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ORIGINAL ARTICLE

Paola Della Torre · Guy Mazué · Arturo Podestà
Donatella Moneta · Umberto Sammartini
Anthony R. Imondi

Protection against doxorubicin-induced cardiotoxicity in weanling rats by dexrazoxane

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Abstract *Purpose*: Dexrazoxane (DZR) protects against anthracycline-induced cardiotoxicity in several laboratory animal species and in patients with breast cancer. Encouraging results have also been obtained in a limited number of pediatric oncology patients. We conducted studies to determine the safety and cardioprotective activity of DZR in the doxorubicin (DOX)-treated weanling rat simulating the rapidly growing immature child. *Methods*: Male weanling rats and young adult rats, 20 days old and 7 weeks old, respectively, were given 1 mg/kg DOX i.v., either alone or with 20 mg/kg DZR, once weekly for 7 weeks. Rats were sacrificed at weeks 8, 12 or 26 following blood collection for hematology and serum chemistry. Hearts were weighed and examined histologically. *Results*: DOX, either alone or with DZR, inhibited growth, and body weight remained below that of controls throughout the 26 weeks of study. There were no biologically significant hematologic changes in either the DOX- or DZR + DOX-treated young rats. DOX caused a slight increase in liver and kidney weights relative to body weight and a slight increase in serum cholesterol and triglycerides in the young rats. These effects were ameliorated or delayed by DZR. DOX, either alone or with DZR, caused a marked atrophy of the testes in the young rats which had recovered by week 26. In the mature rats, DOX caused a significant decrease in the WBC 1 week after the last treatment, and the WBC was significantly lower in the rats given DZR + DOX compared to those given DOX alone. There were marked increases in liver and kidney weight, serum cholesterol and triglycerides in the mature rats given DOX alone but not in those given DZR + DOX. There was also a marked testicular atrophy in the mature rats given either DOX or DZR + DOX but, unlike that observed in the young rats, this had not returned to normal by week 26. DOX-induced cardiotoxicity was less severe in the younger rats than in the mature rats but in both age groups, the lesion progressed rapidly until week 12, 5 weeks after the last dose, and remained relatively stable or progressed slightly thereafter. DZR provided significant cardioprotection in both age groups at all time points examined. Moreover, in both age groups, the severity of the cardiomyopathy in the DZR-treated rats was somewhat less at week 26 than it was at week 12. *Conclusions*: The results indicate that the pharmacologic effects of DZR, including its ability to protect against cardiotoxicity, are similar in immature and adult male animals treated with DOX.

Key words Dexrazoxane · Doxorubicin · Cardiotoxicity

P. Della Torre · G. Mazué · A. Podestà · D. Moneta · U. Sammartini
Worldwide Toxicology, Pharmacia & Upjohn, 20014 Nerviano (MI), Italy

A.R. Imondi (✉)
Pharmaceutical Product Development Division, Battelle Memorial Institute, 505 King Avenue, Columbus, Ohio 43201-2693, USA
Tel.: +1-614-424-7131; Fax: +1-614-424-3716

Introduction

Doxorubicin (DOX) is an important antineoplastic drug in pediatric oncology, but its use has been limited by its propensity to cause cardiotoxicity. Recently, the significance of this side effect in children has received greater emphasis with the recognition that anthracycline cardiotoxicity may not be evident for several years after completing anthracycline therapy [6, 13]. Therefore, a safe and effective drug for the prevention of anthracycline-induced cardiotoxicity in children could play an important role in the treatment of anthracycline-responsive childhood cancers.

Dexrazoxane (DZR), also referred to as ICRF-187 or ADR 529, is an intracellular chelator which protects against doxorubicin-induced cardiotoxicity in patients with breast cancer [12, 14, 15]. Wexler et al. [16] have reported that DZR ameliorates cardiotoxicity in children undergoing doxorubicin therapy for sarcoma, and a preliminary report by Schuler et al. [10] indicates that

DZR is well tolerated and does not interfere with the antineoplastic activity of anthracyclines in children with acute lymphoid leukemia (ALL). Although the ability of DZR to protect against latent cardiotoxicity in pediatric patients remains to be determined, reports such as these are likely to generate additional interest in the use of DZR with anthracycline-containing regimens for pediatric malignancies.

Prior to the initiation of clinical trials, several studies were carried out on DZR in adult laboratory animals treated with anthracyclines to determine its safety and efficacy [2, 3, 5, 8]. The results of these studies demonstrated that DZR is cardioprotective and well tolerated in several animal species. However, there have not been, to our knowledge, any studies on the safety and efficacy of DZR in combination with anthracyclines in rapidly developing young animals. Since children are more sensitive than adults to the cardiotoxic effects of anthracyclines [6] and because there is a growing interest in the use of DZR in pediatric oncology, we conducted a study to evaluate the safety and cardioprotective activity of DZR in weanling rats given DOX. Young adult male rats were also included in the study. The 20:1 dose ratio of DZR to DOX which was used in the reported pediatric sarcoma [16] and ALL [10] studies was used in this experiment.

Materials and methods

Chemicals

DZR and DOX were manufactured by Pharmacia (now Pharmacia and Upjohn; Milan, Italy). DZR was provided as the lyophilized HCl salt and was reconstituted in M/6 sodium lactate. DOX was provided as Adriablastina PFS formulation.

Animals and experimental design

All animal experimentation was conducted in strict compliance with EU and Italian Guidelines for Laboratory Animal Welfare. Young and mature male Sprague Dawley [CrL:CD(SD)BR] rats were obtained from Charles River, Italy. They were housed in groups of two in cages with sawdust bedding in a room with controlled temperature (21 ± 1.5 °C) and humidity (55 ± 15%) and a 12-h light/dark schedule. They were allowed free access to water and 4RF21 GLP pelletted food supplied by Mucedola S.r.l. (Milan, Italy). At the time of the first treatment young animals were 20 days of age and weighed 37–64 g whilst the mature rats were 49 days of age and weighed 204–247 g. Young rats were assigned randomly (24 per group) to one of three groups: control (sodium lactate vehicle + saline), DOX (sodium lactate vehicle + 1 mg/kg DOX), and DZR + DOX (20 mg/kg DZR + 1 mg/kg DOX). The DZR or sodium lactate vehicle was administered 30 min before the DOX or saline. The same experimental and treatment design was used for three groups of 24 mature rats. All doses were given by slow i.v. injection into a tail vein once weekly for 7 consecutive weeks. The first eight survivors per group were killed at weeks 8, 12 and 26 after the first treatment by exsanguination from the abdominal aorta under complete i.p. sodium thiopental anesthesia.

Investigations

Mortality and general condition were observed and individual body weights were recorded. Blood samples were collected for hematology and clinical chemistry. Post mortem examination included necropsies and organ weights of the heart, kidneys, testes and liver. The hearts, quickly removed and fixed in 4% buffered paraformaldehyde, were appropriately dehydrated in ethanol, infiltrated and embedded in methacrylate. Sections (1 μm) were examined microscopically after staining with alkaline toluidine blue. The histopathological evaluation of the hearts was performed using a scoring system described by Solcia et al. [11] in which the cardiomyopathy is expressed as a product of the severity and the extent of the damage. Severity (S) was defined as: *grade 1*, sarcoplasmic microvacuolations and/or inclusions, cellular edema or interstitial edema; and *grade 2*, as grade 1 plus sarcoplasmic macrovacuolations or atrophy, necrosis, fibrosis, endocardial lesions and thrombi. Extent (E) was defined as: *grade 0.5*, fewer than ten altered myocytes; *grade 1*, single altered myocytes; *grade 2*, scattered small groups of altered myocytes; *grade 3*, several small groups of altered myocytes; *grade 4*, groups of altered and confluent myocytes; and *grade 5*, most myocytes affected. The mean total score (MTS) for each group is $\sum(S \times E)$/number of animals.

Statistical analysis

Mean body weight, hematology and clinical chemistry data were analyzed by Bartlett's test for homogeneity of variance, Fisher's and Dunnett's tests for homogeneous data and the Cochran and Cox test for nonhomogeneous data. Relative organ weights (as percentage of body weight) in treated groups were compared with those of the control groups using Student's *t*-test.

The cardiotoxicity data were analyzed using the Kruskall Wallis test, followed by the Dunn one-tailed multiple comparison test to compare the MTS of treated groups with that of the control group and of the DZR + DOX groups with that of the DOX groups, within the same age group and time period.

Results

Toxicity

There were no deaths or treatment-related effects on physical appearance in the younger rats during the 26-week study period. Five of the mature rats which received DOX alone died between weeks 16 and 25, probably due to severe cardiotoxicity and/or nephrotoxicity.

Growth was inhibited in all rats that had received DOX alone and their body weight remained significantly ($P < 0.05$) below that of the controls throughout the 26 weeks of study (Fig. 1). DZR had no effect on the DOX-induced inhibition of growth.

There were no meaningful changes in hematologic parameters in the younger rats (Table 1). There were no clinically important hematologic effects in the older rats, but when compared with the controls, there was a decrease in WBC in older DOX-treated rats at week 8 ($P < 0.05$) that was more pronounced in the DZR + DOX treatment group ($P < 0.01$). The difference in WBC between the DOX and the DZR + DOX groups was highly significant ($P < 0.01$). There was also a slight but statistically significant ($P < 0.01$) anemia throughout the 26 weeks of study in the older rats treated with DOX alone, but this was not observed in the DZR + DOX treatment group after the 8-week observation period.

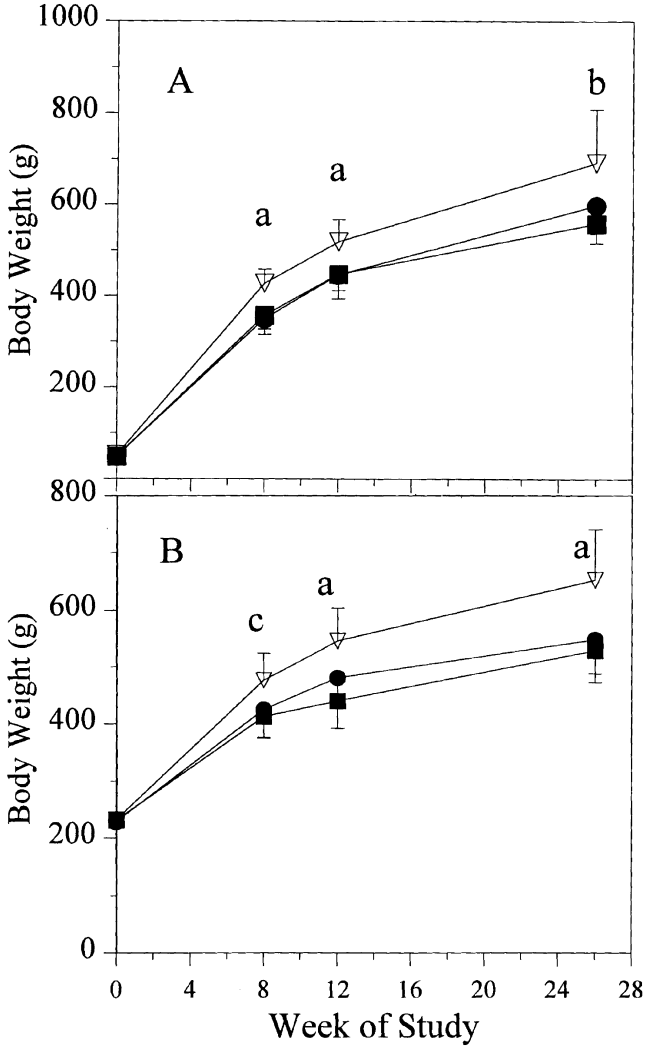

Fig. 1A,B Effect of DZR on the growth of DOX-treated rats; **A** weanling rats, **B** mature rats (▽ vehicle control, ■ DOX alone, ● DZR + DOX). Points are means of 24, 24, 16 and 8 rats at 0, 8, 12 and 26 weeks, respectively, except $n = 3$ for DOX at week 26 in B. Vertical bars are SD. *a* $P < 0.05$ compared to DOX and DZR + DOX, *b* $P < 0.05$ compared to DOX; *c* $P < 0.05$ compared to DZR + DOX

Mean serum cholesterol was elevated by week 26 in the young rats ($P < 0.01$) and by week 8 in the older rats given DOX alone (Table 2). Mean serum triglycerides tended to increase during the 26 weeks in the young rats given DOX alone but in the older rats, the increase was highly significant ($P < 0.01$) by week 8 (Table 2). The hyperlipidemia in both age groups was associated with increases in relative liver and kidney weights. In the young rats, the increase in relative organ weights was not statistically significant until week 26 when the relative liver weight was increased by 13% ($P < 0.05$) and the relative kidney weight by 20% ($P < 0.01$). In the older rats, the relative liver and kidney weights had increased by 20% ($P < 0.01$) and 29% ($P < 0.01$), respectively, by week 8. In both age groups, DZR prevented or delayed the onset of the hyperlipidemia (Table 2) and the increase in liver and kidney weights.

Relative testicular weights in the young rats treated with DOX were significantly below those of the controls through week 12 and were not affected by DZR treatment (Table 3). However, by week 26, the relative testicular weights in the young rats given either DOX or DZR + DOX had recovered completely. In the older rats, relative testicular weights were significantly reduced in both the DOX and DZR + DOX groups ($P < 0.01$), but, unlike that in the younger rats, the atrophy persisted throughout the 26 weeks of study.

Cardiotoxicity

There were no significant treatment-related effects on relative heart weight. In the younger rats, the mean relative heart weights ranged from 0.37% to 0.41% at week 8 to 0.30% to 0.31% at week 26. The corresponding ranges in the older rats were 0.35% to 0.36% at week 8 and 0.31% to 0.36% at week 26. The incidence of measurable cardiomyopathy was 100% in all treatment groups and at all time points except at week 8 when it was 50% in the young rats that had received DZR + DOX (Table 4). Histologically, the lesions in the young rats were similar to those in the older rats and included vacuolar degeneration of the myocytes (sarcoplasmic micro- and macrovacuolations) with a focal

Table 1 Hematological effects of DOX with and without DZR in young and mature male rats (values are means ± SD, $n = 8$ except as otherwise indicated in parentheses)

Age group	Treatment[a]	Red blood cells ($\times 10^3/mm^3$) Week			White blood cells ($\times 10^3/mm^3$) Week		
		8	12	26	8	12	26
Young	Control	7.84 ± 0.37	8.0 ± 0.5	8.8 ± 0.3	10.6 ± 1.73	10.5 ± 2.9	9.9 ± 1.3
	DOX	7.83 ± 0.17	8.1 ± 0.3	8.3 ± 0.3 ($n = 7$)*[1]	10.2 ± 3.10	10.6 ± 2.1	10.8 ± 2.0 ($n = 7$)
	DZR + DOX	7.80 ± 0.42	7.9 ± 0.4	8.8 ± 0.4	8.2 ± 1.86	11.8 ± 4.3	10.4 ± 2.1
Mature	Control	8.4 ± 0.6	8.4 ± 0.3	9.0 ± 0.7	17.1 ± 6.0	11.3 ± 1.2	11.9 ± 4.7
	DOX	7.4 ± 0.4*[2]	7.3 ± 0.7*[2]	7.0 ± 0.8 ($n = 3$)*[2]	11.3 ± 1.7*[1]	9.7 ± 2.8	13.8 ± 4.5 ($n = 3$)
	DZR + DOX	7.6 ± 0.3*[2]	8.0 ± 0.4	8.5 ± 0.5	8.2 ± 1.7*[2,*3]	10.3 ± 2.2	11.6 ± 3.3

*[1] $P < 0.05$, *[2] $P < 0.01$ vs control of same age, *[3] $P < 0.01$ vs DOX of same age
[a] DOX 1 mg/kg i.v. weekly, weeks 1–7; DZR 20 mg/kg, i.v., 30 min before DOX

Table 2 Serum cholesterol and triglycerides in young and mature male rats treated with DOX with or without DZR (values are means ± SD, $n = 8$ except as otherwise indicated in parentheses)

Age group	Treatment[a]	Cholesterol (mg/dl) Week			Triglycerides (mg/dl) Week		
		8	12	26	8	12	26
Young	Control	56 ± 10	65 ± 12	79 ± 20	62 ± 20	67 ± 18	95 ± 37
	DOX	62 ± 16	104 ± 50	124 ± 29**	69 ± 33	124 ± 84	177 ± 122
	DZR + DOX	61 ± 14	74 ± 22	111 ± 34	62 ± 28	107 ± 69	287 ± 286
Mature	Control	56 ± 10	65 ± 12	79 ± 20	62 ± 20	67 ± 18	95 ± 37
	DOX	193 ± 73**	272 ± 103**	242 ± 63 ($n = 3$)*	204 ± 112**	322 ± 183**	264 ± 106 ($n = 3$)**
	DZR + DOX	80 ± 17**	103 ± 36*	124 ± 58	63 ± 22	109 ± 63	137 ± 85

*$P < 0.05$, **$P < 0.01$ vs control of same age
[a] DOX 1 mg/kg i.v. weekly, weeks 1–7; DZR 20 mg/kg i.v., 30 min before DOX

Table 3 Effect of DZR on relative weight of testes in young and mature rats treated with DOX (values are means ± SD testes weight as percentage of body weight, $n = 8$ except as otherwise indicated in parentheses

Age group	Treatment[a]	Week of study		
		8	12	26
Young	Control	0.81 ± 0.09	0.73 ± 0.03	0.54 ± 0.10
	DOX	0.54 ± 0.08*	0.33 ± 0.06*	0.59 ± 0.05
	DZR + DOX	0.55 ± 0.06*	0.38 ± 0.06*	0.53 ± 0.06
Mature	Control	0.83 ± 0.09	0.70 ± 0.07	0.60 ± 0.05
	DOX	0.37 ± 0.04*	0.29 ± 0.04*	0.29 ± 0.06 ($n = 3$)*
	DZR + DOX	0.35 ± 0.03*	0.29 ± 0.06*	0.28 ± 0.18*

* $P < 0.01$ compared to control of same age
[a] DOX 1 mg/kg i.v. weekly, weeks 1–7; DZR 20 mg/kg i.v., 30 minutes before DOX

Table 4 Effect of DZR on DOX-induced cardiomyopathy in young and mature rats

Age group	Treatment[a]	Week of study					
		8		12		26	
		D/E[b]	MTS[c]	D/E[b]	MTS[c]	D/E[b]	MTS[c]
Young	Control	0/8	0	0/8	0	0/8	0
	DOX	8/8	2.1*[2]	8/8	3.8*[2]	8/8	3.8*[2]
	DZR + DOX	4/8	0.6*[4]	8/8	1.8*[1,*3]	7/7	1.3*[4]
Mature	Control	0/8	0	0/8	0	0/8	0
	DOX	8/8	3.5*[2]	8/8	6.5*[2]	3/3	7.3*[2]
	DZR + DOX	8/8	2.0*[2,*3]	8/8	2.8*[1,*4]	7/7	1.6*[2,*4]

*[1] $P < 0.05$, *[2] $P < 0.01$ vs control of same age; *[3] $P < 0.05$, *[4] $P < 0.01$ vs DOX of same age
[a] DOX 1 mg/kg weekly weeks 1–7; DZR 20 mg/kg, 30 minutes before DOX
[b] Damaged hearts/examined hearts
[c] Mean total score of cardiac lesions

distribution (Fig. 2). The lesions were more prominent in the left ventricle and interventricular septum. In both age groups, the cardiac lesions were more severe at 12 and 26 weeks than at week 8. Also, the MTS at each observation period was about 1.5- to 2-fold higher in the older rats than in the younger rats.

The cardiomyopathy in rats given DZR + DOX was histologically similar to that in the rats treated with DOX alone, but the MTS was significantly reduced ($P < 0.01$) by DZR in both age groups and at all observation points. The magnitude of the decrease in the MTS by DZR was 71%, 53% and 66% in the young rats and 43%, 57% and 78% in the older rats at weeks 8, 12 and 26, respectively.

Discussion

Children less than 4 years old are at an increased risk for cardiotoxicity induced by anthracyclines compared to

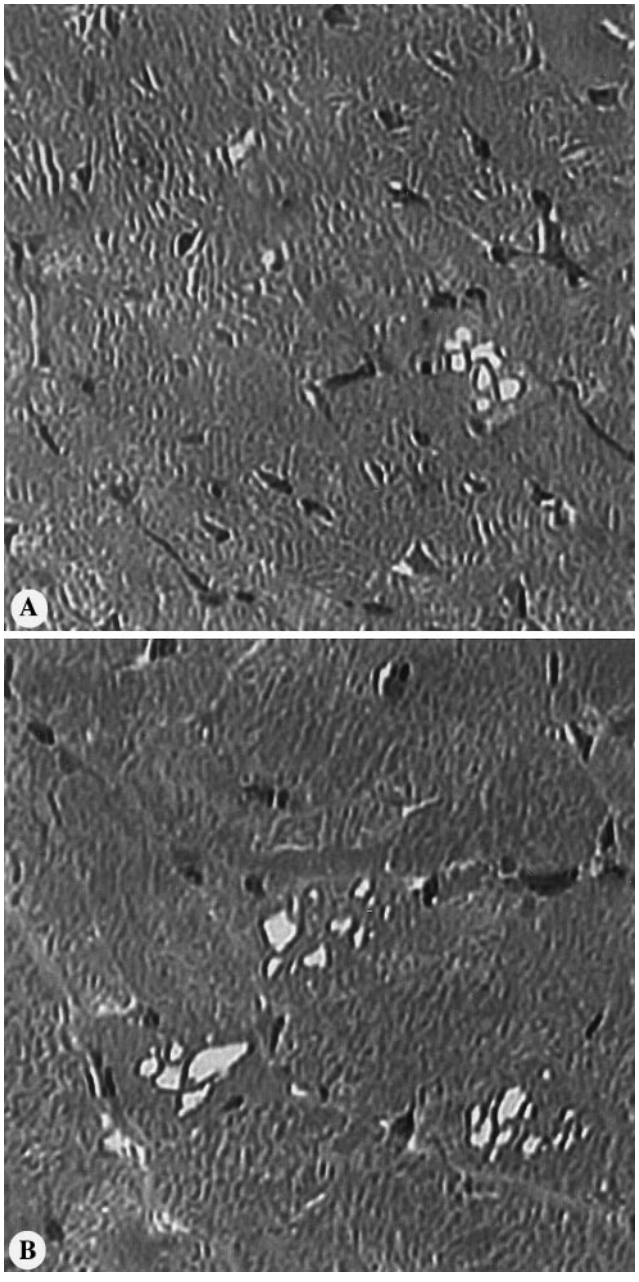

Fig. 2A,B Photomicrographs of myocardium from rats given DOX showing severity grade 2 sarcoplasmic micro- and macrovacuolations. **A** Extent grade 1 (scattered single altered myocytes) with an overall score of 2; **B** extent grade 2 (scattered small groups of altered myocytes) and an overall score of 4 (40×)

older children and adults [6]. In the present study, the severity and extent of the cardiomyopathy in the mature rats was 1.5 to 2 times higher than that in the younger rats. The reason why DOX-induced cardiotoxicity was less severe in young rats than in the mature rats is not entirely clear, but this difference may have been due, at least in part, to the lower total cumulative dose of DOX in the younger rats when expressed in terms of body surface area, i.e. 43.7 mg/m^2 in the younger rats and 53.8 mg/m^2 in the older rats. Although the difference in cumulative dose was only 23%, the more severe cardiomyopathy in the older rats is consistent with the steep dose-response relationship for cardiotoxicity observed in DOX-treated mice by Bertazzoli et al. [1].

The mechanism by which DZR exerts its cardioprotective effect is not completely understood. However, the similarities in the histological appearance of the lesions and in the nature of the response to DZR, suggest that the mechanism is similar in young and adult animals. In addition, the development of the cardiomyopathy in the young and adult rats was similar, that is, with DOX alone, the lesion progressed in severity until week 12, 5 weeks after the last dose, and then remained stable. When DZR was given with the DOX, the cardiomyopathy in both age groups progressed until week 12 and then underwent partial reversal. Reversal of anthracycline-induced cardiomyopathy by DZR has been reported in rabbits treated with daunorubicin [4] and in rats given either DOX or epirubicin [2].

Lipshultz et al. [6] have suggested that the higher risk of anthracycline-induced cardiotoxicity in children may be related to inhibition of myocardial growth by anthracyclines. Results from the present study indicate that DOX did not selectively inhibit growth of the heart in either the younger or older rats since the relative heart weight remained relatively constant in both age groups regardless of treatment. However, it is possible that wet heart weight per se is not sensitive enough to detect effects on the growth or development of some cardiac tissue component important for cardiac function.

Anthracyclines cause testicular atrophy with tubular atrophy and hypospermatogenesis in rats [7]. In the immature rats in the present study, DOX caused a marked atrophy of the testes which was not affected by treatment with DZR. The effect persisted at least until week 12, after which growth of the testes resumed and were comparable in size to those of the controls at week 26. In the older rats, DOX also caused atrophy of the testes which was not affected by treatment with DZR. However, in contrast to the findings in the younger rats, the atrophic testes in the older rats did not recover during the 26-week study period. These results suggest an important difference in the long-term effects on the testes by DOX that has also been reported in humans undergoing cancer chemotherapy [9], that is, DOX treatment in prepubescent males may be less detrimental than it is in young adults.

In conclusion, DZR, at a dose ratio of 20:1, was cardioprotective in both immature and mature male rats treated with DOX, weekly for 7 weeks. The cardioprotective effect of DZR was present for at least 4 months after cessation of treatment. DZR did not exacerbate the toxic effects caused by DOX in either the young or mature rats and delayed or prevented DOX-induced liver and kidney toxicity in both age groups. These results suggest that the pharmacologic effects of DZR are similar in immature and mature male animals treated with DOX.

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