Comparative Study of Doxorubicin, Mitoxantrone, and Epirubicin in Combination with ICRF-187 (ADR-529) in a Chronic Cardiotoxicity Animal Model

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ABSTRACT

In this study doxorubicin, epirubicin, and mitoxantrone were compared for their cardiotoxic potential in a chronic mouse model in an effort to identify and compare their mechanism(s) of toxicity. In addition, the cardioprotective ability of ICRF-187 [(±)-1,2-bis(3,5-dioxopiperazinyl-1-yl)propane] with each anticancer drug was evaluated in this model. The antioxidant capacity (superoxide dismutase, reduced glutathione, catalase, and glutathione peroxidase) was assessed following drug treatment.

Five-week-old BALB/c mice received weekly i.p. injections of each drug or the drug and ICRF-187 over a 3-month period. ICRF-187 was administered 30 min prior to the anticancer drug. The hearts were examined by electron and light microscopy to assess subcellular changes, and the cardiac and hepatic antioxidant levels were measured concurrently. Chronic treatment with these drugs or each combined with ICRF-187 did not change the antioxidant levels relative to the control values. However, all three drugs caused cardiac damage during chronic exposure. Both epirubicin and mitoxantrone caused less severe damage than doxorubicin, and ICRF-187 was the least cardiotoxic of the three. ICRF-187 was cardioprotective for epirubicin and doxorubicin but not for mitoxantrone. These results suggest epirubicin acts by a mechanism similar to that of doxorubicin that is probably mediated by oxygen-free radicals, while mitoxantrone acts by a different mechanism to cause cardiotoxicity.

INTRODUCTION

Doxorubicin is one of the most effective chemotherapeutic drugs used for cancer treatment, but its usefulness is compromised by the development of chronic dose-dependent cardiotoxicity. One approach to overcoming doxorubicin cardiotoxicity is to develop structural analogues which retain the antitumor activity but are less or not cardiotoxic. Two of the most promising drugs that have been developed include epirubicin, an epimer of doxorubicin, and mitoxantrone, an anthracenedione.

Epirubicin has been reported to be less cardiotoxic than its parent drug, doxorubicin, and has comparable antitumor activity (1–3). Mitoxantrone was initially described as noncardiotoxic in animal models (4, 5) with an antitumor activity similar to that of doxorubicin (6), but more recent studies have reported that mitoxantrone is cardiotoxic (7–9). Hence these drugs were chosen for investigation to assess their cardiotoxic potential and to contribute to an understanding of the biochemical mechanisms involved in cardiotoxicity.

There is growing evidence in the literature that implicates oxygen free radicals as a primary mechanism in doxorubicin cardiotoxicity. Doxorubicin can be reduced by cellular flavoenzymes to a semiquinone free radical. This drug radical is postulated to give rise to oxygen free radicals that can initiate cellular damage if they overwhelm the antioxidant defense mechanisms. The cardiac antioxidant defenses, which include superoxide dismutase, catalase, glutathione peroxidase, and reduced glutathione, are intrinsically very low, rendering the heart very susceptible to free radical attack (10, 11). By comparison with doxorubicin, mitoxantrone has been shown to be less susceptible to enzymatic activation to its free radical form and inactive in stimulating oxygen free radical production or lipid peroxidation (12–15). This study is designed to determine whether similar mechanisms of action apply to anthrancenediones and anthracyclines.

Another approach to abrogating doxorubicin cardiotoxicity has been the use of a cardioprotective agent, ICRF-187 (ADR-529), administered just prior to doxorubicin (16, 17). ICRF-187 may protect against cardiac damage by preventing the induction of oxygen free radicals by doxorubicin (18, 19). In contrast to its cardioprotective role ICRF-187 acts synergistically with respect to the cytotoxicity of doxorubicin, actually enhancing its antitumor activity (20, 21). These observations lead to the proposal that the antitumor activity of doxorubicin can be separated from its cardiotoxic action, and these two actions may occur by different mechanisms. ICRF-187 is able to block one mechanism and enhance the other.

This work was undertaken to extend previous observations (18) about the effect of the combination of cardiotoxic drugs and ICRF-187 on the cardiac antioxidant capacity. In this particular study three anticancer drugs (doxorubicin, epirubicin, and mitoxantrone) are compared with respect to their effect on cardiac morphology and antioxidant capacity in a chronic mouse model of cardiotoxicity. The potential cardioprotective ability of ICRF-187 when coadministered with each drug is evaluated.

MATERIALS AND METHODS

Doxorubicin hydrochloride, epirubicin hydrochloride, and ICRF-187 (ADR-529) were obtained from Farmitalia-Carlo (Milan, Italy). Mitoxantrone hydrochloride (Novantrone) was purchased from Lederle Laboratories Division, Cinamid Australia (New South Wales, Australia). All other chemicals were obtained from the sources detailed previously (18).

Experimental Animals. Female BALB/c mice were obtained from the Walter and Eliza Hall Institute's Breeding Laboratories (Melbourne, Australia) at 5 weeks of age and then used in the experiments. Mice were housed in plastic cages and fed a laboratory diet and water ad libitum. Mice were randomly divided into eight treatment groups, each containing four mice which received (a) 0.9% NaCl solution, (b) ICRF-187, (c) doxorubicin, (d) doxorubicin and ICRF-187, (e) epirubicin, (f) epirubicin and ICRF-187, (g) mitoxantrone, and (h) mitoxantrone and ICRF-187. The same treatment protocol utilized to develop a model for chronic doxorubicin cardiotoxicity was used (18). Briefly, each mouse, depending on the treatment group, received weekly i.p. injections over a 12-week period of either 0.9% NaCl solution or ICRF-187 (12.5 mg/kg) 30 min prior to a 0.9% NaCl solution, doxorubicin (1 mg/kg), epirubicin (1 mg/kg), or mitoxantrone (0.2 mg/kg) injection. The total cumulative doses received were 12 mg/kg for both doxorubicin

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The abbreviations used are: ICRF-187 or ADR-529, (±)-1,2-bis(3,5-dioxopiperazinyl-1-yl)propane.
and epirubicin, 2.4 mg/kg for mitoxantrone, and 150 mg/kg for ICRF-187. A lower dose of mitoxantrone than of doxorubicin was used, since mitoxantrone has been reported to be 5–7 times more potent and toxic than doxorubicin in humans (22) and in animal models (4–6). One week after the final injection cycle the mice were sacrificed, the hearts and livers were removed for antioxidant assays, and a portion of the heart was retained for electron microscopy. This study consisted of two experiments in which a total of 6 mice/treatment group (3/experiment) were examined by electron and light microscopy, and the cardiac antioxidant capacity was assessed.

Antioxidant Assays. The mouse livers and hearts were homogenized and centrifuged to obtain a 100,000 ×g supernatant fraction following a modification of the procedure detailed by Doroshow et al. (10), as described previously (18). Aliquots of the tissue homogenate supernatants were stored at −70°C until analysis. However, reduced glutathione is subject to oxidation during long-term storage, and therefore its concentration was determined within 3 days of sample preparation. The reduced glutathione, superoxide dismutase, glutathione peroxidase, and catalase assays were performed as specified before (18) using previously published methods.

Electron and Light Microscopy. The interventricular septum was dissected from the heart immediately after death and cut into 1-mm³ pieces before fixation in 2% glutaraldehyde, 2% paraformaldehyde, and 4% glucose in phosphate buffer. To prevent any deterioration in the heart tissue the whole procedure from death to removal of the heart and placement in the fixative was performed rapidly over a 1–2 min period. Standard postbuffering, osmication, and processing conditions for electron microscopy were followed. For light microscopy examination 1-μm sections were taken from the same epon-embedded blocks used for electron microscopy and stained with toluidine blue O. Specimens were examined blind with a Phillips electron microscope, and the degree of changes in myocardial and endothelial cells was assessed. The frequency and severity of cardiac damage in the myocardial cells were graded according to a scoring system described by Billingham et al. (23). The Billingham grade calculated for each treatment group represents the average of six animals, taking into account any animal variability. Several heart specimens (up to eight) from each animal were assessed and averaged, and the final grade for each treatment group represents this value averaged between six animals.

RESULTS

Morphological Changes. To evaluate the cardiotoxic changes induced by the anthracyclines or mitoxantrone, the effect of these drugs in a chronic toxicity mouse model was examined. Electron microscopy examination of the treated mouse hearts was used to assess whether after chronic exposure to the drugs with or without ICRF-187 they were cardioprotective or cardiotoxic, respectively. The results of this study, depicted in Figs. 1–3, were consistent with our previous investigations (18), in that doxorubicin was cardiotoxic and caused typical anthracycline-induced ultrastructural changes. Epirubicin and mitoxantrone were also cardiotoxic in this mouse model, although the degree of toxicity and the type of subcellular changes varied between the drugs (Figs. 2, A and B, and 3, A and C). Control and ICRF-187-treated mice hearts (Fig. 1, A and B) contained intact mitochondria and an ordered array of myofilibrils as indicated by the parallel alignment of the Z-bands. Slight dilation of the sarcoplasmic reticulum cisternae was present following chronic exposure to ICRF-187 (Fig. 1B).

Chronic epirubicin exposure caused similar ultrastructural changes to doxorubicin, but these changes were much less severe (compare Figs. 2, A and B, and 3A). Electron microscopy examination revealed that epirubicin treatment caused mitochondrial swelling and minor disruption of the cristae, but very little disorganization of the ordered myofilibrillar array was apparent, although minor myofilibrillar lysis was present near the Z-bands. In comparison, doxorubicin induced more pronounced disorganization of the cristae associated with clearing out of the matrix in some mitochondria. These degenerative mitochondrial changes caused by doxorubicin were associated with the appearance of myelin figures. Furthermore, there was marked disruption of the organized myofilibrillar array, including misalignment of the Z-bands and myofilibrillar lysis, leading to focal loss of banding in the myocytes following chronic doxorubicin exposure. Doxorubicin also caused dilation of sarcotubular and t-tubular systems, separation of the adjacent membranes of the intercalated disc, and swelling of the perinuclear area, changes which were absent with epirubicin treatment. Neither epirubicin nor doxorubicin affected the morphology of the endothelial cells. The morphological changes were scored as grade 1 for epirubicin and grade 3 for doxorubicin.

Mitoxantrone was cardiotoxic in this chronic mouse model, with the degree and severity of the morphological changes observed in the myocardium being classified as grade 2, indicating the level of cardiotoxicity lies between epirubicin and doxorubicin. The severity of subcellular changes was less marked in comparison to doxorubicin (compare Figs. 2A, 2B, and 3C). Mitoxantrone treatment induced mitochondrial swelling, partial clearing of the matrix in some mitochondria, and the appearance of myelin figures. Vacuolation and swelling of the cisternae of the sarcoplasmic reticulum and dilation of the t-tubular systems was also evident. Anthracycinedione caused slight myofilibrillar lysis, but disruption of the band registry was not apparent, unlike the effect of exposure to doxorubicin. As was observed for epirubicin, mitoxantrone did not affect the morphology of the intercalated disc or the endothelial cells, or cause swelling of the perinuclear zone. Although mitoxantrone-treated hearts showed many ultrastructural changes similar to those induced by doxorubicin, in comparison, a smaller proportion of the myocytes showed these alterations.

In this study the cardioprotective role of ICRF-187 in combination with each cardiotoxic drug was examined. ICRF-187 was cardioprotective for most of the doxorubicin-induced damage, with the remaining morphological changes present being judged as grade 1, indicating that less than 5% of the myocytes were affected. The subcellular changes were much less severe in comparison to doxorubicin alone (compare Fig. 2, A–C), showing minor mitochondrial swelling and a small degree of myofilibrillar lysis but no disruption of the ordered parallel array. The most pronounced toxicity change still present following doxorubicin and ICRF-187 treatment was dilation of the tubular systems. ICRF-187 was totally protective for the epirubicin-induced changes, with the morphology being evaluated as grade 0 (Fig. 3B). However, ICRF-187 was unable to protect against mitoxantrone-induced damage or affect the degree, severity, or type of subcellular changes observed (compare Fig. 3, C and D). The morphology following mitoxantrone and ICRF-187 treatment was classified as grade 2, and the changes were similar to those described for mitoxantrone alone.

The myocardia of the treated mice were also examined at the light microscopy level to give an overall view of the distribution of cellular damage among individual myocytes and to indicate the number of damaged myocytes involved. Control and ICRF-187-treated animals contain intact myocytes with no vacuolation evident (Fig. 1, C and D). Doxorubicin exposure caused vacuolation and coalescence to form large vacuoles in individual myocytes, replacing the normal contractile components, and the distortion of cross-striations in other myocytes (Fig.
4.4). Pretreatment with ICRF-187 prevented the marked myocytic vacuolization induced by doxorubicin (Fig. 4B). Epirubicin-treated hearts contained vacuolated myocytes scattered throughout the myocardium, and the vacuoles were very small (Fig. 4C). The administration of epirubicin and ICRF-187 protected against vacuolization of myocytes, resulting in morphology similar to that of control or ICRF-187-treated mice. Mitoxantrone exposure induced a lower grade of damage compared with doxorubicin, observed as pale myocytes containing many small vacuoles (Fig. 4D). Pretreatment with ICRF-187 did not prevent the myocytic vacuolization caused by mitoxantrone, so that the pattern of damage was similar to that shown for mitoxantrone alone.

Antioxidant Capacity. Antioxidant levels were assessed in the hearts and livers of mice chronically treated with the drugs. The liver was used as a control because it appears not to be affected by anthracyclines to the same extent as the heart. The antioxidant levels measured included catalase, superoxide dismutase, and glutathione peroxidase activities and reduced glutathione concentration.

The effect of doxorubicin, epirubicin, mitoxantrone, and the combination of each drug with ICRF-187 on the cardiac and hepatic antioxidant capacity is shown in Fig. 5. None of the cardioxic drugs or the drug combinations with ICRF-187 caused any significant change in any of the antioxidants assessed when compared with the control value. This result is in consensus with our previous work evaluating the effect of doxorubicin or doxorubicin and ICRF-187 on cardiac antioxidants (18). Thus, although electron and light micrographs of the treated hearts demonstrated morphological damage caused by the cardioxic drugs, this was not accompanied by a depression or elevation of cardiac antioxidant capacity.

DISCUSSION

This investigation has considered the effect of three anticancer drugs on cardiac subcellular structure, antioxidant capacity, and their interaction with ICRF-187. It was established that all three drugs were cardioxic in this chronic mouse model to varying degrees. Epirubicin was found to be less...
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Fig. 2. Electron micrographs of myocardium after ICRF-187 and doxorubicin treatment. Mice received weekly injections of doxorubicin and/or ICRF-187 over a 12-week period. ICRF-187 was administered 30 min prior to doxorubicin. Cumulative doses were 12 mg/kg for doxorubicin and 150 mg/kg for ICRF-187. A and B, doxorubicin. Mitochondria contain disrupted cristae and there is some clearing out of the matrices. Separation and lysis of myofibrils results in marked disorganization of band registry (A). A loss of myofibrillar structural elements can be seen (B, arrows). Swelling and vacuolization of the tubular systems are evident (*). There is prominent separation of the fascia adherens of intercalated discs (ID). Perinuclear swelling can be seen around the nucleus (B). C, doxorubicin and ICRF-187. Generally, mitochondria and myofibrils are in good condition, but there is minor myofibrillar lysis, swelling of mitochondria, and moderate dilation of t-tubular and sacrotubular systems (*). × 10,000.

Cardiotoxic than doxorubicin, in agreement with previous findings (1–3). Mitoxantrone was evaluated as less cardiotoxic than doxorubicin because the ultrastructural changes were less severe when compared with doxorubicin, in agreement with recent reports in animals (7, 9) and in clinical trials (8, 24, 25).

In this chronic toxicity mouse model the mitoxantrone-induced morphological changes were qualitatively similar to those induced by doxorubicin, as reported in another mouse study (7), but differed from the observations in a rat model, where not all the typical characteristics of anthracycline damage were identified (9). In the latter study mitoxantrone, while it was less cardiotoxic than doxorubicin, caused conspicuous mitochondrial degenerative changes but no sarcotubular dilation or myofibrillar disruption. In clinical trials mitoxantrone induced subcellular changes similar to those induced by doxorubicin (8, 25). The observation that mitoxantrone was cardiotoxic supports the recent reports describing the use of this drug in clinical trials (8) and discounts the initial premise that the drug was not cardiotoxic in animal models (4, 5). In fact it would be quite dangerous in light of these findings to administer mitoxantrone without monitoring for potential cardiotoxicity, especially if the patient has had prior doxorubicin treatment. The reason for the differences in cardiotoxicity of mitoxantrone in animal models may be due to species specificity, the drug dose, treatment protocol, the route of administration, the different procedures used to evaluate cardiotoxicity, or any combination of these factors.

Neither the cardiotoxic drugs nor the drugs in conjunction with ICRF-187 caused any significant effect on the cardiac or hepatic antioxidant capacity of these mice after chronic exposure. These results support the findings of a previous study in which only doxorubicin was evaluated (18) and seem to discount one possible theory for the mechanism of doxorubicin cardiotoxicity. This theory postulated that doxorubicin may depress the cardiac antioxidant levels, particularly glutathione peroxidase, while concomitantly increasing oxygen free radical production, thereby overwhelming the limited cardiac defense system (10). Instead it seems more likely that doxorubicin and
Fig. 3. Electron micrographs of myocardium after ICRF-187 and epirubicin or mitoxantrone treatment. Mice received weekly injections of the anticancer drug or the drug and ICRF-187 over a 12-week period. ICRF-187 was administered 30 min prior to epirubicin or mitoxantrone. Cumulative doses were 12 mg/kg for epirubicin, 2.4 mg/kg for mitoxantrone, and 150 mg/kg for ICRF-187. A, epirubicin. There is mitochondrial swelling, some myofibrillar lysis, and slight dilation of the sacroplasmic reticulum (*). B, epirubicin and ICRF-187. Normal morphology showing intact mitochondria and parallel myofibrillar array. C, mitoxantrone. There is mitochondrial swelling and disruption of cristae alignment (*), dilation of t-tubules and the cisternae of the sacroplasmic reticulum. Arrows, slight myofibrillar lysis but no disorganization of the band registry. D, mitoxantrone and ICRF-187. Similar subcellular changes to mitoxantrone alone. One mitochondrion contains a myelin figure (arrow), indicating mitochondrial degeneration (*), dilation of the tubular systems. × 10,000.

Epirubicin cause cardiac damage by the induction of oxygen free radicals rather than a combined insult on the cellular antioxidant defenses. Furthermore mitoxantrone did not affect the measured cardiac antioxidant capacity, so it does not appear to cause damage by an effect on the myocardial antioxidant defenses.

The cardioprotective agent, ICRF-187, prevented cardiac damage induced by epirubicin but not mitoxantrone, which suggests that epirubicin acts by a mechanism similar to that of doxorubicin, whereas mitoxantrone probably acts by a different mode of action. We have proposed, based on previous findings, that ICRF-187 is cardioprotective by preventing the induction of oxygen free radicals by doxorubicin, probably by complexing iron. Recent evidence has implicated iron as an essential component in the generation of oxygen free radicals by doxorubicin (26, 27). In support of this theory, Hasinoff (28) has shown that ICRF-187 or its hydrolysis product, ICRF-198, can remove iron from a doxorubicin-iron complex. Furthermore, it has been demonstrated that ICRF-187 prevented doxorubicin-induced hydroxyl radical production by perfused rat hearts (19). It is possible, based on the structural similarities between the two anthracyclines, that ICRF-187 prevents epirubicin-induced damage by a similar postulated mechanism.

The observation that ICRF-187 did not completely protect against doxorubicin-induced damage, although it did significantly reduce the severity and incidence, is similar to the reports by others (17, 29–32). In these studies ICRF-187 achieved almost complete protection, but some subjects did show slight morphological damage, evaluated as grade 1 or less based on the Billingham grading system (23), while doxorubicin cardiac lesions were scored as grade 2 or more. The cardioprotection offered by ICRF-187 compared to doxorubicin alone was statistically significant in these cited investigations. In the current work the cardiac damage was assessed as grade 1 for doxorubicin and ICRF-187 and grade 3 for doxorubicin alone.

The reason why epirubicin is less cardiotoxic than doxorubicin is unknown, but it may be related to its ability to generate oxygen free radicals and/or its stimulation of lipid peroxidation.
This concept is supported by studies using acute and chronic models comparing these two drugs, which demonstrated that the hearts exhibited less oxidative stress, measured as endogenous lipid peroxidation and hydroperoxide-initiated chemiluminescence, for epirubicin compared with doxorubicin (1, 33). However, other investigations have been unable to detect any difference in the ability of the two anthracyclines to generate superoxide anions (34) or promote lipid peroxidation (14). Although it must be noted that these later studies were undertaken using in vitro systems composed of hepatic microsomes and the drug or subcellular-free incubations of the drug and iron, Llesuy et al. (1, 33) examined the heart's capacity for lipid peroxidation after drug treatment, which may explain the differences in observations. Alternatively, it has been postulated that doxorubicin may be cardiotoxic by affecting cardiac calcium concentration. In comparison to doxorubicin, epirubicin causes less pronounced inhibition of calcium turnover in cultured heart cells (35) and less inhibition of the Na⁺/Ca²⁺ pump (36), which may explain its lower cardiotoxicity. Another factor contributing to the reduced cardiotoxicity of epirubicin may be the fact that it has pharmacokinetic properties different from those of doxorubicin (3).

Although chemically distinct from anthracyclines, mitoxantrone contains quinone functional groups, which suggests that it may function in a way similar to that of doxorubicin, causing cardiotoxicity by an oxygen free radical-mediated mechanism. However, the observation that ICRF-187 does not prevent drug-induced damage suggests that mitoxantrone acts by a mechanism in the heart different from that of anthracyclines. This is supported by published evidence which has reported that mitoxantrone is not activated to its drug free radical form by cellular reductases (12), it is unable to generate oxygen free radicals (12, 15), and it does not stimulate but actually inhibits lipid peroxidation (13, 14). In contrast, doxorubicin is activated to a semiquinone radical by reductases, and it stimulates oxygen free radical production and lipid peroxidation. These observations collectively suggest that mitoxantrone does not act by a mechanism similar to that of anthracyclines.

However, mitoxantrone does generate a free radical signal by a mechanism different from that of anthracyclines (37, 38).
Mitoxantrone is activated by peroxidases in an oxidative process to a N-centered free radical, and it is not a substrate for the cellular reductases which activate doxorubicin, thus explaining its previous inability to produce oxygen free radicals (12, 38, 39). The mitoxantrone free radical reacts with hydroperoxy fatty acids, thereby inhibiting lipid peroxidation in the propagation stage (13). Also, mitoxantrone inhibits prostaglandin synthesis, probably by interfering with the regulatory processes inherently dependent on hydroperoxy fatty acids (40, 41). The relevance of this mechanism to cardiotoxicity at present is still unclear. Possibly the mitochondrial and tubular calcium levels are altered by a hydroperoxide-mediated process (41), thus affecting mitochondrial function and excitation coupling for muscle contraction. It is probable that the hydroperoxide-mediated mechanism for this drug does not require iron because ICRF-187 was not cardioprotective.

In conclusion, it was demonstrated that epirubicin and mitoxantrone were cardiotoxic in a chronic mouse model. The least cardiotoxic drug was epirubicin, followed by mitoxantrone and doxorubicin, the latter being the most toxic. None of the cardiotoxic drugs or their combination with ICRF-187 affected cardiac antioxidant capacity. ICRF-187 was able to prevent cardiotoxicity by the anthracyclines but not by mitoxantrone, suggesting that anthracenedione causes cardiac damage by a mechanism different from those of epirubicin and doxorubicin.

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