Impact of Co-enzyme Q-10 on Liver Functions and Histology in Isoniazid Induced Rat Model

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Abstract

Background: Tuberculosis is the public health disease of Pakistan. Liver is the site of metabolism for most of the anti-tuberculosis drugs and these agents harm the liver, resulting into elevated liver enzymes following inflammation (hepatitis). Isoniazid (INH) is often being used in experimental studies in animal models for induction of liver injury.

Objective: To assess the hepatoprotective effects of the Co-enzyme Q-10 in rat model with Isoniazid induced hepatotoxicity.

Methodology: A total of 50 Rats of Albino Wistar category were divided in 5 equal groups (A, B, C, D and E) randomly. Group A (control) was kept on normal diet without any intervention whereas group B (experimental negative control) was given INH 100 mg/day for induction of hepatitis. Groups C was administered an oral dose of INH as 100mg+CoQ 100mg/day. The group D rats were given INH 150+ Q-10 100mg/day similarly rats in group E were administered INH 200mg+CoQ 100mg/day. Samples of blood were obtained by scarifying rats at the end of study (1month) LFTs for each group were done, comparing different groups on ANOVA using SPSS 22 version.

Results: There was significant difference in serum AST, ALT, LDH, ALP, GGT and bilirubin levels between various animal groups. The p-value was 0.00 for serum ALT, p-value was 0.000 for serum AST levels while for the difference in serum LDH p-value was 0.000, for serum ALP the p-value was 0.000, whereas p-value was 0. 000 for serum gamma GT levels and the p-value was 0.000 for serum bilirubin levels among the various animal groups that was highly significant statistically.

Conclusion: Co-enzyme Q-10 improved INH induced changes in liver functions and histology.

Key words: LFTs, Coenzyme Q10, INH, Histology.

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Introduction

Coenzyme Q10, a fat soluble compound resembling to vitamins found spread in whole body especially in cardiac, liver, renal and brain tissues.[1] There are various names given to this compound such as Coenzyme Q10, Ubiquinol, ubiquinone, ubidecarenone, CoQ10 and Q10 in simple.1 Millions of people consume Co-enzyme Q10 around the globe from Europe, USA, Russia to Pakistan for Parkinsonism and various neurological disorders, it is an orphan drug approved by the FDA.[1] It has also been reported that co-enzyme Q10 is decreased in other diseases like DM diabetes mellitus, muscular diseases, cancer and cardiac diseases.[2,3] Promising results are observed with the use CoQ10 is DM, breast cancer, HIV, male infertility, migraine, chronic fatigue syndrome, Huntington's disease, myalgia and Lyme disease and these effects are believed to be caused through immunomodulation especially potentiation of immune system.[4,5] Isoniazid (INH) is an essential drug of the intensive therapy for tuberculosis treatment as well as tuberculosis prophylaxis in people at high risk.[6,7] Hepatitis of milder form may occur with a raised liver enzymes to the upper normal limits in about 5% to10% users of INH after initiation of the therapy but this may be converted into severe hepatitis in 0.5% to 1% patients that may present with gastrointestinal upset (anorexia, nausea, vomiting), jaundice leading to hepatic insufficiency if left unchecked.[8] The metabolism of INH is based on acetylation status of the patients which are divided into slow and fast acetylators on the basis of genetic polymorphism. Toxic drug levels may reach in slow metabolizers resulting into liver toxicity in predisposed patients.[9,10,11] INH is often used by scientists to artificially induce the hepatotoxicity in laboratory

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animals to test some hepatoprotective agents, so we also used this agent in our current project on mice to test some beneficial effects of co-enzyme Q10 on liver injury so that it may help the patients of tuberculosis in a similar way as does the vitamin B6 do in saving the INH associated peripheral neuropathy. INH is a very important drug in the management of tuberculosis but hepatitis is a common problem seen in patients on this drug and requires termination of the therapy temporarily till the liver functions tests return to normal levels. The current work was planned to evaluate the protective effects of co-enzyme Q10 on liver injury induced by using the higher doses of an anti-tuberculous drug INH (Isoniazid) in rat model in this way the hepatitis problem may be prevented with the concurrent or adjuvant use of co-enzyme Q10.

Methodology

This was a quasi experimental study, conducted by using non- random sampling while sample selection was made according to previously set inclusion criteria (weight 200-300gm of both genders) and exclusion criteria (weight<200 and >300gm and sick animals). This study was executed from January 2015 to July 2015 at Isra University Hyderabad and the animal house of Agricultural University, Tando Jam, after getting approved from ERC of Isra University. After division into 5 groups animals were administered drugs in a sequence of Group A, 0.9% normal saline, Group B, Isoniazid 100 mg/kg, Group C, Isoniazid 100 mg/kg along with Q-10 at a dose of 100 mg/kg, Group D, was given Isoniazid as 150 mg/kg with Q-10 as 100 mg/kg and Group E, was treated with Isoniazid 200 mg/kg and Q-10 at 100 mg/kg drugs, were administered on once daily dosage regime orally for 6 weeks. Induction of hepatotoxicity was assured with raised hepatic enzymes such as Aspartate transferase (AST), Alanine transferase(ALT), Alkaline Phosphatase (ALP) and Lactate dehydrogenase (LDH), on biochemical analysis. Animals were scarified following cervical dislocation collecting the blood for laboratory analysis for liver enzymes on Hitachi Roche Diagnostics Chemistry Analyzer after centrifugation. Liver from rats of all groups was obtained and slides were made for microscopic examination after fixing with formaldehyde solutions and processing ethyl alcohol and xylene whereas tissue staining was achieved using Hematoxylin and Eosin. SPSS 21 version was used for analysis of ANOVA, keeping 0.05 as significance level for analysis of data.

Results

The serum ALT levels in group A was 24.2±8.6IU/L, 39.4±8.3IU/L in group B and 30.2±7.8IU/L in group C with a highly significant difference p-0.0013. Serum AST was seen 29.6±10.9 IU/L in control group (A), while 89.6±12.0IU/L in group B and 77.4±16.8IU/L in group C (P-value 0.00002) that is highly significant. Serum LDH levels were 59.5±17.9IU/L, 122.2±9.7IU/L and 101.5±14.7IU/L for groups A, B and C respectively and the difference was statistically significant at a p- value of 0.00001. Serum ALP concentration was 50.2±8.2 U/L in group A while in group B it was 114.3±18.6 U/L and it was 94.9±18.2 U/L in group C (P-value 0.00003). Serum $^{\gamma}$-GT was 16.6±3.2IU/L in group A, 58.4±12.2 IU/L in group B and 49.2±6.0IU/L in group C with highly significant difference (0. 000001). Serum levels of Bilirubin were in group A was noted to be 0.46±0.18mg/dl, 2.0±0.61mg/dl in group B while it was 1.73±0.43mg/dl in group C (P-Value 0. 000037). (Table-I) Other groups (D and E) when compared with the control group A and induced group B were also found statistically highly

Table I: Comparison of study parameters between groups A, B and C on ANOVA

Parameters	Group A	Group B	Group C	F-Value	P-value
Serum ALT (IU/L)	24.2±8.6	39.4±8.3	30.2±7.8	8.63	0.0013
Serum AST (IU/L)	29.6±10.9	89.6±12.0	77.4±16.8	55.45	0.00002
Serum LDH (IU/L)	59.5±17.9	122.2±9.7	101.5±14.7	48.56	0.00001
Serum ALP (U/L)	50.2±8.2	114.3±18.6	94.9±18.2	43.53	0.00003
Serum$^{\gamma}$-GT(IU/L)	16.6±3.2	58.4±12.2	49.2±6.0	74.19	0. 00000
Serum Bilirub (mg/dl)	0.46±0.18	2.0±0.61	1.73±0.43	34.42	0. 00003

significant detail given in table-II and III. Histological slides of control group (group A) show normal architecture, hepatocyte cords, capillaries, venules, biliary canaliculi and portal triads as shown in photomicrograph. (Fig-1a)

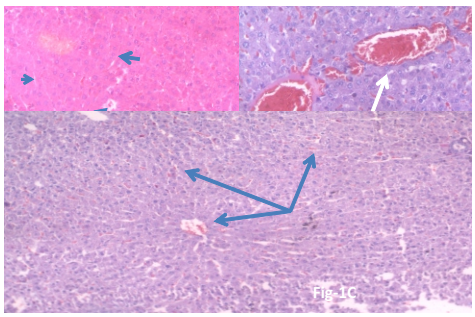
Table II: Comparison of study parameters between groups A, B and D on ANOVA

Parameters	Group A	Group B	Group D	P.Value
ALT (IU/L)	24.2±8.6	39.4±8.3	32.4±6.1	0.001
AST (IU/L)	29.6±10.9	89.6±12.0	80.5±13.2	0.000
LDH (IU/L)	59.5±17.9	122.2±9.7	109.7±14.2	0.000
ALP (U/L)	50.2±8.2	114.3±18.6	99.0±18.6	0.000
γ-GT(IU/L)	16.6±3.2	58.4±12.2	53.6±6.5	0.000
S. Bilirubin (mg/dl)	0.46±0.18	2.0±0.61	1.97±0.43	0.000

Table III: ANOVA of comparison between variable means of groups A, B and E

Parameters	Group A	Group B	Group E	P-Value
ALT (IU/L)	24.2±8.6	39.4±8.3	33.1±9.4	0.002
AST (IU/L)	29.6±10.9	89.6±12.0	82.4±9.6	0.000
LDH (IU/L)	59.5±17.9	122.2±9.7	111.0±15.3	0.000
ALP (U/L)	50.2±8.2	114.3±18.6	101.9±19.2	0.000
?-GT(IU/L)	16.6±3.2	58.4±12.2	55.1±6.3	0.000
S. Bilirubin (mg/dl)	0.46±0.18	2.0±0.61	2.06±0.52	0.000

Figure -1:a. Normal control group A showing normal arrangement of hepatocytes, Fig-1b. INH induced group B showing marked congestion with inflammation, Fig-1c. INH+Q10 treated group C showing reduced congestion and inflammatory changes



Disturbed histology was observed with edematous parenchymal changes with altered architecture in Isoniazid induced hepatotoxicity group B. (Fig-1b) The liver histology was also disturbed in other experimental groups on Isoniazid along with Q-10 (Group C, D and E) but less prominent changes were seen in comparison to group B (INH Induced hepatotoxicity). (Fig-1c)

Discussion

Baskaran UL et al in 2015, used Q-10 against INH and Rifampin induced liver damage and found it as a protective agent that is consistent with our present finding. She reported that Q10 restored the normal antioxidants levels along with reduction of glutathione and lipid peroxidation in rats induced by INH + RIF and it also increased the serum IL-10 and IL-6 to a significant that was reduced by INH + RIF.[10] Although we could not study that much level of parameters in our study that was the difference between the two studies. Amr A. Fouad et al in 2012, studied the effectiveness of Coenzyme Q10 against the Paracetamol (Acetaminophen) induced liver damage and concluded it as a promising agent which reduced serum aminotransferases levels, lipid peroxidation, glutathione reduction, TNF- α (tumor necrosis factor-α) as well as nitric oxide elevations. He also reported the improvement of selenium and zinc ions as well as histopathological damage to liver tissue by acetaminophen along with the reduced expression of nitric oxide synthase, caspase-3 nuclear factor-κBand p53 in the hepatic tissue.[11] Saleh et al, reported combined effects of TA and Coenzyme Q10 on AA induced liver injury exhibits through antioxidant and anti-inflammatory mechanisms especially increasing the GSH levels and free radical- scavenging activity.[12]

That is also consistent with the present findings reported in current study. Eghbal et al, also reported findings consistent with our study, showing protection of liver by the Q10 against hepatic injury induced by statin therapy but he studied isolated hepatocytes in vitro. Although the parameters he studied were more than our study parameters, his work was on glutathione levels, membrane lipid peroxidation, mitochondrial membrane potential, free radical formation and hepatocyte death and free radical formation.[13] Another study by Farsi et al, reported consistent results in terms of the hepatoprotective effect of Co-Q10 but the difference

was that he used Q10 against NALD (non-alcoholic liver disease) while we used INH for liver injury. He evaluated adipokines as well as certain inflammatory markers along with LFTsreporting improved levels of serum AST, ALT, GGT, TNF-α and CRP.[14] These findings from the current study and the previous studies show strong impact of co-enzyme Q10 on hepatic functions and these findings are thought to be due to scavenging of the free radicals that are the most common mediators of drug induced injuries. Lipid peroxidation is not a mechanism responsible for liver injury by the paracetamol but it is helpful protective pathway in non-alcoholic liver disease probably. Tumor Necrosis Factor and C-reactive protein are important mediators and predictors of chronic inflammation their reduced levels by Q1O are the supportive evidences of improvement in inflammatory condition of the liver.

Conclusion

Coenzyme Q10 administration improves the hepatic functions and histology deranged by Isoniazid so this agent may be used as an adjuvant agent to anti- tubercular therapy.

Authors Contribution: SBM: Conception of work and Design of Work. **NQ:** Drafting and Revising. **SS:** Acquisition & analysis **RA:** Analysis of data and drafting. **AAA:** Acquisition & analysis **RA:** Analysis of data and drafting. **AMS:** Drafting and Revising.
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