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Timing of treatment with ICRF-187 and its effect on chronic doxorubicin cardiotoxicity

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Abstract. Studies were conducted to evaluate whether the timing of administration of ICRF-187 [(+)-1,2-bis(3,5 dioxopiperazinyl-1-yl)propane] would influence the degree of cardioprotection provided by this agent against the development of doxorubicin-induced chronic cardiomyopathy. Beagle dogs (8.5–14 kg) received either doxorubicin alone (1.75 mg/kg, i.v., $n = 8$), doxorubicin (1.75 mg/kg) simultaneously with ICRF-187 (35 mg/kg, i.v., $n = 8$), or doxorubicin (1.75 mg/kg) followed 2 h later by ICRF-187 (35 mg/kg, $n = 8$). Control animals received ICRF-187 (35 mg/kg, $n = 4$) or saline ($n = 4$). All animals received a course of seven treatments, each given 3 weeks apart, and were killed 3 weeks after the last treatment. Semiquantitative grading of histologic sections of myocardium showed that as compared with animals treated with doxorubicin alone, the incidence and the severity of the doxorubicin-induced myocardial lesions were reduced in the two groups of animals given doxorubicin plus ICRF-187. However, protection was significantly better in dogs receiving ICRF-187 and doxorubicin simultaneously than in those given ICRF-187 2 h after doxorubicin. These observations were interpreted as indicating that the timing of administration of ICRF-187 with respect to that of doxorubicin is an important factor in determining the degree of cardioprotection and that there is a "time window" in which ICRF-187 exerts optimal effects.

Introduction

A major limitation to the optimal use of anthracyclines such as doxorubicin in cancer chemotherapy is a dose-related cardiomyopathy [3, 19, 20]. Attempts to resolve the problem have included the administration of compounds that would protect the myocardium from the toxic effects of anthracyclines. Pretreatment with one of these, ICRF-187 [(+)-1,2-bis(3,5 dioxopiperazinyl-1-yl)propane], has led to a significant decrease in both the incidence and the severity of chronic daunorubicin- or doxorubicin-induced cardiomyopathy in rabbits [13], rats [17], dogs [10], and miniature swine [11]. These studies have exclusively used a time sequence in which ICRF-187 is given 30 min before the anthracycline. Attempts have been made to define the scope of the protective activity against acute high-dose toxicity by varying the interval between the treatment with ICRF-159 (the racemic mixture of which ICRF-187 is the d-isomer) or ICRF-187 and that with the anthracycline [14, 28]. These studies have suggested that the interval is an important factor in determining the extent of the reduction in toxicity afforded by treatment with ICRF-187 and ICRF-159. Wang et al. [28] reported that the protective effect of ICRF-159 was maximal when it was given 24 h prior to or simultaneously with daunorubicin. Likewise, Herman et al. [14] found that the survival of hamsters was maximal when ICRF-187 was given between 3 h before and 3 h after daunorubicin.

There are no data concerning the relationship between the timing of the administration of ICRF-187 and doxorubicin and the degree of reduction in chronic anthracycline cardiotoxicity. The present study was designed to compare the extent of the cardioprotection obtained when ICRF-187 is given simultaneously with or 2 h after a dose of doxorubicin known to induce chronic cardiomyopathy in beagle dogs. This species was used in these experiments because it has been our experience that beagle dogs are not prone to develop respiratory infection and doxorubicin-induced renal toxicity, in contrast to rodents. In addition, cardiac lesions produced by doxorubicin are more consistent in the dog than in other species [10, 11, 13–17].

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Materials and methods

Experimental procedures. Adult beagle dogs (1.5–2 years old) of either sex, weighing between 8.5 and 14 kg, were assigned to three treatment groups of eight animals (groups 1–3) and two control groups of four animals (groups 4 and 5). Dogs in groups 1–3 received i. v. injections of 1.75 mg/kg of doxorubicin. The animals in groups 2 and 3 were given i. v. injections of 35 mg/kg of ICRF-187 simultaneously with (group 2) or 2 h after doxorubicin administration (group 3). Dogs in the control groups received 35 mg/kg of ICRF-187 (group 4) or saline (group 5) i. v. without doxorubicin. After dosing, dogs were returned to their pens, observed daily, and weighed weekly. All drug injections were given into the cephalic vein at 3-week intervals, and the experiment was terminated 3 weeks after the seventh treatment period (21 weeks). Lyophilized doxorubicin, ICRF-187, and the combination of ICRF-187 and doxorubicin (Adria Laboratories, Columbus, Ohio) were reconstituted in normal physiological saline to a concentration of 1.25 mg doxorubicin/ml and 25 mg ICRF-187/ml just prior to their use.

Clinical laboratory determinations. Blood samples for complete blood cell counts and serum chemistry screens were obtained from the jugular vein prior to the first dosing (control), before each subsequent treatment, and 3 weeks after the seventh drug injection. The hematologic and clinical chemistry determinations were performed by MET-PATH Laboratories (Rockville, Md.). A two-tailed, paired-sample *t*-test was used for statistical analysis to determine treatment-related differences in clinical chemistry and hematologic results.

Procedures for terminal study. At 3 weeks after the seventh doxorubicin dose (total cumulative dose, 12.25 mg/kg), the animals were euthanized and the entire heart and samples of the small intestine, kidney, liver, skeletal muscle, and diaphragm were excised and fixed in neutral buffered 10% formalin. Three blocks of tissue (left ventricular free wall, papillary muscles, and ventricular septum) were embedded in glycol methacrylate plastic resin. Sections of plastic-embedded tissues were stained with hematoxylin-eosin or toluidine blue. All noncardiac tissues were embedded in paraffin and stained with hematoxylin-eosin. The frequency and severity of doxorubicin-induced myocardial lesions were assessed by light microscopic evaluation of sections stained with toluidine blue. Lesions were graded on the following scale on the basis of the percentage of myocytes showing myofibrillar loss and cytoplasmic vacuolization: 0, no damage; 1+, less than 10% involvement; 2+, 10%–24% involvement; 3+, 25%–49% involvement; and 4+, 50% or greater involvement. The cardiomyopathy score reported for each animal represents the mean value for all three sections rounded to the nearest whole number. Sections were evaluated without knowledge of the treatment given to the dogs. A Kruskal-Wallis rank test [18] was used to determine the significance of differences in the severity of cardiomyopathy scores among treatment groups.

Table 1. Effect of ICRF-187 treatment on the incidence and severity of doxorubicin-induced chronic cardiomyopathy in beagle dogs

Group	Number of animals	Severity of lesions				
		0	1+	2+	3+	4+
Doxorubicin	8	0	0	1	6	1
Doxorubicin/ICRF-187, Simultaneous*, **	8	4	4	0	0	0
Doxorubicin/ICRF-187, doxorubicin after 2 h*	8	0	6	2	0	0
ICRF-187*	4	4	0	0	0	0
Saline*	4	4	0	0	0	0

Dogs received a total of 7 doses, each given 3 weeks apart, of either doxorubicin (1.75 mg/kg, i. v.) and/or ICRF-187 (35 mg/kg, i. v.) and were killed 3 weeks after the last injection

* Score significantly lower than that of the group receiving doxorubicin alone; $P < 0.001$, ranking test (Kruskal-Wallis)

** Score significantly lower than that of the group receiving ICRF-187 2 h after doxorubicin; $P < 0.05$, ranking test (Kruskal-Wallis)

Results

General toxicity and weight changes

Three dogs given doxorubicin alone died during the course of the study: one died 3 weeks after the sixth treatment period, and the other two died 2 and 7 days following the seventh doxorubicin dosing, respectively. Although the exact cause of death of these animals could not be determined at necropsy, it seems likely that acute sepsis was a contributing factor in at least two of these animals.

Loss of hair was noted in most dogs given doxorubicin with or without ICRF-187. It began around the snout after the second dose and became more extensive as the doxorubicin treatment continued. Dogs given ICRF-187 or saline without doxorubicin did not develop any alopecia. Mean body weights in the groups of animals receiving doxorubicin or ICRF-187 and doxorubicin were similar at the beginning and at the end of the experiment (i. e., animals did not show statistically significant changes in body weight during this period). These weights were: doxorubicin alone, 11.4 ± 1.9 kg initial weight and 10.5 ± 2.0 kg final weight; doxorubicin given simultaneously with ICRF-187, 10.7 ± 1.4 kg initially and 11.3 ± 2.1 kg finally; doxorubicin followed in 2 h by ICRF-187, 11.6 ± 0.8 kg initially and 11.9 ± 1.5 kg finally; and ICRF-187 alone, 11.7 ± 1.4 kg initially and 13.4 ± 1.7 kg finally. In contrast, the saline-control group animals did increase significantly in body weight during the course of the study, from 11.0 ± 0.7 to 13.4 ± 0.5 kg ($P < 0.05$).

Gross anatomic changes

At necropsy, two dogs treated with doxorubicin alone (one of which had died and one of which was euthanized at the end of the study) had excess fluid in the abdominal, pleural, and pericardial cavities. Few consistent gross anatomic alterations were found in any of the other animals.

Myocardial alterations

The myocardial lesions found in the present study (Table 1) were similar to those described previously in beagle dogs with anthracycline cardiomyopathy [10]. Such lesions are also similar to those that develop under comparable circumstances in humans [3], miniature swine [11], rabbits [13], and rats [15]. The two primary myocyte alterations observed by light microscopy were cytoplasmic vacuolization and myofibrillar loss. Both of these alterations were observed in progressively larger numbers of cells as the lesions increased in severity. The vacuolization,

which is due to dilatation of the sarcoplasmic reticulum, involved the formation of multiple clear vacuoles that filled the cytoplasm of the affected cells and frequently caused these cells to appear larger than normal [10]. The myofibrillar loss resulted in a pale but nonvacuolated appearance of the cytoplasm. Both the vacuolization and the myofibrillar loss often were found together in the same cells.

Myocyte alterations were observed in the hearts of all eight animals given doxorubicin alone. Seven of the eight dogs in this group had lesion scores ranging from 3 to 4+. In contrast, the lesion scores were 0 in four animals and 1+ in the other four animals in the group receiving ICRF-187 and doxorubicin simultaneously. Myocardial lesions were found in the hearts of all eight dogs given ICRF-187 2 h after doxorubicin. However, six of these animals had only minimal alterations (lesion score, 1+) whereas the other two had mild lesions (lesion score, 2+). Highly significant differences ($P < 0.001$) in cardiomyopathy scores (Table 1) were found between the group receiving doxorubicin alone and the groups given ICRF-187 simultaneously with or 2 h after doxorubicin. Likewise, a significant difference in lesion severity was found between the group receiving ICRF-187 and doxorubicin simultaneously and the group given ICRF-187 2 h after doxorubicin ($P < 0.05$). No cardiac lesion was found in the animals given ICRF-187 or saline without doxorubicin.

Pathology of non-cardiac tissues

Alterations were found in the small intestine, liver, and kidney of the three dogs that died prior to termination of the study. Mild to moderate hepatic and renal congestion were consistent findings in these animals. In two of the animals, hemorrhage was associated with the congestion. Lesions in the small intestine included loss of the epithelial cells of the villi (one animal) and severely necrotizing superficial ulcers (two animals). Minimal to mild gastrointestinal alterations were noted in two of the five surviving animals receiving doxorubicin alone (lymphocytic infiltration at the tips of the villi). Gastrointestinal alterations were found in six of eight animals receiving ICRF-187 and doxorubicin simultaneously (lymphocytic infiltration at the tips of the villi) and in one of eight animals receiving ICRF-187 2 h after doxorubicin (minimal superficial ulcer). No histological alteration was observed in the animals given ICRF-187 or saline.

Clinical chemistries and hematologic determination

When the experiment was terminated, the serum concentrations of glucose, urea nitrogen, creatinine, bilirubin, total lipids, total protein, triglycerides, uric acid, cholesterol, sodium, potassium, calcium, and chloride and both the activities of serum glutamate-oxalate transaminase, alkaline phosphatase, and glutamate-pyruvate transaminase and the white blood cell counts in all groups given doxorubicin with or without ICRF-187 were not significantly changed from the control values obtained before drug administration.

Significant changes were found in the serum concentrations of lactic dehydrogenase (LDH) and iron and in certain hematologic values. Serum LDH determinations revealed an increase in values from the beginning (control values obtained before the first injection) to the end of the experiment (final values) in the groups receiving doxorubicin alone (95 ± 35 and 324 ± 185 U/l, respectively) and in those receiving ICRF-187 either simultaneously with doxorubicin (85 ± 30 and 240 ± 167 U/l, respectively) or 2 h after doxorubicin (79 ± 42 and 272 ± 89 U/l, respectively). There was no significant difference in the final LDH values among these three groups. The corresponding initial and final LDH values were 58 ± 40 and 86 ± 14 U/l for animals given ICRF-187 alone and 69 ± 22 and 113 ± 15 U/l for those given saline. Total serum iron concentrations were depressed in all groups receiving doxoru-

Table 2. Serum iron, red blood cell count, hemoglobin, and hematocrit values measured before (initial) and 3 weeks after administration of the final (seventh) dose of doxorubicin alone or in combination with ICRF-187

Groups	Total serum iron (μg/dl)		Red blood cells ($\times 10^6$/mm^3)		Hemoglobin (g/dl)		Hematocrit (%)	
	Initial	Final	Initial	Final	Initial	Final	Initial	Final
Doxorubicin	198±24[a]	124±12*	7.1±0.7[a]	6.0±0.6*	18.3±1.7[a]	14.3±1.4*	51.5±4.7[a]	41.1±4.5*
Doxorubicin/ ICRF-187, simultaneous	194±35	105±21*	7.5±0.3	6.4±0.6*	18.6±0.6	15.2±1.2*	53.6±1.8	45.9±3.7*
Doxorubicin/ ICRF-187, doxorubicin after 2 h	170±29	91±32*	7.3±0.1	6.4±0.4*	18.8±0.9	15.4±0.8*	53.5±1.0	44.9±2.9*
ICRF-187	183±43	188±16	7.1±0.4	7.0±0.5	17.2±0.9	17.6±0.5	49.5±2.7	50.0±1.6
Saline	208±45	228±64	6.9±0.3	7.2±0.2	17.7±0.6	17.4±1.3	51.3±1.0	49.2±4.0

Dogs received a total of 7 doses, each given 3 weeks apart, of either doxorubicin (1.75 mg/kg, i.v.) and/or ICRF-187 (35 mg/kg, i.v.) and were killed 3 weeks after the last injection

[a] All data are given as mean values ± SD

* Significantly different from the initial value; $P < 0.05$, paired-sample t-test

bicin, irrespective of treatment with ICRF-187 (Table 2). Significant decreases in red blood cell counts, hemoglobin concentration, and hematocrit were also found in the doxorubicin-treated groups (Table 2). No significant alteration in any clinical chemistry or in any hematologic value was found over the course of the study in groups given saline or ICRF-187 without doxorubicin.

Discussion

In the present study, the time of ICRF-187 dosing was varied so as to define better the scope of the protective activity that this compound exerts on chronic doxorubicin cardiotoxicity. The characteristics and the severity of the myocyte alterations observed in the present series of dogs were comparable with those previously noted in dogs receiving doxorubicin either in 7 doses of 1.75 mg/kg given at 3-week intervals or in 15 doses of 1 mg/kg given weekly [10, 16]. In these studies, pretreatment with ICRF-187 30 min prior to either doxorubicin or daunorubicin caused significant decreases in both the incidence and the severity of the cardiomyopathy [10, 16].

A comparison of the data from animals receiving ICRF-187 simultaneously with doxorubicin or 2 h after the latter drug showed that significant cardioprotection was obtained with both of these schedules of administration (Table 1). In both groups the cardiomyopathy scores were significantly lower than those in animals given doxorubicin alone ($P < 0.001$). Among these two groups, cardiomyopathy scores were significantly lower in the animals receiving doxorubicin and ICRF-187 simultaneously ($P < 0.05$). This degree of reduction in the incidence and severity of the lesions observed when the agents are given simultaneously is comparable with that reported previously in dogs given ICRF-187 30 min prior to doxorubicin [10, 16]. Thus, the protection provided by ICRF-187 against chronic doxorubicin toxicity in beagle dogs is more effective when this agent is given at times closer to doxorubicin administration.

A somewhat similar finding was reported by Filippi et al. [5], who also observed time-dependent variations in ICRF-187 cardioprotection in mice treated chronically with doxorubicin according to the protocol developed by Bertazzoli et al. [2]. A reduction in cardiac damage was found when ICRF-187 was given as early as 2 h prior to doxorubicin and as late as 1 h after the anthracycline; however, protection was optimal when the compound was given from 30 min before to 15 min after doxorubicin [5].

Wang et al. [28] examined the survival of mice given ICRF-159 over a period ranging from 96 h before to 48 h after a single high dose (10 mg/kg) of daunorubicin. They found that survival was enhanced when ICRF-159 was given from 48 h before to 24 h after daunorubicin but was maximal when the compound was given 24 h before or at the same time as the anthracycline [28]. Similar differences in protection were observed when hamsters were given 100 mg/kg of ICRF-187 at various times before or after the administration of a single dose of 25 mg/kg of daunorubicin [14]. Although some increase in survival was noted in animals treated up to 48 h before or 6 h after receiving daunorubicin, the best protection was obtained when ICRF-187 was given between 3 h before and 3 h after the anthracycline [14]. There are differences in the major toxic effects induced by acute high doses (gastrointestinal, bone marrow toxicity) and chronic low doses (cardiotoxicity) of anthracyclines. Nevertheless, the studies cited above and the present study indicate the existence of a "time window" in which ICRF-159 and ICRF-187 exert maximal protection against either acute or chronic anthracycline toxicity. Such observations suggest that there is a certain interval that lapses between anthracycline administration and the onset of the biochemical effects by which these agents induce cellular alterations.

Doxorubicin is rapidly taken up by tissues from the plasma [29] and can be detected in the heart for prolonged periods [25]. However, in dogs, treatment with ICRF-187 does not alter the pharmacokinetic profile of doxorubicin [1]. It appears that if doxorubicin is given without being followed within a short time by an adequate dose of ICRF-187, it will initiate myocardial damage that is not prevented or reversed by the subsequent administration of free-radical scavengers (*N*-acetylcysteine or vitamin E) [16, 21] or ICRF-187 itself (which does not function as a free-radical scavenger). Considerable evidence indicates that a most important mechanism in this process is the formation of oxygen free radicals [8, 22, 26]. These highly reactive radicals are formed and initiate peroxidative activity quickly, and as a result, free-radical scavengers are of little use in preventing the chronic anthracycline cardiotoxicity [16, 21].

It has been postulated that the protective effect of ICRF-187 against doxorubicin-induced cardiac damage is ultimately related to the ability of this agent to penetrate into cells, where its two dioxopiperazine rings undergo hydrolytic opening to form a diacid diamide derivative (ICRF-198) [9]. This derivative, which strongly binds iron, could act as an intracellular chelator of the iron needed to catalyze the anthracycline-mediated formation of oxygen free radicals [6]. It is not known to what extent the differences in animal survival or in cardiomyopathy scores reflect the kinetics of the iron-chelation process that is presumed to constitute the basis of the pharmacologic activity of ICRF-187. Pharmacokinetic studies in mice (100 mg/kg) and dogs (12.5 mg/kg) showed that the plasma half-life of ^{14}C-labeled ICRF-187 was short (1.5 and 3 min, respectively) and that the tissue distribution and elimination were rapid [23, 24]. In dogs, the highest concentrations of ICRF-187 were found in the liver (100 μg/g) and kidney (31 μg/g) within 2 h of administration [24]. During that same period a maximal cardiac concentration of 6 μg/g tissue was attained. Both the parent compound and unidentified metabolites were detected in tissues, plasma, and urine [24].

Other studies have shown that the uptake of ICRF-187 into isolated beating rat myocytes proceeds rapidly and that 65% of the parent compound is converted to the diacid diamide metabolite (ICRF-198) [4] within 0.5 min of administration. Doroshow et al. [4] concluded that the kinetics of ICRF-187 are dominated by rapid entry of the intact drug into cells followed by an almost immediate conversion by hydrolysis to a compound that possesses metal-

chelating properties. However, no data are available concerning the extent and time course of cardiac iron chelation occurring as a result of in vivo administration of ICRF-187.

In addition to differences in timing of the administration of ICRF-187, the present study utilized a higher dose of this agent (35 mg/kg) than was used in previous studies with dogs (25 or 12.5 mg/kg) [10, 16]. Under certain circumstances, the combination of a bisdiketopiperazine agent with an anthracycline can provoke increased noncardiac toxicity as observed in mice (increased lethality) and in hamsters (greater bone marrow suppression) [7, 12]. In patients, the combination of a high dose of ICRF-159 and doxorubicin caused more bone marrow suppression than when either agent was given alone [27]. In the present study, red blood cell counts, hematocrit, hemoglobin, and serum iron concentrations declined to a similar extent in all groups of dogs given doxorubicin, whether or not they also received ICRF-187.

The conclusions of the present study can be summarized as follows: (1) treatment with ICRF-187 provided protection against the cardiotoxicity induced by the chronic administration of low doses of doxorubicin to beagle dogs; (2) the degree of cardioprotection was higher when ICRF-187 was given simultaneously with doxorubicin than when it was given 2 h after the latter agent – thus, the timing of administration of ICRF-187 with respect to that of doxorubicin is an important factor in determining the degree of cardioprotection; and (3) there is a "time window" in which ICRF-187 exerts optimal effects in preventing doxorubicin-induced chronic cardiomyopathy.

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