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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

18-972

Summary Basis of Approval

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FEB 2 1984

NDA 13-972

Drug Generic Name
Amiodarone hydrochloride

Applicant
Wyeth Laboratories
Philadelphia, PA

Drug Trade Name
Cordarone

I INDICATIONS FOR USE

Cordarone is indicated only for the treatment of the following documented, life-threatening recurrent ventricular arrhythmias when these have not responded to documented adequate doses of other available antiarrhythmics or when alternative agents could not be tolerated

1 Recurrent ventricular fibrillation

2 Recurrent hemodynamically unstable ventricular tachycardia

As is the case for other antiarrhythmic agents, there is no evidence from controlled trials that the use of Cordarone favorably affects survival Cordarone should be used only by physicians familiar with and with access to (directly or through referral) the use of all available modalities for treating recurrent life-threatening ventricular arrhythmias, and who have access to appropriate monitoring facilities, including in-hospital and ambulatory continuous electrocardiographic monitoring and electrophysiologic techniques Because of the life-threatening nature of the arrhythmias treated, potential interactions with prior therapy, and potential exacerbation of the arrhythmia, initiation of therapy with Cordarone should be carried out in the hospital

II DOSAGE FORM, ROUTE OF ADMINISTRATION AND RECOMMENDED DOSAGE

Amiodarone is formulated as 200 mg white to slightly cream-colored tablets, scored on one side and embossed "Ives" "4188" on the reverse side It is intended for oral administration

Because of the unique pharmacokinetic properties, difficult dosing schedule, and severity of the side effects if patients are improperly monitored, Cordarone should be administered only by physicians who are experienced in the treatment of life threatening arrhythmias, who are thoroughly familiar with the risks and benefits of Cordarone therapy, and who have access to laboratory facilities capable of adequately monitoring the effectiveness and side effects of treatment

In order to insure that an antiarrhythmic effect will be observed without waiting several months, loading doses are required. A uniform, optimal dosage schedule for administration of Cordarone has not been determined. Individual patient titration is suggested according to the following guidelines for life-threatening ventricular arrhythmias, such as ventricular fibrillation or hemodynamically unstable ventricular tachycardia.

Close monitoring of the patients is indicated during the loading phase, particularly until risk of recurrent ventricular tachycardia or fibrillation has abated. Because of the serious nature of the arrhythmia and the lack of predictable time course of effect, loading should be performed in a hospital setting. Loading doses of 800 to 1600 mg/day are required for 1 to 3 weeks (occasionally longer) until initial therapeutic response occurs (Administration of Cordarone in divided doses with meals is suggested for total daily doses of 1000 mg or higher, or when gastrointestinal intolerance occurs) If side effects become excessive, the dose should be reduced Elimination of recurrence of ventricular fibrillation and tachycardia, along with reduction in complex and total ventricular beats, usually occurs in most patients within 1-2 weeks but occasionally can take longer

Upon starting Cordarone therapy, an attempt should be made to gradually discontinue prior antiarrhythmic drugs When adequate arrhythmia control is achieved or if side effects become prominent, the Cordarone dose should be reduced to 600 to 800 mg/day for one month and then to the maintenance dose, usually 400 mg/day Some patients may require larger maintenance doses, up to 600 mg/day, and some can be controlled on lower doses Cordarone may be administered as a single daily dose, or in patients with severe gastrointestinal intolerance, as a b i d dose. In each patient, the chronic maintenance dose should be determined according to antiarrhythmic comma-effect as assessed by symptoms, Holter recordings, and/or programmed electrical stimulation and by patient tolerance Plasma concentrations may be helpful in evaluating nonresponsiveness or unexpectedly severe toxicity

The lowest effective dose should be used to prevent the occurrence of side effects. In all instances, the physician must be guided by the severity of the individual patient s arrhythmia and response to therapy When dosage adjustments are necessary, the patient should be closely monitored for an extended period of time because of the long and variable half-life of Cordarone and the difficulty in predicting the time required to attain a new steady-state level of drug Dosage suggestions are summarized below

	Loading Dose (Daily)	Adjustment and Maintenance Dose (Daily)	
Ventricular Arrhythmias	1 to 3 weeks	1 month	usual maintenance
	800 to 1600 mg	600 to 800 mg	400 mg

III MANUFACTURING AND CONTROLS

A Drug Preparation and Testing

Manufacture of the new drug substance is performed by two subsidiaries

The route(s) of synthesis are adequately described and ample data are presented to support the assigned structure of the amiodarone molecule

Adequate tests and specifications are provided for the release and acceptance by the manufacture of the finished dosage form to assure the identity, strength, quality and purity of the new drug substance

The finished dosage form is manufactured by another subsidiary The controls over the manufacturing procedures of the finished dosage form give adequate assurance of the identity, strength, quality and purity of the finished dosage form Retesting of the bulk tablets is done before packaging to confirm assurance characteristics and properties

B Stability Studies

The applicant has provided satisfactory stability data to support a 3-year (36-month) expiration dating in approved packaging Intent to extend this period has been made as stability studies progress and data are submitted

C Methods Validation

Validation studies have been performed by the designated laboratories of the laboratory operations branch and the methods with certain adopted recommendations have been found suitable for control and regulatory analysis

D Labeling

All labels and labeling are in accord with the technical requirements of prescription drug labeling

The trade name is not in conflict with the name of any other drug

E Establishment Inspection

Evaluation of the operations of the firms involved in this application indicates compliance with GMPs, and includes inspections of all establishments producing the new drug substance and finished dosage forms

F Environmental Impact Analysis Report

A report has been submitted showing that further environmental impact analysis consideration is not necessary

IV PRECLINICAL PHARMACOLOGY

A Antiarrhythmic Activity

Amiodarone exhibits antiarrhythmic activity in several experimental animal models Following acute i v administration to rodents, amiodarone protected against chloroform-induced ventricular fibrillation, and calcium chloride and aconitine-induced ventricular tachycardias, in isolated rat hearts it prevented ischemia-reperfusion arrhythmias (Lubbe et al , 1974) In dogs acute i v treatment with amiodarone suppressed ventricular arrhythmias induced by epinephrine barium chloride, aconitine, cardiac glycosides, and coronary artery ligation, and it was effective against acetylcholine-induced atrial fibrillation (Charlier and Deltour, 1970) Pretreatment of rats and dogs with amiodarone for 1 to 4 weeks prevented ischemia-related ventricular tachycardias and fibrillation (Lubbe et al , 1974 Rosenbaum et al , 1976)

B Cardiac Electrophysiology

Acute intravenous administration of amiodarone caused a dose-dependent sinus rate slowing in dogs which was neither influenced by atropine nor β-blockade Also amiodarone increased intra-atrial and A-V nodal conduction times and refractory periods without changing conduction velocity within the His-Purkinje system or ventricular contractile tissue (Cabasson et al , 1976)

Following chronic oral administration, amiodarone increased the action potential duration of atrial, ventricular, and Purkinje fibers, and slightly reduced the maximum rate of depolarization without altering the resting membrane potential or action potential amplitude (Singh and Vaughan-Williams 1970) In dogs and rabbits, atrial and ventricular refractory periods were increased following chronic oral dosing Amiodarone also decreased the spontaneous frequency of the sinus node by increasing action potential duration (Goupil and Lenfant, 1976) In in vitro experiments using voltage clamp in both amphibian and mammalian cardiac tissues, amiodarone decreased outward K^+-mediated currents and decreased reactivation kinetics of inward currents (Neliat et al , 1982) Simultaneous intraperitoneal administration to rabbits of 5 mg thyroxine (less than a rabbit's daily requirement) with amiodarone for 3 weeks prevented the effects of amiodarone on action potential duration whereas pretreatment with iodine in an amount equal to that found in amiodarone did not alter the action potential duration (Singh and Vaughan-Williams 1971)

C Other Cardiovascular Effects

In anesthetized dogs amiodarone, studied at doses ranging from 2 5 to 20 mg/kg i v , caused a fall in systemic and coronary vascular resistance, a decrease of systolic and diastolic blood pressures (Charlier et al , 1973, Singh et al , 1976, Petta and Zaccneo, 1971), intracoronary artery administration is associated with modest decreases of left ventricular dp/dt (Kobayashi et al , 1983) Amiodarone increased stroke volume, while variable effects on left ventricular end-diastolic pressure have been reported Amiodarone i v decreased myocardial oxygen consumption in a dose-dependent manner (Charlier, 1971), and reversed both electrical and biochemical indices of experimental myocardial ischemia

Amiodarone non-competitively inhibits both alpha- and B-receptor-mediated actions of catecholamines (Bautnier et al , 197b, Polster and Broekhuysen, 1976) Studies using B-receptor binding techniques have shown that this inhibition is associated with a decrease in the density of B-receptors (Nokin et al , 1983a and b)

D Mode of Action

Amiodarone's antiarrhythmic action is attributable to its ability to increase myocardial refractory periods while not appreciably affecting the cardiac action potential maximum upstroke velocity, and to its conduction slowing properties in nodal tissue Antiadrenergic actions may also contribute to the antiarrhythmic effects of amiodarone.

E Pharmacokinetics and Metabolism

Early studies using ^{131}I-labeled amiodarone showed that following oral administration to the rat, the drug was well absorbed and identified no organ as preferentially accumulating amiodarone Recent studies employing HPLC methods, however, showed that after i v administration amiodarone exhibited a long (but shorter than in humans) terminal plasma half-life in rats and dogs (approximately 8 5 and 9 hours, respectively), with an apparent volume of distribution of 30 and 3b l/kg, respectively (Riva et al , 1982a Broekhuysen et al , 1978), and that amiodarone was greatly concentrated in adipose tissue, with a fat to blood ratio of approximately 1000 at 1o hours Metabolism of amiodarone has been less extensively studied in animals than in man In humans, the N-desethyl analogue of amiodarone has been identified as a principal metabolite (Latini et al , 1983)

F Toxicology

1 Acute Toxicity

The median lethal dose (LD_{50}) of amiodarone in both mice and rats was greater than 3000 mg/kg by the oral route and greater than 450 mg/kg by the intraperitoneal route. For rats, two LD_{50} values of 135 mg/kg and 150 mg/kg were obtained in two separate studies. The estimated oral LD_{50} value for amiodarone in dogs was greater than 5000 mg/kg.

Signs of acute toxicity in rodents after parenteral administration of amiodarone included CNS stimulation followed by sedation, tremors, convulsions and respiratory difficulties. For dogs, emesis and paresis of the hind limbs were noted with oral dosing.

2 Subchronic and Chronic Toxicity

Subacute oral toxicity studies of up to 3 months in duration were conducted in rats. Animals receiving daily doses of 75 or 150 mg/kg of amiodarone for up to 4 weeks showed a marked deterioration in general health, increased mortality, an altered ECG (increased PR interval and QTc segment, prolonged QRS complex, elevated T-wave), hypercholesterolemia, azotemia, elevated thyroxine (T_4) levels and a decreased triiodothyronine (T_3)/T_4 ratio, elevated liver enzymes (SGPT, alkaline phosphatase) and organ weight changes (lung and adrenal increased, reproductive organs and thymus decreased). Microscopic examination revealed an accumulation of foamy macrophages in the mesenteric lymph node with spreading to the spleen, liver and lungs. In another study it was demonstrated that the mesenteric lymph node and lung lesions induced by amiodarone were totally reversible within 2 weeks after termination of treatment. No adverse effects were observed with doses of 37.5 mg/kg or lower of amiodarone.

In the 3-month rat study there was increased mortality, reduced body weight gains, anemia and azotemia at daily doses of 200 mg/kg or greater. Histopathologic examination showed centrilobular congestion of the liver at doses of 200 mg/kg or greater and myocardial lesions (unspecified) at 300 mg/kg. Other than hypertrophic changes of the thyroid gland, no microscopic lesions were evident at 100 mg/kg.

In a 104-week chronic toxicity/carcinogenicity rat study, amiodarone caused a statistically significant dose-related increase in the incidence of thyroid tumors (follicular adenoma and/or carcinoma) at oral doses of 5, 15 and 50 mg/kg/day There was no evidence of goiter (antemortem observations) although elevated thyroid weights were found at 52 and 104 weeks for the high dose group males Thyroid stimulating hormone (TSH) levels were not monitored

Rats receiving 50 mg/kg/day showed a decreased rate of body weight gain during the first 78 weeks of study

Slightly lowered red blood cell parameters (packed cell volume, hemoglobin and erythroid cell count) were found during the first 52 weeks of study in rats from the highest dose group (50 mg/kg) This change was noted particularly in the high dose males

Changes in biochemistry parameters found during the first 52 weeks of study included elevated serum cholesterol levels and increased alkaline phosphatase (AP) activity in rats (males and females) from the highest dose group An exception was found during study week 51 when the AP activity of the high dose group males was lower than that of the controls

Organ weight changes found after 52 weeks of treatment included a marginal increase in liver weight of the high dose males and a trend toward increased thyroid weights of the high dose males.

Histopathology after 26 and 52 weeks of treatment revealed a slight increase in the incidence of foamy alveolar macrophages which was "sometimes associated with pneumonitis" in the lungs of rats from the highest dose group (50 mg/kg) This finding was most prominent in the 50 mg/kg males after 52 weeks of treatment In addition, an increase in aggregates of eosinophilic macrophages in the lymph nodes of high dose rats (male and females) after 52 weeks of treatment was found

A further investigation of the effect of amiodarone on thyroid function was undertaken with the identical dose levels used in the rat carcinogenicity bioassay, i e , 0, 5, 15 and 50 mg/kg/day (See Amendment to NDA-18,972 submitted May 17, 1985) Dosing was conducted for at least 3 months (102 days), with plasma samples being obtained on days 15, 29, and 102 for determination of thyroxine (T_4), triiodothyronine (T_3) and TSH levels

Analysis of plasma samples revealed increased T_4 levels from day 15 to day 102 in rats receiving 15 and 50 mg/kg/day Triiodothyronine (T_3) levels were slightly lower only in the high dose males on day 102 TSH levels

were increased in a dose-related manner Rats dosed with 50 mg/kg had elevated TSH levels by study day 15, continuing throughout the 102-day study. A trend toward increased TSH levels was apparent by day 102 in the low and mid dose groups

Thyroid hyperplastic changes observed with amiodarone in mice (up to 21 months dietary administration at same doses as in rat) also suggest increased TSH stimulation although a significant tumorigenic response was not observed in that species

Subacute oral toxicity studies were conducted in dogs at dose levels of amiodarone ranging from 30 to 150 mg/kg Dogs receiving 100 mg/kg for 1 month showed a decrease in body weight gain and food consumption which resulted in the moribund sacrifice of one female and elevations in serum enzyme levels (SGPT, SGOT, LDH), cholesterol, triglycerides and urinary pH Postmortem examination revealed increases in adrenal and liver weight, the disappearance of the thymus gland and a generalized dyslipidosis In another study, dogs receiving 150 mg/kg (5 days/week) of amiodarone for 3 months exhibited excessive salivation and signs of gastrointestinal distress (i e , vomiting, diarrhea, anorexia) which was accompanied by some loss in body weight The leukocyte count increased in a dose-related manner at each dosage level (30 and 150 mg/kg) and high dose dogs showed decreases in neutrophils and increases in lymphocytes during the end of the study Apart from occasional increases in BUN, SGPT, alkaline phosphatase and cholesterol reported in several high dose dogs, clinical chemistry values were generally similar to the control values Postmortem examination revealed hypertrophy of the thyroid in one high dose dog and necrosis of the stomach in another

In a chronic (9 months) oral toxicity study in dogs, amiodarone caused no clinical signs of toxicity at daily dose levels of 30 and 60 mg/kg Serum cholesterol levels were increased in the high dose group and terminal serum free fatty acids increased at both dose levels Increases in blood and tissue iodine levels and in protein-bound iodine were found in drug-treated dogs Histopathology was unremarkable

A 3-month oral toxicity study with amiodarone (10, 20, 50, or 150 mg/kg) in pigs demonstrated that the drug was well tolerated at doses up to 50 mg/kg Dose levels of 150 mg/kg caused ataxia, hypotonia and lack of weight gain Two high dose animals died within 1 1/2 months and autopsy showed gastritis and gastric ulceration The remaining pigs at the high dose level were sacrificed in extremis at 2 1/2 months Histopathological lesions of the liver and endocrine (pituitary, thyroid, adrenal) glands were present in these animals

Other than anemia in one treated animal, amiodarone (50 mg/kg) appeared to be well tolerated in a chronic (10 months) oral toxicity study in pigs The results of histopathological examinations were not reported in this study, however No drug-related postmortem gross abnormalities were found

A 6-week intravenous toxicity study in rabbits at doses of 5, 10, or 25 mg/kg revealed anemia, hyperlipidemia and hypercholesterolemia at the high dose level. Non dose-related hepatic degenerative lesions were found in rabbits from each treated group (2/8 low, 2/8 mid, 1/8 high)

3 Effects on Reproduction

Amiodarone had no adverse effect on fertility or mating performance when administered to male or female rats at daily oral doses up to 30 mg/kg Higher doses of the drug (60 and 90 mg/kg) adversely affected female fertility and significantly decreased litter size and litter weight For the F1 generation offspring (F2 pups), those obtained from the high dose amiodarone group were less viable and gained less weight than their control counterparts for the first 10 days postpartum, but developed normally thereafter

The teratogenic potential of orally administered amiodarone was investigated in mice, rats and rabbits

In Sprague-Dawley rats, 200 mg/kg of amiodarone administered on days 1 to 21 of gestation caused maternal toxicity and marked embryotoxicity, therefore, no conclusions regarding teratogenicity could be made. With 90 mg/kg of amiodarone administered prior to mating, during mating and through gestation day 19, fertility decreased and preimplantation loss increased Increased fetal resorption and growth retardation (mainly delayed skeletal ossification) at 90 mg/kg were indicative of drug-induced embryotoxicity In Wistar rats, however, doses of up to 100 mg/kg administered on gestation days 1 to 15 produced no embryotoxicity or skeletal abnormalities Amiodarone was not teratogenic in rats at any dose level

Mice receiving 5, 50 or 100 mg/kg of amiodarone on gestation days 1-15 showed a dose-related reduction in litter size and an increase in the number of fetal resorptions There was no suggestion of drug-related teratogenicity In another study employing a different mouse strain, up to 100 mg/kg administered during days 1-15 of gestation was neither teratogenic nor embryotoxic

In rabbits, amiodarone administered orally during gestation days 1-18 at doses up to 100 mg/kg was not teratogenic In a second rabbit study (employing a different strain), intravenous administration of 5, 10, or 25 mg/kg amiodarone during days 8 to 16 of gestation caused maternal death at the high dose level and a non-dose-related increase in the number of resorptions at the two higher dose levels No fetal abnormalities were observed

In a perinatal and postnatal development study in (Sprague-Dawley) rats, pregnant dams gained less weight during gestation at a dose level of 90 mg/kg amiodarone Weanling body weight and neonatal survival were also reduced at this dose level Dose levels of 10 and 30 mg/kg produced no adverse effects

4 Mutagenic Potential

Amiodarone was not mutagenic in the Ames test (TA 1535, 1537, 1538, 98 or 100) performed with or without metabolic activation Amiodarone was also negative in the micronucleus test, and was not lysogenic to bacterial indicator strains GY 5027 or GY 4015

V. CLINICAL PHARMACOLOGY

Summaries of the clinical pharmacology studies are included in Appendix I and referenced publications are listed in Appendix IV

A Pharmacokinetics/Pharmacodynamics

The clinical use of amiodarone as an antiarrhythmic agent predated by over a decade the availability of reliable assay methodology

Early studies by Broekhuysen and co workers (1969) gave some indication of the complexity of amiodarone pharmacokinetics, but their measurements were not specific for amiodarone since they followed the total radioactivity of ^{131}I beled amiodarone More recently, however, HPLC te iques have allowed accurate measurement of both amiodarone and its metabolite, desethylamiodarone, provid ng a clearer profile of the drug's pharmacokinetics

1 Single-Dose Pharmacokinetics (i v and oral)

In a randomized, crossover study, dolt et al (1983d) evaluated the pharmacokinetics of amiodarone in 6 healthy male volunteers after the administration of 3 single

doses (1) 400 mg given as an i v. infusion over 10 minutes, (2) 400 mg oral formulation, Cordarone[a],* and (3) 400 mg oral formulation, Cordarone X[a] *

Blood samples were collected up to 84 days after i v dosing and up to 63 days after oral dosing, the second and third treatments were administered at least 1 month after amiodarone could no longer be detected. Assays were performed using a highly sensitive HPLC methodology with a limit of sensitivity of 5 ug/l Table 1 summarizes the findings in this study

TABLE 1 PHARMACOKINETIC PARAMETERS OF AMIODARONE IN SIX VOLUNTEER SUBJECTS AFTER SINGLE 400 mg DOSES

Parameter	Mean ± SD	Range
Volume of distribution (Vd_{SS})** (l)	4936 ± 3290	1375 - 11081
Volume of distribution (Vd_{SS})** (l/kg)	61 8 ± 30 5	20 6 - 112 0
Clearance** (l/hr)	8 6 ± 1 86	6 5 - 11 14
Terminal half-life** (days)	24 8 ± 11 7	9 3 - 44 1
Time to peak concentration (hr)		
Cordarone	5.1 ± 2 3	1 5 - 8 5
Cordarone X	5 9 ± 1 7	2 5 - 7 0

**Described by polyexponential function after i v dosing

The results demonstrated that amiodarone has a very large and variable volume of distribution and a low total clearance from plasma and blood with a prolonged and highly variable mean terminal elimination half-life of 25 days

Data after single dosing are consistent with the biphasic elimination profile noted after chronic dosing

Figure 1 illustrates a typical plasma elimination profile after a 400 mg i v dose in 1 subject and the superior fit of a 4-exponent curve compared with either a 3-exponent curve or power function

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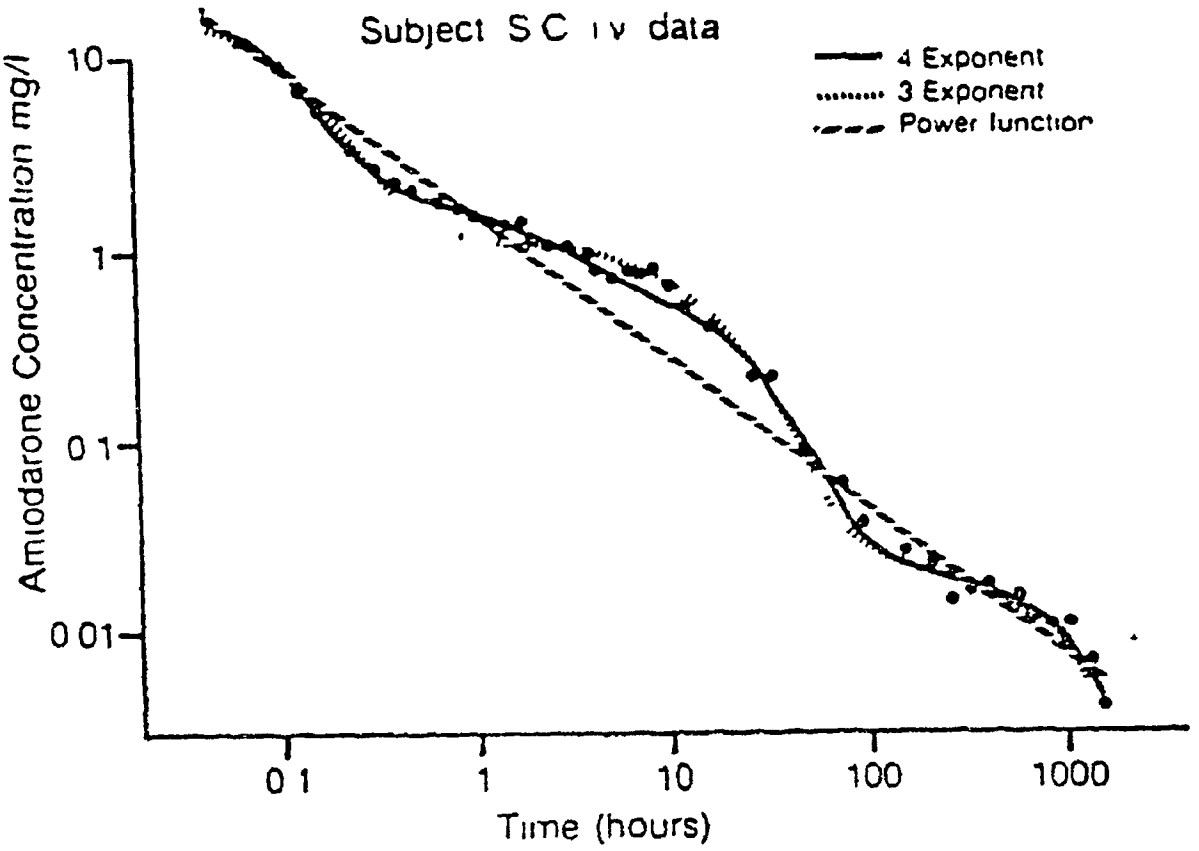
* Cordarone and Cordarone X are oral preparations of amiodarone, the former is recrystallized from toluene, while the latter is recrystallized from ethanol Cordarone is used in Europe and the U S , whereas Cordarone X is used in the U K

FIGURE 1 PLASMA CONCENTRATION-TIME CURVE AFTER I V DOSING



(Holt, unpublished)

The highly sensitive assay and the long-term collection of specimens make the data from the Holt study the most persuasive description of the kinetics of the drug to date

Four other i v./oral single-dose crossover studies have been performed (Andreasen et al , 1981, Anastasiou-Nana et al , 1982, Riva et al , 1982b, Sanofi, unpublished internal report, 1984) The Sanofi study in 12 normal volunteers showed results very similar to those of Holt Table 2 summarizes these findings.

TABLE 2 MEAN (±SE) SINGLE-DOSE PHARMACOKINETIC DATA FROM SANOFI

Parameter	i v (5 mg/kg)	Tablet (200 mg x 2)
T_{max} (hrs)	---	4 7 ± 0 9
C_{max} (mg/l)	---	0 543 ± 0 298
AUC/dose (100 x hr/l)	3 3 ± 0 0	2 1 ± 0 7
C_{max}/body weight (1000 mg/lekg)	---	8 03 ± 5 36
AUC/body weight (1000 hr/lekg)	0 45 ± 0 17	0 30 ± 0 13
$t_{1/2}$ (days)*	18 ± 4 6	-
clearance (l/hr)*	9 42 ± 1 38	-
V_{dss} (l)*	5950 ± 2100	-

* additional Sanofi data from unpublished report (N=5, mean _ S D)
Note Limit of assay sensitivity was 5 ug/l
AUC = area under the plasma concentration-time curve,
V_{dss} = vol of distribution at steady state $t_{1/2}$ = half-life,
C_{max} = peak plasma conc , T_{max} = time to peak plasma conc

In the other three studies (Andreasen et al., 1981, Anastasiou-Nana et al. 1982, Riva et al., 1982b), amiodarone concentrations were measured for a maximum of up to only 96 hours post-dosing, leading to a marked underestimation of the half-life ($t_{1/2z}$) In addition, these studies were limited in their ability to define amiodarone elimination by the poor sensitivity and specificity of their assay methodology.

Results from these studies are summarized in Table 3

TABLE 3 SUMMARY OF I.V./ORAL PHARMACOKINETICS

Author	No. of Subjects	Dose	Blood Samples	Assay Sensitivity	Results
Andreasen et al. (1981)	7 patients	400 mg i v 400 mg p o. (after 2-4 days washout)	up to 96 hrs up to 24 hrs	100 µg/l	Tmax = 7 3±2.3 (hr) Vd = 400 (l/kg)
Anastasiou-Nana et al. (1982)	4 patients	150 mg i.v 200/400 mg p o. (after 3-4 days washout)	up to 16 hrs up to 30 hrs	100 µg/l	Vd = 1.0±0.1 (l/kg) Cl = 10 7±3 3 (l/hr) t1/2 i v = 4 4±0 6 (hr) p.o = 16 9±6 4
Riva et al (1982b)	3 volunteers	150 mg i v 400 mg p.o (after 3 weeks washout)	up to 32 hrs up to 50 hrs	20 µg/l	Vd = 12 9±4.0 (l/kg) Cl = 35 7±7 1 (l/hr) $t1/2_z$ i.v = 17.4±4 6 (hr) p.o. = 35.9±37 9

Note Clearance (Cl) and volume of distribution (V_d) are based on i v data
$t_{1/2}$ = half-life,
T_{max} = time to peak plasma conc

In several additional studies, peak plasma concentrations ranged from 0.5 to 14 mg/l for single oral doses of 200 to 1600 mg (Canada et al., 1981, Kannan et al., 1982, Haffajee et al , 1981)

2 Absorption and Absolute Bioavailability of the Marketed Formulation

The iv/oral studies described above all measured the absolute bioavailability of amiodarone

Table 4 summarizes their findings

TABLE 4 ABSOLUTE BIOAVAILABILITY OF ORAL AMIODARONE

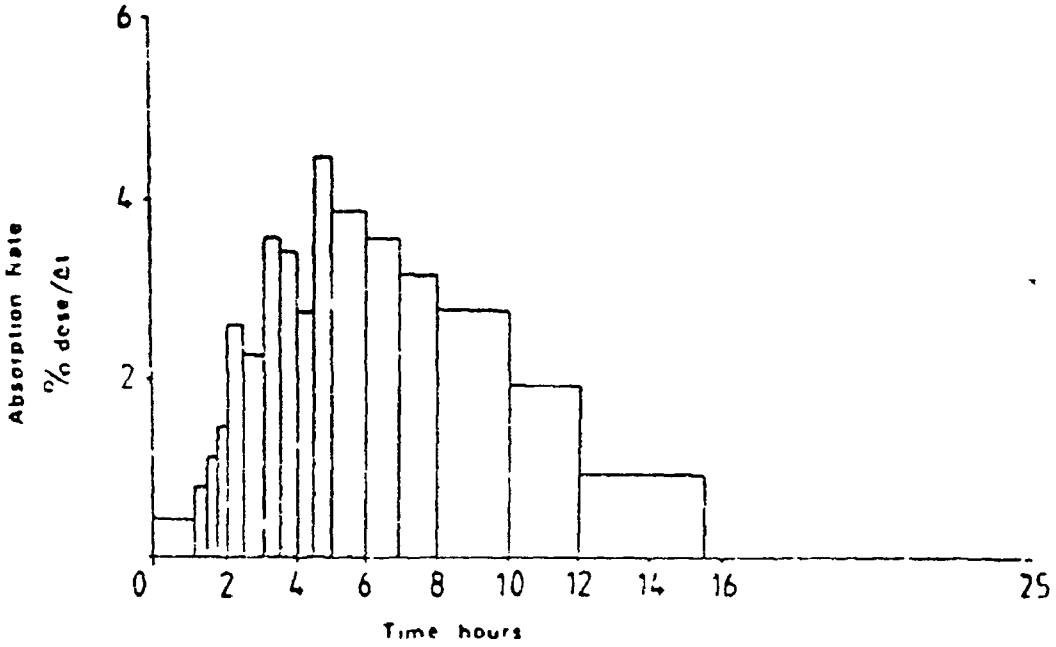
Author	Preparation	Mean Value (±SD)	Range
Holt et al (1983d) AUC_{∞} p o / AUC_{∞} i v	Cordarone	35 ± 9%	22 - 46%
	Cordarone X	35 ± 13%	19 - 55%
Andreasen et al (1981) (24 hr time/ concentration curve)		43 ± 19%	---
Anastasiou-Nana et al (1982)		34.5 ± 12.6%	---
Riva et al (1982)		58 ± 33%	---
Sanofi* unpublished report, 1984 AUC_{∞} p o / AUC_{∞} i v	Cordarone (400 mg)	65 ± 26%	22 - 104%
	Cordarone X (400 mg)	80 ± 22%	29 - 105%
	Oral solution of amiodarone (400 mg)	68 ± 20%	43 - 105%

*Mean ± SE

Peak plasma levels were not attained until a mean of approximately 3 to 7 hours after oral dosing (Andreasen et al , 1981, Holt et al , 1983d, Sanofi unpublished report, 1984)

Figure 2 presents the absorption rate over time in 1 subject after oral dosing with amiodarone

FIGURE 2 ORAL DOSING ABSORPTION RATE VS TIME



(Holt et al , 1983d)

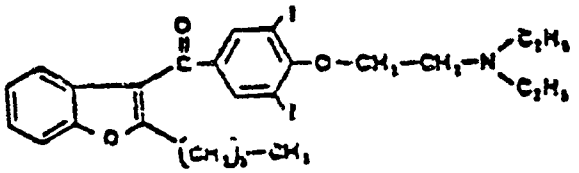
Absorption continued for up to approximately 15 hours post-ingestion, suggesting it occurred across the entire GI tract. Recycling might complicate this question, since the possibility of entero-hepatic recirculation has been suggested by several investigators who have demonstrated bile levels 10 to 50 times that of plasma levels 2 hours post-dosing in a small number of patients (Andreasen et al , 1981, Gobbato et al , 1982).

The bioavailability after oral administration was very variable and may have been due to incomplete absorption across the GI mucosa, since the apparent hepatic extraction ratio was relatively low (0 13) (Holt et al , 1983d) However, first-pass effect of the drug in the gut or liver cannot be excluded

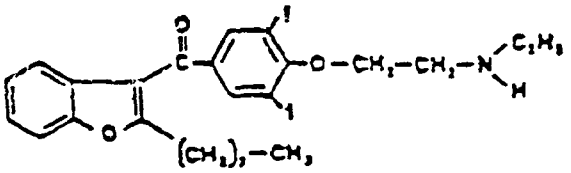
3 Metabolism

To date, one major metabolite, desethylamiodarone, has been identified (Flanagan et al , 1982a) There is no information available on the pharmacological activity of this derivative in man The plasma concentrations of desethylamiodarone attained during chronic amiodarone therapy were similar to those seen for the parent compound and the kinetics are probably limited by the rate of formation (Holt et al , 1983d) Figure 3 presents the chemical structures for amiodarone and desethylamiodarone

FIGURE 3 STRUCTURES OF AMIODARONE AND DESETHYLAMIODARONE



AMIODARONE



DESETHYLAMIODARONE

4 *Excretion*

Studer et al (1979) postulated that the main excretory pathway was not urinary, but biliary, as less than 20% was excreted as urinary iodide up to 56 days after single oral dosing with 400 mg of amiodarone

Andreason et al (1981) demonstrated that for 2 hours after I V dosing, urinary excretion of unchanged amiodarone was negligible or possibly below the limits of their assay detection (less than 0 1 mg/l), while plasma levels were about 2 mg/l Iodide concentration in the urine after I V administration of amiodarone suggested that only 5% of the orally administered drug was eliminated in the urine after biotransformation

Harris et al (1983b) evaluated 10 patients with normal renal function receiving chronic treatment with 359±235 mg/day and found that the urinary concentrations of parent drug and metabolite were very low Table 5 summarizes their mean plasma and urinary drug levels for these patients

TABLE 5 - MEAN (±SD) PLASMA AND URINARY CONCENTRATIONS OF AMIODARONE AND DESETHYLAMIODARONE IN 10 PATIENTS

Parameter	Amiodarone	Desethylamiodarone
Plasma conc (mg/l)	2 08 ± 1 46	1 48 ± 0 90
Urinary conc (mg/l)	0 029 ± 0 027	0 149 ± 0 132

These data support the contention that the kidney is not a major route of elimination for either amiodarone or its metabolite

The possibility of an enterohepatic circulation was suggested by a preliminary study by Andreasen et al (1981), performed in 1 patient undergoing endoscopic examination, who had received 400 mg i v of amiodarone A rapid increase in the concentration of amiodarone in the bile was observed which at 2 hours reached a concentration about 50 times that in plasma Gobbato et al (1982) also demonstrated in 2 surgical patients that bile levels 2 hours after a single oral dose of 600 mg were 10 to 30 times those in plasma

5 Pharmacokinetics During Chronic Treatment

Holt et al (1983d) measured levels of amiodarone and desethylamiodarone in 8 patients following cessation of chronic oral therapy (greater than 2 months) The mean (±SD) elimination half-life was 52 6 ± 23 7 days for amiodarone and 61 2 ± 31 1 days for its metabolite, desethylamiodarone Table 6 shows the half-lives for these 8 patients, some of whom displayed approximately a 4-fold difference in their values

TABLE 6 TERMINAL ELIMINATION HALF-LIVES OF AMIODARONE AND DESETHYLAMIODARONE FOLLOWING CESSATION OF LONG-TERM ORAL THERAPY (N=8)

Patient	Maintenance Dose (mg/day)	Duration of Therapy (mo)	Terminal Elimination Half-Life (days)	
			Amiodarone	Desethyl-amiodarone
GR	200	2	54	60
JM	600	12	49	60
TB	200	20	74	92
RW	200	18	45	34
NS	400	25	107	118
PS	400	52	44	53
HL	600	18	42	53
DA	400	11	26	20
Mean	375	19 8	52 6	61 3
±SD	166 9	14 8	23 7	31 1

(Holt et al , 1983d)

Blood samples collected during the first few days in 4 patients following withdrawal of therapy, however, showed an initial halving of drug levels over the first 2 5 to 10 days, indicating a biphasic elimination In addition, this initial phase was followed by an unexplained rebound in plasma concentrations of amiodarone and desethylamiodarone at approximately 20 days

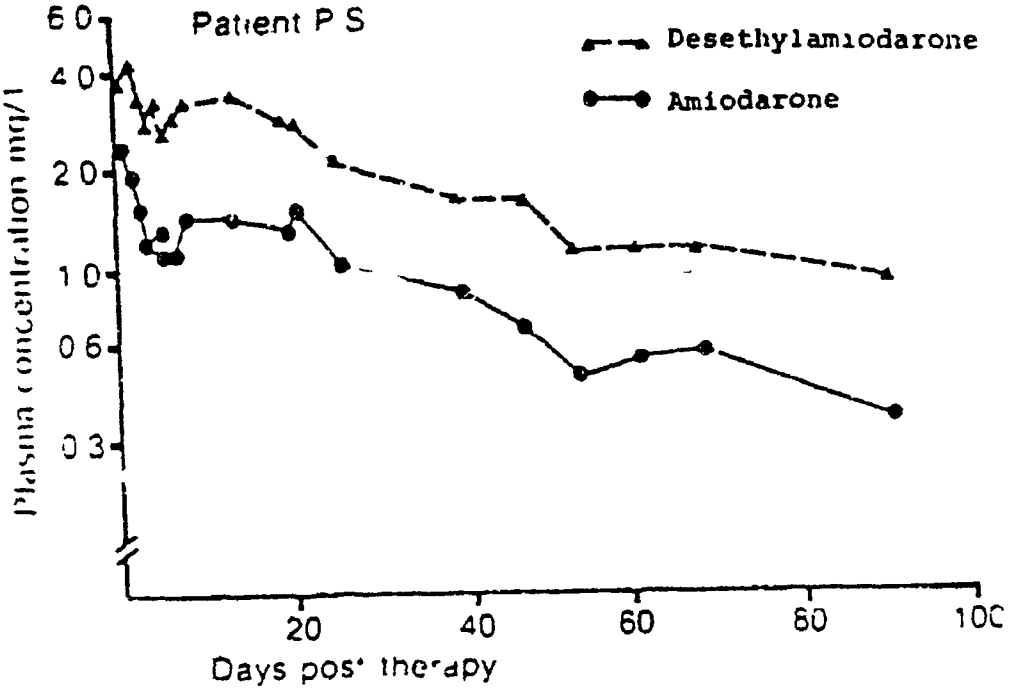
Table 7 shows the initial and terminal elimination of drug for 3 of the patients evaluated Figure 4 shows a typical plasma profile (patient P S)

TABLE 7 ELIMINATION FOLLOWING CESSATION OF LONG-TERM THERAPY WITH AMIODARONE

Patient	Days	
	Initial halving	Terminal half-life
RW	10 0	45
NS	7 5	107
PS	4 0	44
Mean ±	7 2	65 3
SD	3 0	36 1

(Holt et al , 1983d)

FIGURE 4 ELIMINATION OF AMIODARONE AND DESETHYLAMIODARONE IN ONE PATIENT AFTER CHRONIC DOSING



(Holt et al., 1982, unpublished)

In patient NS, with the longest terminal half-life, the antiarrhythmic efficacy of amiodarone persisted for 18 weeks following cessation of therapy, consistent with the clinical observations of other investigators such as Rosenbaum et al (1976)

Staubli et al (1983) demonstrated a similar prolonged half-life of elimination for amiodarone ranging from 21 to 78 days (mean 41±13 days) in 14 petients who had continued chronic amiodarone therapy ranging from 180 to 880 days

Preliminary data from Haffajee et al. (1981) suggested that when loading doses are given, apparent steady-state plasma levels are reached in approximately 2 to 4 weeks indicating achievement of steady state levels may be related to the initial elimination phase, rather than to the prolonged terminal disposition of the drug Theoretically, without loading doses steady state can be expected to be achieved in approximately 3 to 4 times the terminal half-life, or after 150 to 200 days of maintenance dosing

Chronic dosing is associated with mean amiodarone blood levels of approximately 1 0 to 3.5 mg/l for maintenance doses ranging from 200 to 600 mg/day (Holt et al , 1982, Boppana et al , 1983) More recently Falik et al (1987) reported that a loading dose of 1 4 g/day for 7 days followed by 200-400 mg/day over 10 months among 92 patients resulted in apparent steady-state plasma levels of 2 4 mg/l However, inasmuch as plasma levels were not given at the end of loading dosing (7 days) one cannot determine if steady state was achieved

The ratio of the parent compound to metabolite is approximately 1 0 (Holt et al , 1983a) in patients on long-term amiodarone treatment. During the initial days of therapy, however, metabolite levels are relatively low and a ratio of 0 3 or less has been observed (Storey et al , 1982a)

6 Iodine Metabolism

Administration of amiodarone causes a large increase of serum organic and inorganic iodine In addition to desethylamiodarone, amiodarone is metabolized to several, as yet unidentified, iodinated or dehalogenated metabolites (Staubli, 1985). At steady state these metabolites plus inorganic iodine account for approximately 2/3 of the total circulating serum iodine, 1/4 of which is inorganic iodine (Staubli, 1983, Staubli, 1985). The iodine released from amiodarone and its metabolites can raise the serum inorganic iodine levels to approximately 40 times normal (Rao, 1980, Staubli, 1985)

In 15 patients receiving 300 mg amiodarone for 6 months, urinary iodine increased from 2.14±0.4 umol/day to 87±7 umol/day (011 mg/day), a 40-fold increase above pre-amiodarone values, while renal iodine clearance remained unchanged (Rao, 1986) Since 300 mg amiodarone HCl contains 112 mg iodine by weight, these results suggest that approximately 10% of the iodine in the administered amiodarone is freed to inorganic iodine (Rao, 1986), a value which corresponds closely to that found by Broekhuysen (1969) who determined radioactive urinary iodine following the administration of radioiodinated amiodarone In 6 patients in whom the serum terminal elimination of amiodarone was 44±12 days (range 35-68 days), the terminal elimination half-life of iodine and the iodine-containing metabolites that is, other than amiodarone and desethylamiodarone) as 98±40 days (range 57 to 160 days, Staubli, 1985) High serum iodine levels are responsible for at least a portion of the thyroid dysfunction cases reported among amiodarone-treated patients, and this prolonged elimination half-life of iodine-containing metabolites probably contributes to the observation that recovery to normal thyroid function requires several weeks to months upon discontinuation of amiodarone (Leger, 1984, Raeder, 1985)

7 Dose Proportionality

Holt et al (1983d and unpublished data) showed a linear relationship between dose and the mean concentrations of amiodarone and desethylamiodarone in 197 patients receiving at least 1 month of chronic therapy with 100, 200, 400 or 600 mg of amiodarone daily, between-subject variation at each dose was, however, large Note that each patient was evaluated on only a single dosage, i e , the classic crossover dose-proportionality study was not carried out Table 8 summarizes the mean concentration at each dose level

TABLE 8 RELATIONSHIP BETWEEN DAILY MAINTENANCE DOSE OF AMIODARONE AND PLASMA CONCENTRATIONS OF AMIODARONE AND DESETHYLAMIODARONE

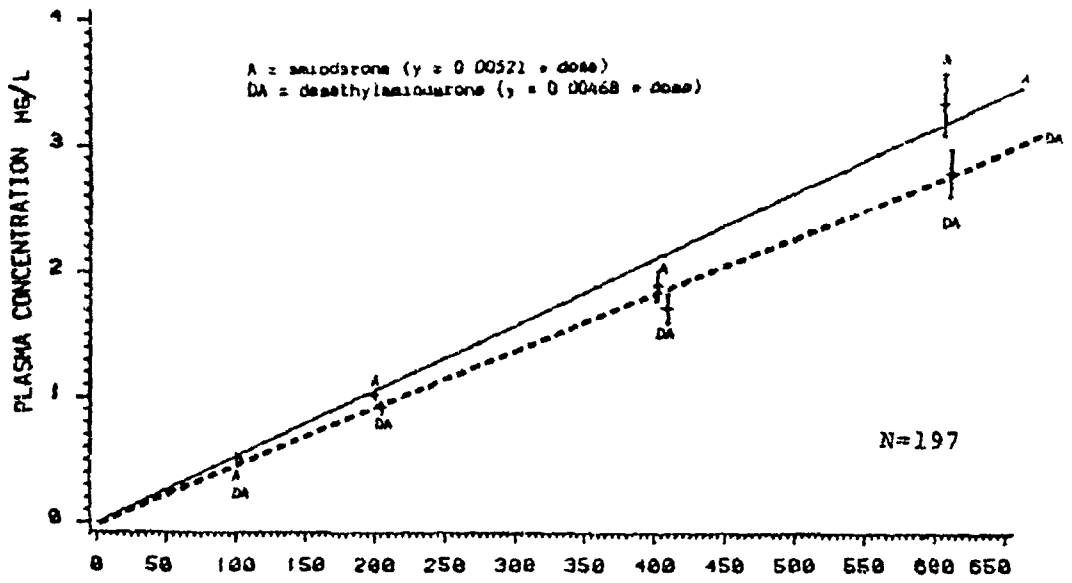
Daily dose (mg)	N	Plasma concentration (mg/l) Amiodarone mean ± SD	CV%	Desethylamiodarone mean ± SD	CV%
100	15	0 52 ± 0 20	38	0 56 ± 0.24	38
200	103	1 05 ± 0 41	42	1 04 ± 0 33	32
400	51	1 91 ± 0 80	40	1 77 ± 0 64	37
600	27	3 36 ± 1 23	50	2 80 ± 1 05	43

CV - coefficient of variation (Holt et al , 1983d and unpublished data)

There was a good correlation between the plasma amiodarone concentrations and dose ($r = 0.76$). In addition, the correlation coefficient for the plasma amiodarone concentration vs desethylamiodarone concentration was 0.88. A straight line relating plasma concentration to daily dose, fitted through the zero ordinate origin, showed that for every 100 mg dose increase there is a corresponding 0.52 mg/l and 0.47 mg/l increase in amiodarone and desethylamiodarone concentration, respectively.

Figure 5 shows the relationship of steady-state concentrations (mean ± SEM) and dose in these 197 patients.

FIGURE 5 STEADY-STATE PLASMA AMIODARONE CONCENTRATIONS VS DAILY MAINTENANCE DOSE OF AMIODARONE



(Holt et al., 1983, unpublished)

Boppana et al (1983) and Rotmensch et al (1983a), reporting on the same group of patients, have also shown a linear relationship between dose and plasma concentrations. Table 3 summarizes the mean steady-state plasma concentrations, duration of treatment and body weight for the 3 maintenance doses evaluated (200, 400 and 600 mg/day) by the Boppana and Rotmensch group. The groups had similar weights and duration of treatment.

TABLE 9 MEAN PLASMA CONCENTRATIONS DURING CHRONIC DOSING

A Dose (mg/day)	200	400	600
N	10	44	23
Duration (mo)	5.1 ± 2 9	6.4 ± 5.4	4.0 ± 2 4
Body Weight (kg)	77 ± 13	74 ± 12	79 ± 2 4
A (mg/l)	1 30 ± 0 57	2 40 ± 0.95	3.65 ± 1.50
DA (mg/l)	0 82 ± 0.30	1 43 ± 0 41	1 77 ± 0 66

A = amiodarone
DA = desethylamiodarone

(Boppana et al , 1983, Rotmensch et al , 1983a)

Haffajee et al (1983b and unpublished) have also found a good correlation between maintenance serum concentrations and weight-related doses of amiodarone

In these studies, which made use of patient steady-state values without attempting to use crossover designs to minimize patient variability, amiodarone showed dose proportionality over the range of 100 to 600 mg per day

8 Tissue Concentrations

Holt et al (1983b) measured tissue concentrations using samples obtained from 3 patients during surgery and from 5 deceased patients who had been on chronic amiodarone therapy.

Table 10 shows the mean concentrations in various tissues of amiodarone (A) and its desethyl metabolite (DA)

TABLE 10 MEAN CONCENTRATIONS OF AMIODARONE (A) AND ITS DESETHYL METABOLITE (DA) IN VARIOUS TISSUES

Tissue	Tissue concentrations (mg/kg wet weight) A	DA
liver	311	1814
fat	236	o5
lung	115	540
spleen*	114	3do
myocardium	25	90
kidney	22	oo
thyroid	13	6o
skeletal muscle	12	28
skin	8	20
cornea	7	5o
brain	6	46

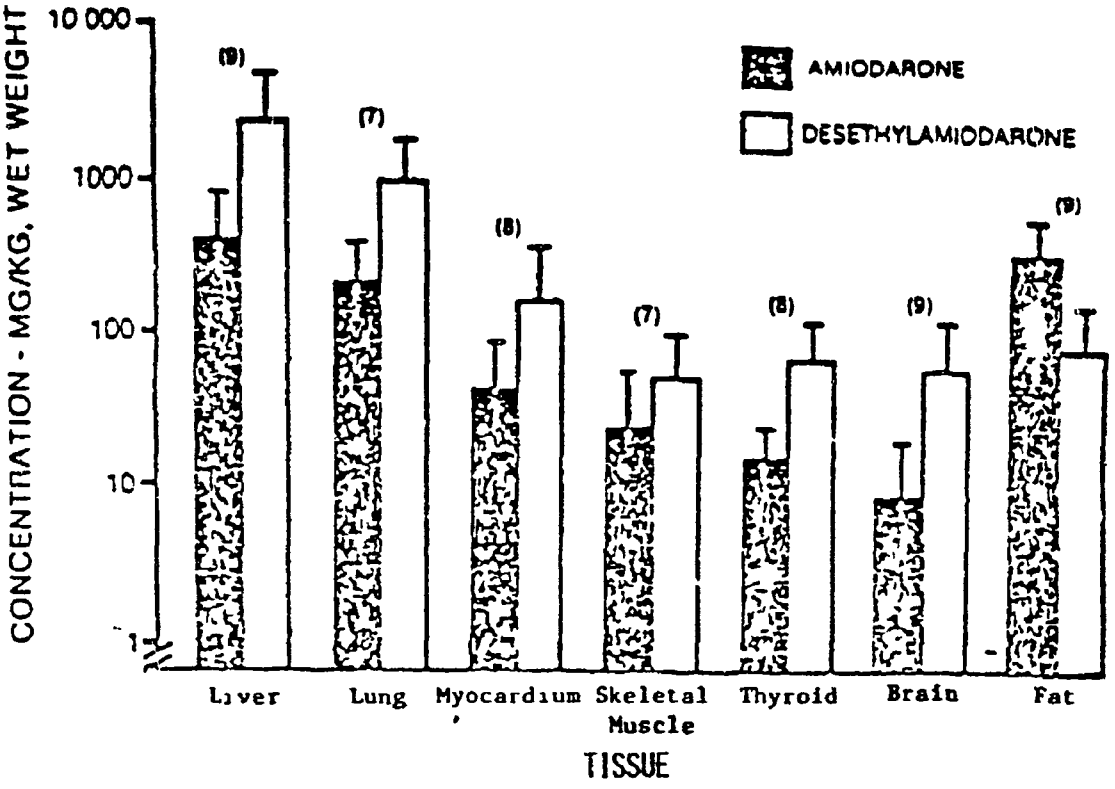
From Holt et al 1983o (N=8)
From *Adams et al 1983 (N=7)

Mean (±SD) plasma concentrations were 1 7 ± 0 6 mg/l for A and 1 9 ± 0 8 mg/l for DA

With the exception of fat, the ratio of A/DA was lower in tissue than in plasma, the overall range for plasma was 0 64 to 1 09 (mean of approximately 1 0) and for tissue, 0 12 to 0.70 (mean = 0 28) In contrast, the mean ratio of A/DA for fat was 4 8

Figure 6 presents the mean concentration of amiodarone and desethylamiodarone in a variety of postmortem tissues

FIGURE 6 MEAN (±SE) TISSUE CONCENTRATIONS



(Holt et al., 1983d) N=9

Note Numbers in parentheses are the number of observations

In general, although there were large differences in absolute values of tissue drug levels among the patients due to differences in the dose and duration of therapy, the pattern of tissue distribution was almost identical in each patient (i e , highly perfused organs such as the liver, lung and spleen had the largest concentrations of both compounds)

High fat concentrations of amiodarone are consistent with its lipid solubility, and fat represents a poorly perfused tissue reservoir of drug Slow elimination from these deep tissue deposits may explain the long terminal half-life and persistence of drug effect observed with this compound after dosing has been discontinued

9 Pharmacodynamics

a Relationship of Blood Levels to Efficacy

There is good correlation between the dose of amiodarone and serum concentration of amiodarone during chronic therapy at doses of 100 to 600 mg/day (see Section V A.7) and there are many documented cases of arrhythmia recurring when amiodarone dosage has been reduced. Some studies have tried to address the correlation between serum drug level and clinical efficacy, but this is difficult in a context of life-threatening arrhythmias and a much delayed change in serum concentration following changes in dose. The typical dose-response studies relating dose or blood level to control of frequent ventricular premature beats (VPBs) seen with most antiarrhythmics have not been carried out for amiodarone and would be difficult to justify, as the VPB population is not the target for the drug, patients with both VPBs and ventricular tachycardia/ventricular fibrillation (VT/VF) who would be a target population, therapy must be directed at the VT/V so that dose-finding for effects on VPBs cannot be carried out. Nonetheless, it is possible to describe the serum concentration where effects are usually seen.

Several investigators have reported a correlation of serum amiodarone levels to antiarrhythmic effect. Mostow et al (1984) observed that trough serum amiodarone concentrations greater than 2.0 ug/ml were associated with a significant decrease in frequency of premature ventricular complexes (PVCs) per hour (p less than 0.01) and paired PVCs per day (p less than 0.02) when compared with serum levels less than 2.0 ug/ml cutpoint. Frequency of VT episodes did not show a consistent relation to blood level. Based on this study of 25 patients with complex ventricular arrhythmias, these authors concluded that measuring serum levels may serve as a useful adjunct to ambulatory ECGs in monitoring amiodarone therapy during the maintenance phase when data were obtained. Results are summarized in Table 1.

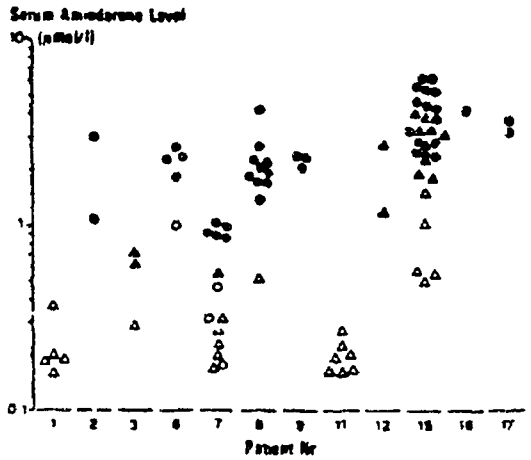
TABLE 11 SIGNIFICANCE OF AMIODARONE SERUM CONCENTRATIONS OF 1 5ug/ml AND 2.0 ug/ml

	1 5 µg/ml Cutpoint			2 0 µg/ml Cutpoint		
Arrhythmia	less than 1 5 (n = 109)	greater than 1 5 (n = 109)	p value	less than or equal to 2 0 (n = 153)	greater than 2.0 (n = 65)	p value
PVCs/hour	39	24	less than 0 02	40	12	less than 0 01
Paired PVCs/day	11	5	less than 0 04	11	2	less than 0 02

n = number of ambulatory electrocardiograms in each group, NS = not significant, PVCs = premature ventricular complexes VT ventricular tachycardia
From Hostow et al 1984

Staubli et al (1983) observed effective arrhythmia control (elimination of VT by Holter, suppression of symptoms and ectopic focus of supraventricular arrhythmia [SVA]) in 12 patients of 17 who could be evaluated Of these 17 patients, 16 were treated for arrhythmias and one for angina In 5 patients (4 could not be evaluated and one was treated for angina), whose amiodarone concentration was measured during periods of ineffective and effective therapy, amiodarone concentration was always higher when arrhythmia was controlled Only 2 patients (both had no on-therapy serum amiodarone concentrations, and were not controlled at serum levels measured off-therapy) still experienced arrhythmias at serum amiodarone levels above 0 5 µmol/l, and none of the 12 patients had arrhythmias at levels above 1 5 µmol/l (=1 0 mg/l) (Figure 7) These data, predominantly in atrial arrhythmias, appear to give a low estimate of the serum concentrations needed to control ventricular arrhythmias

FIGURE 7 SERUM AMIODARONE LEVEL VS ARRHYTHMIA CONTROL (STAJBLI et al , 1983)



Solid symbols indicate controlled and open symbols uncontrolled arrhythmias ● ○ observations during intake of amiodarone ▲ △ observations after cessation of therapy

Many investigators have observed marked variation of amiodarone serum levels within groups of responders and nonresponders, as well as overlap between the two groups, indicating that nonresponsiveness is not the result of unusual kinetics in most cases Harfajee et al (1983a) administered a mean loading dose of 1150 mg/day (800-1600 mg/day) for 21 days (8-28 days) in 173 patients and at the end of the loading phase or when consistent suppression of arrhythmias was seen (or sooner if severe adverse effects were observed), amiodarone serum levels were measured If the level was greater than 2 5 mg/l, the maintenance dose was reduced (generally to 200 to 600 mg/day) to achieve a level of 1 to 2 5 mg/l Serum concentrations did not distinguish between responders and nonresponders (1 7 vs 1 9 mg/l, respectively, in ventricular arrhythmias and 1 5 vs 1 9 mg/l, respectively, in supraventricular arrhythmias), and tended to be higher in the nonresponders, presumably reflecting attempts to elicit a response (See Table 12)

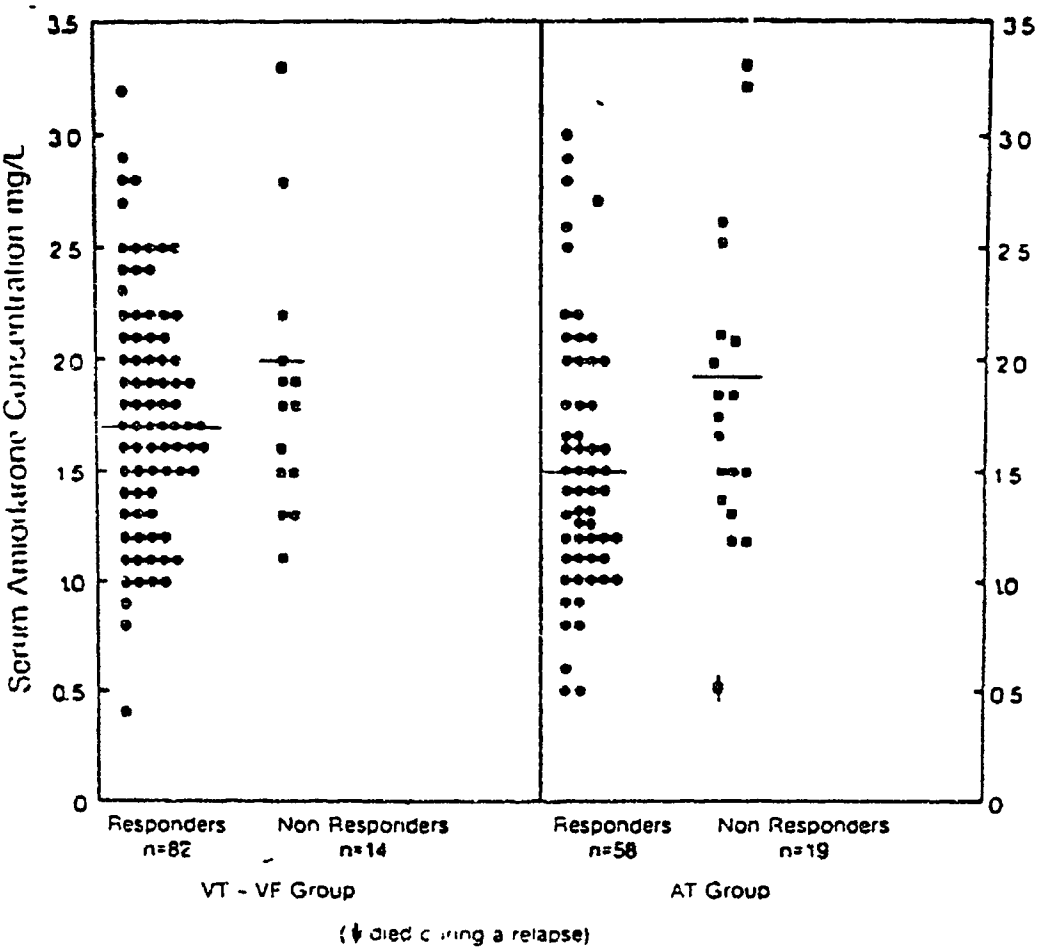
TABLE 12 AMIODARONE CONCENTRATION OF RESPONDERS AND NONRESPONDERS (HAFFAJEE et al., 1983b)

Arrhythmia	No Pts	No of Responders	Follow-up (months)	Maintenance dose (mg/day)	Maintenance Serum Amiodarone conc (mg/l)	No of Non Responders	Follow up (months)	Maintenance dose (mg/day)	Maintenance Serum Amiodarone conc (mg/l)
Sustained ventricular tachycardia	50	38	1 5-53 (mean 10 9)	200-600 (mean 371±145)	0 4-3 3 (mean 1 8±0 7)	12	1 5-15 (mean 2 5)	400-800 (mean 500±175)	1 1-2 8 (mean 1 9±0 7)
Unsustained VT and high-grade VEA	18	17	1 5-36 (mean 8 9)	200-600 (mean 370±141)	1 0-2 5 (mean 2 0±0 6)	1	11	400	1 5
Recurrent A Fib-flutter	48	41	1 5 49 (mean 10 1)	200-600 (mean 349±122)	0 5-3 0 (mean 1 5±0 6)	7	1 5 23 (mean 6 7)	200-600 (mean 460±135)	0 5-3 3 (mean 1 7±0 7)
Paroxysmal SVT	6	4	4 23 (mean 9 8)	400-600 (mean 500)	1 4-2 8 (mean 2 0)	2	9 and 23 months	400 and 600	1 8 and 3 2

conc = concentration, VT = ventricular tachycardia VEA = ventricular ectopic activity, SVT = supraventricular tachycardia
A fib-flutter = atrial fibrillation flutter

Figure 8 shows arrhythmia response vs maintenance serum amiodarone concentrations in 173 patients receiving oral amiodarone ranging from 200 to 400 mg/day (mean 382±146 mg/day) for 2 to 62 months (mean 19.3 months). Interpatient variability is clearly demonstrated. Most responses in VT/VF are seen at serum concentrations of 1.0 to 2.5 mg/l.

FIGURE 8 ARRHYTHMIA RESPONSE VS PLASMA AMIODARONE CONCENTRATION

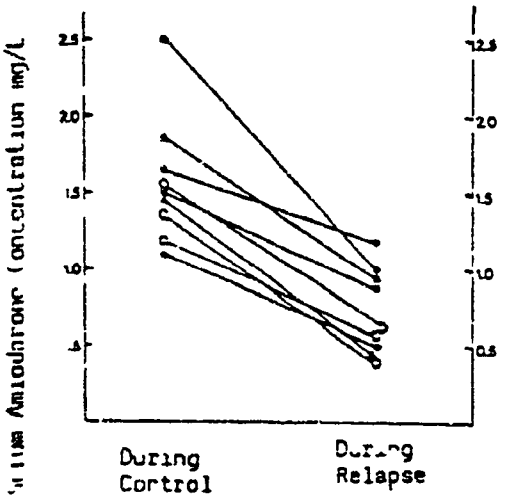


(Haffajee et al , 19d3a)

AT = atrial tachycardia
VT/VF = ventricular tachycardia/ventricular fibrillation

In a small number of patients (4 treated for atrial fibrillation [AF] and 4 for nonsustained VT) in Haffajee's series, serum concentration was observed to be less than or equal to 1 mg/l during relapse and control was restored when doses were increased and serum concentrations rose above 1 mg/l, a fifth AF patient had a relapse at 1 2 mg/l that was controlled with a higher dose (Figure 9)

FIGURE 9 RELAPSE VS PLASMA CONCENTRATION



(Haffajee et al , 1983a)

Most patients receiving 200 to 600 mg/day of amiodarone thus had steady-state serum amiodarone concentrations of 1 to 2 5 mg/l, but there was considerable intersubject variation Arrhythmia responses, when they occurred, were seen in this dose range, the 33 nonresponders, with one exception, had amiodarone concentrations greater than 1 mg/l and 11 had concentrations of at least 2 0 mg/l These data do not indicate, of course, whether the nonresponders could respond at still higher doses They do show that in this series, poor absorption or unusual kinetics was not the reason for nonresponse

Gradoys et al. (1983) also found no difference in serum amiodarone levels between responders and nonresponders treated for refractory supraventricular tachycardia The mean serum concentration among the 121 patients was 2 0 and was correlated with total daily dose Stewart et al (1984) found a mean amiodarone serum concentration of 2 4 ± 0 17 mg/l in a group of 41 patients treated with 505 ± 179 mg/day for 14 ± 6 8 months and serum level 2 5 ± 0 51 mg/l in the 7 patients among the 41 who were unresponsive

Rotmensch et al (1983a) showed that a total of 11 of 12 patients (92%) had no recurrence of their supraventricular arrhythmias at plasma concentrations of 1 5 ± 0 6 and 1 0 ± 0 4 mg/l, for amiodarone and its desethyl metabolite, respectively Forty-five of 52 patients with ventricular arrhythmias (87%) had no recurrence of their arrhythmia at plasma level of 2 5 ± 1 1 and 1 5 ± 0 6 mg/l for the parent compound and its metabolite, respectively The 7 nonresponders had similar plasma levels, 2 7 ± 1 1 mg/l for amiodarone and 1 6 ± 0 6 mg/l for the desethyl derivative

There are a number of possible explanations for the similarity of plasma concentrations in responders and nonresponders It is possible that plasma levels of amiodarone do not correspond to some more relevant tissue level, such as myocardial concentration of the drug More likely amiodarone simply behaves like other antiarrhythmics and indeed, as with other drugs, not every abnormal rhythm responds to it, even at maximally tolerated doses

Given the considerable individual variability of plasma concentration following a given dose, plasma concentration measurements may be useful in identifying unresponsive patients whose levels may be unusually low (1 mg/l or less), and who might benefit from a dose increase or better compliance, or responsive patients with unusually high levels, who might avoid eventual toxicity or reduce toxicity they are already suffering and retain response at a lower dose Since serum amiodarone levels are not reliable until the patient has reached steady state, serial concentrations would not be useful in evaluating the unresponsive patient during the loading phase

b Relationship of Blood Levels and Adverse Effects

Despite the likelihood that some adverse drug reactions (ADR, i e , neurological and gastrointestinal) are dose-related (Section VII B 5) and that amiodarone dose and plasma concentration are correlated (Section V A 10), the measurement of serum amiodarone levels has not yet been shown to be a very useful tool in monitoring or predicting toxicity When all side effects were tallied in 173 patients, Haffajee et al (1983a) found amiodarone serum levels among patients experiencing adverse reactions to be slightly, but not significantly, higher than those among patients without adverse effects (2 0 vs 1 8 mg/l) Similarly, Graboys et al (1983) found considerable overlap in serum amiodarone concentration in 121 patients with and without ADR On the other hand, Boppana et al (1983), using the same patient population, reported a mean (±SD) steady-state plasma amiodarone concentration in patients with adverse reactions as 3 1 ± 1 2 mg/l (N=2o) vs 2 3 ± 1 3 mg/l (N=38) in those free of adverse effects, a fairly sizable difference.

Table 13 summarizes serum level data and adverse effects noted by Haffajee and associates during long-term treatment (up to 53 months) in 173 patients.

TABLE 13 CLINICAL SIDE EFFECTS NOTED DURING LONG-TERM AMIODARONE THERAPY IN 173 PATIENTS

Side effect	N	%	Serum concentrations (mg/l)
Sun sensitivity	30	17	0 o-4 3 (mean 2 3)
CNS (tremor, ataxia, nightmare, paresthesia, headache, hair loss)	2o	15	0 8-3 6 (mean 1 o)
GI (constipation, anorexia or nausea)	2O	12	0 8-4 4 (mean 2 0)
Exacerbation of heart failure	7	4	1 1-2 3 (mean 1 6)
Impotence	5	2	1 2-2 . (mean 1 8)
Profound sinus node depression	5	2	2 6, 2 5, 2 4, 1 7
Proximal muscle weakness	3	2	2 8, 1 4, 1 3
Clinical hyperthyroidism	3	2	4 3, 1 7, 1 4
Clinical hypothyroidism	3	2	4 1, 1 8, 1 4
Pulmonary fibrosis	1	0 5	1 5
Total experiencing one or more side effects	44	25	0 6-4 8 (mean 2 0)

(Haffajee et al 1983a)

Data suggest that there may be a relationship between amiodarone serum concentration and some specific symptoms Harris et al. (1983) observed that increased liver enzymes correlated well with higher blood levels in 15 patients (p less than 0 001), while other symptoms (corneal deposits and facial pigmentation) were both dose and duration dependent in 140 patients who had taken amiodarone for an average of 2 years (mean daily dose = 360 mg) Contrary to the findings by Harris, however, the Haffajee group found no correlation between asymptomatic elevations in liver enzymes and serum concentrations of drug in 35 patients who developed these abnormalities

In a group of 3o patients who, at some time during follow-up, had serum amiodarone concentrations both above and below 2 5 mg/l, Haffajee et al found that the incidence of gastrointestinal and neurological symptoms was lower at amiodarone levels less than 2 5 mg/l Although the authors reported no significant increase in GI side effects with the higher plasma concentration (greater than n2 5 mg/l), this probably was erroneous, i e , the increased incidence (from 1 to 7) was significant Table 14 summarizes the distribution of side effects observed by Haffajee in those patients

TABLE 14 SUMMARY OF SIDE EFFECTS VS PLASMA CONCENTRATION

Side Effect	less than 2 5 mg/l	greater than or equal to 2 5 mg/l	p (Chi-square)
Sun sensitivity	11	8	NS
CNS	3	11	-- less than 0 05
GI	1	7	NS
CHF	0	0	--
Other	4	8	NS
Total no of patients with side effects*	1o	22	NS

*A patient may have more than 1 ADR (Haffajee et al , 1983b)

Fraser et al (unpublished report) showed that peripheral neuropathy was associated with long-term treatment (greater than 18 months) and elevated plasma concentrations of amiodarone and especially desethylamiodarone (mean 3 0 mg/l) in patients given maintenance doses of amiodarone of 400 to 600 mg/day In general, it was more common in older patients Sural nerve biopsy showed drug

concentrations 80 times higher than those found in plasma These peripheral nerve levels were much higher than those observed in patients treated with amiodarone without clinical evidence of peripheral neuropathy

Heger et al. (1982) examined the plasma and red blood cell hemolysate (RCH) levels of amiodarone and its metabolite, and their association with adverse effects in 28 patients of a group of 55 during chronic dosing Patients received a mean daily dose of 444 mg for at least 1 month The mean (±SD) plasma concentrations of amiodarone and desethylamiodarone were 3 00 ± 1 42 mg/l and 2 43 ± 1 22 mg/l, respectively In plasma, amiodarone levels were slightly greater than desethylamiodarone levels, whereas in the same patients (N=28), the RCH had higher metabolite concentrations than parent drug (3 65 vs 1 38 mg/l, respectively) Adverse effects (anorexia, nausea, weakness, unsteady gait and impotence) occurred in 9 of the 28 patients who, when compared to the other 19 patients free of adverse effects, had significantly higher RCH levels of amiodarone (2 05 vs 0 78 mg/l) and desethylamiodarone (6 55 vs 2 28 mg/l), although doses of amiodarone were not significantly different It was concluded that the concentration of amiodarone and its metabolite in RCH may represent intracellular or membrane-bound drug and may be a better marker for some adverse effects of the drug than plasma levels

The significance of the high tissue concentrations of the parent drug and metabolite, especially in liver and lung, and their relationship to amiodarone-induced adverse effects is under investigation Heger et al (1983a) could not predict the occurrence of pulmonary toxicity on the basis of cumulative dose or duration of treatment and stated that their data do not suggest that lung tissue accumulation is predictable based on plasma amiodarone levels Pulmonary toxicity occurred in 8 patients with plasma amiodarone concentrations available at the time of detection of pulmonary toxicity, but for 2 of these patients the concentrations were not unusually high (2 32 and 3 40 µg/ml) In the 196 patients treated, mean amiodarone concentrations were 1 45 + 0 50 and 3 78 + 1 61 after doses of 200 and 600 mg/day, respectively (Heger et al , 1983a) The development of blue skin discoloration was related to the cumulative dose and duration of therapy amiodarone tissue levels were similar, however, in 6 patients

with skin discoloration (2 96 ± 0 96 mg/l) and 8 unaffected patients (2 63 ± 1.63 mg/l) These were patients from a total of 53 who received long-term treatment (greater than17 months)

In 4 patients who had amiodarone-induced facial pigmentation, Holt et al (1982) studied tissue amiodarone concentrations associated with this adverse effect compared to unaffected skin in the same patient Biopsy results are summarized in Table 15

TABLE 15 AMIODARONE (A) AND DESETHYLAMIODARONE (DA) CONCENTRATIONS IN BIOPSY SAMPLES FROM PATIENTS WITH AMIODARONE-INDUCED FACIAL PIGMENTATION

Patient	Concentration A/DA (mg/kg wet weight)	
	Affected skin (Facial)	Control skin (Forearm or chest wall)
1	119/539	17 4/72 5
2	185/1018	19 7/116
3	167/229	18 3/46/3
4	502/1590	35 3/45 5
Mean ±SD (A)	243 ± 175	24 7 ± 8 5
(DA)	844 ± 594	70 1 ± 33 1

(Holt et al , 1982, unpublished)

Particularly high tissue levels of the parent drug (A) and especially the desethyl metabolite (DA) are associated with this adverse effect Amiodarone and its desethyl metabolite are usually present in high concentrations in tissues rich in macrophages Ultrastructurally, high levels of iodine attributed to these 2 compounds have been detected in secondary lysosomes when tissues are scanned by energy dispersion analysis of x-rays These findings have been reported in a variety of cells including dermatocytes, pneumocytes, hepatocytes, leukocytes and Schwann cells

Though the mechanism of amiodarone-related toxicity is not yet established, histochemical and electron microscopic studies suggest that the underlying pathology may be due to an alteration of lipid metabolism leading to a generalized lipoidosis, probably related to accumulation of the drug and its metabolite in tissue an accumulation that may not always correlate well with plasma concentrations

Side effects seem to be generally more common when plasma levels greater than 2.5 mg/l are maintained for a long time, but correlation of plasma levels and adverse effects is poor, and there is an overlap of plasma concentration between patients with and without adverse reactions. In some reports, however, where objective measurements can be made to evaluate specific adverse effects, such as liver enzyme elevations or peripheral nerve conduction, there may be a relationship between plasma levels and adverse effects. It may be possible to avoid very high plasma levels by monitoring. When adverse effects are observed, monitoring of plasma levels at that time may be useful in confirming the association of symptoms and amiodarone-induced toxicity. Routine monitoring of plasma levels cannot at present be said to forstall or reduce toxicity, especially for the potentially life-threatening pulmonary and arrhythmogenic adverse effects, or for possibly irreversible skin discoloration.

c. Additional Tests Used to Monitor Therapy

Other studies have evaluated parameters of potential use in identifying the response to amiodarone. Debbas et al. (1984) observed a correlation between plasma and myocardial concentration of amiodarone and prolongation of QTc. However, Rosenbaum et al. (1976) and Harris et al. (1981) did not find that QTc prolongation was closely related to antiarrhythmic effect. In addition, plasma and myocardial levels by the Debbas group did not correspond with those by other investigators indicating assay differences. Harris showed that 85% of 70 arrhythmia patients on chronic amiodarone treatment had repolarization changes but QTc did not alter significantly. PR and RR intervals increased (mean 33 msec [p less than 0.01], mean 132 msec [p less than 0.001], respectively). These changes were greatest with the highest plasma levels of amiodarone and its metabolite, but overall, the correlation was weak. Furthermore, it may be difficult to measure QTc interval accurately especially in the presence of myocardial disease, other antiarrhythmics and U waves. Other investigators (Nademanee et al., 1982c) have found correlations between reverse T_3 (rT_3) and antiarrhythmic effect. However, stress and intercurrent illnesses are also known to elevate rT_3 and may limit usefulness of this assay. Red blood cell concentrations of amiodarone and the desethyl metabolite have also been studied (Heger et al. 1983 and 1984). Until such results are confirmed in prospective studies with a larger

number of patients, it is unclear now useful these tests are in the routine follow-up of patients treated with amiodarone. Clinical evaluation and ambulatory Holter monitoring are presently the most reliable methods of adjusting dose and judging efficacy

d Onset of Action

Acute antiarrhythmic effects of amiodarone have been postulated to result, in part, from the nonspecific adrenolytic properties of the drug, whereas the long-term action may be related to prolongation of the action potential duration in all cardiac tissues with the consequent lengthening of the effective refractory periods (Singh et al , 1983a) Observed changes in A-V nodal conduction and refractoriness during acute dosing, however, may not be attributable solely to the antiadrenergic effects For example, Gloor et al (1982) raised the question as to whether or not acute changes in the S-A and A-V nodes following i v amiodarone in dogs may involve the blockade of the slow calcium channel Further work must be performed to elucidate the mechanisms involving the acute electrophysiological changes induced by amiodarone In contrast, the electrophysiological effects after long-term therapy described above are reasonably uniform and consistent

The unusually long half-life of amiodarone and intersubject variability make it difficult to precisely define the time to onset of initial and maximal antiarrhythmic effect in an individual patient Nevertheless, some general comments can be made The time-course of the electrophysiologic response to amiodarone has been discussed in several papers Early studies in animals showed a stepwise increase in effective refractory period (ERP) as a function of time at a constant amiodarone dose (Singh et al , 1970)

Fananapazir et al (unpublished) compared the timing of the onset of action and peak effect of oral and intravenous preparations of amiodarone on the ventricular effective refractory period Twenty-one patients received oral doses of amiodarone, 600 mg or 1200 per day Another 17 patients were first treated with an i v infusion (5 mg/kg) over 30 minutes, followed by 1000 mg infused over the next 24 hours, and then an oral daily dose of 1200 mg Although the investigators observed marked interpatient variations, generally, the onset of refractory period prolongation in patients receiving only oral amiodarone occurred in 1 to 3 days, and in

17 of the 21 patients after 24 hours. In contrast, i v. amiodarone prolonged the refractory period within 6 hours and in 9 of the 12 patients within the first 30 minutes. At the end of the first 24 hours of therapy, refractory period prolongation was significantly greater with i.v. than with oral amiodarone The timing of the peak effect following the i.v loading and 2 oral doses was similar (i.v. 6 days, 600 mg oral 8 days, 1200 mg oral 7 days). A greater peak effect was achieved with the 1200 mg oral dosage regimen than with the 600 mg schedule

Nademanee et al (1983a) reported that in 20 patients with resistant ventricular arrhythmias, monitored by 24-hour serial Holters, levels of serum amiodarone and rT_3, a latency period of 3 to 4 days was observed for the onset of PVC suppressant effects whether or not an i.v bolus of 5 mg/kg amiodarone preceded oral daily dosing with 1600 mg/day (The i v bolus, 350 mg for a 70 kg man, may have been too small to make a difference when added to the large loading dose.) A similar latency with respect to sustained PVC suppression or significant slowing of ventricular tachycardia cycle length was evident after a continuous i v amiodarone infusion of 50 mg/hour for 120 hours followed by oral dosing with 1200 mg/day Nademanee et al concluded that the overall effects of the i v infusion regimen on latency were statistically indistinguishable from those of the oral loading doses

Rakita and associates (1983a) noted elimination of all but infrequent ventricular ectopic beats (VEB) (less than 6/min) after 11 to 12 days in patients treated with loading doses of 1400 mg/day

McKenna et al (1983b) treated 24 hypertropic cardiomyopathic patients with 800 to 1200 mg/day for a 1-week loading period, followed by 400 mg/day for 1 month and then 200 to 600 mg/day After 1 week, Holters showed a significant decrease in the number of patients with frequent and complex VEB and VT. Results were similar after 1 month and slightly better after 1 year Paroxysmal SVA were essentially eliminated, and 4 of 8 patients converted from atrial fibrillation to sinus rhythm (3 during loading phase)

Singh and Nademanee (1983b) judged onset of action according to symptoms and reduction in ventricular tachycardia (VT) and VEB on Holter recordings. In 18 patients with recurrent atrial or ventricular arrhythmias, amiodarone was given at doses of 600 to 1400 mg/day. Response was apparent within 2 to 3 weeks although in individual patients, maximal response was not seen until 2 to 5 months. Interestingly, rT_3 increased linearly for 2 to 5 months, to reach a level in responders of 2 to 4 times baseline, rT_3 was more reliable than heart rate, T_4 or QTc in predicting onset of action and response.

Kaski et al. (1981) observed a latency of 9.5 ± 4.5 days in 11 patients with daily episodes of VT; average loading dose at the time of arrhythmia suppression was 918 mg/day. They also observed that suppression of VT was usually preceded by a decrease in the number of daily episodes and slowing of the heart rate during each episode. A longer latency (12 to 16 days) was seen in patients with clinical signs of severe heart failure.

In the Detailed Study conducted by Ives (see Section VI), Holter responses showed a marked reduction in VT after 8 to 14 days and in couplets and VEB after more than 14 days of loading treatment (mean initial loading dose for all patients was 1081 ± 37.7 mg/day for 24 ± 4.6 days). The reduction in VEB from baseline appeared to improve with increasing duration of maintenance treatment (60 ± 11.1% reduction from baseline after 3 months or less of treatment vs 70 ± 13.7% after more than 3 months' maintenance therapy), although fewer patients were represented in the latter treatment intervals.

Despite differences in patient populations, dosage regimens and methods of assessment, the above studies suggest that amiodarone's antiarrhythmic effect may be noted as early as 3 days (72 hours) but more often takes 1 to 3 weeks, even with a loading dose regimen. Due to variation among patients (difference in attaining steady state), some may show initial and peak antiarrhythmic effects much later than the above. Prolongation of the effective refractory period has been shown to occur as soon as 24 hours after oral dosing. Antiarrhythmic response probably increases to its full potential effect some time later, depending on the achievement of steady state. Some patients (particularly those treated for supraventricular tachyarrhythmias) may respond with reduction in heart rate after 1 or 2 loading doses (Graboys et al., 1983), this probably reflects the antiadrenergic properties of amiodarone

e. Rationale for Loading Phase

The above studies defining onset of action initially used high loading doses. Because of amiodarone's long half-life and large volume of distribution, loading doses are required to achieve effective drug concentrations reasonably promptly (Holt et al., 1983d). Heger and coworkers (1983a) found significantly higher plasma and red blood cell concentrations of amiodarone (A) and desethylamiodarone (DA) after 2 to 15 days of treatment with 1600 mg/day vs 800 mg/day (Table 16)

TABLE 16 AMIODARONE CONCENTRATION DURING LOADING (HEGER et al , 1983a)

	800 mg/day						1600 mg/day					
	Plasma			Red cell			Plasma			Red cell		
Day	A	DA	DA/A	A	DA	DA/A	A	DA	DA/A	A	DA	DA/A
2	0.60 ± 0.26	0 13 ± 0.10	0.22	0.11 ± 0.04	0.10 ± 0.05	0.91	1 46 ± 0.50	0.36 ± 0.14	0.25	0 45 ± 0.20	0.33 ± 0 16	0 73
5	1.08 ± 0.30	0.28 ± 0.12	0.26	0.33 ± 0.04	0.42 ± 0.24	1.27	2.38 ± 0.64	0.92 ± 0.32	0.39	0.77 ± 0.2[illegible]	0.87 ± 0.33	1 13
10	1.44 ± 0.53	0.71 ± 0.20	0.49	0.44 ± 0.17	0.72 ± 0.19	1.64	2.71 ± 0.76	1.33 ± 0.68	0 49	1.08 ± 0 48	1.52 ± 0 74	1.41
15	1 68 ± 0 41	0.78 ± 0.23	0.47	0.43 ± 0.06	0.88 ± 0.23	2.05	2.73 ± 0.93	1.40 ± 0 66	0.51	1.20 ± 0.35	1 73 ± 0 45	1.46

While they demonstrated that use of a high loading dose (1600 mg/day) would achieve higher drug concentrations earlier, this study did not determine whether the antiarrhythmic effect was also achieved more promptly. Fananapazir and associates (unpublished) observed a greater peak effect, as assessed by prolongation of effective refractory period, with 1200 than with 600 mg/day after 6 to 7 days of oral amiodarone. Several other investigators addressed arrhythmia response. Thiesen et al. (1983), in a dosage regimen essentially lacking a high-dose loading phase (600 mg/day for 1 week, reduced thereafter to maintenance level), found elimination of Lown arrhythmia classes IVa and b in only 12/22 patients after 1 week, which then increased to 15/22, 17/24 and 23/28 patients after 1, 3 and 6 to 12 months, respectively, perhaps showing a slow attainment of optimal response without a loading dose (it is also possible there was spontaneous improvement over so long a period).

Rakita et al. (1983b) demonstrated the need for high loading doses to shorten the time to control ventricular arrhythmias (VT) in 40 patients refractory to other antiarrhythmic or pacemaker therapy. Patients were assessed by weekly 24-hour Holter monitoring and control was defined by complete elimination of all VT, except for isolated PVCs (less than 6/min). Table 17 summarizes these investigators' findings. The three loading dose regimens were superior to the regimen lacking one, but there was no clear difference among the three even though one (number III) gave a dose almost twice the other two.

Even with relatively high oral loading doses, arrhythmia suppression may not be achieved until 8 days to 4 weeks (mean 17 days) after initiation of therapy (Haffajee et al , 1983b) The reason for such a delay in the onset of drug effect is not known.

f Duration of Action

Consistent with amiodarone's long half-life, early studies in animals showed that reduction of heart rate, systemic arterial pressure and tension-time index persisted for 5 weeks after amiodarone was discontinued (Charlier et al., 1968) Subsequently, studies addressed the gradual decrease in antiarrhythmic effects and recurrence of arrhythmia after discontinuation of amiodarone Singh and Nademanee (1983b) observed recurrence of arrhytnmia in hospitalized patients (5 with ventricular and 4 with supraventricular arrhythmias) 2 to 20 weeks following controlled withdrawal of amiodarone, arrhythmia recurrence corresponded with the fall in serum rT_3 concentration (Figure 10)

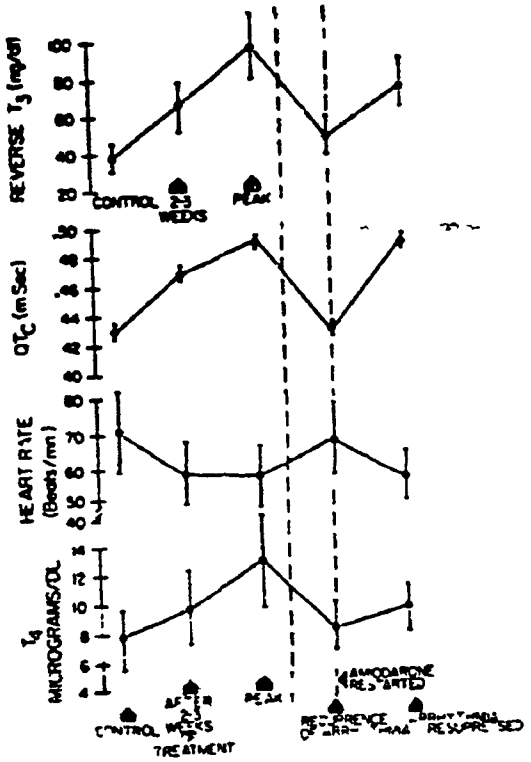
TABLE 17 NUMBER OF DAYS AND DOSAGE REQUIRED FOR CONTROL OF VENTRICULAR TACHYCARDIA
(LOADING VS. NON-LOADING REGIMEN)

Group	Dosage Regimen	N	Mean Days to Control	Mean Dose to Control (g
I	200 mg/day x 1 week ____ 400 mg/day x 1 week ____ 600 mg/day x 1 week ____ increased up to 800 mg/day x 4 weeks and then titrated down by 200 mg/day/week if controlled	8	23.5 ± 12.3	11.5 ± 6.36
II	Initial oral loading dose on Day 1 of 1400 mg ____greater than 800 mg/day x 6 days, then 200 mg increase or decrease depending on achievement of control	16	11.5 ± 6.08*	10.84 ± 6.82
III	Initial loading with 1400 mg x 1 week dose continued up to 4 weeks if needed. At the end of 7-day dosing periods if control reached ____ reduction to 200 mg/day. If control lost ____ repeat 1400 mg/day x 1 week ____ reduction to 400 mg/day	9	12.1 ± 6.75*	11 00 ± 8.34 This
IV	i.v. loading with 5 mg/kg x 1 day ____ 800 mg/day. Doses changed at weekly intervals depending on control	7	11 7 ± 7.08*	10.42 ± 6.46 then

* = statistically significant
Group I vs. II less than 0.02
Group I vs. III less than 0.05
Group I vs. IV less than 0.01

(Rakita et al., 1983b and personal communications)

FIGURE 10 RESPONSE TO INITIATION AND DISCONTINUATION OF AMIODARONE (SINGH AND NADEHANEE, 1983b)



Within a mean of 11 days (range 3 to 28 days) of resuming therapy, control was reestablished, in contrast to an initial latency of 2 to 5 months when amiodarone was first administered Since amiodarone was restarted upon recurrence of arrhythmia (2 to 20 weeks), patients probably still had remaining tissue stores and a shorter latency for reestablishing control would not be unexpected

The prolonged antiarrhythmic effect of amiodarone coincided with a similarly prolonged persistence of the electrocardiographic changes caused by the drug (Pritchard et al , 1974) Holt et al (1983c) found that the antiarrhythmic efficacy of the drug lasted up to 18 weeks following cessation of therapy in one patient with a prolonged half-life of 107 days

In general, antiarrhythmic effects may persist for weeks or months after amiodarone withdrawal and the effects of a dosage adjustment may similarly be delayed, the difficulty is that the time of recurrence is highly variable and unpredictable, a considerable problem if life-threatening arrhythmias are involved

g Minimal Effective Dose

The minimal effective dose has not been rigorously defined but clearly varies from person to person, as recurrent arrhythmias have appeared following dosage reduction from various effective doses Dosage must be based on individual responses, weighing the severity of the arrhythmia and tolerance In addition, other possible factors should be taken into consideration, including body weight, age and underlying cardiac status (e g , CHF)

h Rationale for Daily Dosing Regimen

As efficacy may be related to the changes which are seen in the more rapidly perfused tissues, once-daily dosing is recommended despite the long terminal elimination half-life. Furthermore, the risk of breakthrough arrhythmia is minimized and patient compliance is facilitated by daily dosing

10. Miscellaneous

a Protein Binding

Andreasen et al. (1981) reported technical difficulties in the measurements of plasma protein binding of amiodarone. Similarly, Holt et al (1982, unpublished) encountered problems using the conventional techniques of equilibrium dialysis and ultracentrifugation, however, they used an alternate approach measuring salivary levels as an indirect measurement of the free concentration Their preliminary results demonstrated that the drug is highly protein-bound (o 98%) A more recent study by Lalloz et al (1984) confirmed these findings Using ^{125}I-labeled amiodarone, the compound was described as strongly and highly bound (approximately 96%), specifically, to the albumin and β_2-lipoprotein fractions Amiodarone binding was reduced by quinidine, amitriptyline, and cefazolin but the binding of digoxin or warfarin was not affected by amiodarone

D Renal Insufficiency

Harris et al. (1983b) evaluated 2 patients with chronic renal failure who were receiving chronic amiodarone therapy while being treated by hemodialysis or peritoneal dialysis. For both patients, amiodarone and the desethyl metabolite concentrations were within the expected range for the doses they were taking, and these levels did not fluctuate during dialysis. Neither the parent compound nor the metabolite was detected in the dialysate, probably reflecting their large volume of distribution and poor water solubility, and only minimal amounts were recovered in the urine.

In these patients, the ratio of metabolite to parent drug was in the range of 0.8 to 1.2 (approximately 1.0 has been found in patients on long-term therapy), suggesting that the biotransformation of the drug is not significantly altered in patients with renal insufficiency.

In their study of 5 patients with chronic renal insufficiency maintained on regular hemodialysis, Bonati et al. (1983) obtained kinetic information for amiodarone and its N-dealkyl metabolite during amiodarone treatment for supraventricular arrhythmias. Unfortunately, these investigators did not monitor blood levels of amiodarone and its metabolite long enough. The only meaningful information provided by this study was the observation that amiodarone was not detected in the dialysate or in the dialyzer membrane, i.e., amiodarone is nondialyzable.

C Placental Transfer and Breast Milk Concentrations

Several investigators (Candelpergher et al. 1982, Pitcher et al., 1983, McKenna et al., 1983a) have demonstrated that there is limited placental transfer of amiodarone and its desethyl metabolite, ranging from 10 to 25% and 25 to 50%, respectively.

Candelpergner et al. (1982) reported some ECG changes and bradycardia in the newborn. In addition, Haffajee et al. (personal communication) monitored a woman receiving amiodarone during the course of her pregnancy who gave birth to a small hypothyroid infant.

Gobbato et al. (1982) and McKenna et al. (1983a) observed a wide variation in the concentrations of amiodarone and desethylamiodarone in the breast milk throughout the day. In general, levels were high, suggesting that breast feeding could expose the nursing infant to a significant dose of drug.

d. Saliva and Bile Levels

Holt et al (unpublished) and Gobbato et al. (1982) found that salivary levels of drug were low, whereas Gobbato et al., 1982 reported biliary levels 10 to 30 times that of plasma

11 Conclusions of Pharmacokinetics and Pharmacodynamics

The data reveal the following pharmacokinetic and pharmacodynamic characteristics of amiodarone

a It is slowly absorbed after oral administration with a time to reach peak plasma concentration (T_{max}) in the range of 3 to 7 hours

b Amiodarone has absolute (compared to i v) bioavailability of 35-65% in various studies and shows great individual variation.

c. One metabolite, desethylamiodarone, has been identified which displays formation rate-limited elimination kinetics, and for which the pharmacological activity in man has not been established

d. Plasma levels with chronic dosing show dose-proportional steady-state plasma concentrations in the range of 0.5 to 3.5 mg/l at maintenance doses of 100 to 600 mg/day, with a roughly 0.5 mg/l increase for each 100 mg/day. Those are means, however, and include considerable individual variability

e Amiodarone has a large volume of distribution (about 5000 liters) because of extensive accumulation of amiodarone in adipose tissue and highly perfused organ (especially liver, lung and spleen).

f Amiodarone has negligible renal excretion but considerable excretion into bile with levels of drug in the bile 10-to 30-fold greater than in plasma, there is thus a possibility of enterohepatic recirculation

g. Amiodarone has low total plasma clearance of approximately 8 l/hr. It shows a biphasic elimination pattern with a long terminal half-life ($t_{1/2z}$) after single dosing in normals a terminal elimination of approximately 25 days is observed, again with considerable variability Following cessation of chronic oral therapy, plasma levels of amiodarone decline by half over a period of 2 5 to 10 days followed by a rebound at 12 to 21 days, before settling into the terminal elimination phase, with a half-life ranging from 26 to 107 days (mean of approximately 53 days and most patients in the 40-55 day range) For the metabolite, after chronic dosing the mean terminal half-life was estimated at 61 days This final phase probably represents very slow clearance from deep, poorly perfused tissue compartments such as fat, while the initial elimination may represent the turnover from more highly perfused organs, presumably including the sites where amiodarone has its effect. This would fit with the observation that arrhythmias can respond within weeks of therapy and can return within a few weeks after the drug is stopped, suggesting that the biologically pertinent half-life may be the shorter (but still several days to a week or more) initial elimination phase

h There is limited transplacental transfer of parent compound and its metabolite but secretion of high levels of amiodarone and desethylamiodarone into breast milk

i There is a low concentration of amiodarone in saliva

j Amiodarone is highly protein bound (about 96%) to the albumin and β_2-lipoprotein fractions

k Significant correlations between steady-state blood levels of drug and some adverse reactions may exist, but a clear relationship has not been demonstrated for most adverse effects In general, serum levels below 2 5 mg/l may be associated with better tolerance of the drug Though the mechanism of amiodarone-related toxicity is not established, histochemical and electron microscopic studies show alteration of lipid metabolism in the pattern of a generalized lipoidosis, probably related to tissue accumulation of the drug and its desethyl metabolite

l Arrhythmia control has been seen with plasma concentrations ranging from 0.6 to 3 mg/l (and with doses of 200 to 600 mg/day), in treated cases, effectiveness has not correlated with blood levels as nonresponders have had plasma concentrations similar to those in responders Thus, non-response does not usually seem to be caused by poor absorption or rapid metabolism, rather, it seems to relate to the innerent responsiveness of the patient's particular arrhythmia. Recurrence of arrhythmia, however, obviously does occur when plasma concentrations fall and, specifically, has been observed in some responsive patients whose plasma levels fell below 1 0 mg/l

m In adults, the onset of antiarrhythmic effect is usually observed in about 1 to 3 weeks with loading doses and after a longer period if no loading dose is used Even with loading doses responses may be enhanced over several months

n The duration of action has been reported as up to several months after discontinuation of therapy in one patient with an extremely prolonged amiodarone plasma half-life (107 days), but on the average, antiarrhythmic efficacy may persist for up to 1 month depending on the body stores of drug

B Mechanism of Action

1. Electrophysiology

Amiodarone is a Vaughan-Williams Class III antiarrhythmic agent The predominant effect of the drug is a prolongation of the action potential (Elizari et al , 1980, Singh et al , 1980) and increased refractoriness in sinus node tissue, the slope of phase 4 prepotential is reduced (delaying the point where critical potential is reached) In contractile and Purkinje tissues, the rate and amplitude of the upstroke* (phase 0) is not affected The net result is prolongation of the action potential duration and refractoriness (i e , delay of repolarization) without impairment of depolarization (Singh et al , 1970)

* In one recent study (Mason et al , 1982) preliminary animal data did demonstrate some slowing of the rate of depolarization

Voltage clamp experiments performed on atrial and ventricular fibers (Neliat et al., 1982) showed that amiodarone's predominant effect is the decrease of outward K^+-mediated current. More precisely, in ferret ventricular fibers, the decrease of outward K^+ current reaches 25% and 42%, respectively, for amiodarone concentrations of 2.10^{-5} and 2.10^{-4} M.

Although electrophysiologic studies in man following I.V. and chronic oral administration showed similar effects, in general, effects were more pronounced after oral treatment (Touboul et al., 1982). Some differences were observed, however, in electrophysiologic changes following acute and chronic therapy. Acute effects were dominated by increased A-V nodal conduction time with prolonged refractoriness of the A-V node (Singh et al., 1983a). Long-term treatment was associated with effects on all electrically active cardiac tissues (Donaldson et al., 1982).

Generally in man, the sinus rate is slowed by about 10%, and SA conduction is depressed (Wellens et al., 1976, Rasmussen et al., 1979, Fineman et al., 1982). In some cases, retrograde conduction within the SA junction is suppressed (Touboul et al., 1979). Brown et al. (1978), however, showed good response to amiodarone (200 to 600 mg/day for up to 9 months) in 5 refractory patients with bradycardia-tachycardia syndrome. These patients showed no evidence of return of severe sinus bradycardia. Atrial and ventricular monophasic action potential durations (Olsson et al., 1973) and effective refractory periods are increased (Waxman et al., 1982). A-V nodal conduction time is increased, as evidenced by a lengthening of the A-H interval by about 10%, and the functional and effective refractory periods of the A-V node are prolonged. The infranodal conduction time (H-V interval) usually does not vary, but there have been slight increases in several cases (Rasmussen et al., 1979, Waxman et al., 1982). The relative effective refractory period of the His-Purkinje system increases after administration of amiodarone (Touboul et al., 1976). In patients with Wolff-Parkinson-White (WPW) syndrome, amiodarone increases the refractory period of the A-V accessory pathways (antegrade and retrograde) (Rowland et al., 1980). Table 18 summarizes the electrophysiologic effects of amiodarone.

TABLE 18 SUMMARY OF AMIODARONE ELECTROPHYSIOLOGY

	Automaticity	Conduction	Refractoriness
SA node	-	0 (or -)	0 (or +)
Atrium	-	-	+
AV node	-	-	+
Accessory patnway	0 (?)	-	+
His-Purkinje	0	0 (or -)	+
Ventricle	-	-	+

0 = no effect, + = increased, - = decreased. (Camm and Bexton, 1983)

Amiodarone exerts a widespread action on myocardial tissue, as well as on S-A, A-V, and abnormal accessory conduction pathways These changes are, in general, similar to those found in vitro In the human His-Purkinje system, amiodarone does not significantly depress conduction as do Class I antiarrhythmics Therapeutic doses prolong the QT interval on the surface ECG by about 10% independently of changes in heart rate (Touboul et al., 1982).

The uniform action on both specialized and ordinary myocardial cells appears to be a unique property of amiodarone In comparison, quinidine and quinidine-like compounds do not always depress A-V node conduction, while B-blockers have no significant effect on conduction in ordinary myocardial cells (other than A-V junction). Digitalis derivatives and verapamil may increase conduction in accessory pathways, although increased ventricular rate on verapamil may be due to a reflex response to systemic hypotension

2 Hemodynamics

Cote et al (1979) found that in patients undergoing diagnostic cardiac catheterization, intravenous amiodarone decreased mean arterial pressure, left ventricular end-diastolic pressure, and systemic vascular resistance with a mild but significant increase in the cardiac index. In addition, coronary vascular resistance decreased and coronary sinus flow increased significantly, confirming animal studies showing amiodarone to be a potent coronary and peripheral vasodilator. Despite falls in the systemic vascular resistance, reflex tachycardia was not observed

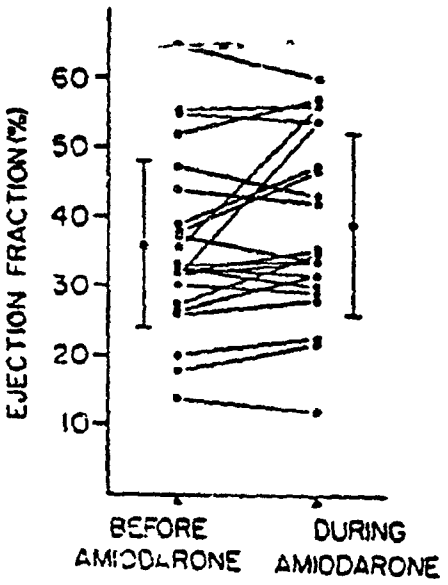
After long-term oral dosing with amiodarone in the therapeutic dose range of 200-600 mg/day, Singh et al. (1983a) and Haffajee et al. (1983a) demonstrated no significant decrease in left ventricular ejection fractions even when the basal ejection fraction was markedly reduced. Figure 11 shows left ventricular ejection fraction data before and during chronic amiodarone treatment from these 2 studies.

3. Antiadrenergic Effect

Amiodarone causes a mild sinus bradycardia and a 10% increase in PR intervals which may be attributed, in part, to an antiadrenergic effect. It is a mild noncompetitive antiadrenergic agent which relaxes smooth muscle, including coronary and peripheral arteries, reducing systemic vascular resistance (SVR) (Vastesager et al , 1967, Salvador et al., 1979, Jewett et al., 1980).

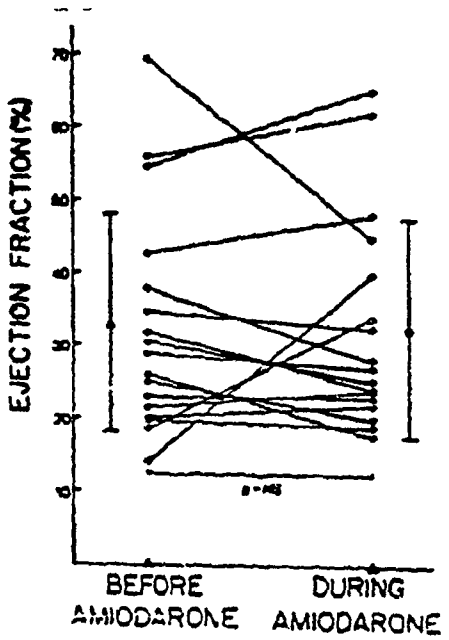
FIGURE 11 LEFT VENTRICULAR EJECTION FRACTIONS IN PATIENTS PRE- AND POST-AMIODARONE TREATMENT

N = 25



(Singh et al , 1983a)

N = 17



(Haffajee et al , 1983a, mean pre-dosing 32 8 ± 15 4% and mean post-dosing 32 6 ± 14.8%)

4. Amiodarone and Thyroid Function

The amiodarone molecule contains 37% (by weight) iodine, to the extent that deiodination occurs, iodide effects on the thyroid are possible including hyperthyroidism and hypothyroidism. Amiodarone apparently can affect peripheral deiodination of T_4 to the major metabolically active T_3 (Burger et al., 1976, Jonckheer et al., 1978, Freedberg et al , 1970, Pritchard et al., 1975). Like some other substances or factors which interfere with normal metabolism (e.g. starvation or inflammation), amiodarone inhibits the peripheral and intracellular thyroxine metabolic pathways, and instead of active T_3, an increased amount of the metabolically inactive reverse T_3 (rT_3) is produced Whether this relates in any way to the arrhythmic action of amiodarone is unclear, although the effect of amiodarone upon the action potential of individual cells in cardiac muscle and upon the surface ECG is very similar to effects produced by thyroxine depletion, i e., depolarization currents are not altered, but repolarization currents are delayed It has been suggested that increases in rT_3 levels may constitute a useful technique for monitoring the drug's antiarrhythmic efficacy and toxicity, but rT_3 is a labile measurement that can easily be affected by other concomitant drugs or intercurrent illness, thereby making the reliability of its usage still questionable. For example, Holt et al. (1984) showed that although rT_3 is elevated during amiodarone treatment, patients not receiving the drug had a wide range of rT_3 concentrations which often overlapped with those of the amiodarone-treated patients

C. Drug Interactions

Amiodarone interacts with a number of other drugs, viz warfarin, digoxin, phenytoin, quinidine, procainamide, β-blockers lidocaine, and aprindine For warfarin, digoxin and the antiarrhythmics, the interaction appears to be related to amiodarone's effect in altering the pharmacokinetics of the drugs, but the interaction with β-blockers is probably due to an additive effect, especially in individuals who have sick sinus syndrome or partial A-V block. Patients taking any of these drugs concomitantly with amiodarone should be carefully monitored and the doses of the concomitant drugs reduced accordingly or discontinued If amiodarone is discontinued due to treatment failure, other antiarrhythmic therapy should be initiated cautiously, since amiodarone's long half-life may give rise to significant interactions