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Dexrazoxane for the Prevention of Cardiac Toxicity and Treatment of Extravasation Injury from the Anthracycline Antibiotics

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Abstract

The cumulative cardiac toxicity of the anthracycline antibiotics and their propensity to produce severe tissue injury following extravasation from a peripheral vein during intravenous administration remain significant problems in clinical oncologic practice. Understanding of the free radical metabolism of these drugs and their interactions with iron proteins led to the development of dexrazoxane, an analogue of EDTA with intrinsic antineoplastic activity as well as strong iron binding properties, as both a prospective cardioprotective therapy for patients receiving anthracyclines and as an effective treatment for anthracycline extravasations. In this review, the molecular mechanisms by which the anthracyclines generate reactive oxygen species and interact with intracellular iron are examined to understand the cardioprotective mechanism of action of dexrazoxane and its ability to protect the subcutaneous tissues from anthracycline-induced tissue necrosis.

Keywords

Dexrazoxane; anthracycline; doxorubicin; oxidative stress; iron; chelator; cardiac toxicity; extravasation injury

INTRODUCTION

The anthracyclines doxorubicin and daunorubicin, discovered over forty years ago, continue to be widely used in clinical oncology, particularly in the treatment of adult hematologic malignancies, including acute myelogenous leukemia, and both Hodgkin's and non-Hodgkin's lymphoma [1]. Most treatment programs for breast, ovarian, and gastric carcinomas, bone and soft tissue sarcomas, and a wide range of childhood malignancies also include an anthracycline antibiotic [1]. Doxorubicin is currently employed primarily for the

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CONFLICT OF INTEREST

Declared none.

treatment of solid tumors, whereas daunorubicin is routinely used during chemotherapeutic induction of the acute leukemias. Although the acute side effects associated with anthracycline administration, such as myelosuppression, alopecia, and damage to the gastrointestinal mucosa play an important role in the use of this class of drugs, the toxicity that produces greatest concern is a unique, potentially fatal form of cumulative cardiac damage [2].

An understanding of the biochemical underpinnings of anthracycline cardiac toxicity, based on the ability of this drug class to generate reactive oxygen species in essentially all subcellular compartments in the heart [3], and to release iron from intracellular iron binding proteins [4], played a critical role in the development and eventual regulatory approval of dexrazoxane (ICRF-187; Zinecard®), an ironchelating derivative of EDTA with its own anticancer activity, that blocks the cardiac toxicity of the anthracyclines in a wide range of animal models [5,6]. Prospective, randomized clinical trials demonstrated that dexrazoxane is highly effective in reducing the cardiac toxicity of doxorubicin in both adults and children without inhibiting the therapeutic effects of the anthracyclines significantly [7–9]. Furthermore, recent clinical studies have found that dexrazoxane is also capable of decreasing the severe local tissue injury that accompanies the leakage of the anthracyclines out of the intravascular space [10, 11]. In this review, the various biochemical features of both anthracycline and dexrazoxane metabolism that help to explain the protective effects of dexrazoxane on the anthracycline-treated heart and on tissues exposed to an accidental anthracycline infiltration are examined.

MECHANISMS OF ANTHRACYCLINE CARDIAC TOXICITY AND ITS PREVENTION BY DEXRAZOXANE

Anthracycline-Induced Production of Reactive Oxygen Species in the Heart

Doxorubicin, daunorubicin, and all the other clinically useful anthracyclines are anthraquinones that undergo futile cycles of reduction and oxidation (so-called redox cycling) of their quinone moieties in essentially all intracellular compartments, including the nucleus and the mitochondrion, leading to the formation of reactive oxygen species (ROS) [12]. The one-electron reduction of the anthracyclines was initially described in hepatic microsomal systems [13] but was later shown to play a central role in the cardiac toxicity of this class of drugs [14, 15]. Anthracycline-induced ROS can damage intracellular lipid membranes and sodium and calcium transporters in the heart [16–18]. One-electron reduction of the anthracycline quinone in the heart is catalyzed by cardiac flavin dehydrogenases including cytochrome P-450 reductase, NADH dehydrogenase (complex I of the mitochondrial electron transport chain), and xanthine oxidase [19–21]. In blood vessels, nitric oxide synthase can catalyze doxorubicin redox cycling with the subsequent production of superoxide and a decrease in nitric oxide [22, 23]. Furthermore, doxorubicin can directly inhibit nitric oxide synthase activity [23, 24] which could significantly change vascular tone [25]. Doxorubicin can also be reduced in the heart by oxymyoglobin, leading to the production of strong oxidant species [26]. actively transporting anthracyclines and anthracycline metabolites into the bile [1].

The dismutation of anthracycline-induced superoxide anions yields hydrogen peroxide. Either the anthracycline semiquinone or reduced metal ions such as iron can then reductively cleave hydrogen peroxide to produce the hydroxyl radical, one of the most reactive chemical species known [27]. It is now commonly accepted that reduced metals are critical components in the formation of toxic freeradical intermediates that contribute to the cytotoxicity of the anthracyclines [28].

To confirm that oxygen radicals are formed in the heart after doxorubicin treatment, isolated perfused beating rat hearts have been exposed to doxorubicin; electron spin resonance has been used to detect hydroxyl radicals. In this setting, the hydroxyl radical is found after exposure of the heart to doxorubicin levels (1 μM) attained in the clinic following standard intravenous bolus administration of a dose of 60 mg/m^2 [29]. Thus, it seems clear that doxorubicin can trigger the formation of ROS *in vivo* and that this occurs at concentrations that are associated with the development of cardiac toxicity.

ROS formation is also a consequence of normal aerobic metabolism (such as the functioning of the mitochondrial respiratory chain) and is a common mechanism of action for several naturally-occurring toxins; hence, most mammalian cells have extensive defenses against ROS [30]. The enzymes superoxide dismutase, catalase, and glutathione peroxidase reduce superoxide, hydrogen peroxide, and lipid hydroperoxides, respectively, to water or non-toxic lipid alcohols without the formation of more reactive free radical species. However, enzymatic defenses against oxidant stress are not equally distributed throughout the body. For instance, the concentration of glutathione is greater in the liver than in most other organs. Catalase activity is lower in the heart than in the liver [14, 31]. The specific activities of many flavoproteins that metabolize the anthracyclines to free radicals vary from tissue to tissue. These variations in drug activation and enzymatic defense provide a degree of tissue specificity with respect to anthracycline toxicity. Thus, anthracycline cardiac toxicity may be enhanced by low catalase levels in the heart, coupled with the large amount of mitochondria and myoglobin in that organ, both of which increase ROS production by the anthracyclines. The sensitivity of cardiac glutathione peroxidase to free radical attack [14, 32], which limits detoxifying capacity in the heart at the time that anthracycline treatment initiates ROS formation [29], may underlie the special sensitivity of the heart to anthracyclines. It has recently been shown, further, that transgenic mice homozygous for deletion of the glutathione peroxidase gene are significantly more sensitive to anthracycline cardiac toxicity, and that transgenic mice overexpressing glutathione peroxidase in the heart are resistant to heart damage from doxorubicin [33, 34]. Finally, although anthracyclines are metabolized by hepatic dehydrogenases, generating ROS, the liver has a robust system to detoxify ROS and is also capable of

To understand the cardiac toxicity of the anthracyclines, critical changes in calcium handling in heart muscle that are associated with anthracycline exposure must also be explained [35–39]. Calcium levels regulate the force of heart muscle contraction. The two major sites for the beat-to-beat regulation of calcium concentration are the sarcoplasmic reticulum and mitochondria. Sarcoplasmic reticulum avidly binds calcium that is rapidly released during depolarization of the sarcoplasmic membrane. Cardiac mitochondria accumulate calcium if it is available in preference to making ATP. One possibility is that anthracyclines might

chelate calcium and thus alter the distribution of this metal ion. However, doxorubicin does not chelate calcium within its physiologic concentration range. The cardiac pathology of anthracycline toxicity reveals that a major site of damage after drug exposure is the sarcoplasmic reticulum, which is also a major site of calcium regulation. Doxorubicin-induced damage to the sarcoplasmic reticulum produces calcium release [39, 40]; calcium is then taken up by the mitochondria, decreasing ATP production. This sequence would account for lower ATP levels and accumulation of calcium and calcium-related damage within the mitochondria following anthracycline treatment.

Doxorubicin stimulates ROS formation in cardiac sarcoplasmic reticulum, cytosol, and mitochondria [41, 42]. The non-redox active anthracycline, 5-iminodaunorubicin, does not generate ROS in sarcoplasmic reticulum or mitochondria and is markedly less cardiotoxic than other anthracyclines [43]. Doxorubicin induces peroxidation of the sarcoplasmic reticulum lipid and oxidant-related sulfhydryl loss that is associated with a decrease in both high-affinity calcium binding and the force of contraction [17, 35]. Redox cycling of doxorubicin also selectively inhibits critical sulfhydryl groups on the ryanodine-sensitive calcium channel of the sarcoplasmic reticulum resulting in enhanced channel activation and subsequent alterations in calcium homeostasis [44, 45]. Thus, anthracycline redox cycling can produce oxidative damage to the sarcoplasmic membrane with subsequent loss of the capacity of this membrane to bind calcium, disrupting the linkage between electrical excitation and contraction in the heart.

Anthracyclines, Iron, and Dexrazoxane

Although scavengers of ROS are potent inhibitors of doxorubicin-induced cardiac injury in animal models [15], the initial studies of reactive oxygen scavengers as cardioprotectants were unsuccessful in humans [46]. However, the heart is rich in iron proteins, such as ferritin and those in the mitochondrial electron transport chain, that are capable of donating their metal to catalyze hydroxyl radical formation. Doxorubicin has been found to release iron from ferritin by slowly abstracting iron from the ferritin shell directly [47], or more rapidly by releasing iron following conversion of the anthracycline to its semiquinone, which releases iron under hypoxic conditions directly, or through the reducing power of the superoxide anion in air [48, 49]. Doxorubicin can also induce the release of non-heme, non-ferritin iron from microsomes [50–52], and can increase the uptake of iron by a transferrin receptor-mediated process, enhancing intracellular iron availability [53]. The hydroxyquinone structure of the anthracyclines provides a site for chelation of metal ions, especially ferric iron. Iron anthracycline complexes possess a wide range of biochemical properties *in vitro* [54]. These complexes can cause oxidative destruction of membranes and oxidize critical sulfhydryl groups. It remains unclear, however, whether these tight-binding iron-anthracycline complexes produce toxic effects intracellularly [55], or whether iron-dependent, anthracycline-stimulated free radical formation is responsible for hydroxyl radical formation in tissues.

These studies suggested that an effective way to interfere with the generation of highly reactive oxidants after anthracycline exposure would be to pretreat with a chelating agent that could sequester iron, minimizing free radical reactions. The iron chelator dexrazoxane

has been shown to prevent doxorubicin-induced lipid peroxidation [56] and cardiac toxicity in many animal models [6]. Randomized clinical trials in humans have confirmed the ability of dexrazoxane to markedly decrease heart damage from doxorubicin [57, 58]. Dexrazoxane is an effective iron chelator *in vivo*; during phase I studies it caused a tenfold increase in urinary clearance of iron [59]. Dexrazoxane is also a prodrug; it must undergo hydrolysis to become an effective iron chelator. The hydrolysis to ICRF-198, the major iron-binding metabolite of dexrazoxane, can occur spontaneously at physiologic pH but is markedly enhanced after uptake into cardiac myocytes with conversion of the parent drug to ICRF-198 in less than 60 seconds [60]. The parent drug is very lipid soluble and enters cells by passive diffusion. ICRF-198 has been demonstrated to efflux iron from iron-loaded myocytes; these studies suggest that the same chelating ability may be available to remove iron that has been released from cardiac iron storage proteins [60].

Additional studies have amplified our understanding of the role of iron in the mechanism of anthracycline-induced cardiac toxicity [61–64]. Down-regulation of cellular iron uptake by overexpression of the wild-type hemochromatosis gene in MCF-7 breast cancer cells decreases doxorubicin-induced reactive oxygen production and apoptosis [65]. Furthermore, rats fed a diet that is iron-enriched demonstrate dramatically enhanced cardiac apoptosis and mitochondrial injury after treatment with doxorubicin [66]. The alcohol metabolite of doxorubicin, doxorubicinol, which is produced by the two-electron reduction of the C-13 side chain carbonyl group, has been demonstrated to cause the delocalization of low molecular weight Fe^{2+} species from the iron-sulfur center of aconitase in a redox-dependent fashion. These effects of doxorubicin metabolites suggest that iron-dependent reactions occur that may not be directly related to the formation of reactive oxygen species. This could help to explain the utility of dexrazoxane, compared to free radical scavengers that do not chelate iron, in the prevention of both acute and chronic anthracycline cardiotoxicity [52].

Potential Roles of Other Biochemical and Pharmacologic Effects of Dexrazoxane on Anthracycline Cardioprotection

Although the data supporting the role of iron chelation in the mechanism of cardioprotection by dexrazoxane are substantial [67–69], other direct or indirect actions of this agent have been postulated to contribute to its protective effect on the anthracycline-treated heart. Recent studies suggest that in addition to its ability to chelate iron, dexrazoxane has direct antioxidant properties both *in vitro* and *in vivo* [70]. This effect can be demonstrated against both peroxynitrite and peroxyl radicals in the plasma of patients treated with an anthracycline. Dexrazoxane can also prevent the acute repression of cardiac mitochondrial gene expression by doxorubicin in the rat [71], as well as a doxorubicin-related shift in cardiac mitochondrial metabolism from fatty acid oxidation to a compensatory oxidation of lactate and glucose by pyruvate dehydrogenase [72]. Whether or not these effects are ROS-related is unknown. In recent studies, chronic doxorubicin administration in murine models has been shown to decrease the phosphorylation of Akt and Erk in the heart; dexrazoxane pretreatment significantly blocks the downregulation of these pro-survival pathways by doxorubicin and, thus, may play an important role in preventing the progression of cardiomyocyte apoptosis [73, 74]. It has recently been proposed that the cardioprotective effects of dexrazoxane are due to the inhibition of topoisomerase II β , limiting doxorubicin-related

DNA damage [75]; however, these studies were performed in a rapidly-dividing myocyte cell culture model that does not reflect the biochemistry of the adult heart. Furthermore, a dexrazoxane derivative that has no effect on topoisomerase function has recently been demonstrated to lack cardioprotective properties [76]. The potential contribution of each of these effects of dexrazoxane to its cardioprotective activity continues to be an area of active investigation.

CLINICAL ANTHRACYCLINE CARDIAC TOXICITY AND ITS PREVENTION BY DEXRAZOXANE

The cardiac toxicity exhibited by doxorubicin and the other anthracyclines is unique in terms of its pathology and mechanism [2, 77]. Although the major limiting factors in the clinical use of anthracyclines in adults are bone marrow suppression and mucositis, for certain patients cardiac toxicity can develop while the individual's tumor is still responding to the anthracycline. Furthermore, synergistic cardiac toxicity has been demonstrated for the combination of doxorubicin and trastuzumab [78,79], an antibody directed against the *HER2/neu* oncoprotein, which is highly active in the treatment of advanced breast cancer [80]. The potentiation of anthracycline-induced heart damage by trastuzumab has eliminated its concurrent use with doxorubicin in the population of patients whose tumors exhibit high levels of *HER2/neu* expression, a group that could benefit most from this combination [81]. Finally, children appear to be more sensitive to the cardiac toxicity of the anthracyclines, and this has become a significant problem in the use of doxorubicin in pediatric oncology [82–84].

Cardiac toxicity has been best documented for doxorubicin administered as an intravenous bolus dose of 45 to 60 mg/m² every 21 to 28 days. Using this schedule, cardiac toxicity develops as a result of cumulative injury to the myocardium. With each dose of doxorubicin there is progressive injury to the heart that increases steadily based on the total dose of drug delivered. The major changes observed in myocytes are dilation of the sarcoplasmic reticulum and disruption of myofibrils. Early in the development of this toxicity these changes appear focally in scattered myocytes surrounded by normal-appearing cells. As the toxicity progresses, the frequency of these altered cells increases until a significant proportion of the myocardium is involved.

The risk of congestive heart failure from the anthracyclines is low at total doses of doxorubicin below 250–300 mg/m² or 600–700 mg/m² of daunorubicin [85, 86], although cases of fatal congestive cardiomyopathy have been observed after a single dose of doxorubicin. Above these doses, the risk steadily accelerates. For doxorubicin, the most commonly used total dose limit applied in the past has been 450–500 mg/m², at which the risk of clinically-evident cardiac toxicity has generally been believed to be 1% to 10%. However, recent large trials that have evaluated heart function with radionuclide-gated cardiac blood pool scans strongly suggest that subclinical reductions in ejection fraction can be detected routinely after 250–300 mg/m² doxorubicin [87, 88]. It is also important to note that congestive heart failure may occur many months after the discontinuation of doxorubicin. Children are clearly at risk of developing congestive heart failure many years

after discontinuing doxorubicin even if treated long-term with an angiotensin-converting enzyme inhibitor [89].

Dexrazoxane is the first and only agent that has been demonstrated to block the development of anthracycline-induced cardiac toxicity in the clinic; controlled clinical trials have proven that this drug dramatically reduces the incidence of cardiac toxicity in patients with breast cancer without significantly altering the antitumor activity of anthracycline-containing combinations [57, 90–92]. Patients receiving dexrazoxane have had, for the most part, an equivalent response rate and duration of time to disease progression, as compared to those not receiving dexrazoxane. Dexrazoxane-treated patients had significantly smaller decreases in left ventricular ejection fraction at each dose level of doxorubicin, and their cardiac biopsies reflected less histologic change. These results have been confirmed in trials with both doxorubicin and its analogue epirubicin and led to the approval of dexrazoxane by the United States Food and Drug Administration as a cardioprotectant in patients receiving >300 mg/m² of doxorubicin [93].

When administered prior to an anthracycline bolus, dexrazoxane is often given at a dose of 500 mg/m²; it has a biphasic disappearance pattern with a short (<1 hr) initial half life, and an elimination phase of over 8 hr [94]. It is rapidly metabolized in humans and in experimental animal models to its ring-opened metabolites, that serve as the critical iron-binding species *in vivo* [95]. To maintain its cardioprotective properties while reducing drug-related granulocytopenia, the currently recommended dose of dexrazoxane is ten times the doxorubicin dose on a mg per mg basis administered no more than 30 minutes before the anthracycline infusion is initiated.

This approach is also applicable to pediatric patients with sarcomas receiving doxorubicin [83] as well as children receiving doxorubicin as part of their induction therapy for acute lymphocytic leukemia [96]. Long-term follow-up studies from two pediatric leukemia cohorts have shown that when dexrazoxane pretreatment was combined with all doses of doxorubicin, left ventricular wall thickness and fractional shortening were significantly better than in patients who received doxorubicin alone; furthermore, there was no apparent adverse effect of dexrazoxane therapy on event-free survival from leukemia in those patients receiving the cardioprotective agent [9, 97].

ANTHRACYCLINE EXTRAVASATION INJURY: TREATMENT WITH DEXRAZOXANE

Extravasation during intravenous administration of most anthracyclines leads to severe, local perivascular damage that can continue to progress over weeks to months, causing pain and permanent dysfunction of the involved area. Pathologically, soft tissue necrosis is associated with dermatitis-like epidermal changes and thrombosis of venules; overall, the process resembles that observed in ionizing radiation injury [98]. The anthracyclines have been shown to bind locally to tissues and can still be detected in high levels based on their characteristic fluorescence at the base of a drug-induced ulcer in the soft tissues of the hand or forearm months later [99–101]. These lesions are very difficult to treat and may significantly delay the administration of additional chemotherapy. Skin grafting is usually

not successful unless preceded by extensive excision of the involved tissue. Debridement of necrotic tissue must be undertaken with extreme caution during the initial phases of extravasation injury, and local wound care to prevent infection is critical [102, 103]. Although a wide range of treatments have been employed immediately after extravasation in an attempt to lessen the injury, including ice, steroids, vitamin E, dimethyl sulfoxide (DMSO), and bicarbonate [104–106], none were found to be unequivocally effective.

More recently, however, dexrazoxane has been used to treat acute anthracycline extravasations with excellent results [107–109]. These initial case reports were based on studies in pre-clinical models that revealed that after subcutaneous administration in mice, necrosis from an anthracycline could be prevented by systemic treatment with dexrazoxane beginning three hours after experimental extravasation, and continuing for multiple doses [110]. It is likely that multiple doses of dexrazoxane are required because, while the extravasated anthracycline is tightly bound to tissues, dexrazoxane is rapidly cleared from the plasma [11]. When dexrazoxane was compared to other agents (DMSO, hydrocortisone, and N-acetylcysteine), it was the only compound that effectively inhibited damage to subcutaneous tissues from an anthracycline antibiotic. Mechanistic studies in this model system, however, have not clarified the precise mechanism of protection provided by dexrazoxane, since dexrazoxane was successful in preventing extravasation injury in transgenic mice expressing a mutant topoisomerase II α gene, suggesting that a dexrazoxane-topoisomerase interaction was not essential for the drug's protective effects [111]. In light of the broad range of oxidant-dependent toxicities that dexrazoxane can ameliorate in animal model systems (including bleomycin pulmonary fibrosis, alloxan-induced diabetes, and acetaminophen-related liver injury), it seems likely that its iron chelating and direct antioxidant properties more likely underlie its ability to prevent tissue injury from the anthracyclines [11,70].

These pre-clinical studies formed the basis for two prospective, single arm clinical trials of intravenous dexrazoxane to prevent long-term injury from anthracycline extravasation [10]. One trial was performed in Denmark, the other recruited patients from 36 oncology units in Europe. The diagnosis of anthracycline extravasation was confirmed by fluorescence microscopy of required tissue biopsies in all protocol entrants. Patients were treated beginning no more than 6 hours following extravasation with a daily, intravenous infusion of 1000, 1000, and 500 mg/m² of dexrazoxane over 1–2 hrs for three consecutive days; dexrazoxane was administered in the arm opposite to that in which the extravasation had occurred. In the two trials, a total of 57 patients were entered, 75% of whom had either breast cancer or lymphoma. The treatment program was dramatically successful; only one patient required surgical resection, and 39 patients had no sequelae following extravasation. Modest hematological toxicity, consistent with the chemotherapies administered and the hematopoietic toxicity of dexrazoxane itself, was observed. This remarkable outcome led to the rapid approval of dexrazoxane as an antidote for anthracycline extravasation injury in Europe and in the United States [110].

CONCLUSION

In this review, we have examined the molecular mechanisms by which dexrazoxane blocks doxorubicin-related damage to the heart as well as prevents drug-related extravasation injury. These mechanisms include chelation of free iron to decrease the production of reactive oxygen species, direct antioxidant effects, protection of cardiac mitochondrial metabolism, as well as the protection of critical cardiac signal transduction cascades. Importantly, the clinical cardioprotection provided by dexrazoxane has recently been shown to benefit children receiving anthracycline-containing chemotherapeutic programs without producing any adverse impact on therapeutic efficacy, even when treatment with the cardioprotective agent is initiated with the first dose of doxorubicin. This approach should now become the standard of care in pediatric oncology. Furthermore, convincing evidence is now available to demonstrate that dexrazoxane can effectively prevent the devastating consequences of the extravasation of doxorubicin outside the vascular system into the subcutaneous space. Dexrazoxane should also be considered the standard of care for this indication. Based on the recent pediatric experience future studies should address whether dexrazoxane could be added to doxorubicin-containing chemotherapy in adults from the first dose of the anthracycline, rather than waiting to initiate cardioprotection until 300 mg/m² of doxorubicin have been delivered.

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ABBREVIATION

ROS Reactive Oxygen Species

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