Introduction

Anthracycline antibiotics are among the most effective and widely used antineoplastic agents. Their clinical usefulness is, however, largely limited by a cumulative dose-related cardiotoxicity and other non-cardiac toxicities (25). The precise mechanisms of anthracycline cardiotoxicity have not been elucidated as yet. It is believed that cardiotoxic and possibly other cytotoxic actions of anthracyclines are caused, at least partly, by production of oxygen free radicals (39). This has been experimentally demonstrated both in vitro (13,27) and in vivo (29). Apart from other approaches to mitigate anthracycline cardiotoxicity (e.g. modification of the dosage schedule) (43), a number of cardioprotectants have been tested with equivocal results. Dexrazoxane (ICRF-187), a bisdioxopiperazine compound originally developed as an antitumour agent (8), is the only clinically approved drug for the prevention of anthracycline cardiotoxicity (44). The protective effect appears to be due to either removal of iron from anthracycline-iron complexes and/or binding of free iron in cardiomyocytes. Thus the catalytic role of iron in generation of oxygen free radicals is diminished (14,34,44). Dexrazoxane is usually reported not to affect anthracyclines antitumour activity and not to increase the incidence of non-cardiac toxicities (28,15,45).

Sodium 2,3-dimercaptopropane-1-sulphonate (DMPS), a dithiol orally active chelating agent with low toxicity (11), may hypothetically chelate iron (22), and due to two –SH groups it may act as an antioxidant (4). Thus, DMPS may not only scavenge oxygen free radicals, but it may also prevent their formation. In this study the authors tested apos-99

ORIGINAL ARTICLE

EFFECT OF SODIUM 2,3-DIMERCAPTOPROPAINE-1-SULPHONATE (DMPS) ON CHRONIC DAUNORUBICIN TOXICITY IN RABBITS: COMPARISON WITH DEXRAZOXANE

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Summary: A possible protective action of DMPS (a dithiol chelating agent) against chronic daunorubicin toxicity in rabbits in comparison with dexrazoxane was investigated. The rabbits were divided into five groups: control (saline, 1 ml/kg i.v.), daunorubicin (3 mg/kg i.v.), DMPS (50 mg/kg i.v.); the remaining two groups were pre-treated either with dexrazoxane (60 mg/kg i.p.) or DMPS (50 mg/kg i.v.) 30 min before administration of daunorubicin (3 mg/kg i.v.). Drugs were given once a week for 10 weeks. Routine biochemical parameters were determined in weeks 1, 5 and 11. In the 11th week, invasive haemodynamic parameters were measured, then the rabbits underwent autopsy, cardiac tissue was examined by light microscopy and scored semiquantitatively. The contents of calcium, potassium, magnesium, iron and selenium were measured in the left heart ventricle. DMPS administered alone was well tolerated and did not cause any major signs of toxicity. It decreased the cardiac content of calcium, but did not affect the iron concentration. In contrast to dexrazoxane, DMPS pre-treatment did not prevent the decline in body weight in weeks 8–11 caused by daunorubicin, actually worsened mortality (26.7% vs 40.0%), did not ameliorate daunorubicin-induced nephrotic syndrome, and did not prevent the occurrence of the severe myocardial lesions. Unlike dexrazoxane, a lack of protective effect of DMPS against chronic daunorubicin toxicity in rabbits was demonstrated. The underlying cause may consist in the fact that DMPS does not efficiently chelate tissue iron and thus may not prevent the formation of oxygen free radicals.

Key words: 2,3-dimercaptopropane-1-sulphonate; Daunorubicin; dexrazoxane; Cardiotoxicity; Nephrotoxicity; Rabbit
sible protective action of DMPS against chronic daunorubicin toxicities, primarily against cardiotoxicity, in rabbits. The action of DMPS was compared with that of a reference agent – dexrazoxane.

Material and methods

Animals. Medium size Chinchilla male rabbits (weight range 2.80–3.30 kg at the beginning of the experiment) were used. The experiments complied with the “European Convention for the Protection of Vertebrate Animals Used for Experimental and other Scientific Purposes” (1) and were under the supervision of the Ethical Committee of the Faculty of Medicine in Hradec Králové.

Origin of drugs and chemicals. Daunorubicin (Cérubidine, Laboratoires Roger Bellon, France), 2,3-dimercapto-propane-1-sulphonic acid, sodium salt (Sigma Chemie, Czech Republic), dexrazoxane (Cardioxane, Eurocetus, Netherlands), sodium pentobarbitone (Nembutal Sodium, Abbott, USA), heparin (Heparin inj., Léčiva, Czech Republic), aqua pro inj. (Biotika, Slovakia), saline (Solutio natrii chlorati isotonica, Biotika, Slovakia)

Experimental design. A total number of 57 rabbits was divided into five groups: 1. control (n=15, saline 1 ml/kg i.v.); 2. daunorubicin (n=15, 3 mg/kg i.v.); 3. DMPS (n=12, 50 mg/kg i.v.); 4. dexrazoxane + daunorubicin (n=5, 60 mg/kg i.p. + 3 mg/kg i.v., 30 min interval); 5. DMPS + daunorubicin (n=10, 50 mg/kg i.v. + 3 mg/kg i.v., 30 min interval). Drugs or their combinations were given once a week for 10 weeks. Blood samples were withdrawn at least after 12 hr fasting in weeks 1 (initial value), 5 and 11 (final value), and biochemical parameters were determined in plasma/serum.

Biochemical parameters. The following biochemical parameters were determined in plasma/serum using a Hitachi 717 analyser (Japan): sodium, potassium, calcium, chloride, magnesium, phosphate, glucose, urea, creatinine, uric acid, bilirubin, lactate dehydrogenase (LD), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK), alkaline phosphatase (ALP), cholesterol, triglycerides, proteins incl. electrophoresis.

Invasive haemodynamic measurement. At the end of the experiment the rabbits were anaesthetized with sodium pentobarbitone (25 mg/kg i.v.). Polyethylene catheters (1.6/2.4 mm; filled with heparinized saline, 10 IU/ml) were introduced into the right femoral artery and through the left carotid artery into the left cardiac ventricle, respectively. The catheters were connected to Gold Statham P 23 ID pressure transducers (USA). The mean arterial blood pressure, left ventricular pressure, and left ventricular differential pressure (dP/dt max) were recorded following a 15 min equilibrium period after an instrumentation with the use of a polygraph Biomedica C6b (Italy) and a differentiator (VÚFB Prague, Czech Republic).

Histological examination. Tissue blocks of transversally sectioned heart ventricles (the region under the atria) were fixed by immersion in 10% buffered formalin. Paraffin sections (7 µm) were regularly stained with Masson’s blue triple. A 5-point scale of morphological changes was applied for light microscopic semiquantitative evaluation of myocardial lesions.

Myocardial elements content assay. Calcium, potassium, magnesium, iron and selenium content were measured in samples of the dried myocardial tissue after microwave digestion with nitric acid and hydrogen peroxide. Calcium, magnesium, and selenium were determined by atomic absorption spectrophotometry using an Unicam Sollar analyser 959 (USA). Potassium and iron were measured photometrically using an Eppendorf Efox 5053 (Germany) and Hitachi 717 (Japan), respectively.

Statistical analysis. The data are expressed as the mean ± SEM for n observations. The homogeneity of variances between groups was tested by F test and the appropriate unpaired t-test was used for the following comparisons: daunorubicin and DMPS groups were compared to the control group; “treated” groups (i.e. dexrazoxane + daunorubicin and DMPS + daunorubicin) were compared with the daunorubicin group. Changes in data within groups (i.e. the 5th and 11th weeks in comparison with the 1st week) were tested by the paired t-test. A χ² test was used to determine the significance of differences in the severity of cardiomyopathy scores between groups. P < 0.05 was used as the level of statistical significance.

Results

General toxicity. Treatment with DMPS did not prevent a decline in body weight caused by daunorubicin administration starting in week 9 (Fig. 1). Mortality encountered in the daunorubicin group achieved 26.7%, DMPS co-administration actually worsened it to 40.0%. In contrast, no mortality was observed in rabbits pre-treated with dexrazoxane. Growth curve displayed nearly the same shape as in the control group.

Biochemical parameters. Important changes in biochemical parameters are summarized in Table 1. These changes, characteristic for the nephrotic syndrome induced by daunorubicin, were partly reduced by dexrazoxane, but not by DMPS co-administration. Other measured parameters either did not show any consistent changes or the changes were difficult to interpret (e.g. changes in CK activity were affected by repeated i.m. injections).
Invasive haemodynamic measurement. Daunorubicin significantly depressed left ventricular contractility indicated by a decrease in dp/dt max (Table 2). DMPS itself did not change this parameter. Pre-treatment with both dexrazoxane and DMPS tended to attenuate depressive effect of daunorubicin. None of the treatment regimens changed significantly the mean blood pressure.

Postmortem examination. Marked signs of congestion - ascites, pleural effusion and hydropericardium - were observed in 26.7% of rabbits treated with daunorubicin and in

Tab. 1: Important changes of biochemical parameters during the experiment.

| Parameter | Week | Control (n=15) | Daunorubicin (n=15) | DMPS (n=12) | Dexrazoxane + daunorubicin (n=5) | DMPS + daunorubicin (n=10) |
|-----------|------|---------------|---------------------|-------------|---------------------------------|-----------------------------|
| urea (mmol/l) | 1 | 7.9 ± 0.3 | 7.4 ± 0.5 | 9.7 ± 0.3c | 7.1 ± 0.5 | 6.5 ± 0.8 |
| creatinine (µmol/l) | 1 | 91.2 ± 4.1 | 90.1 ± 6.6 | 90.9 ± 1.9 | 87.4 ± 6.5 | 90.0 ± 3.7 |
| cholesterol (mmol/l) | 1 | 1.0 ± 0.1 | 1.3 ± 0.2 | 1.2 ± 0.1 | 1.3 ± 0.1 | 1.5 ± 0.1 |
| triglycerides (mmol/l) | 1 | 1.0 ± 0.1 | 1.4 ± 0.3 | 0.9 ± 0.1 | 0.7 ± 0.1d | 1.0 ± 0.1 |
| protein (g/l) | 1 | 62.3 ± 1.1 | 63.0 ± 1.1 | 64.7 ± 0.8 | 60.5 ± 0.5 | 62.6 ± 1.0 |

Electrophoresis (%)

| Albumin | α1-globulin | α2-globulin | β-globulin | γ-globulin |
|---------|-------------|-------------|------------|-----------|
| 1 | 66.3 ± 1.0 | 5.6 ± 0.6 | 6.7 ± 0.4 | 11.0 ± 1.1 |
| 5 | 69.3 ± 1.1 | 5.7 ± 0.4 | 6.0 ± 0.2 | 10.6 ± 0.9 |
| 11 | 66.7 ± 1.7 | 5.7 ± 0.2 | 6.7 ± 0.5 | 8.7 ± 0.6 |

Note: values not measured due to interference between fractions of albumin and α1-globulin compared to: * - initial value, c - the control group, d - the daunorubicin group (P < 0.05)

Tab. 2: Parameters of the invasive haemodynamic measurement at the end of the experiment (week 11).

| Group | dp/dt max (mmHg/s) | Mean blood pressure (mmHg) |
|-------|-------------------|---------------------------|
| Control (n=15) | 9855 ± 548 | 94 ± 2 |
| Daunorubicin (n=11) | 5565 ± 803c | 86 ± 5 |
| DMPS (n=12) | 10073 ± 645 | 98 ± 3 |
| Dexrazoxane + daunorubicin (n=5) | 6975 ± 548 | 102 ± 5 |
| DMPS + daunorubicin (n=6) | 6420 ± 465 | 87 ± 4 |

c - compared to the control group (P < 0.05)
20.0% of animals pre-treated with DMPS. In other groups of rabbits no clear signs of congestion were visible.

**Histopathology.** The evaluation of myocardial damage is summarised in Table 3. The normal appearance of the myocardial tissue of control rabbits is shown in Fig. 2. Daunorubicin caused the disperse toxic damage of the rabbit myocardium followed by proliferation of fibrotic tissue as a reparative process (Fig. 3). The pre-treatment with dexrazoxane prevented the occurrence of this severe damage (Fig. 4) in comparison with DMPS pre-treatment, where the results were similar to or worse than the results in daunorubicin group (Fig. 5). DMPS itself did not cause any significant changes in the myocardium, i.e. the appearance of the heart tissue resembled the normal stage.

**Myocardial content of elements.** Daunorubicin caused a significant increase in the content of calcium and a significant decrease in potassium and magnesium concentration. Cardiac levels of iron and selenium were not significantly changed (Table 4). DMPS decreased calcium concentration by more than one third as compared to the controls, tended to decrease potassium and magnesium concentration. The concentration of iron and selenium was not significantly affected. Dexrazoxane pre-treatment prevented “calcium overload” induced by daunorubicin, other changes in cardiac elements concentration induced by daunorubicin were not significantly affected, though some tendency to a decrease in iron and selenium concentration was observed. DMPS co-administration also prevented an increase in calcium concentration induced by daunorubicin; levels of other elements were not practically changed by DMPS pre-treatment.

### Tab. 3: Histological evaluation of the damage of myocardium scored according to the 5-point scale.

| Group                        | n  | 0 | 1 | 2 | 3 | 4 | P   |
|------------------------------|----|---|---|---|---|---|-----|
| control                      | 15 | 8 | 7 | 0 | 0 | 0 |     |
| daunorubicin                 | 13 | 0 | 1 | 8 | 3 | 1 | <0.05<sup>c</sup> |
| DMPS                         | 12 | 0 | 12| 0 | 0 | 0 | NS<sup>c</sup>   |
| dexrazoxane + daunorubicin   | 5  | 0 | 3 | 2 | 0 | 0 | NS<sup>c</sup>   |
| DMPS + daunorubicin          | 8  | 0 | 1 | 4 | 2 | 1 | NS<sup>c</sup>   |

NS – not significant; c - compared to the control group (<sup>χ²</sup> test); d – compared to the daunorubicin group (<sup>χ²</sup> test)

### Tab. 4: The content of selected elements in the left heart ventricle. Values are expressed in µmol/g of dry tissue (selenium in nmol/g).

| Element   | Control (n<sub>1</sub>=15) | Daunorubicin (n<sub>2</sub>=13) | DMPS (n<sub>3</sub>=12) | Dexrazoxane + daunorubicin (n<sub>4</sub>=5) | DMPS + daunorubicin (n<sub>5</sub>=8) |
|-----------|---------------------------|-------------------------------|------------------------|--------------------------------------------|-------------------------------------|
| Calcium   | 9.3 ± 1.0                 | 16.2 ± 2.4<sup>c</sup>       | 5.9 ± 0.7<sup>c</sup>  | 9.1 ± 0.4<sup>d</sup>                      | 7.4 ± 1.3<sup>d</sup>               |
| Potassium | 253.6 ± 8.8               | 225.3 ± 5.0<sup>c</sup>      | 226.6 ± 17.1           | 226.7 ± 13.8                              | 213.3 ± 12.2                       |
| Magnesium | 33.7 ± 1.5                | 28.6 ± 0.9<sup>c</sup>       | 27.6 ± 2.7             | 29.7 ± 0.9                                | 28.9 ± 1.8                         |
| Iron      | 3.0 ± 0.3                 | 2.8 ± 0.2                    | 3.0 ± 0.4              | 2.5 ± 0.1                                 | 3.0 ± 0.8                          |
| Selenium  | 6.7 ± 1.7                 | 10.9 ± 2.5                   | 8.5 ± 1.0              | 8.3 ± 0.5                                 | 10.4 ± 1.1                         |

c - compared to the control group (<i>P</i> < 0.05); d - compared to the daunorubicin group (<i>P</i> < 0.05)
Fig. 2: Control group (score 0) – normal appearance of the myocardium; typical cross-striated myofibrils fill the cytoplasm of cardiomyocytes except the endoplasm (a pale-stained region) around the nucleus (N); the capillaries (around each muscle fiber) are marked by chain of erythrocytes. Masson’s blue trichrome, Mag. 1152x.

Fig. 3: Daunorubicin group (score 4) - numerous degenerated (d) or destroyed cardiomyocytes (white spaces) are gradually replaced by granulation tissue pointed up by conspicuous nuclei of macrophages (M) and scattered lymphocytes, and later by collagen fibers (arrows). Remaining, relatively undamaged myocytes in these foci possess mostly the intensely eosinophilic cytoplasm. Masson’s blue trichrome, Mag. 1152x.

Fig. 4: Dexrazoxane-daunorubicin group (score 1) – large number (strips) of cardiomyocytes with intensely eosinophilic cytoplasm (darker stained - E) and scattered groups of degenerated/necrotic cells (D). Masson’s blue trichrome, Mag. 1152x.

Fig. 5: DMPS-daunorubicin group (score 4) – degenerated (necrotic) cardiomyocytes (white spaces) are replaced by granulation tissue and macrophages (M) – the healing process results in formation of the fibrotic scars marked by thick collagen fibers (arrows). There was no marked difference in microscopic picture of the myocardium damage in DMPS-daunorubicin and daunorubicin group. Masson’s blue trichrome, Mag. 1152x.
Discussion

Using the rabbit model of chronic anthracycline cardiotoxicity, which has been widely used in the studies of various protectants (6,9,12,16,17,40,41), the present authors studied a possible protective action of DMPS against daunorubicin toxicity, especially cardiotoxicity. The selected dose of DMPS, i.e. 50 mg/kg i.v., is comparable (molar basis) with the usual dexrazoxane doses in fixed combinations with anthracyclines (weight ratio 20:1) (23).

General toxicity, postmortem examination. Daunorubicin caused a significant decrease in body weight, especially in the last three weeks of the experiment (Fig. 1). Unlike DMPS, dexrazoxane pre-treatment normalized the growth curve of rabbits. Similarly, mortality induced by daunorubicin (26.7%) was prevented by dexrazoxane. This is consistent with the results of other experimental studies (16,19). In contrast, DMPS co-administration actually worsened mortality induced by daunorubicin (40.0%). Unlike DMPS, dexrazoxane prevented the occurrence of fluid accumulation in all pre-treated animals.

Biochemical parameters. The most marked changes in biochemical parameters demonstrated a nephrotoxic action of daunorubicin. Pathogenesis of anthracycline nephrotoxicity is not clear as yet. Most studies support a role of oxidative stress and lipid peroxidation (10,31,32,42); some authors, however, emphasize other mechanisms, e.g. interference with DNA metabolism (5). Partial protection against daunorubicin nephrotoxicity by dexrazoxane noted in the present study suggests a certain role of oxygen free radicals in its pathogenesis. In contrast, DMPS failed to prove any nephroprotective action. In blood, DMPS is rapidly oxidized to disulfide forms (30). In the kidney, disulfides may be reduced to the parent DMPS involving a glutathione (GSH)-disulfide exchange reaction (35). This may ensure the intracellular chelating activity of reduced DMPS, but at the expense of the GSH content and subsequent attenuation of antioxidant mechanisms involving GSH. Moreover, iron chelating activity of DMPS in renal tissue was not demonstrated in rats given DMPS in a cumulative dose 1.26 g/kg i.p. during 3 week interval (38).

Invasive haemodynamic measurement. Chronic daunorubicin cardiomyopathy manifested by a significant decrease in dP/dt max - a parameter of left ventricular contractility (26). DMPS alone did not change this parameter. Both dexrazoxane and DMPS pre-treatment partially non-significantly diminished a decrease in cardiac contractility induced by daunorubicin. Daunorubicin-induced decrease in cardiac contractility was not accompanied by a significant decrease in the mean blood pressure, possibly by a countereacting activation of vasoconstrictor mechanisms (3).

Histopathology. In compliance with some previous studies (17,18,40) conspicuous differences in the extent and severity of the myocardial damage were found mainly between daunorubicin and dexrazoxane-daunorubicin groups. Though the differences between the pre-treated groups and the daunorubicin group were not statistically significant (Table 3), unlike DMPS, dexrazoxane prevented the severe myocardial damage. In comparison with the above-mentioned studies (17,18,40), presence of many necrotic cells accompanied by mononuclear infiltrate (macrophages and scattered lymphocytes), and followed by proliferation of the fibrotic tissue were characteristics of daunorubicin-induced cardiomyopathy in our long-lasting (11 weeks) experiment.

Myocardial content of elements. A significant increase in myocardial calcium concentration (calcium overload) caused by daunorubicin observed in this study has been a well-documented feature of anthracycline cardiotoxicity. This may result from the block of calcium-release channels in sarcoplasmic reticulum and subsequent accumulation of calcium (37), and from the inhibition of transport systems regulating calcium movement (33). Calcium overload induced by daunorubicin was prevented by pre-treatment with both dexrazoxane and DMPS. However, the underlying mechanisms of the preventive action seem to be different for individual drugs. By binding intracellular iron dexrazoxane decreases harmful cellular biochemical effects induced by anthracyclines, i.e. oxygen-derived free radicals production (14,34,44), lipid peroxidation and subsequent damage of cellular membrane systems whose integrity is essential for cellular calcium homeostasis (46). Lesser extent of myofibrilar damage was seen also in this study as dexrazoxane prevented occurrence of the severe myocardial damage, i.e. stage 3 and 4 (necrosis of the cells) (Table 3, Fig. 4). In contrast, DMPS prevented calcium overload produced by daunorubicin possibly by direct chelation of calcium ions (Table 4). On the other hand, the present study did not prove any iron chelating action of DMPS, which was proposed hypothetically (22) and demonstrated in in vitro experiments (24). However, in in vivo studies, DMPS, used even in higher doses than in the present study, did not markedly change iron content in various tissues including the cardiac one (36,38). A tendency to an increase in selenium concentration in daunorubicin group may possibly reflect an up-regulation of antioxidant enzyme gene expression and an increase in glutathione peroxidase (GSH-Px) activity in response to oxidative stress. This has been demonstrated in various models of anthracycline cardiotoxicity (21,47). GSH-Px has been shown to serve as a major metabolic form of selenium against oxidative stress (7). Unlike DMPS, pre-treatment with dexrazoxane partially (non-significantly) attenuated an increase in selenium concentration. This may reflect partial reduction of oxidative stress induced by daunorubicin.

Conclusions

Data obtained in the present study suggest that DMPS does not appear to be an efficient iron chelator in vivo, and as the result, in a dose used in this study it did not demonstrate an effective action against daunorubicin toxicity in rabbits.
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