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DISPOSITION OF AMIODARONE AND ITS PROXIMATE METABOLITE, DESETHYLAMIODARONE, IN THE DOG FOR ORAL ADMINISTRATION OF SINGLE-DOSE AND SHORT-TERM DRUG REGIMENS

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ABSTRACT:

A comparative study of the plasma disposition and tissue distribution of amiodarone and its proximate metabolite, desethylamiodarone, for a single oral dose and short-term oral dosage regimens was conducted in the dog. Four groups of male mongrel dogs (six per group) received one of the following oral dosage regimens: single dose of 40 mg amiodarone/kg; 40 mg amiodarone/kg/day for 10 days and then 30 mg/kg/day for 4 days; 40 mg amiodarone/kg/day for 10 days, 30 mg/kg/day for 4 days, and then no treatment for 14 days; and 40 mg amiodarone/kg/day for 10 days, 30 mg/kg/day for 4 days, and then 20 mg/kg/day for 5 days/week for 2 weeks. The plasma and tissue amiodarone and desethylamiodarone concentrations were determined by HPLC. The plasma concentration of amiodarone was greater than that of desethylamiodarone for the four dosage regimens. The apparent plasma elimination half-life of amiodarone was prolonged following repeated drug administration (3.2 days) compared with a single drug dose (7.5 hr). There was extensive extravascular distribution of amiodarone and desethylamiodarone resulting in progressive tissue accumulation of drug and metabolite for the short-term regimens. For most of the dosage regimens, the concentration of amiodarone was greater than that of desethylamiodarone in left and right ventricles, thyroid gland, adipose tissue, and kidney, whereas the parent drug and metabolite concentrations were similar in lung, liver, and brain. There was predominant accumulation of amiodarone in adipose tissue and desethylamiodarone in lung. After cessation of amiodarone administration, there was rapid elimination of parent drug and metabolite from all tissues, except for amiodarone from adipose tissue. It would appear that adipose tissue serves as a reservoir for amiodarone, which could explain the prolonged plasma elimination half-life of the drug after repeated administration.

Amiodarone, an iodine-containing benzofuran derivative, is an efficacious antiarrhythmic drug for the treatment of life-threatening ventricular tachyarrhythmias (1). Although the clinical use of this drug has been increasing, its pharmacology has not been completely elucidated. Human and experimental animal studies have demonstrated that amiodarone has unusual pharmacologic properties including: differential pharmacokinetics for acute *vs.* chronic therapy; delayed onset of antiarrhythmic action with chronic oral therapy; differential cardiac electrophysiologic actions for acute iv therapy compared with chronic oral treatment; persistent antiarrhythmic action after cessation of pharmacotherapy; broad spectrum of therapeutic effects including suppression of ventricular and supraventricular arrhythmias and antianginal action; toxic effects on a variety of organ systems including the heart, lungs, liver, thyroid gland, kidneys, central nervous system, skin, and eyes; a pharmacologically-active metabolite, *viz.* desethylamiodarone, that has antiarrhythmic effects and produces pulmonary toxicity; and a questionable relationship between plasma (tissue) drug concentration and therapeutic/toxic effects (see reviews: 1–3).

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The pharmacokinetics of amiodarone have been studied in the human (see reviews: 1–3), rat (4, 5), rabbit (6), and dog (7, 8). The disposition of amiodarone is complex. There is low and variable bioavailability of amiodarone for oral drug administration (22 to 86%) (2). Elimination of amiodarone occurs primarily by drug biotransformation, with less than 1% of the dose excreted unchanged in the urine (2). Biotransformation involves *N*-deethylation of amiodarone to give desethylamiodarone, which is pharmacologically active (8, 9) and is the major metabolite found in the plasma of the human and several other mammalian species (2). The very high lipid solubility of amiodarone can explain, at least in part, its extensive accumulation in lipophilic tissues and consequent large apparent volume of distribution (0.9 to 148 liters/kg in the human) and very small amount of drug that undergoes renal excretion (2, 3). The plasma elimination half-life of amiodarone depends on the dosage regimen, such that, in the human, the half-life is in the range of 3 to 80 hr for a single dose and up to 100 days after the cessation of chronic amiodarone treatment (2), which may be due to the extensive extravascular distribution of the drug rather than to any limited capacity of the amiodarone-metabolizing systems (3). The pharmacokinetics of amiodarone in healthy volunteers are not different from those in patients with cardiac arrhythmias, but no coexisting liver or cardiac failure (2). The complex pharmacokinetics of amiodarone have contributed to the controversy regarding the existence of a plasma amiodarone concentration-response relationship (3, 10).

In our laboratory, we have been investigating the antiarrhythmic and electrophysiologic properties of amiodarone in the

dog with subacute myocardial infarction and reproducibly-inducible ventricular arrhythmias. Presently, there is a paucity of knowledge about the disposition of amiodarone in the dog for a chronic oral dosage regimen that produces antiarrhythmic effects. Furthermore, it is necessary to know the disposition of a drug in the experimental animal species in which the pharmacodynamics, including mechanism, are being studied in order to determine whether there are important pharmacokinetic-pharmacodynamic relationships, including the existence of a therapeutic range for plasma amiodarone (and desethylamiodarone) concentration. The objective of our investigation was to conduct a comparative study of the plasma and tissue concentrations of amiodarone and its proximate metabolite, desethylamiodarone, in the dog for oral administration of single-dose and short-term regimens of amiodarone. The regimens were selected based on the findings of a preliminary investigation which demonstrated that in order to achieve in dogs a plasma amiodarone concentration similar to that observed in patients who received 10 mg amiodarone/kg/day for 10 days, followed by 7.5 mg/kg/day for 4 days, and then 5 mg/kg/day for 5 days/week (11), it was necessary to administer to the dog a dosage regimen 4 times that given to the human (12).

Materials and Methods

Drugs and Chemicals. Amiodarone hydrochloride and desethylamiodarone hydrochloride were obtained from Sanofi (Montpellier, France) *via* Ayerst Laboratories (Montreal, Canada). All chemicals used in the HPLC methods for the quantitation of amiodarone and desethylamiodarone were spectrophotometric or HPLC grade, and were obtained from a variety of commercial sources. The daily doses of amiodarone were administered in the form of the hydrochloride salt, were given in gelatin capsules, and are reported as the hydrochloride salt.

Experimental Protocol. Male mongrel dogs (20.7 ± 2.6 kg) were studied in accordance with the principles and guidelines on the care and use of experimental animals of the Canadian Council on Animal Care. Four groups of dogs (six per group) received one of the following oral once-daily amiodarone dosage regimens: single dose of 40 mg amiodarone/kg (single dose); 40 mg amiodarone/kg/day for 10 days and then 30 mg/kg/day for 4 days (14-day regimen); 40 mg amiodarone/kg/day for 10 days, 30 mg/kg/day for 4 days, and then no treatment for 14 days (14-day regimen/elimination); and 40 mg amiodarone/kg/day for 10 days, 30 mg/kg/day for 4 days, and then 20 mg/kg/day for 5 days/week for 2 weeks (28-day regimen). Blood samples were obtained from a forelimb vein by venipuncture at selected times after the single drug dose, and at 24 hr after selected daily doses, as well as at other selected times for the short-term regimens. Each blood sample was placed in a heparin-containing tube, centrifuged at 1350*g* for 10 min, and the plasma was stored at −20°C until analyzed. At 24 hr after the single dose, at 24 hr after the last dose of the 14-day regimen and of the 28-day regimen, and on the last day of the 14-day regimen/elimination, a blood sample was obtained before each animal was terminated with an overdose of sodium pentobarbital. Myocardial tissue samples were removed from the walls of the left and right ventricles. Samples of lung, liver, thyroid gland, and kidney were dissected from the same respective anatomical location for all animals. Adipose tissue from the abdominal region and the brain were excised. All tissue samples were frozen immediately in liquid nitrogen and stored at −20°C until analyzed.

Quantitation of Amiodarone and Desethylamiodarone. Plasma and tissue amiodarone and desethylamiodarone concentrations were measured by reverse-phase HPLC methods using UV-Visible spectrophotometric detection (13–15). Each sample was analyzed in triplicate. The lower limit of quantitative sensitivity was 0.05 μg amiodarone (or desethylamiodarone) per ml plasma and 1.0 μg amiodarone (or desethylamiodarone) per g wet tissue weight. The within-day coefficient of variation of the methods did not exceed 8.0% for amiodarone and 7.2% for desethylamiodarone.

Data Analysis. The amiodarone and desethylamiodarone concentration data are presented as group means ± SD. The drug and metabolite concentration data for plasma, obtained just before animal termination, and each tissue were compared across the four treatment groups by randomized-design one-way analysis of variance followed by Newman-Keuls test for a significant F statistic, using transformed data if there was heterogeneity of variance in the data (16). Amiodarone and desethylamiodarone concentration data of each treatment group were compared across plasma, obtained just before animal termination, and tissues by repeated-measures analysis of variance and Newman-Keuls test. Plasma and tissue parent drug concentrations were compared with the respective metabolite concentrations by Student's t test for paired data (two-tailed). Two groups of data were considered to be statistically different when $p < 0.05$. Model-independent kinetic analysis was performed to determine the half-life of the apparent terminal elimination phase of the plasma amiodarone and desethylamiodarone concentration-time curves of the individual dogs. Least-squares linear regression analysis of the appropriate log-linear data was conducted to determine the apparent elimination rate constant (k_e), and the apparent elimination half-life was calculated by the equation: $t_{1/2} = 0.693/k_e$.

Results

The plasma amiodarone and desethylamiodarone concentration-time curves for the single dose of amiodarone are presented in fig. 1. Although there was appreciable interanimal variability in the data as shown by the SD values, the amiodarone concentration was greater ($p < 0.05$) than that of desethylamiodarone for the 1.5 to 24 hr interval. The plasma amiodarone concentration appeared to be maximal at 3 hr; for the individual animals, the range of maximal plasma amiodarone concentration and time of occurrence was 1.0 to 4.0 μg/ml and 2 to 10 hr, respectively. The apparent plasma elimination half-life was 7.5 ± 3.2 hr for amiodarone, and could not be calculated for desethylamiodarone due to the very low plasma concentrations.

The plasma amiodarone and desethylamiodarone concentration-time curves for the 14-day amiodarone regimen and the 14-day drug regimen followed by a 14-day drug elimination period are presented in the *upper* and *lower panels*, respectively, of fig. 2. The amiodarone concentration was greater ($p < 0.05$) than that of desethylamiodarone throughout the drug treatment period and during the drug elimination period. The respective amiodarone and desethylamiodarone concentrations at day 14

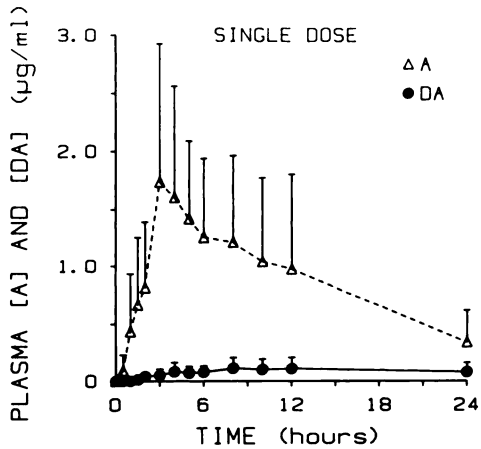

FIG. 1. *Plasma amiodarone and desethylamiodarone concentration-time curves in the dog for a single oral dose of amiodarone.*

Six dogs received a single oral dose of 40 mg amiodarone/kg. The data are presented as the mean ± SD. Statistical differences are reported in the text.

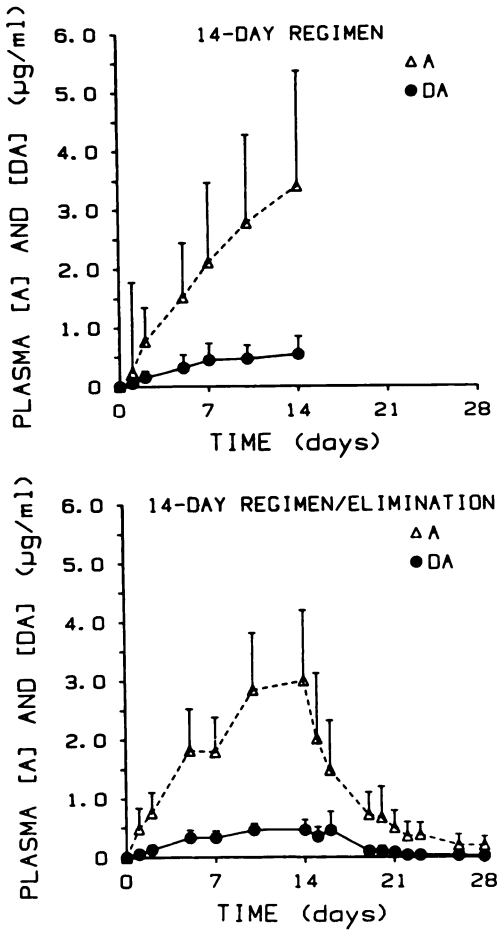

FIG. 2. *Plasma amiodarone and desethylamiodarone concentration-time curves in the dog for a 14-day oral amiodarone regimen (upper panel) and a 14-day oral amiodarone regimen/14-day elimination period (lower panel).*

Six dogs received a 14-day oral amiodarone regimen (40 mg amiodarone/kg/day for 10 days and then 30 mg/kg/day for 4 days) and six dogs received a 14-day oral amiodarone regimen (40 mg amiodarone/kg/day for 10 days and 30 mg/kg/day for 4 days) followed by 14 days of no treatment. The data are presented as the mean ± SD. Statistical differences are reported in the text.

were not statistically different between the two regimens. The elimination of amiodarone and desethylamiodarone from plasma appeared to be monoexponential as assessed by log-linear analysis of the individual animal data. The apparent plasma elimination half-life values were 3.2 ± 0.8 days and 3.5 ± 2.8 days for amiodarone and desethylamiodarone, respectively, and were not statistically different.

The plasma amiodarone and desethylamiodarone concentration-time curves for the 28-day amiodarone regimen are presented in fig. 3. The plasma amiodarone concentration was greater ($p < 0.05$) than the desethylamiodarone concentration throughout the 28-day study. The amiodarone concentration appeared to be maximal at day 14, and then declined during the next 14 days of treatment, as expected for the lower daily maintenance dose of the drug. Likewise, the desethylamiodarone concentration decreased during the last 14 days of treatment. There was, however, no significant change in amiodarone concentration from day 21 to day 28, as was also the case for desethylamiodarone. These findings indicated that apparent

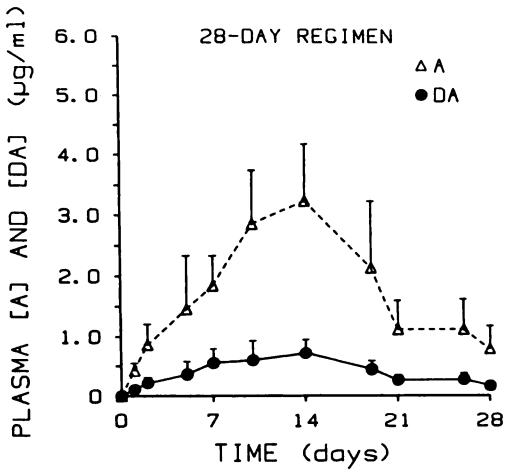

FIG. 3. *Plasma amiodarone and desethylamiodarone concentration-time curves in the dog for a 28-day oral amiodarone regimen.*

Six dogs received a 28-day oral amiodarone regimen (40 mg amiodarone/kg/day for 10 days, then 30 mg/kg/day for 4 days, followed by 20 mg/kg/day for 5 days/week for 2 weeks). The data are presented as the mean ± SD. Statistical differences are reported in the text.

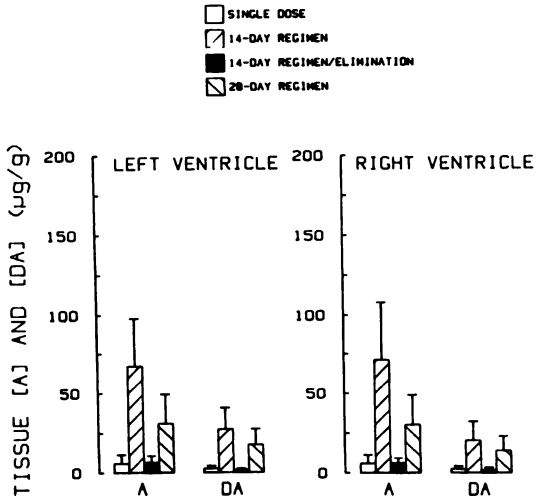

FIG. 4. *Left ventricle and right ventricle amiodarone and desethylamiodarone concentrations in the dog after oral administration of a single dose of amiodarone, 14-day amiodarone regimen, 14-day amiodarone regimen/14-day elimination period, and 28-day amiodarone regimen.*

Four groups of dogs (six per group) received one of the following oral amiodarone dosage regimens: single dose of 40 mg amiodarone/kg; 40 mg amiodarone/kg/day for 10 days and then 30 mg/kg/day for 4 days; 40 mg amiodarone/kg/day for 10 days, 30 mg/kg/day for 4 days, and then no treatment for 14 days; 40 mg amiodarone/kg/day for 10 days, 30 mg/kg/day for 4 days, and then 20 mg/kg/day for 5 days/week for 2 weeks. The data are presented as the mean ± SD. Statistical differences are reported in the text.

steady-state conditions were achieved during the last week of the 28-day regimen.

The amiodarone and desethylamiodarone concentration data in the left and right ventricles for the four amiodarone dosage regimens are presented in fig. 4. The concentrations of the parent drug and its *N*-deethylated metabolite were greater ($p < 0.05$) for the 14-day and 28-day regimens compared with the 14-day regimen/elimination protocol and single drug dose. For the

individual dosage regimens, the amiodarone concentration in each tissue was greater ($p < 0.05$) than the desethylamiodarone concentration.

The lung, liver, and thyroid gland amiodarone and desethylamiodarone concentration data are presented in fig. 5. In the lung, the amiodarone and desethylamiodarone concentrations were greater ($p < 0.05$) for the 14-day and 28-day regimens compared with the single dose and 14-day regimen/elimination. For the liver, the parent drug concentration was greatest ($p < 0.05$) for the 14-day regimen compared with the other three regimens. This also appeared to be the case for desethylamiodarone. For the thyroid gland, the amiodarone and desethylamiodarone concentrations were greatest ($p < 0.05$) for the 14-day regimen compared with the other three dosage protocols. For the individual regimens, the amiodarone concentration appeared to be similar to that of desethylamiodarone in the lung and liver. For the thyroid gland, however, the amiodarone concentration was greater ($p < 0.05$) than that of desethylamiodarone for all four regimens.

The adipose tissue, kidney, and brain amiodarone and desethylamiodarone concentrations for the four amiodarone regimens are presented in fig. 6. In adipose tissue, the amiodarone and desethylamiodarone concentrations were greater ($p < 0.05$) for the 14-day and 28-day regimens compared with the single dose and 14-day regimen/elimination protocol, whereas for each dosage regimen, the amiodarone concentration was much greater ($p < 0.05$) than that of desethylamiodarone. In kidney, the amiodarone and desethylamiodarone concentrations were greatest ($p < 0.05$) for the 14-day regimen compared with the other three dosage regimens; within each dosage regimen, the amiodarone concentration was greater ($p < 0.05$) than the desethylamiodarone concentration. For brain, the amiodarone and desethylamiodarone concentrations were greatest ($p < 0.05$) for the 14-day regimen compared with the other three dosage protocols; within the individual dosage regimens, the amiodarone concentration was similar to that of desethylamiodarone.

For each dosage regimen, there was the following rank order of tissue and plasma amiodarone concentrations ($p < 0.05$): single dose—kidney ≈ lung ≈ adipose tissue > other tissues > plasma; 14-day regimen, 14-day regimen/elimination, and 28-day regimen—adipose tissue > other tissues > plasma. The rank order of tissue and plasma desethylamiodarone concentrations was the following ($p < 0.05$): single dose, 14-day regimen, and 28-day regimen—lung > other tissues > plasma; 14-day regimen/elimination—all tissues > plasma.

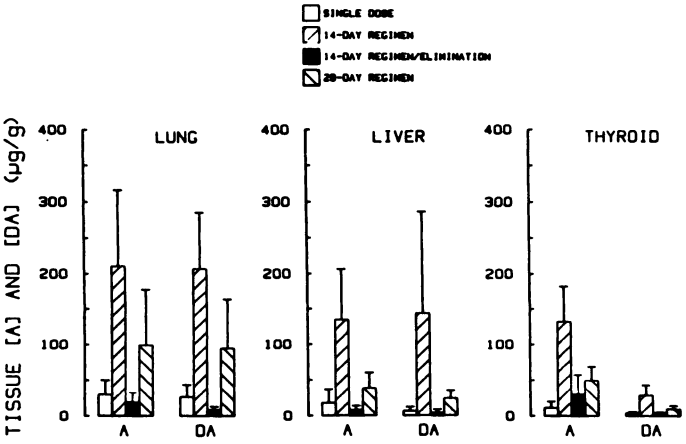

FIG. 5. *Lung, liver, and thyroid gland amiodarone and desethylamiodarone concentrations in the dog after oral administration of a single dose of amiodarone, 14-day amiodarone regimen, 14-day amiodarone regimen/14-day elimination period, and 28-day amiodarone regimen.*

The data are presented as the mean ± SD (six dogs per group). Statistical differences are reported in the text.

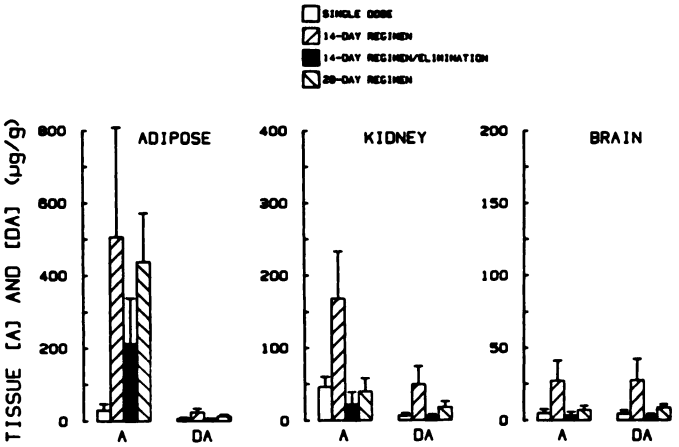

FIG. 6. *Adipose tissue, kidney, and brain amiodarone and desethylamiodarone concentrations in the dog after oral administration of a single dose of amiodarone, 14-day amiodarone regimen, 14-day amiodarone regimen/14-day elimination period, and 28-day amiodarone regimen.*

The data are presented as the mean ± SD (six dogs per group). Statistical differences are reported in the text.

The tissue/plasma concentration ratios of amiodarone and desethylamiodarone for the four regimens are presented in table 1. For the purpose of clarity, only the mean values are reported. The desethylamiodarone ratios of the 14-day regimen/elimination protocol were calculated for two dogs only, as plasma desethylamiodarone was not measurable for the other four animals in the group. Comparison of the amiodarone data with those of desethylamiodarone for each tissue indicated that, in general for the four regimens, the tissue/plasma concentration ratio was greater for desethylamiodarone in left and right ventricles, lung, liver, and brain, whereas the tissue/plasma ratio was greater for amiodarone in adipose tissue. Furthermore, the desethylamiodarone tissue/plasma concentration ratio appeared to be highest in lung for the four regimens, whereas the amiodarone tissue/plasma ratio appeared to be highest in adipose tissue for the three short-term regimens.

Discussion

There are few studies on the disposition of amiodarone in an experimental animal species in which the pharmacodynamics of the drug also have been investigated. Our objective was to conduct a comparative study of the plasma disposition and tissue distribution of amiodarone and its proximate metabolite, desethylamiodarone, for a single oral dose and short-term oral dosage regimens. The amiodarone dosage regimens used in our study are high compared to conventional therapeutic doses for the human. The 28-day amiodarone regimen in our dog study was 4 times greater than the regimen that was administered in a 28-day study of the plasma disposition and antiarrhythmic effect of amiodarone in patients with ventricular arrhythmias (11). In this clinical study, suppression of ventricular arrhythmias was achieved and maintained, and apparent steady-state plasma

TABLE 1

Tissue/plasma concentration ratios of amiodarone (A) and desethylamiodarone (DA) for the four dosage regimens

The data are presented as mean values: single dose ($n = 5$ for A, $n = 4$ for DA); 14-day regimen ($n = 6$ for A and DA); 14-day regimen/elimination ($n = 6$ for A, $n = 2$ for DA); 28-day regimen ($n = 6$ for A and DA).

Dosage Regimen	Drug or Metabolite	Tissue/Plasma Concentration Ratio							
		Left Ventricle	Right Ventricle	Lung	Liver	Thyroid Gland	Adipose Tissue	Kidney	Brain
Single dose	A	20	16	103	52	45	122	307	19
	DA	41	37	409	115	51	83	99	66
14-Day regimen	A	23	23	73	44	47	223	62	9
	DA	55	44	442	281	63	51	97	54
14-Day regimen/ elimination	A	28	34	94	33	214	1015	172	14
	DA	46	78	243	57	82	126	145	70
28-Day regimen	A	41	40	126	50	73	623	50	11
	DA	121	94	664	162	65	90	118	61

amiodarone concentration between 0.6 and 0.5 μg/ml was attained by day 21 of the 28-day study. In our dog study, plasma amiodarone concentration appeared to reach a plateau between 1.0 and 0.8 μg/ml during the last week of the 4-week regimen. Therefore, the results of our study confirm the findings of our preliminary investigation (12) that the 4-fold larger oral amiodarone dosage regimen in the dog was required to achieve plasma amiodarone concentration comparable to that observed in the human.

Our study was conducted in normal dogs, as it has been shown that the plasma pharmacokinetics of amiodarone are not different between patients and healthy volunteers (2). The eight tissues that were examined in our study were selected for the following reasons (1–3): left ventricle and right ventricle are sites of therapeutic action of amiodarone; lung, liver, and thyroid gland are common sites of toxic action of amiodarone; adipose tissue may act as a storage site for amiodarone because of the very high lipid solubility of the drug; kidney is a potential site of accumulation of amiodarone; and brain is a site of extravascular distribution and potential toxicity of the drug.

Plasma amiodarone concentration was greater than that of desethylamiodarone throughout the time-course studies for the single drug dose and the three short-term dosage regimens, even though there was appreciable interanimal variability in the plasma amiodarone concentration data. These results are consistent with the time-course data during and after 37-day oral administration of 400 mg amiodarone/day to the dog (7) and the single time-interval data after acute oral administration of 35 mg amiodarone/kg to the anesthetized, instrumented dog with acute myocardial infarction (8), 6-week oral administration of 20 mg amiodarone/kg/day to the rabbit (6), and 13-day oral administration of 25, 50, and 100 mg amiodarone/kg/day to the rat (5). However, during chronic oral amiodarone treatment in the human, the plasma desethylamiodarone concentration accumulates relative to that of amiodarone (3, 11), such that the desethylamiodarone/amiodarone concentration ratio approaches unity (3, 11) or is greater than one (17). In our dog study, the apparent plasma elimination half-life of amiodarone was dependent on the dosage regimen (single dose, 7.5 hr; 14-day regimen, 3.2 days), but the plasma elimination half-life values of amiodarone and desethylamiodarone after the 14-day regimen were similar (3.2 days and 3.5 days, respectively), which is consistent with the data for the human (2, 3).

The tissue amiodarone concentrations were dose-dependent, as has been observed in patients who received oral amiodarone therapy for varying time periods (15). Amiodarone concentrations in the tissues decreased during the 14-day elimination period, resulting in tissue concentrations that usually were similar to those for the single oral dose. The exception was adipose tissue, in which the amiodarone concentration remained elevated. For the 28-day regimen, the tissue amiodarone concentrations usually were less than those for the 14-day regimen, which is consistent with the lower daily maintenance dose of the drug (20 mg/kg/day). One important exception was adipose tissue, in which the concentration of amiodarone was similar for the 14-day and 28-day regimens. The differential distribution of amiodarone in adipose tissue compared with other tissues is consistent with the very high lipid solubility of amiodarone, its extensive extravascular distribution into adipose tissue, and the poor blood perfusion of this tissue relative to other tissues such as the heart and lung (3). The persistence of amiodarone in adipose tissue may explain, at least in part, the prolonged antiarrhythmic effect and plasma elimination half-life after the cessation of chronic oral treatment (1–3), in which there would be slow redistribution of the drug from the adipose tissue into the plasma. For desethylamiodarone, the tissue concentrations also were dependent on the amiodarone dosage regimen. Tissue desethylamiodarone concentrations decreased during the 14-day elimination period, resulting in concentrations that usually were similar to those of the single dose.

The rank order of tissue and plasma concentrations of amiodarone and desethylamiodarone for the four dosage regimens demonstrates that there was extensive extravascular distribution of the parent drug and its proximate metabolite from the systemic circulation into highly blood-perfused and poorly blood-perfused tissues, resulting in high tissue concentrations. The tissue/plasma concentration ratios indicate selective uptake of amiodarone into adipose tissue as compared with desethylamiodarone, and selective uptake of desethylamiodarone into left and right ventricles, lung, liver, and brain as compared with amiodarone. The tissue concentrations and tissue/plasma concentration ratios together indicate that there was predominant distribution of amiodarone into adipose tissue and of desethylamiodarone into lung. Furthermore, the data indicate that the adipose tissue acts as a reservoir for amiodarone, as the change in drug concentration from the end of the 14-day regimen to the end of the 14-day elimination period (60% decrease) was the least of all the tissues studied. These findings are consistent with the tissue distribution data reported for the rabbit (6) and the rat (5). In the human, there is preferential accumulation of amiodarone in adipose tissue, liver, and lung and preferential accumulation of desethylamiodarone in liver and lung (15, 17, 18).

In the dog, the amiodarone concentration in individual tissues was greater than the desethylamiodarone concentration, except for lung, liver, and brain, in which the drug and metabolite concentrations were similar. These findings are similar to those reported for the rabbit (6), but are different from the data for the rat (5), in which the amiodarone concentration was greater than the desethylamiodarone concentration for all tissues studied. Furthermore, these results in the dog are appreciably different from the data obtained in the human, in whom the tissue desethylamiodarone concentration is greater than the amiodarone concentration except for adipose tissue (15, 17, 18). The reason for these differences in the tissue concentrations of amiodarone and desethylamiodarone among the dog, the rat, and the human is not known, but it may be due to species differences in the affinity of the individual tissues for the parent drug and its proximate metabolite. This species difference in the pharmacokinetics of amiodarone indicates the necessity of characterizing the plasma disposition and tissue distribution of amiodarone and its cardioactive metabolite, desethylamiodarone, in the experimental animal species in which the pharmacodynamics, including mechanism of action, of amiodarone are to be studied. This is very important if drug (and metabolite) concentration-response relationships are to be assessed.

The results of this study of the plasma disposition and tissue distribution of amiodarone and its proximate metabolite, desethylamiodarone, are being used as the basis for selecting short-term and chronic oral amiodarone dosage regimens for the investigation of the antiarrhythmic effects of amiodarone in the dog with subacute myocardial infarction and reproducibly-inducible ventricular arrhythmias. In this regard, we recently have demonstrated with this canine preparation that oral administration of 40 mg amiodarone/kg/day for 10 days, followed by 30 mg/kg/day for 4 days, and then 20 mg/kg/day for 6 weeks produced antiarrhythmic effects at the end of the first week of treatment, with plasma amiodarone and desethylamiodarone concentrations of 1.6 and 0.3 μg/ml, respectively (19). This dosage regimen maintained its antiarrhythmic effect for several weeks with apparent steady-state plasma amiodarone and desethylamiodarone concentrations in the range of 1.6 to 1.3 μg/ml and 0.3 to 0.2 μg/ml, respectively. At the end of the 8-week study, the non-infarcted left ventricle amiodarone and desethylamiodarone concentrations were 34.0 and 20.8 μg/g, respectively. The plasma and left ventricle amiodarone and desethylamiodarone concentrations were comparable to the data reported in this article. This amiodarone dosage regimen currently is being used in the experimental canine preparation with ventricular arrhythmias to investigate the mechanism of the antiarrhythmic action of amiodarone.

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