

THE EFFECTS OF CARVEDILOL AND Q10 ON ISOPRENALINE-INDUCED CARDIOTOXICITY: ELECTROCARDIOGRAPHIC, BIOCHEMICAL AND HISTOPATHOLOGICAL EVALUATION IN RATS.

BY

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Abstract

Objective: To assess the therapeutic effect of combining of Carvedilol and Q10 on electrocardiographic, biochemical and histopathological changes in isoprenaline induced myocardial infarction. Methods: Myocardial infarction was induced in rats by subcutaneous (s.c) injection of isoprenaline (85mg/kg) for two consecutive days at an interval of 24 h. Rats were treated orally (p.o) with Carvedilol at dose (5 mg/kg/day) and Q10 at dose (10 mg/kg/day) for a period of 14 days. At the end of experiment electrocardiographic, biochemical and histopathological changes were monitored from control and experimental groups. Results: ISP intoxicated rats showed a significant tachycardia , elevation ST and prolongation of QTc (i.e. ST, QTc & HR) due to conduction abnormalities, increased serum creatine kinase isoenzyme-MB (CK-MB) Treatment with Carv+Q10 significantly improved the ISP induced alteration in ECG, biochemical and histopathological changes. Conclusions: The present result shows that treatment with Carv+Q10 significantly attenuates myocardial infarction in ISP-intoxicated rats.

1. Introduction

Cardiovascular disease (CVD), predominantly myocardial infarction, remains the principal cause of death in both developed and developing countries. It will be the most important cause of mortality worldwide by 2020(Rajadurai and Prince 2007). Myocardial infarction (MI) occurs when the blood supply to a part of the heart is interrupted, causing death of heart tissue (Upaganlawar, Patel *et al.* 2012). It is an acute condition of necrosis of the myocardium that occurs as a result of imbalance between coronary blood supply and myocardial demand (Upaganlawar, Patel *et al.* 2012).Inflammation is a key process involved in mediating myocardial tissue damage after an ischemic event. Neutrophils infiltrate the infarcted area where they can promote myocardial cell damage through the release of proteolytic enzymes and the production of reactive oxygen species (ROS). Inflammation may also increase the risk of recurrent ischemic events by destabilizing atherosclerotic plaques and making them prone to rupture (Jordan, Zhao *et al.* 1999).The development of myocardial ischemia and infarction is a dynamic process with the widespread occurrence of coronary atherosclerosis and involvement of oxidative stress in the humans. Among several

pharmacological interventions to protect heart against oxidative stress, the use of antioxidants is most promising (Ojha, Bhatia *et al.* 2011).

Isoprenaline (ISP) [1-(3, 4-dihydroxyphenyl)-2-isopropylaminoethanol hydrochloride] is a synthetic β -adrenergic agonist and its subcutaneous injection induces irreversible cellular damage and ultimately myocardial infarction in rats. The acute hemodynamic and electrocardiographic changes in isoprenaline induced myocardial infarction resemble closely to those occurring in patients with myocardial infarction (Yousefi, Soraya *et al.* 2013). Therefore, the rat model of isoprenaline induced myocardial infarction offers a reliable non-invasive technique for studying the effects of various potentially cardioprotective agents (Fathiazad, Matlobi *et al.* 2012).

It produces myocardial necrosis which caused cardiac dysfunction, increased lipid peroxidation along with an increase in the level of myocardial lipids, altered activities of the cardiac enzymes and antioxidants (Karthikeyan, Bai *et al.* 2007).

Carvedilol is a non-selective α_1 - and β -receptor blocker initially used in the treatment of hypertension. In addition to its antihypertensive property, carvedilol has been shown to significantly reduce morbidity and mortality in heart failure and post-AMI patients (Liu, Zhang *et al.* 2013).

Therefore the present study was designed to study the effect of Carvedilol and Q10 treatment on the myocardial infarction induced by supramaximal doses of isoprenaline. And study its therapeutic efficacy by studying the biochemical marker, electrocardiographic and histopathological changes.

2. Materials and methods

2.1. Drugs and chemicals

1. Carvedilol (Multiapex pharma, Cairo, Egypt). It was obtained as a gift. Carveilol was used as a drug to treat myocardial necrosis in rats. It was dissolved by the initial addition of dimethyl sulphoxide (DMSO), followed by the addition of normal saline (the final concentration of DMSO was less than 0.5%).
2. Co-enzyme Q10 (Mepaco pharma, Cairo, Egypt). Co-enzyme Q10 was used as a drug to treat myocardial infarction in rats. It was dissolved in distilled water oral administration.
3. Isoprenaline (Sigma-Aldrich Co., St Louis, MO, USA).

Isoprenaline is (RS)-4-[1-hydroxy-2 (isopropylamino)ethyl]benzene-1,2-diol, C₁₁H₁₇NO₃, It is white crystalline powder. It was dissolved in saline at concentration of 85mg/kg to be injected s.c. for 2 consecutive days to induce myocardial infarction.

2.2. Experimental animals

Male Sprague-Dawley rats (200-220 g) obtained from Nile Co. for Pharmaceutical and Chemical industries (Cairo, Egypt) were used in the present study. Rats were housed in faculty of Pharmacy, Ain-Shams University, in an air-conditioned atmosphere, at a temperature of 25 °C with alternatively 12 hour light and dark cycles. Animals were acclimated for 2 weeks before experimentation. They were kept on standard pellet diet and water *ad libitum*.

The study was carried out according to the guidelines of the Ethics Committee, Faculty of Pharmacy, Ain-Shams University.

2.3. Induction of myocardial infarction

Myocardial infarction was induced in rats by subcutaneous injection of 85 mg/kg isoprenaline hydrochloride dissolved in saline once daily for two successive days. The selected route and dose were chosen from published literatures (**Priscilla and Prince 2009**).

2.4. Experimental design.

After acclimatization, the animals were randomly divided into the following groups consisting of 8 rats each:

Group 1 (control): rats was injected with normal saline (1ml/kg) subcutaneous (S.C.) on the 1st and 2nd day and then received DMSO /distilled water (vehicle for Carvedilol/ Q10) orally for 14 days.

Group 2 Carv(5mg/kg) +Q10(10mg/kg) : rats was injected with Normal saline (1ml/kg) subcutaneous (S.C.) on the 1st and 2nd day at an interval of 24 h then received Carv (5mg/kg)+Q10 (10/kg) in DMSO/distilled water orally for 14 days(**CHANDER HASS YADAV and KHANAM 2014**).

Group 3 (ISP): rats was injected with ISP (85 mg/kg, S.C.) in normal saline on the 1st and 2nd day at an interval of 24 h then received DMSO/distilled water orally for 14 days(**Dusek, Rona et al. 1971**).

Group 4 ISP+ Carv (5mg/kg) + Q10 (10mg/kg): rats was injected with ISP (85 mg/kg, S.C.) in normal saline on the 1st and 2nd day at an interval of 24 h then received Carv (5mg/kg)+Q10 (10mg/kg) in DMSO/distilled water for orally 14 days.

Twenty-four hours after the last treatment, animals were anesthetized with urethane intraperitoneal at dose (1.5 g/kg) (**Field, White et al. 1993**) for ECG monitoring. Thereafter, blood samples were collected from the retro-orbital plexus. Serum was separated by centrifugation at 4000 rpm for 4 min and stored at -20⁰C until analysis for the estimation of CK-MB activity. Rats were then sacrificed by decapitation and the hearts were rapidly isolated, and preserved in 10% formalin for histological examination.

2.5. Measurements of ECG changes

Electrocardiograph was recorded at the beginning of the experiment to ensure the normal ECG pattern of the rats according to method of (**Mladěnka, Hrdina et al. 2009**) At the end of the experiment, ECG was recorded in urethane anesthetized rats 48 h after ISP injection using Bioscience ECG recorder (Bioscience, Washington, USA). Anesthetized rats were placed in the supine position on a board and needle electrodes were inserted beneath the skin for the limb lead at position II (right forelimb to left hind limb). Every recording lasted for at least 5 min. ECG recording speed was 50 mm/s and the voltage was 1 mV/cm. Noise was minimized by a digital filter. Analysis of ECG waves was done to calculate heart rate (beats/min), ST segment (mV) and QTc interval (ms). QTc interval was calculated from Bazett's equation. For each parameter, measurements were done at three non-consecutive, randomly chosen points in every 5 min recording. The results are reported as mean of the three randomly selected segments.

2.6. Biochemical assays

The collected serum was used for the estimation of cardiac marker enzyme creatinine kinase-MB (CK-MB), standard enzymatic kits according to method of Gerhardt & Waldenström (Gerhardt and Waldenström 1979).

2.7. Histopathology

After sacrifice, the heart was rapidly dissected out and washed immediately with saline and fixed in 10% buffered formalin. The fixed tissues were embedded in paraffin and serial sections (5 μ m thick) were cut. Each section was stained with hematoxylin and eosin (H&E) according to Bancroft & Gamble (Ashoush, El-Batawy *et al.* 2013). The sections were examined under the light microscope (Olympus BX10, Tokyo, Japan) for histopathological changes and photomicrographs (Olympus DP12 camera, Japan) were taken.

2.8. Statistical analysis

All the values are expressed as mean \pm S.D. Statistical significance between more than two groups was tested using one-way ANOVA followed by Tukey–Kramer as a post-hoc test as appropriate using computer based fitting program (Prism, Graphpad). The 0.05 level of probability ($P \leq 0.05$) was used as the criterion for significance.

Results

3.1. Effect of Carvedilol and Q10 on ECG changes in isoprenaline-induced myocardial infarction in rats

Electrocardiograph tracing showed normal cardiac activity in the control and Carv+Q10 treated rats. Rats in ISP-intoxicated group showed several ECG changes including tachycardia, ST-segment elevation and prolongation of QTc intervals as compared to the control group. Such ECG abnormalities were obviously improved in the ISP-intoxicated animals treated with the Carv+Q10 as evidenced by normalization of heart rate, ST-segment and QTc intervals compared to ISP-intoxicated group (Table 1).

Table (1): ECG parameters of rats treated with Carvedilol and Q10 and/or isoprenaline (ISP).

Treated groups	ST segment (mV)	QTc interval (ms)	Heart rate (beat/min)
Control	0.10 \pm 0.005	0.31 \pm 0.015	329.9 \pm 7.90
Carv+Q10	0.10 \pm 0.009	0.31 \pm 0.005	313.8 \pm 10.17
ISP (85mg/kg)	0.25 \pm 0.037 ^a	0.50 \pm 0.045 ^a	453.3 \pm 27.33 ^a
ISP (85mg/kg)+ (Carv/Q10)	0.15 \pm 0.033 ^b	0.35 \pm 0.035 ^b	305.0 \pm 36.19 ^b

Data are the mean \pm S.D. (n =8).

a:Significantly different from the control

b:Significantly different from **ISP-intoxicated** group respectively at $P \leq 0.05$ using ANOVA followed by Tukey-Kramer as a post-hoc test.

3.2. Effect of Carvedilol and Q10 on biochemical change that associate isoprenaline-induced myocardial infarction in rats

Isoprenaline increased serum CK-MB activity by 110% as compared to the normal group. Carv+Q10 treatment decreased serum CK-MB activity by 41.8% as compared to the isoprenaline-intoxicated group (Table 2 and Fig 1).

Table (2): Cardiotoxicity marker of rats treated with Carv+Q10 and/or isoprenaline (ISP).

Treated groups	CK-MB
Control	148.7±19.33
Carv+Q10	124.2.4±20.31
ISP (85mg/kg)	311.7 ±44.12 ^a
ISP (85mg/kg)+ (Carv+Q10)	181.4 ±20.85 ^b

CK-MB, Creatine phosphokinase isoenzyme-MB.

Data are the mean±S.D. (n=8)

a: Significantly different from the control

b: Significantly different from ISP-intoxicated group respectively at $P \leq 0.05$ using ANOVA followed by Tukey-Kramer as a post-hoc test.

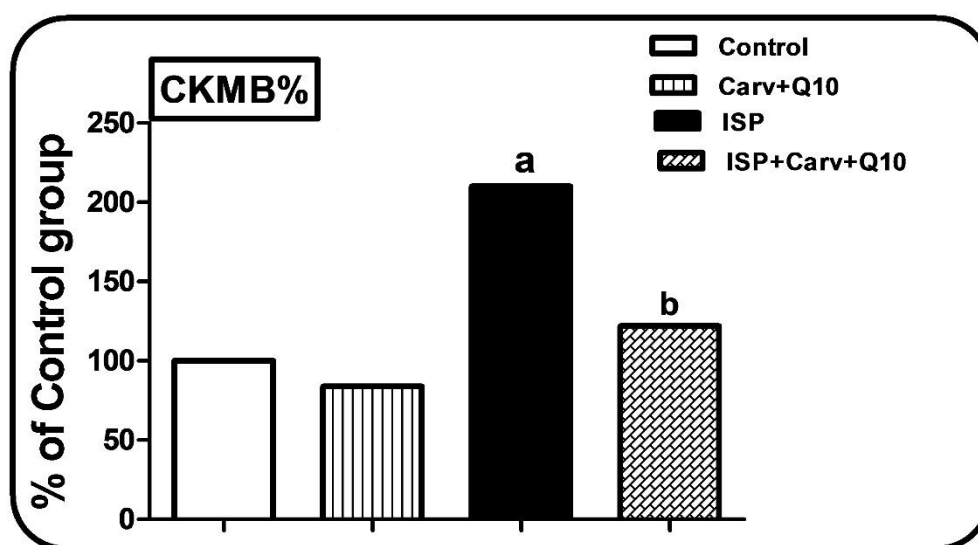


Fig. (1): Effect of Carv+Q10 on *CK-MB* in ISP-intoxicated group as percentage of control group.

a or b: Significantly different from the control or ISP-intoxicated group respectively at $P \leq 0.05$ using ANOVA followed by Tukey-Kramer as a post-hoc test.

3.3. Effect of Carv+Q10 on histopathological changes that associate isoprenaline-induced myocardial infarction in rats

To further characterize the Cardiotoxicity induced by isoprenaline, histopathological examination of heart tissue was done. Hearts from control and Carv+Q10 treated rats showed regular cell distribution and normal myocardium architecture (Fig 2A and 2B). Histological examination of hearts from ISP-intoxicated animals revealed marked myocardial degeneration (D) in the form of myofibrillar loss, cytoplasmic vacuolization (V), inflammatory cell infiltration (I), edema (E) and congestion (Fig. 2C). Interestingly, pretreatment of ISP-intoxicated rats with Carv+Q10 almost preserved the normal myocardium architecture (Fig. 2D).

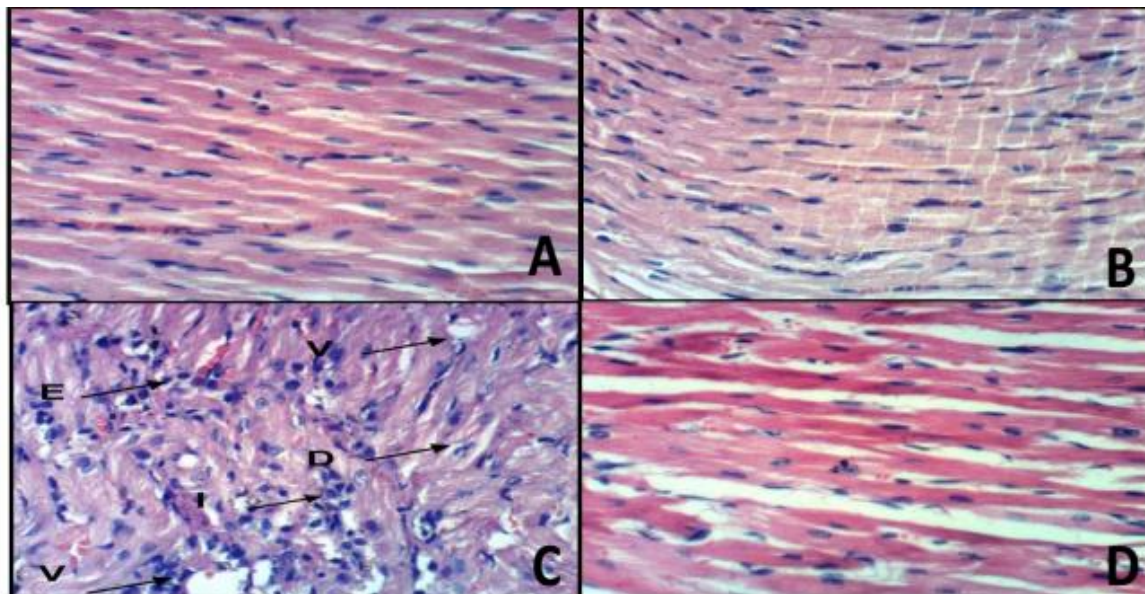


Fig2. Effect of Carv/Q10 treatment on ISP-induced histological alterations of the heart tissue (x200). Photomicrographs of haematoxylin and eosin stained sections of heart depicting (A) control group, (B) Carv/Q10 treated group, (C) ISP treated group (85mg/kg) and (D) ISP (85 mg/kg) + Carv/Q10 treated group. (A)&(B) show normal histoarchitecture of the rat heart. (C) Show ISP-induced myofibrillar loss, cytoplasmic vacuolization, inflammatory cell infiltration, edema and congestion. (D) Show that Carv/Q10 treatment prevented

4. Discussion

MI induced by injection of ISP is a standardized model to study the beneficial effects of numerous drugs and antioxidants. In the present study, we found that Carvedilol and Q10 treatment exerts a strong improvement in ISP induced MI in rats. The ECG is considered the single most important initial clinical test for diagnosis of myocardial ischemia and infarction. Its correct interpretation is usually the basis for immediate therapeutic interventions and/or subsequent diagnosis tests. In the present study, ISP intoxication shows significant alterations in ECG patterns. The characteristic ECG findings were elevation of ST-segment and QTc interval. These alterations could be due to ISP auto oxidation and generation of free radicals which further produced oxidative stress. Increased oxidative stress causes loss of cell membrane function in injured myocardium (**Holland and Brooks 1977**). This elevation reflects the potential difference in the boundary between ischemic and non-ischemic zones (**Patel, Upaganlawar et al. 2010; Li, Xie et al. 2012**). Furthermore, ST-segment elevation was observed in patient with acute myocardial ischemia and in experimental model of ISP in rats (**Peacock, Hollander et al. 2007; Punithavathi and Stanely Mainzen Prince 2011**).

Treatment with Carvedilol and Q10 in ISP-intoxicated rats significantly prevented the altered ECG pattern towards normal suggesting the cell membrane stabilizing potential of Carvedilol and Q10 which might be due to their potent antioxidant property which is in agreement with previous reports (**Cheng, Kamiya et al. 2001**).

In the present study ISP-intoxicated rats showed MI which is evident by significant increase in heart rate. These changes in hemodynamic parameter indicated the activation of sympathetic nervous system which is in line with previous reports (**Alcaraz, Fernandez et al. 2003**).

Treatment with Carvedilol and Q10 significantly attenuated these changes in hemodynamic parameter which are evidenced from improvements in heart rate (**Bullinga, Alharethi et al. 2005**).

Additionally, ISP-induced myocardial injury was further manifested by the significant elevation in activities of serum CK-MB enzyme; due to leakage from tissue to blood serum as a result of damaged or destroyed cardiomyocytes, as well as, the cells damaged because of insufficient supply of oxygen and oxidative damage of myocardium which render the cell membrane fragile, porous, or ruptured. The increased levels of these enzymes are indicative of severity of cell necrosis and ISP mediated peroxidative myocyte injury. The increase in activities of these enzymes is in agreement with previous studies (**Kannan and Quine 2013**).

On the other hand, Carvedilol and Q10 treatment significantly ameliorated ISP-induced CK-MB enzymes activities elevations. Furthermore, it almost preserved the normal architecture of the heart which in consonance with previous studies (**Brunner, Faber et al. 2000**).

This present findings are strongly suggestive of potent antioxidant activity of Carvedilol against ISP-induced oxidative stress in MI as previous investigations (**Hori and Nishida 2009**).

Histopathologic examination of cardiac tissues correlated with the observed biochemical and ECG changes as the protective effects of Carvedilol and Q10 on histopathological changes of myocardium were further supported by light microscopic observations. Subsequent to isoprenaline administration, significant myonecrosis,

edema, and infiltration of inflammatory cells were observed in light microscopic examination of the myocardium. These histopathological perturbation in isoprenaline-intoxicated rats are attributed to a decline in oxygen supply with paramount rise in wall-stress(Ojha, Bhatia et al. 2011)

However, Carvedilol and Q10 treatment to ISP-intoxicated rats has shown resistance towards necrosis, edema, and inflammation and protected cardiomyocytes from the deleterious effects of isoprenaline. Such effects can be explained by previously reported anti-oxidant and anti-inflammatory potentials of Carvedilol and Q10 (Alcaraz, Fernandez et al. 2003). Rats which received Carvedilol and Q10 treatment exhibited a normal myocardial histology, which is suggestive of the fact that Carvedilol and Q10 (5mg & 10mg/kg/day) do not render any significant adverse effects on myocardium and is safe for myocardial cells.

5. Conclusion

The present study demonstrated that subcutaneous injections of isoprenaline produced myocardial infarction in rats as evident by the release of myocyte injury markers in serum. Myocardial lesions were associated with decreased antioxidant defense status in the heart electrocardiographic, histopathological changes and release of CK-MB. In addition, the present study provided experimental evidence that Carvedilol and Q10 maintained the antioxidant activity and improved cardiac performance following high-dose isoprenaline administration. This finding might be a scientific support to understand the beneficial effects of Carvedilol and Q10 on improvement of myocardial injury, in which oxidative stress has long been known to contribute to the pathogenesis.

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تأثير الكارفيديلول والكيو 10 على سمية القلب المحدثه بواسطة الايزوبرينالين:تقييم رسم القلب و الكيمياء الحيوية و الانسجة المرضية في الجرذان

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تقييم التأثير العلاجي من الجمع بين مادة الكيوتن و الكارفيديلول على التغيرات الحادثة في رسم القلب الكهربى electrocardiographic، والكيمياء الحيوية والنسجية المرضية في مرض احتشاء عضلة القلب المحدث نتيجة لحقن مادة الإيزوبرينالين. الأساليب: تم استحداث مرض احتشاء عضلة القلب في الجرذان عن طريق حقن ٨٥مجم/كجم إيزوبرينالين تحت الجلد لمدة يومين متتاليين بفترة لفاصلة ٢٤ ساعة ثم تم علاج فئران التجارب بمادتين الكارفيديلول و الكيوتن ١٠,٥مجم/كجم/يوم عن طريق الفم لمدة ١٤ يوم متتالية ، تم قياس التغيرات الحادثة في الرسم الكهربى للقلب في اليوم السابع عشر من بدايه التجربه ثم تم رصد التغيرات البيوكيميائية والتشريحية المرضية. النتائج: أظهرت المجموعة المرضيه من الفئران تغيير كبير في نمط تخطيط القلب (ST,Qtc & HR) و ذلك بسبب تشوهات التوصيل، وكذلك زيادة تركيز الكرياتين كيناز (CK-MB) في الدم وتشوه في انسجة القلب myofibrillar. اما في المجموعة المعالجة بمادتي الكيوتن و الكارفيديلول فقد حدث تحسن كبير في الرسم الكهربى للقلب والتغيرات التشريحية المرضية و كذلك نقص في تركيز الكرياتين كيناز ، . الاستنتاجات: ادى تناول مادتي الكيوتن و الكارفيديلول الى التحسن في مرض احتشاء عضلة القلب في الفئران الناجم عن حقن مادة الأيزوبرينالين.