant as assessed by Independence sample "t" test and *p*-value was >0.05 (table-2).

The serum CK & LDH remained within normal range in G3 & G4 treated with therapeutic doses (1mg/kg/day) of simvastatin for 90 days, Co Q10 (5mg/kg/day) was also given in addition to simvastatin to G4 for similar period of time, the *p*-value was >0.05 (table-1) . Surprisingly the histolopathologic examination showed mild to to simvastatin therapy.

In our study simvastatin was used only for 14 days in toxic doses and for 90 days in therapeutic doses. Severe myopathy was observed as indicated by raised biochemical markers and undeniable histopathalogical evidence in the case of the former and mild to moderate histological damage with normal serum CK and LDH levels in the case of later. Studies in the past have proven that statin induce

muscular adverse effects can occur with normal biochemical markers[3].

To our knowledge at least two studies have been previously published; they tried to explore the possible beneficial role of Co Q10 on statin induced myalgias. Out of these, one trial has shown positive impact on simvastatin tolerability and significant pain reduction was documented. In this comparative study 32 patients were randomly given either vitamin E 400 IU/day or Co Q10 100mg/day for 30 days[9]. The pain intensity score was measured on the basis of Brief Pain Inventory at base line. There was a decline in score from a mean of 5 to 3 in patients who received Co Q10 and increased to 4.7 from 4 in vitamin E treated group (p<0.05). However the subjects were not getting standardized doses and type of statin where as in present study the animals were standardized to simvastatin only.

The other research project which was carried out on comparatively larger number of patients showed insignificance of Co Q10 in statins related muscular effects. In this placebo controlled study the 44 patients complaining of myalgias with simvastatin therapy were selected[10]. Simvastatin was withdrawn for two weeks and at the same time patients were started to either Co Q10 200mg/day or placebo. Simvastatin was rechallenged and continued for 12 weeks. The researchers found insignificant difference between the groups continuing simvastian treatment for 3 months (82% placebo vs 73% Co Q10) and no change in myalgia score was noticed[10].

This inconsistent response of Co Q10 supplementation in improving the symptoms of statin induced muscular damage has created ambiguity about the mechanism involved in the genesis of this problem. Many studies have documented a noticeable reduction in serum levels of Co Q10 in patients receiving statins[15] but whether this decline in serum levels also leads to a reduction in the intra-cellular levels in the affected muscles has given mixed results especially when statins are used for a short period of time[5,16]. Furthermore, the raised plasma Co Q10 levels achieved by exogenous administration of the same does not necessarily reflect the tissue concentration[17]. If this is so then only deficiency of Co Q10 cannot be the sole reason for the development of myopathic changes that are observed even when statins are used for a relatively short duration.

Most of the previous studies that have reported success in reversing the adverse muscular effects of statins by using Co Q10 have been carried out on humans[18] where as we selected rabbits for our project which was consistent with the work of Nakahara et al[19], who used simvastatin in a dose of 50 mg/kg to rabbits in their experimental set up to observe simvastatin induced myopathy in rabbits. However the rise in serum CK in our work was about 50% less in magnitude as opposed to this work which was possibly due to a different breed of rabbits used in our study. Furthermore, the sample size used in human studies was small and possibility of a placebo response cannot be entirely ruled out.

The dosage and bioavailability issues can also contribute in the variable response of Co Q10 supplementation in correction of statin induced myalgias. In our study the dose that was used for prevention as well as reversal of statin induced muscular toxicity was about four times greater than the dose of Co Q10 used in previous studies yet literature search reveals that even a dose 30 times that of the usual dose can be tolerated without any appreciable side effects[20]. So may be further studies with much higher doses can be tried to rule out inadequate dose administration as the reason behind therapeutic failure.

Another possible reason behind the mixed response of Co Q10 therapy is genetic differences between patients and different species. Up to our knowledge no study has been conducted to explore the genetic differences in the response to Co Q10 supplementation. However, pharmacogenomic experiments has documented

genetic differences related to amplified risk of statin induced myopathy[21,22].

CONCLUSION

The current study on animal model has confirmed that simvastatin causes muscular injury. It is further revealed that these muscular adverse effects are dose related and reflected as raised serum creatinine kinase and LDH levels, followed by structural changes in muscle tissue. However it is worth mentioning here that these adverse muscular effects can occur even with normal biochemical markers.

We have established that probably the development of statins induced myopathy was not linked to serum Co Q10 levels because concomitant use of Coenzyme Q10 could not prevent the muscular toxicity caused by both toxic and therapeutic doses of simvastatin.

In the closing words we can say that our study did not elucidate the beneficial effects of Co Q10 supplementation in myopathy induced by both toxic and therapeutic doses of simvastatin in rabbits and in our opinion all such positive reports are anecdotal in nature. However further work needs to be instituted on this very important topic.

CONFLICT OF INTEREST

The authors of this study reported no conflict of interest.

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