Effect of octreotide in the prevention of doxorubicin cardiotoxicity

Doksorubisine bağlı kardiyotoksisitenin önlenmesinde oktreotidin etkisi

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ABSTRACT

Objective: A precise method for prevention from doxorubicin cardiotoxicity is not known. We examined whether octreotide has a protective effect against doxorubicin cardiotoxicity.

Methods: New Zealand rabbits (n=44) were divided into 4 groups according to drugs given: Group A (n=12) doxorubicin and octreotide, Group B (n=12) only doxorubicin, Group C (n=10) only octreotide and Group D (n=10) only saline. Effects of the drugs were evaluated in terms of histopathological score, fractional shortening (FS) and prolongation of the QTc interval.

Results: Mean pathological score for cardiotoxicity (Group A: 3.7±0.5, Group B: 3.9±0.3), prolongation of QTc (Group A: from 244.5±21.2ms to 282.9±25.9ms, p<0.0001; Group B: from 248.5±17.7ms to 298.3±13.7ms, p<0.00001) and the rate of decrease in FS (Group A: from 34.4 ± 2.0 to 28.0 ± 2.0, p<0.05; Group B: from 35.1 ± 1.9 to 24.8 ± 1.3, p<0.05) were higher in Group B when compared to Group A, but only difference in the rate of decrease in FS was statistically significant (p<0.001). None of these variables changed significantly in groups C and D.

Conclusion: In this preliminary study, octreotide seems not to reduce doxorubicin cardiotoxicity. On the other hand, a consistent tendency of decreased cardiotoxicity in octreotide+doxorubicin group was observed, although only the difference in FS decrease was significant. Further investigations are needed to address the issue of the extent and the mechanisms of this effect. *(Anadolu Kardiyol Derg 2005; 5:18-23)*

Key words: Doxorubicin, cardiotoxicity, prevention, octreotide

ÖZET

Amaç: Doksorubisine bağlı kardiyotoksisinin önlenmesi konusunda kesin bir yöntem bulunmamaktadır. Bu deneysel çalışmada oktreotidin doksorubisine bağlı kardiyotoksisitenin önlenmesindeki etkinliği incelenmiştir.

Yöntemler: Çalışma Yeni Zelanda tavşanları (n=44) üzerinde yapılmış olup denekler 4 gruba ayrılmışlardır. Bunlardan A grubuna (n=12) doksorubisin ve oktreotid, B grubuna (n=12) sadece doksorubisin, C grubuna (n=10) sadece oktreotid ve D grubuna sadece serum fizyolojik verilmiştir. Kardiyotoksisite, histopatolojik toksisite skorlaması, fraksiyonel kısalmadaki (FK) azalma ve QTd intervalindeki uzama derecesi ile değerlendirilmiştir.

Bulgular: B grubunda, patolojik incelemede sonucundaki ortalama kardiyotoksisite skoru (A grubu: 3.7±0.5, B grubu: 3.9±0.3), QTd uzaması miktarı (A grubu: 244.5±21.2ms'den 282.9±25.9ms'ye, p<0.0001; B grubu: 248.5±17.7ms'den 298.3±13.7ms'ye, p<0.00001) ve FK'daki azalma (A grubu: 34.4 ± 2.0'den 28.0 ± 2.0'ye, p<0.05; B grubu: 35.1 ± 1.9'den 24.8 ± 1.3'e, p<0.05) A grubuna göre daha fazla olduğu saptanmakla beraber, bu parametrelerden sadece FK kısalmaları arasındaki fark istatistiki olarak anlamlı düzeyde olmuştur (p<0.001). C ve D gruplarında ise bu üç parametreden hiçbirinde anlamlı bir değişiklik saptanmamıştır.

Sonuç: Bu deneysel çalışmada oktreotid doksorubisin kardiyotoksisitesini belirgin azaltmamıştır. Ancak, sadece FK'daki azalma anlamlı olmakla beraber, 3 inceleme yönteminde de oktreotid grubunda kardiyotoksisitede azalma eğilimi gözlenmiştir. Oktreotidin bu etkisinin derecesi ve mekanizmaları, ile doksorubisine bağlı kardiyoyoksisitenin mekanizmaları konusunda başka araştırmaların yapılması gerekmektedir. *(Anadolu Kardiyol Derg 2005; 5: 18-23)*

Anahtar kelimeler: Doksorubisin, kardiyotoksisite, korunma, oktreotid

Introduction

Doxorubicin is an antineoplastic antibiotic, in the anthracycline group, which is now a part of standard chemotherapeutic regimens for many hematopoietic malignancies and solid tumors. However, the development of dose dependent cardiomyopathy has greatly limited its use (1). Myocardial damage as seen on myocardial biopsy, increases linearly with increasing cumulative dose of doxorubicin (2), but clinically the incidence of cardiotoxicity is more apparent at cumulative doses greater than 400-450mg/m2 (3). Furthermore, individual toxic doses may vary. Myocardial dysfunction years after the therapy have also been recognized (4,5). Thus, myocardial protection during doxorubicin treatment should remain being the goal to enhance the beneficial effects of the drug and to minimize the risk of short and long-term cardiac problems.

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The mechanisms for anthracycline-induced myocardial injury are not clear but several theories most of which have a common pathway of mediation of oxygen radicals have been proposed (1, 6-8). One possible mechanism involves the disturbance of calcium and sodium exchange caused by an interaction with the mitochondrial membrane to form a complex that inactivates the electron transport chain, which leads to the production of free oxygen radicals (9). Some studies have suggested that doxorubicin inhibits calcium accumulation by sarcoplasmic reticulum and mitochondria, and causes the release of preaccumulated calcium (10). Suitable calcium antagonists such as gallopamil or cyclosporine A may diminish cardiotoxic effects of anthracyclines (11,12). Somatostatin, which is a naturally occurring tetradecapeptide that has numerous physiologic effects, was shown to decrease inward calcium current in some studies (13-15).

This experimental study was undertaken to determine whether octreotide, a somatostatin analogue, has a protective effect against doxorubicin cardiomyopathy.

Materials and Methods

Animals

Forty-four male, New Zealand white rabbits weighing 2.7-3.4 kg (2.8±0.4) were housed separately in stainless steel cages in a room with 20-220C temperature and 55±5% humidity. They were provided a diet of standard rabbit pellets and water ad libitum. All animals were observed in quarantine for at least 2 weeks before the study to allow adaptation to the environment and to eliminate sick animals.

All animal procedures were performed in compliance with the guidelines of our medical institute and with the approval of the Ethic Committee for Animal Studies.

Study methods

Animals were randomized into four groups: Group A (n=12) received doxorubicin and octreotide, Group B (n=12) received only doxorubicin, Group C (n=10) received only octreotide and Group D (n=10) received only saline. Doxorubicin was given to each animal in groups A and B (2 mg/kg) once a week for 10 weeks with a 24 G venous catheter via marginal or median vein. Animals in groups C and D were given saline at the same dose (1 ml/kg) in the same manner. Octreotide was given subcutaneously to each animal in groups A and C everyday (5mgr/kg/day in 3 divided doses) during 10 weeks. The same amount of saline was given to animals in groups B and D subcutaneously.

Blood samples were taken to determine hematological parameters every two weeks. Doxorubicin was discontinued for one week in rabbits with low hemoglobin (<7 gr/dL) or white cell count (<3000/mm3) to avoid the loss of animals.

Pathology

Whenever an animal died before the completion of the study a necropsy was performed within 12 hours of the death of the animal. At the end of the study, surviving animals were sacrificed with pentobarbital sodium. The entire heart was excised from all animals and fixated in 10% formalin. Tissue samples obtained from the ventricular septum, left ventricular free wall and left ventricular papillary muscles were embedded in paraffin. Tissue sections of 4-5 μm in thickness were taken and stained with hematoxylin and eosin. The frequency and severity of doxorubicin-induced cardiac toxicity were assessed by light microscopic examination of left ventricular tissue. The histopathological changes (number of muscle cells showing myofibrillar loss and cytoplasmic vacuolization) were graded on a scale from 0 to 4: Grade 0- no damage; grade 1- involvement of less than 5% of cells; grade 2- involvement of 6-25% of cells; grade 3- involvement of 26-49% of cells; grade 4- involvement of more than 50% of cells. A single score between 0 and 4 was given to each animal after evaluation of all three myocardial sections according to the most affected segment. Specimens were evaluated by an experienced pathologist without prior knowledge of the treatment given to the animals.

Echocardiography

All animals were evaluated by echocardiography at the beginning and living animals were re-evaluated at the end of the study before they were sacrificed. The echocardiograms were obtained using a 5MHz transducer (Hewlett-Packard Sonos 2000 country). Rabbits were sedated with ketamine (35 mg/kg) and placed in supine position after the ventral area of the chest had been shaved. After identification of the apical impulse, the transducer was placed on the same intercostal space and M-mode echocardiogram of the left ventricle was recorded at the level of mitral chordae tendinea using the 2-D image to assure a view as perpendicular as possible to the long-axis of the left ventricle. Left ventricular end-systolic and end-diastolic diameters (ESD and EDD, respectively) were measured and fractional shortening (FS) was calculated for each animal [FS=(EDD-ESD)/EDD].

An operator experienced in animal echocardiography performed examinations in a blinded fashion.

Electrocardiography

Electrocardiograms (ECG) from extremity leads were obtained at the beginning and every two weeks during the study. The tracings were analyzed under a magnifying glass and QT intervals were measured from the onset of the Q wave to the end of the T wave and corrected QT (QTc) intervals were calculated for each lead [QTc=RR interval/(QT interval)1/2]. Then the QTc intervals obtained from each lead were averaged to find the final QTc interval of each animal. The leads where the onset of the QRS complex or the end of the T wave could not be determined were ignored.

Statistical analyses

The ordinal results (histopathological scores) of four groups were analyzed using Kruskal-Wallis test. Fractional shortenings and QTc values and the rate of change of these were analyzed using one-way ANOVA. Post-hoc analysis between the groups was done using Newman-Keuls test. The differences between the groups with ordinal variables were determined using Mann-Whitney U test. Student`s t test was used to determine the significance of the change in continuous variables within the same group. A p value of <0.05 was considered significant.

Results

Experimental considerations

Three animals in Group A and 4 animals in Group B died before the end of the study: two of general weakness and weight loss, 2 of generalized edema and signs of congestive heart failure; and 3 of them died suddenly without any clinical signs. Cumulative doxorubicin doses given to these animals are shown in Table 1. Among the surviving animals, 2 in Group B had leg ede-

ma. All of the rabbits in groups A and B had alopecia starting from the head and spreading to the interscapular area and in some animals to the legs. Two animals in Group A and 5 animals in Group B had local necrosis in the ear because of extravasation of doxorubicin.

Microscopic myocardial changes

Light microscopic examination revealed two prominent and characteristic alterations in doxorubicin treated animals (groups A and B); cytoplasmic vacuolization and myofibrillar loss (Fig. 1). The vacuolization involved the formation of multiple, clean, membrane limited vacuoles that filled the cytoplasm of the affected cells and often caused them to appear larger than normal. The loss of myofibrils resulted in a pale but nonvacuolated appearance of the cytoplasm. In many instances both vacuolization and myofibrillar loss occurred in the same cell. Both findings were seen with greater frequency as the severity of the lesion increased. Histopathological scores for each animal are shown in Table 1. The findings pointed out the significant impairment in doxorubicin treated groups (A and B) when compared with groups C and D in both of which no animal showed any histopathological change ($p<0.0001$). Although the mean histopathological score of Group A was lower than that of Group B (3.7±0.5 vs. 3.9±0.3) this difference was not statistically significant ($p=0.3$).

Echocardiography

Table 1 shows the FS values at the beginning and end of the study. Because 3 animals in Group A and 4 animals in Group B died during the study, FS results of these animals are excluded from statistical analysis. Fractional shortening values of Group A and B decreased significantly from 34.4 ± 2.0 to 28.0 ± 2.0 ($p<0.05$) and from 35.1 ± 1.9 to 24.8 ± 1.3 ($p<0.05$), respectively, whereas the changes in groups C (from 33.2 ± 2.5 to 33.9 ± 2.2) and D (from 35.4 ± 2.5 to 34.9 ± 2.8) were not significant. When compared, the rate of decrease in FS in Group B was significantly higher than that of Group A ($p<0.001$) (Fig. 2).

Electrocardiography

Table 2 shows the mean QTc intervals of four groups at the beginning and every two weeks of increments in doxorubicin dose. The results of animals, which died during the study, were not included in statistical analyses. When the change in QTc between the basal and the last values were compared for each group, significant prolongations were determined in both Group A ($p<0.0001$) and Group B ($p<0.00001$), whereas the changes in are were not significant in groups C and D (Fig. 3). Although mean QTc prolongation was higher in Group B (%16.9) than in Group A (%15.0), this difference wasn't significant (p@0.25). When the QTc values of each measurement were compared with the initial values in groups A and B, the prolongation became significant after 8mg/kg cumulative doxorubicin use in both groups ($p<0.01$ and $p<0.001$ respectively).

Discussion

Use of the antineoplastic doxorubicin continues to be limited by its cumulative dose-related cardiotoxicity. Formation of

Table 1. Echocardiographic and histopathological results of animals

GROUP	Animal #	Doxo.	HPS	FS 1	FS 2	GROUP	Animal #	Doxo.	HPS	FS 1	FS2
	1	20	3	35	30		25	0	0	33	36
	2	20	4	33	29		26	0	0	33	35
	3	20	3	38	30		27	0	0	38	36
	4	20	4	34	27		28	0	0	35	37
	5	20	4	37	29		29	0	0	32	33
A	6	12	3	35	NA	C	30	0	0	35	34
	7	16	4	33	NA		31	0	0	34	30
	8	20	4	32	28		32	0	0	33	33
	9	20	4	33	26		33	0	0	29	31
	10	16	4	31	NA		34	0	0	30	34
	11	20	4	35	29						
	12	20	3	33	24						
	13	20	4	35	24		35	0	0	34	35
	14	20	4	37	26		36	0	0	32	32
	15	20	4	35	26		37	0	0	36	37
	16	12	3	34	NA		38	0	0	35	36
	17	20	4	33	24		39	0	0	37	35
B	18	16	4	36	NA	D	40	0	0	31	34
	19	20	4	32	23		41	0	0	35	30
	20	14	4	37	NA		42	0	0	39	37
	21	20	4	38	27		43	0	0	37	33
	22	20	4	35	24		44	0	0	38	40
	23	14	4	32	NA						
	24	20	4	36	25						

Doxo.: Cumulative doxorubicin dose (mg/kg), FS1: fractional shortening before the therapy (%), FS2: fractional shortening at the end of the study (%),
HPS: histopathological score in a scale from 0 to 4, NA: Non applicable since these animals died before the end of the study

free radicals and intracellular calcium overloading are the major proposed mechanisms in the pathogenesis of anthracycline-induced cardiotoxicity (15,16). The mechanisms of intracellular calcium accumulation are not clear. It was suggested that doxorubicin interferes with the calcium accumulation activity of the sarcoplasmic reticulum (10). Chugun et al. (17) reported that doxorubicin impairs the calcium handling of sarcoplasmic reticulum and this contributes to doxorubicin induced late cardiotoxicity. It was also suggested that interference with mitochondrial calcium regulation and irreversible decrease in mitochondrial calcium loading capacity causes calcium accumulation and loss of myocardial function in doxorubicin-treated patients (11,18). It was proposed that suitable calcium antagonists such as cyclosporine A, which is an antagonist of calcium dependent pore formation and gallopamil, which acts via slow calcium channels, may prevent doxorubicin cardiotoxicity (11,12). On the other hand, somatostatin was shown to decrease inward calcium current in guinea-pig atria (13,15). Lin et al. (19) suggested that octreotide, an analogue of somatostatin, inhibits transmembrane calcium influx. We have previously shown that octreotide decreased the interventricular septum thickness in hypertrophic obstructive cardiomyopathy, which suggests that decrease in inward calcium current may have a role (20).

In this study, histopathological cardiotoxicity score, decrease in FS and prolongation of QTc interval were used to evaluate cardiac impairment in order to detect doxorubicin cardiotoxicity and protective effect of octreotide.

Histopathological examination is the most sensitive method of early detection of anthracycline cardiotoxicity (2).) However there was no difference in favor of the protective effect of octreotide in histopathological score between groups (p=0.3).

Table 2. Corrected QT intervals after different total doxorubicin doses

Groups	QTc0,ms	QTc1,ms	QTc2,ms	QTc3,ms	QTc4,ms	QTc5,ms
A(Doxo+Oct)	244.5 ±21.2	246.1 ±18.6*	253.5 ± 18.8†	266.4 ±21.5†	278.5 ±24.5†	282.9 ±25.9†
B(Doxo)	248.5 ±17.7	249.4 ±17.5*	262.3 ±17.9†	273.0 ±18.4†	291.8 ±12.8†	298.8 ±13.7†
C(Oct)	243.6 ±18.9	243.7 ±16.6*	244.4 ±15.9*	243.5 ± 18.5*	242.3 ±18.8*	244.6 ±18.9*
D(Control)	243.8 ±17.6	243.8 ±17.5*	242.9 ±19.8*	246.6 ±17.9*	245.9 ±16.8*	245.4 ±17.8*

QTc0, QTc1, QTc2, QTc3, QTc4, QTc5: Corrected QT intervals at the beginning and after 4mg/kg, 8mg/kg, 12mg/kg, 16mg/kg and 20mg/kg doses of doxorubicin respectively;
Doxo: Doxorubicin; Oct: Octreotide

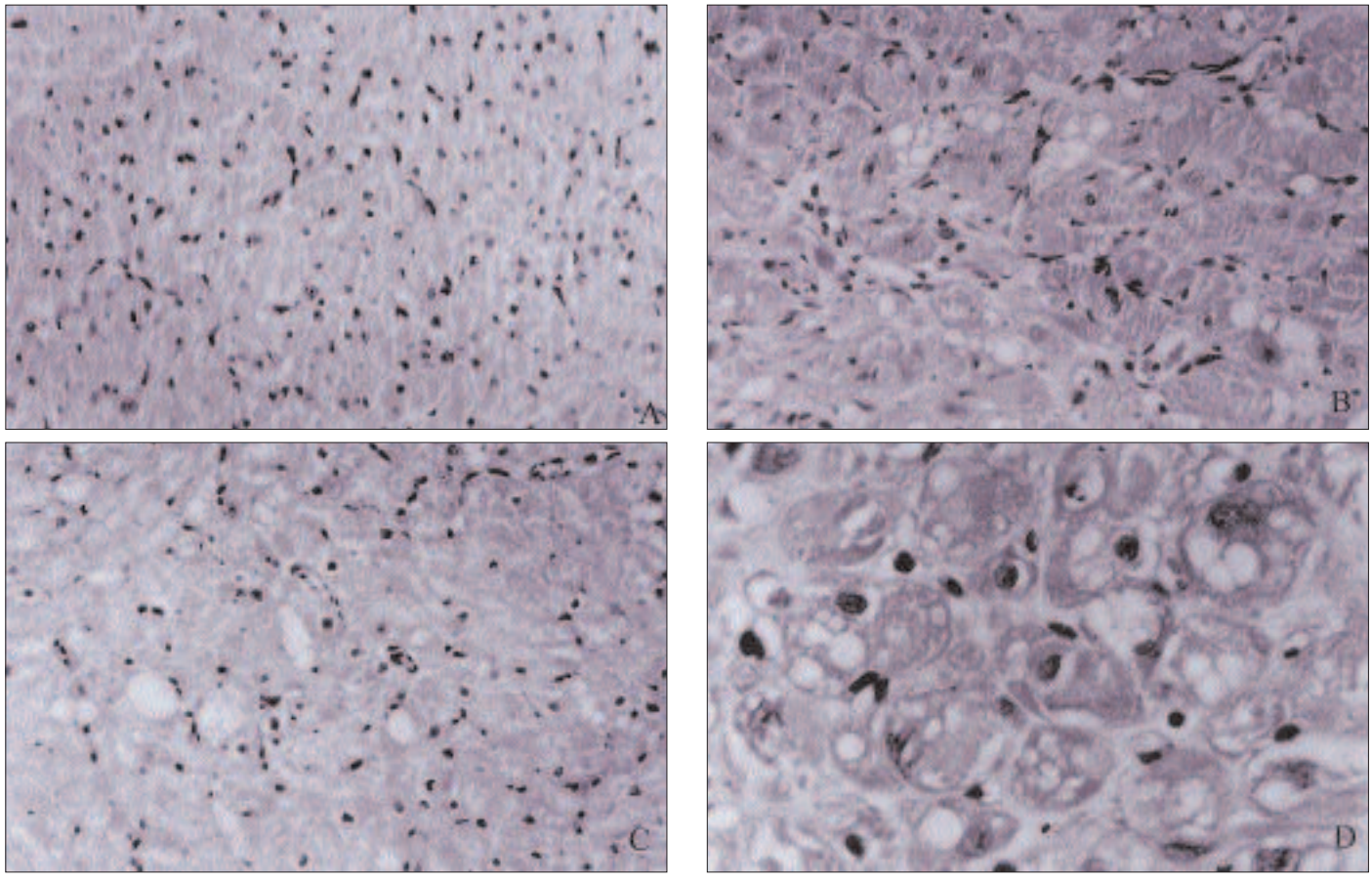

Figure 1. Pictures of specimens obtained from the left ventricle. A- normal histological appearance from an animal in Group C (octreotide only) (H-E stain, X 400); B- a specimen of an animal in Group B (doxorubicin only) with prominent intracellular vacuolization and pale areas indicating myofibrillar loss 4 (H-E stain, X 400); C- a specimen of an animal in Group A (doxorubicin + octreotide) also indicating severe impairment (H-E stain, X 400) D-a more detailed (H-E stain, X 1000) picture of severe impairment of cardiac tissue of an animal in Group B.

QT interval is a measurement of the duration of ventricular repolarization. Jensen et al. (21) showed the impairment of ventricular repolarization early in doxorubicin cardiotoxicity and also suggested that prolongation of QT interval reflects the cardiotoxic effect of this drug. In our study the rate of prolongation of QTc intervals from pretreatment values to the values at the end of the study were 15% in group A and %16.9 in group B, and this difference between the groups was not significant either (p=0.25). Ohmura et al. (15) showed that somatostatin shortens the duration of the action potential in a single atrial cell but in the octreotide group (Group C) no significant change in QTc was observed during the study. Interestingly, in both doxorubicin treated groups the QTc prolongation became significant after 8mg/kg total doxorubicin dose that was early stage of the therapy. Although it is not clear if that QTc prolongation would persist in the long-term after the discontinuation of doxorubicin, this method could be used for detection of patients who are at higher risk for cardiomyopathy development.

Echocardiography is another important tool in the detection of anthracycline cardiotoxicity (22, 23). Bu'Lock et al. (24) demonstrated that regular monitoring of left ventricular FS could identify patients at higher risk of subsequent cardiotoxicity. In our study FS decreased significantly in both Group A and Group B. Although histopathological impairment was severe, the FS decreased at intermediate levels in both groups. This finding was consistent with the earlier histopathological impairment. The rate of fall in FS in Group A was significantly lower than that of Group B ($p<0.001$), which favors the possible protective effect of octreotide.

In our study, evidence of cardiotoxicity was less in Group A than Group B in only echocardiographic examination . It should be emphasized that this difference in FS was small, although significant, and may be considered in the spectrum of intraobserver variability. When we look at the results of our methods together, this study may be concluded as a "negative" study in which octreotide is not efficient in the protection of doxorubicin cardiotoxicity. On the other hand, the consistent tendency of decreased cardiotoxicity in octreotide group with all of these 3 methods should not be ignored. In an animal study by Herman et al. (25) the cumulative dose of doxorubicin was 12-14 mg/kg and the histopathological grades were 3 in all of the dogs with a similar histopathological grading method. In the present study the higher histopathological scores may due to higher cumulative doses of doxorubicin administered to rabbits. One other possible explanation of severe histopathological impairment is the use of most potent cardiotoxic anthracycline doxorubicin. In the study of Polverino et al. (12) in which gallopamil was suggested to have protective effects on anthracycline cardiotoxicity, the anthracycline used was epirubicin, which is less potent than doxorubicin in terms of cardiotoxic effects. Thus, the use of the most potent cardiotoxic anthracycline at high doses might have limited protective effect of octreotide which was significant in histopathological and electrocardiographic examinations.

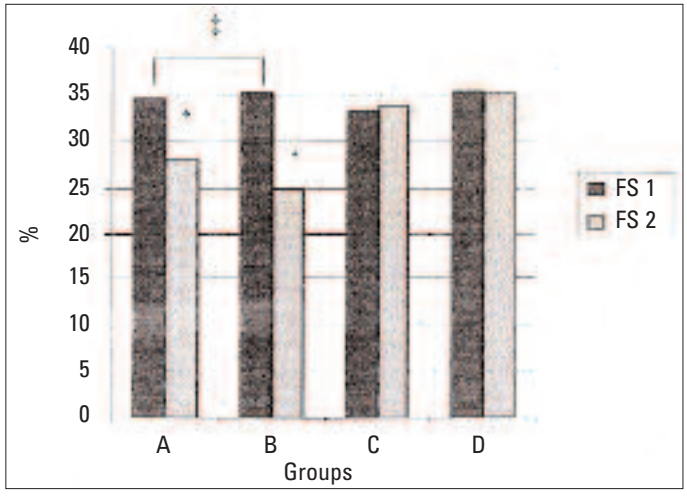

Figure 2. The changes in fractional shortening before (FS1) and after (FS2) treatment in studied groups of animals

FS: fractional shortening, *: the differences in the FS between groups A and B are significant; $p<0.05$,

‡: the difference in the rate of FS decrease between group A and B is significant, $p<0.001$

Limitations

The present study was not designed as a mechanistic investigation. Rather, it focused on description of a phenomenon. This study provides insight to the potential protective effects of octreotide in doxorubicin cardiotoxicity. It is also not clear if octreotide has an effect on the oncologic efficacy of doxorubicin. The current study should be considered as a preliminary investigation.

Conclusion

In the small group of animals included in this study, octreotide seems not to have a serious protective effect against doxorubicin cardiotoxicity. On the other hand, a consistent tendency of decreased cardiotoxicity with octreotide was observed with 3 different evaluation methods we used, although only decrease in FS was significant. Future investigations carried out on larger groups and in different animal models are needed to address the issue of the extent and the mechanisms of this effect as well as the mechanisms of doxorubicin cardiotoxicity.

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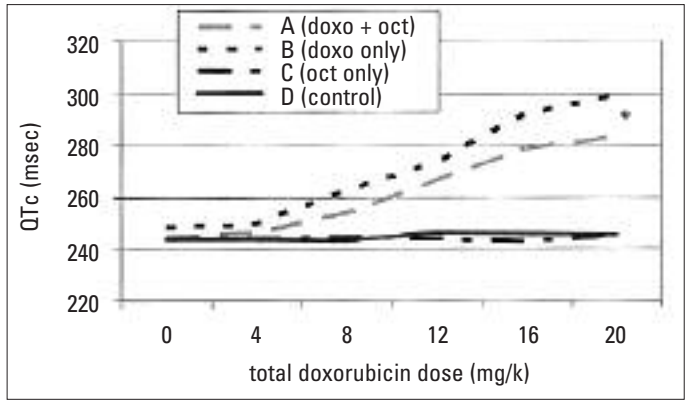

Figure 3. Mean QTc intervals measured at the beginning and at every two weeks of increments in doxorubicin dose.

*The difference between the rate of QTc prolongation from baseline to the end of the study of Group A was not different significantly from that of Group B (p=0.25)
Doxo: doxorubicin; oct:octreotide; QTc: Corrected QT interval

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