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Abstract

Protective effects of clinically used drugs against adriamycin (ADM)-induced toxicity were studied in ICR mice. The control mice, which were administered 15 mg/kg of ADM twice, survived 7.48 +/- 1.99 days (mean +/- S.D.). The survival times of mice treated with the following drugs, expressed as a percent of that of the control group, were 293.6% for coenzyme Q10 (Co Q10, 2 mg/kg), 402.2% for dextran sulfate (MDS, 300 mg/kg), 121.6% for flavin adenine dinucleotide (20 mg/kg), 236.3% for adenosine triphosphate disodium (50 mg/kg), 213.7% for reduced glutathione (100 mg/kg), 121.6% for phytonadione (50 mg/kg), 155.2% for inositol nicotinate (Ino-N, 500 mg/kg), 335.5% for nicomol (1000 mg/kg), 157.5% for nicardipine (10 mg/kg) and 123.3% for dipyridamol (50 mg/kg). Anti-hyperlipemic agents such as MDS, nicomol, Ino-N and Co Q10 strongly protected against the ADM-induced toxicity, and the mice administered these drugs lived significantly longer than the control mice. The mechanism of the protective effect was discussed.

KEYWORDS: adriamycin-toxicity, survival time, protective effect, coenzyme Q10, dextran sulfate, nicomol, inositol nicotinate

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Protection against Adriamycin (Doxorubicin)-Induced Toxicity in Mice by Several Clinically Used Drugs

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Protective effects of clinically used drugs against adriamycin (ADM)-induced toxicity were studied in ICR mice. The control mice, which were administered 15 mg/kg of ADM twice, survived 7.48±1.99 days (mean±S.D.). The survival times of mice treated with the following drugs, expressed as a percent of that of the control group, were 293.6% for coenzyme Q_{10} (Co Q_{10}, 2 mg/kg), 402.2% for dextran sulfate (MDS, 300 mg/kg), 121.6% for flavin adenine dinucleotide (20 mg/kg), 236.3% for adenosine triphosphate disodium (50 mg/kg), 213.7% for reduced glutathione (100 mg/kg), 121.6% for phytonadione (50 mg/kg), 155.2% for inositol nicotinate (Ino-N, 500 mg/kg), 335.5% for nicomol (1000 mg/kg), 157.5% for nicardipine (10 mg/kg) and 123.3% for dipyridamol (50 mg/kg). Anti-hyperlipemic agents such as MDS, nicomol, Ino-N and Co Q_{10} strongly protected against the ADM-induced toxicity, and the mice administered these drugs lived significantly longer than the control mice. The mechanism of the protective effect was discussed.

Key words : adriamycin-toxicity, survival time, protective effect, coenzyme Q_{10}, dextran sulfate, nicomol, inositol nicotinate

Adriamycin (ADM), an anthracycline antibiotic, has shown a marked activity against a wide range of human neoplasms, but its clinical use has been limited because of the risk of severe dose-dependent cardiotoxicity (1, 2). The mechanisms of ADM-induced cardiotoxicity have been reported to be inhibition of mitochondrial functions (3-5), interference with DNA-directed DNA or RNA synthesis (6-8), inhibition of membrane Na^+-K^+-ATPase (9), calcium accumulation in the myocardium (10), and the production of lipid peroxides due to membrane damage (11). However, the precise mechanism is not completely understood.

In order to reduce ADM-induced toxicity, the use of the following drugs has been reported: coenzyme Q_{10} (4, 12-17), α-tocopherol (18, 19), selenium (20), digoxin (21), sulfhydryl groups (22), EDTA (23, 24), dextran sulfate (25), and radical scavengers (24). In the present study, we examined the effects of drugs used clinically for the treatment of ADM-induced toxicity.

Materials and Methods

Animals. Five-week-old male ICR mice weighing between 25 and 30g were used in all experiments. They were fed a standard rat and mouse chow diet (Oriental Yeast Co., Ltd. Tokyo) and housed in plastic cages on an automatically maintained 12-h light-dark-cycle. Food and water were provided *ad libitum*.

Chemicals. Adriamycin hydrochloride was purchased from Kyowa Hakko Kogyo Co., Ltd. (Tokyo). Coenzyme Q_{10} (Co Q_{10} powder) and injectable Co Q_{10} (Co Q_{10} E-0216-019, containing 1.8 mg phospholipid, 30 mg polyglycol and 45 mg sorbitol/ml of citrate buffer, pH 7.4) were kindly donated by Eisai Co., Ltd. (Tokyo). Dextran sulfate (Medical Dextran Sulfate, MDS) was kindly donated by Kowa Shinyaku Co., Ltd. (Nagoya). Flavin adenine dinucleotide (FAD) was purchased from Tanabe Seiyaku Co., Ltd. (Osaka), adenosine triphosphate disodium (ATP) from Kowa Shinyaku Co., Ltd. (Nagoya), panthethine from Daiichi Seiyaku Co., Ltd. (Tokyo), cytochrome C (Cyt-C) from Meiji Seika Co., Ltd. (Tokyo), ascorbic acid (VC) from Fuso Pharmaceutical Ind., Ltd. (Osaka), edetate sodium calcium (EDTA) from Nissin Pharmaceutical Co., Ltd. (Yamagata), 1, 3-dimethylurea (DMU) from Nakarai Chemicals Co., Ltd. (Kyoto), reduced glutathione (GSH) from Yamanouchi Pharmaceutical Co., Ltd. (Tokyo), tiopronin from Santen Pharmaceutical Co., Ltd. (Osaka), phytonadion (VK1) and menatetrenone (VK2) from Eisai Co., Ltd. (Tokyo), clofibrate from Sumitomo Chemical Co., Ltd. (Osaka), inositol nicotinate (Ino-N) from Yoshitomi Pharmaceutical Ind. Co., Ltd. (Osaka), nicomol from Kyorin Pharmaceutical Co., Ltd. (Tokyo), nicardipine and dipyridamole from Yamanouchi Pharmaceutical Co., Ltd. (Tokyo), diltiazem from Tanabe Seiyaku Co., Ltd. (Osaka), nifedipine from Takeda Chem. Ind. Co., Ltd. (Osaka), verapamil from Eisai Co., Ltd. (Tokyo), pindolol from Sankyo Co., Ltd. (Tokyo), disopyramide from Roussel Medica Co., Ltd. (Tokyo), and propranolol from Sumitomo Chemical Co., Ltd. (Osaka).

Experimental design. All mice were injected intraperitoneally with ADM at a dose of 15 mg/kg on days 0 and 4 (day 0=day of first ADM administration). In the drug-treated groups, the drug to be tested was administered from day -3 to day 6 once a day. The test drug was given 2 h before ADM administration on days 0 and 4. For some drugs, the same experiment was repeated in different seasons, Exp. 1, Exp. 2 and Exp. 3, in consideration of the bio-rhythm in ADM-induced toxicity. In the control group, saline was administered instead of the drugs. All drugs tested by oral administration (p.o.) were suspended in 0.5% carboxymethyl cellulose solution (CMC sol.). Injectable drugs were dissolved in sterilized saline or distilled water and administered intraperitoneally (i.p.) or subcutaneously (s.c.).

Statistics. Survival times were expressed as the mean±S.D. Significance of the differences between means was determined by Student's t test.

Results

After an intraperitoneal injection of 15 mg/kg of ADM on days 0 and 4, the control mice survived for 5.5 - 20.0 days (7.48 ± 1.99, N=54). In this group, no mouse survived more than 30 days. Table 1 shows the effect of Co Q_{10} on the survival time of ADM-administered mice. All groups treated p.o. with Co Q_{10} (CMC sol.) showed a significantly longer survival time than the control group. Mice of the group treated with 10 mg/kg of Co Q_{10} (CMC sol.) survived for the longest period (16.8±10.3 days) of all the mice studied, and the survival time was significantly longer in this group than in the control group ($p<0.01$). Most of the groups treated p.o. or s.c. with Co Q_{10} (E-0216-019), except the group treated p.o. with 2 mg/kg of the drug, showed a significantly longer survival time than the control group.

Table 2 shows the effect of MDS on the survival time of ADM-administered mice. In all groups treated p.o. with MDS, survival times were not significantly different from the survival time of the control group. However, most of the groups treated s.c. with MDS, except the group receiving 20 mg/kg of the drug, showed a significantly longer survival time than the control group. The group treated s.c. with 300 mg/kg of MDS survived the longest (28.6±3.1) of all the mice studied and survived significantly longer than the control group ($p<0.01$). Four of five mice in this group survived for more than 30 days.

Table 3 shows the effect of various protectors on the survival time of ADM-administered mice. The groups treated with FAD

Table 1 Effect of Co Q_{10} on the Survival Time of ADM-Administered Mice[a]

Protectors	Experiments	Dose (mg/kg)	Route	Survival time		30-day survivors
				Days (mean±S.D.)	% (T/C)	
Co Q_{10}	Exp. 1	2	p.o.	15.4±10.7***	205.9	6/22
(CMC sol.)	Exp. 2	2	p.o.	13.8±11.2**	293.6	3/10
		10	p.o.	16.8±10.3***	224.7	6/22
		50	p.o.	9.5±3.9**	126.3	0/11
Co Q_{10}[b]		2	p.o.	7.9±3.1	105.6	0/10
(E-0216-019)		2	s.c.	10.0±6.1**	133.7	0/10
		10	p.o.	14.8±9.7***	198.1	2/11
		10	s.c.	11.6±8.3***	155.1	1/20
		50	p.o.	11.3±6.7***	151.1	2/16
		50	s.c.	12.3±9.7***	164.6	2/16

a: All mice were injected intraperitoneally with 15 mg/kg of ADM on days 0 and 4 (day 0=day of first ADM administration). In the drug-treated groups, the drug to be tested was administered from day -3 to 6 once a day. The test drug was given 2 h before ADM administration on day 0 and 4. In the control group, saline was administered instead of the drugs.

b: Injectable Co Q_{10} containing 1.8 mg phospholipid, 30 mg polyglycol and 45 mg sorbitol/ml of citrate buffer (pH 7.4).

The values with asterisks are significantly different from the values obtained in the control group (**$p<0.02$, ***$p<0.01$).

Table 2 Effect of MDS on the Survival Time of ADM-Administered Mice[a]

Experiments	Dose (mg/kg)	Route	Survival time[b]		30-day survivors
			Days (mean±S.D.)	% (T/C)	
	20	p.o.	10.5±5.7	144.3	0/11
	60	p.o.	8.8±4.8	118.4	0/11
	100	p.o.	13.6±11.6	178.9	3/10
Exp. 1	300	p.o.	11.4±7.5	150.5	0/9
Exp. 2	300	p.o.	10.6±8.4	139.5	1/10
	600	p.o.	7.7±1.8	106.9	0/10
	1500	p.o.	7.2±1.9	94.7	0/10
	20	s.c.	10.5±7.1	143.2	1/11
Exp. 1	60	s.c.	14.6±10.1*	200.5	2/11
Exp. 2	60	s.c.	16.7±8.3***	219.7	2/10
Exp. 1	100	s.c.	15.4±9.8*	202.6	2/10
Exp. 2	100	s.c.	7.4±1.4***	148.9	0/10
Exp. 1	300	s.c.	28.6±3.1***	402.2	4/5
Exp. 2	300	s.c.	15.6±11.2*	205.2	3/10
Exp. 3	300	s.c.	17.2±9.4***	235.2	2/11
	600	s.c.	10.1±2.3***	140.3	0/10
	1500	s.c.	10.8±7.9***	142.1	1/10

a: Experimental design represented in this Table is the same as in Table 1.

b: The values with asterisks are significantly different from the values obtained in the control group (*$p<0.05$, ***$p<0.01$).

(20 mg/kg, s.c.), ATP (50 mg/kg, i.p.), GSH (100 mg/kg, i.p. and 250 mg/kg, s.c.), VK1 (50 mg/kg, s.c.), Ino-N (500 mg/kg, p.o.) and nicomol (200 and 1000 mg/kg, p.o.) showed a significantly longer survival time than the control group. All the groups treated p.o. with 200 mg/kg of nicomol survived significantly longer than the control groups.

Table 3 Effect of Various Protectors on the Survival Time of ADM-Administered Mice[a]

Protectors	Dose (mg/kg)	Route	Survival time[b]		30-day survivors
			Days (mean±S.D.)	% (T/C)	
FAD	4	p.o.	6.0±2.8	78.9	0/11
	20	p.o.	9.2±8.6	120.8	1/11
	20	s.c.	9.4±2.9**	121.6	0/5
	20	i.p.	5.2±0.6	82.3	0/11
ATP	50	i.p.	14.9±12.1*	236.3	2/9
Pantethine	200	i.p.	7.1±4.3	112.7	0/10
Cyt-C	5	i.p.	6.8±5.7	107.9	0/10
VC	500	s.c.	6.2±2.0	80.2	0/5
EDTA	100	p.o.	7.2±8.1	114.3	1/10
DMU	100	p.o.	5.4±1.1	86.4	0/10
	500	p.o.	12.6±12.1	200.0	3/10
GSH	100	s.c.	9.2±7.5	195.7	1/10
	100	i.p.	13.5±11.6**	213.7	3/10
	250	s.c.	14.2±6.6***	183.7	0/5
	500	i.p.	6.2±2.3	98.1	0/10
Tiopronin	500	s.c.	8.8±3.7	113.8	0/5
VK1	50	s.c.	9.4±3.4*	121.6	0/5
VK2	50	s.c.	7.2±4.3	93.1	0/5
Clofibrate	250	p.o.	11.6±10.4	150.1	1/5
Ino-N	500	p.o.	12.0±6.9**	155.2	0/5
Nicomol	40	p.o.	9.1±3.6	117.7	0/10
Exp. 1	200	p.o.	17.7±7.9***	232.9	2/10
Exp. 2	200	p.o.	23.0±9.6***	297.5	3/5
Exp. 3	200	p.o.	11.1±10.1*	236.1	2/10
	1000	p.o.	25.5±8.3***	335.5	6/10

a: Experimental design represented in this Table is the same as in Table 1.
b: The values with asterisks are significantly different from the values obtained in the control group (*$p<0.05$, **$p<0.02$, ***$p<0.01$).

Table 4 Effect of Various Vasodilators on the Survival Time of ADM-Administered Mice[a]

Protectors	Dose (mg/kg)	Route	Survival time[b]		30-day survivors
			Days (mean±S.D.)	% (T/C)	
Nicardipine	10	p.o.	11.5±7.3*	157.5	1/10
Dipyridamole	40	p.o.	9.0±0.7**	123.3	0/10
	50	i.p.	9.4±2.9*	121.6	0/5
Diltiazem	10	p.o.	6.7±1.7	91.8	0/10
Nifedipine	10	p.o.	7.1±2.2	97.3	0/10
Verapamil	10	p.o.	7.1±1.4	97.3	0/10
Pindolol	10	p.o.	7.0±2.8	90.6	0/6
Disopyramide	200	p.o.	6.7±2.7	86.2	0/6
Propranolol	5	s.c.	5.2±1.6*	67.3	0/5

a: Experimental design represented in this Table is the same as in Table 1.
b: The values with asterisks are significantly different from the values obtained in the control group (*$p<0.05$, **$p<0.02$).

The group treated p. o. with 1000 mg/kg of nicomol survived the longest (25.5±8.3), and 6 of 10 mice in this group survived for more than 30 days.

Table 4 shows the effect of various vasodilators on the survival time of ADM-administered mice. Significantly longer survival times than that of the control group were found in the groups treated p.o. with nicardipine and p.o. and i.p. with dipyridamole. The group treated s. c. with propranolol showed a significantly shorter survival time than the control group ($p<0.02$).

Discussion

The main mechanism of ADM-induced cardiotoxicity is thought to be the insufficiency of mitochondrial functions in the heart (3-5). The factors that lead to this state are indicated to be the inhibition of DNA-directed DNA or RNA synthesis and protein synthesis of the myocardiac cells (6-8). The administration of Co Q_{10}, FAD and ATP (cardiac metabolism activators) protected against the ADM-induced toxicity and resulted in a significantly longer survival time than the control value. However, the administration of panthethine and Cyt-C did not show any protective effect.

ADM is thought to inhibit Co Q_{10} dependent enzymes in the mitochondrial succinoxidase and NADH-oxidase electron transfer systems by its structural interaction with Co Q_{10} (12, 13). Co Q_{10} has been reported to be useful in inhibiting ADM-induced acute toxicity (4, 15-16), and in improving mitochondrial functions (14, 26), the circulation system (4) and lipid peroxidation (16, 17). However, α-tocopherol, which has an action like that of Co Q_{10}, has been reported both to inhibit (11,18,19) and not to inhibit the ADM-induced toxicity (20, 27). In the present study, the administration of α-tocopherol did not protect against ADM-induced toxicity, but further examination is under way. Mimnaugh *et al.* (24) reported that the insufficiency of mitochondrial functions was due to radical formation in the membrane. Scavengers of reactive oxygen such as superoxide dismutase, reduced-glutathione and 1, 3-dimethylurea diminished the ADM-stimulated lipid peroxidation *in vitro*, indicating that superoxide radicals and the hydroxyl radical participated in the peroxidation reactions. Chelating agents such as EDTA did not show a protective effect in the present experiment. However, Herman *et al.* (23) reported that chelating agents prevented the marked increase in perfusion pressure and suggested that the removal of certain cations by chelating agents may reduce the toxicity. Glutathione levels in the heart mitochondria may play an important role in the modulation of ADM-induced toxicity, and soluble sulfhydryl groups have been reported to offer protection against the toxicity (22).

In the present study, anti-hyperlipemic agents such as MDS, nicomol, ino-N and Co Q_{10} strongly protected the animals against the ADM-induced toxicity and resulted in a significantly longer survival time than the control value. The results suggest that these drugs may stabilize membrane lipid against the damage due to lipid peroxidation (11, 16, 17, 28) or protect the pathway to thromboxane A2 or leucotriene via production of arachidonic acid (29). The last important factor causing insufficiency of the circulation system is the accumulation of Ca^{++} or Na^{+} ions in cardiac cells (10). The administration of a Ca^{++} antagonist showed little protective effect against ADM-induced toxicity. As cardiac failures have been reported as a side effect of some vasodilators such as disopyramide (30) and propranolol (31, 32), the use of vasodilators for preventing ADM-induced toxicity may be in question.

In the present study, we examined the

protective effects of various drugs on the survival time of ADM-treated mice, but further examination must be done on the biochemical and pharmacological aspects.

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