

It is evident from Table 5b that in the Global Survey the most frequent reasons for discontinuation of amiodarone treatment due to cardiovascular side effects were cardiac arrhythmias and CHF. It is always difficult to distinguish therapy failure and adverse effects, but 13 patients were identified as having definite increases in ventricular tachycardia (10) or torsades de pointe (3), most of these patients were receiving digoxin and/or other antiarrhythmics in addition to amiodarone. As noted above, exacerbation rates of 5% have been reported in several series.

Terminations due to Gastrointestinal ADR

In the Global Survey, among 399 patients who discontinued treatment because of an ADR, 34 listed gastrointestinal ADR as the primary cause (refer to Table 57)

TABLE 57 DISCONTINUATION OF AMIODARONE FOR GASTROINTESTINAL ADR (Global Survey)

Description of ADR	No Pts Discontinued	% of Treated (N=4802)	% Pts Discontinued (N=399)
Nausea and Vomiting	19	0.4	4.8
Anorexia	3	less than 0.1	0.8
Constipation	5	0.1	1.3
Stomach Function Dis	5	0.1	1.3
Noninf Gastroenteritis	1	less than 0.1	0.3
Intestinal Obstruction	1	less than 0.1	0.3
Total	34	0.7	8.5

Terminations due to Hepatic Adverse Reactions

In the Global Survey of 4802 patients, 15 (0.3%) discontinued therapy for hepatic ADR, 6 had chronic passive congestion and 3 had elevated liver enzymes (refer to Table 58)

TABLE 58 DISCONTINUATION OF AMIODARONE DUE TO HEPATIC ADR (Global Survey)

Description of Adverse Reaction	No Pts Discnt	% of Treated (N=4802)	% Pts Discnt (N=399)
Elevated Transaminase/LDH	3	less than 0.1	0.8
Chronic Passive Congestive Liver	5	0.1	1.5
Liver Disorder	2	less than 0.1	0.5
Other*	4	less than 0.1	1.0
Total	15	0.3%	3.8%

*Other includes hepatomegaly, jaundice, hepatic coma, acute necrosis of liver (granulomatous hepatitis)

Terminations due to Dermatologic ADR

In the Global Survey of 4802 patients, therapy was discontinued in 21 patients (0.4%) because of dermatologic ADR including photosensitivity in 4 patients. Sun barrier creams may afford some protection, but not complete filtering of all wavelengths. The dermatologic ADR in the Global Survey are summarized in Table 59.

TABLE 59 DISCONTINUATION OF AMIODARONE DUE TO DERMATOLOGICAL ADR (Global Survey)

Description of ADR	No Pts Discnt	% All Treated (N=4802)	% Pts Discnt (N=399)
Photosensitivity	4	0.2	2.3
Nonspecific Skin Erupt	1	0.1	1.0
Pruritus	2	less than 0.1	0.5
Hyperhidrosis	2	less than 0.1	0.5
Others	4	0.1	1.0
Total	21	0.4	7.0

Terminations due to Thyroid ADR

Of 4802 patients treated, 13 (0.3%) discontinued therapy because of hypothyroidism and 2 (0.04%) for hyperthyroidism

Terminations due to Miscellaneous ADR

Table 60 lists miscellaneous terminating ADR that occurred in a small number of patients and that were not classified in any of the body systems described previously.

TABLE 60 DISCONTINUATION OF AMIODARONE DUE TO MISCELLANEOUS ADR (Global Survey)

Description of Adverse Drug Reaction	Total (%)	% Treated Discont.	% Pt Discont (N=399)
Unk. Cause Morb/Mort	4	0.1	1
Nutritional Marasmus	4	0.1	1
Muscle/Ligament Dis	4	0.1	1
General Symptoms	2	less than 0.1	0.5
Eosinophilia	2	less than 0.1	0.5
Smell Taste Disturbance	2	less than 0.1	0.5
Others*	16	0.3	4
TOTAL	34	0.7	8.5

*Others One patient each - edema, sialoadenitis, tinnitus, integument/tissue symptom, dist phosphorus metabolism, hemorrhagic condition, agranulocytosis (of questionable relationship to amiodarone, patient was also on procainamide), neuropathy in diabetes, malignant hypertension, arteritis, salivary secretion dis, pyrexia unknown origin, renal failure, Reiter's syndrome, abnormal finding-skull/head, neurohypophysis dis

The outcome of patients discontinued for ADR in the Global Survey was evaluated and is summarized in Table 61. In the majority of patients (71%) symptoms resolved or improved following discontinuation of therapy or dose reduction.

TABLE 61 OUTCOME OF ADR

Outcome	No (%) Patients (N=399)
ADR resolved	198 (50%)
ADR improved	84 (21%)
ADR unchanged	59 (15%)
ADR worsened	16 (4%)
Death due to ADR*	6 (2%)
Unknown	36 (9%)

*Respiratory deaths attributed to interstitial or fibrotic problem

4 Response of Adverse Reactions to Dose Reduction and Temporary Discontinuation

Forty-nine (49) of 241 patients (20%) in the Detailed Study, and 251 of 1024 patients in the Global Survey (25%) had either dose reduction or temporary interruption of therapy due to ADR. The outcome of ADR on dose reduction or temporary discontinuation of amiodarone is summarized in Table 62.

TABLE 62 SUMMARY OF ADR RESPONSE TO DOSE REDUCTION OR TEMPORARY INTERRUPTION OF THERAPY

	Total No Patients	Improved/ No Recur	No Change/ Recur	Worsened	Unknown
Detailed Study	49	31 (63%)	12 (24%)	0	6 (12%)
Global Survey	251	68 (27%)	130 (52%)	20 (8%)	33 (13%)

Generally, symptoms necessitating dose changes were neurologic or gastrointestinal which tended to occur at high doses during the loading phase. Most side effects resolved when the amiodarone dose was reduced or when therapy was interrupted temporarily, ADR did not recur immediately upon resumption of therapy at a somewhat lower dose. Occasionally some symptoms (such as skin pigmentation or peripheral neuropathy) may persist.

Although the safety profile of high and low doses of amiodarone has not been systematically studied, ADR do respond to dose reduction and the patients seem to tolerate lower doses better than higher doses.

5 Adverse Reactions vs Dose and Duration of Therapy

To use amiodarone properly, the desired antiarrhythmic response must be achieved with minimal toxicity. The relationship of side effects to amiodarone dose and duration of therapy is an important factor in adjusting therapy to minimize toxicity.

Conclusions regarding effects of dose and duration that can be made from Ives data are limited by the following points:

1. Effects of dose and duration cannot be separated completely as high doses were given early during the loading phase and generally patients had progressive dose reductions with continued therapy.

- 2 High doses, as used during loading, were administered for a much shorter period of time compared with lower maintenance doses
- 3 Because of amiodarone's long half-life, a new steady-state would be achieved sometime (i.e., 2-4 weeks) following dose adjustment. Therefore, the dose at onset of symptoms is difficult to define
- 4 No common dosage regimen was followed

Nevertheless, the following points can be made from the data regarding dose and duration of therapy for particular side effects

Pulmonary toxicity - The cases reported in the U.S. tended to occur at doses greater than 400 mg/day (in the Global Survey, mean dose of 614 mg/day, following 223 days of treatment). However, the European clinical experience, as reported by Sanofi, showed that this ADR occurred at doses less than or equal to 400 mg/day in 36 of 54 cases. This, too, is hard to interpret, however, European clinicians have generally used lower doses of amiodarone. Available data do not allow one to predict the incidence of pulmonary toxicity at various maintenance doses, nor are there data to determine whether the cumulative dose, which is distorted by the inclusion of high loading doses, increases risk of this reaction. Although the duration of therapy in the cases reported in the Global Survey as well as by Sanofi was generally greater than 6 months, some patients may develop pulmonary ADR earlier. Mason's survey suggests that the rate of pulmonary toxicity does increase up to about 7 months, but is then fairly steady at a rather high rate of almost 20%.

The relationship of pulmonary reactions to dose and duration was evaluated in 51 patients (data from 3 patients were not available) reported by Sanofi. Pulmonary reactions occurred at low doses (26 of 51) on less than or equal to 200 mg) as well as at higher doses. Sanofi data are summarized in Table 03.

TABLE 63 PULMONARY TOXICITY DOSE-TIME RELATIONSHIP
(Sanofi Data)

Dose*	N*	less than or equal to 3 mos	greater than 3 mos less than or equal to 6 mos	greater than 6 mos less than or equal to 1 yr	greater than 1 yr
less than or equal to 200	26	2	3	7	14
greater than 200 less than or equal to 400	10	2	0	3	5
greater than 400 less than or equal to 600	11	1	4	6	0
greater than 600 less than or equal to 800	4	0	2	2	0
Total	51	5	9	18	19

*Data from 3 patients not available.

Gastrointestinal ADR (usually nausea and vomiting), occurred most frequently during the loading phase and were related to high doses (greater than 600 mg/day) in the Detailed Study. Reduction in dosage usually led to a lessening or disappearance of gastrointestinal ADR. In the Global Survey, patients discontinued for gastrointestinal ADR were withdrawn after a mean of 170 days of treatment. This suggests that most gastrointestinal symptoms appearing early are tolerated and/or resolve. However, in a small number of patients with persistent, severe symptoms, therapy is eventually discontinued.

Neurological ADR were usually fatigue, lack of coordination or abnormal gait. In the Detailed Study symptoms developed on doses above 500 mg/day (most greater than or equal to 600 mg/day) after 2-3 months of therapy. Patients who discontinued treatment for neurological ADR in the Global Survey were also on a moderately high dose (555 mg/day) at the time of termination and had been treated for 5 months.

Cardiovascular ADR are usually not related to the total daily dose or to duration of therapy. Ventricular tachycardia occurring early in treatment (within 3 months) in the Detailed Study and Global Survey possibly represented therapeutic failure. The dose relationship of occurrence of ventricular tachycardia was evaluated in 22 patients (with dose information). VT occurred in 18 of 22 patients at doses above 400 mg/day.

Dermatological reactions occurred at mean doses of 440 to 541 mg/day in the Detailed Study and Global Survey. Blue-gray skin discoloration was reported in 7 patients (but was not the primary reason for termination) after a relatively long duration of therapy (418 days in Global Survey) and high cumulative dose (273 g). It is possible that the incidence of this reaction would have been even higher if patients had been treated for a longer period of time (mean duration of treatment in the Detailed Study and Global Survey was 470 and 195 days, respectively). No relationship existed between dose or duration of therapy and photosensitivity.

No relationship existed between dose or duration of therapy and development of thyroid toxicity, and ocular ADR.

Tables 64 and 65 list mean total daily doses (TDD), mean duration of therapy and the mean cumulative dose of the most common adverse drug reactions in the Global Survey and the Detailed Study, respectively.

TABLE 64 DOSE AND DURATION OF TREATMENT FOR ADR
(Global Survey)

BODY SYSTEM	SYMPTOMS	NO. PTS.	MEAN TDD* (MG/D)	MEAN DUR RX* (DAYS)	TOTAL CUH DOSE* (G)
Gastrointestinal	Nausea, Vom	68	488	140	66
	Anorexia	28	556	244	124
Neurological	Malaise, Fatigue	41	515	138	73
	Coordination	28	561	207	129
	Abnl Invol Mov	22	524	137	71
Cardiovascular	CHF	36	627	115	68
	V. Tach	35	808	73	35
Pulmonary	Pulm infiltrate	35	673	218	140
	Pulm fibrosis	32	601	228	133
Dermatological	Solar Derm	20	435	347	188
	Slate gray	7	440	418	273
	Discoloration				
Thyroid	Hypothyroidism	13	567	212	115
	Hyperthyroidism	2	200	1041	254
Ocular	Corneal deposit	15	500	340	178
	Visual disturbance	18	519	224	142

* Values represent dose and duration of treatment when therapy was discontinued. Data listed for all patients experiencing ADR, including primary and contributory reasons for termination.

TABLE 65 ONSET OF ADR vs. DOSE AND DURATION OF TREATMENT FOR ADR
(Detailed Study)

BODY SYSTEM	NO PTS	MEAN TDD* (MG/D)	MEAN DURATION OF THERAPY (DAYS)*
Ocular			
Corneal deposits, Pigment, Degen	79	431	164
Visual disturb, Distort	21	444	305
Neurological			
Malaise, Fatigue	21	610	117
Abnl Invol Mov	15	600	147
Coord	14	511	260
Abnl Gait	13	854	126
Dizziness, Giddiness	12	720	90
Gastrointestinal			
Nausea, Vomiting	32	742	65
Constipation	12	640	20
Dermatological			
Solar Dermatitis	22	414	291
Thyroid			
Hypothyroidism	4	375	N A
Hyperthyroidism	2	500	N A
Cardiovascular			
Congestive heart failure	5	500	139
Cardiac arrhythmias	5	720	57
SA node dysfunction	4	800	18

*Values represent doses and duration of treatment at the onset of symptoms
N A = not available

L Laboratory Tests

The laboratory tests included routine blood tests (biochemical and hematology), liver function tests, thyroid function tests, chest X-ray, and electrocardiogram (ECG). No clinically significant abnormalities were found in the routine blood analysis. The remaining laboratory tests are discussed below.

1 Liver Function Tests

When laboratory tests of all patients were evaluated, minor elevations of SGOT, bilirubin, and alkaline phosphatase were noted which decreased spontaneously in most patients while continuing treatment (refer to Table 60). The isolated elevations seen (see above) were not reflected in a consistent mean change.

TABLE 60 LIVER FUNCTION TESTS (Detailed Study)

DURATION OF RX	No Pts	Bilirubin* (mg%)	No Pts	Alk Phos* (IU/l)	No Pts	SGOT* (IU/l)
Baseline	186	0.64 \pm 0.03	189	94.6 \pm 3.1	198	38.6 \pm 5.4
Loading Phase (Days)						
1-7	25	0.57 \pm 0.09	26	91.0 \pm 5.3	32	42.5 \pm 11.4
8-14	38	0.65 \pm 0.13	38	83.1 \pm 5.5	43	35.1 \pm 5.5
greater than 14	62	0.56 \pm 0.03	67	97.1 \pm 8.0	69	32.6 \pm 1.8
Maint Phase (Mos)						
less than or equal to 6	150	0.63 \pm 0.03	161	96.6 \pm 3.1	169	43.1 \pm 2.4
greater than 6 less than or equal to 12	100	0.75 \pm 0.08	110	112.8 \pm 7.1	110	54.6 \pm 6.8
greater than 12 less than or equal to 18	48	0.56 \pm 0.03	49	93.9 \pm 4.6	49	38.4 \pm 3.1
greater than 18 less than or equal to 24	25	0.71 \pm 0.11	25	114.5 \pm 8.6	26	40.7 \pm 5.4
greater than 24	18	0.80 \pm 0.19	19	103.2 \pm 10.4	19	47.2 \pm 8.4

*Mean \pm SEM

2 Thyroid Function Tests

Thyroid function tests obtained in the Detailed Study showed a considerable increase of rT₃, a modest increase in T₄, and no appreciable change in T₃. Table 67 summarizes the results.

TABLE 67 THYROID FUNCTION TESTS (Detailed Study)

Duration of RX	No. Pts.	T ₄ (ng/dl)	No. Pts.	T ₃ (ng/dl)	No. Pts.	rT ₃ (ng/dl)
Baseline	122	8.43±0.20	83	113.8±6.0	41	31.8±4.8
Loading Phase (Days)						
1-7	20	8.80±0.33	14	69.4±10.0	11	42.0±6.2
8-14	10	9.71±0.58	14	95.6±6.0	7	32.6±7.3
greater than 14	41	10.82±0.49	36	138.2±40.2	28	133.5±35.1
Maint Phase (Mos)						
less than or equal to 6	100	10.63±0.30	89	108.3±4.4	54	91.2±16.9
greater than 6 less than or equal to 12	81	11.29±0.31	72	107.7±3.9	44	73.2±4.3
greater than 12 less than or equal to 18	39	11.18±0.62	32	108.2±5.2	14	86.4±3.5
greater than 18 less than or equal to 24	23	9.53±0.73	20	126.2±31.1	1	1.1
greater than 24	16	10.20±1.43	12	88.2±11.5	1	3.1

3 Chest X-Ray Results

Chest X rays were reviewed for the presence of interstitial infiltrates, for opacities not stated to be interstitial, diffuse or attributed to CHF, and for changes described as due to CHF. Not all patients had baseline and treatment chest X-ray reports, only 429 of 1024 patients in the Global Survey and 229 of 241 patients in the Detailed Study had chest X-ray reports. These are summarized as follows

TABLE 68 CHEST X-RAY ABNORMALITIES DEVELOPED ON AMIODARONE*

Chest X-Ray Abnormality	No. Pts.	
	Total No. Pts.	With Normal Baseline CXR
<u>Global Survey</u>		
Interstitial Infiltrate	26	13
Opacity	33	13
CHF	21	1
<u>Detailed Study</u>		
Infiltrate	16	6

*Abnormality not present on baseline CXR, but present on amiodarone

4. Electrocardiographic Results

Electrocardiographic changes in the Detailed Study were evaluated and are summarized in Table 69.

TABLE 69 EFFECTS OF AMIODARONE ON ECG
(Detailed Study)

Study Phase	No Pts	Vent Rate (bpm)	PR (sec)	QRS (sec)	QT* (sec)
Baseline	213	81.0	0.18	0.10	0.40
Loading	113	69.9	0.20	0.11	0.45
Maintenance	172	65.9	0.21	0.11	0.45

*QTc changes were not calculated

As seen from Table 69, there was a 20% decrease in sinus rate and 10% increase in QT and PR intervals

D Deaths

Since amiodarone was used in patients with severe cardiac disease and life-threatening arrhythmias unresponsive to other medications, it was expected that a number of amiodarone-treated patients would die because of the underlying disease.

Among the 4802 patients in the Global Survey, 625 (13%) died while taking amiodarone. Table 70 lists the primary cause of death according to body system.

TABLE 70 PRIMARY CAUSE OF DEATH

Cause	No. of Pts	% of Pts Treated (n=4802)	% of Deaths (n=625)
Cardiovascular	500	10.4%	80.0%
Respiratory	47	1.0%	7.5%
Cerebrovascular	19	0.4%	3.0%
Cancer	10	0.2%	1.6%
Miscellaneous	49	1.0%	7.8%

Most deaths (80%) were due to cardiovascular causes. The higher percentage of deaths due to cardiovascular cause reflect the severity of the underlying disease in this patient population. These are summarized in Table 71

TABLE 71 PRIMARY CARDIOVASCULAR CAUSES OF DEATH

Cause	No Pt
Ventricular arrhythmias, unwitnessed/sudden death	274
Pump failure (CHF and shock)	138
Acute ischemic heart failure	48
Miscellaneous cardiovascular causes	40

Among the 625 deaths, 86 were listed as "respiratory" causes (primary or contributory), 57 of them showing an infectious, bronchial or hemodynamic etiology, whereas 29 cases were presented as potential amiodarone toxicity or etiology not definitely established. These cases were reviewed in detail and were judged as probably due to pulmonary edema (11 cases), pneumonia (3 cases) or fibrosis/alveolitis (15 cases). Only the latter were considered likely cases of pulmonary toxicity.

It is difficult to determine the number of patients with drug-related deaths. Amiodarone-related exacerbation of arrhythmia was observed in one death in the Global Survey. In addition, there was a total of 21 deaths related to pneumonitis (15 patients died on therapy and 6 died after discontinuing amiodarone). Therefore, of 4802 patients treated, a total of 22 (0.5%) died of a drug-related cause.

F Conclusions

On the basis of the Global Survey of 4802 patients which supplied data on 399 patients who discontinued amiodarone treatment because of an adverse drug reaction (ADR) and 625 who died during such therapy, the Detailed Study of 241 patients, the Mason survey, a literature review, and the French experience, the following conclusions can be made:

The Detailed Study indicated that ADR occurred frequently (175 of 241 patients, or 73%, developed one or more ADR), but these usually improved with dosage reduction. However, 14 of the 241 patients (5.8%) did require temporary withdrawal of amiodarone and 17 (7.1%), permanent withdrawal because of ADR. Other experience shows a similar very high rate of ADR with discontinuation rates of about 15%.

The most common ADR among the 241 patients were corneal microdeposits (109 patients or 44.4%). Only 2 of these required discontinuation of treatment because of visual disturbance. In the Global Survey 33 of the 4802 patients (0.7%) discontinued therapy because of ocular ADR, usually because of visual disturbance probably related to the corneal deposits. In general, the ocular ADR were mild and well tolerated, and less than 1% of patients had to discontinue amiodarone treatment.

Neurological ADR were commonly reported (40- to 60% of patients on amiodarone). These were dose-related, often occurring during the loading phase, and usually responded to dose reduction. In the Detailed Study 116 of the 241 patients (48.1%) developed neurological side effects (malaise, fatigue, tremor, etc.) but none required discontinuation of treatment. Among the 399 patients in the Global Survey whose therapy was interrupted because of an ADR, 71 had neurological ADR as the primary cause for treatment discontinuation.

A third common class of side effects involved the gastrointestinal system. Sixty-seven patients (28%) in the Detailed Study reported GI ADR, but only 2 (0.3%) required termination of therapy. These ADR included nausea, vomiting, anorexia and constipation. Usually patients responded to dosage reduction and/or symptomatic treatment. In the Global Survey 34 of the 399 patients who discontinued treatment were listed to have GI ADR as the primary cause. As with the neurological ADR, the GI side effects tended to occur early during amiodarone treatment, and were possibly related to the high loading dosage regimen.

Dermatological ADR also occurred fairly frequently during amiodarone treatment. In the Detailed Study 44 patients (18%) developed skin side effects with 22 of these being photosensitivity. Slate-gray discoloration of the skin occurred less frequently, and appeared to be related to the total cumulative dose and duration of treatment. Whereas no patient in the Detailed Study required termination of treatment, 21 patients (0.4%) in the Global Survey discontinued amiodarone because of dermatological ADR.

More important were the cardiovascular and pulmonary ADR associated with amiodarone. In the Detailed Study 33 patients (13.7%) developed cardiovascular ADR, including 6 (2.5%) who had an aggravation of their arrhythmia. In the Global Survey 97 patients (2%) developed cardiovascular side effects which required termination of treatment. Recognizing that patients treated with amiodarone had severe, often life-threatening arrhythmias, amiodarone has a favorable cardiovascular safety profile. This is further corroborated by the literature, which reports exacerbation rates of up to 5%.

The second serious and potentially life-threatening ADR is pulmonary toxicity. In the Detailed Study, 5 patients (2.1%) developed pneumonitis. Two of these temporarily discontinued treatment, and were rechallenged, whereas 3 permanently terminated therapy. One of the latter 3 patients died 2 months after withdrawal of amiodarone. Therefore, the incidence of death due to amiodarone pneumonitis was one of 241 patients (0.4%). In the Global Survey, 110 patients with pulmonary toxicity (about 2%) and 15 deaths due to pulmonary fibrosis-alveolitis were identified among the 4802 patients. In addition, 95 patients (0.2%) discontinued treatment because of pulmonary toxicity probably induced by amiodarone. Six of these patients subsequently died after treatment was withdrawn. Therefore, in the Global Survey a total of 21 deaths (0.4%) occurred which could be attributed to pulmonary toxicity of amiodarone.

A review of published and unpublished cases of pulmonary disease among patients on amiodarone was performed by Sanofi Pharmaceuticals (France). Among 102 cases of pulmonary symptoms, data in 54 suggested an association to amiodarone treatment. Five of these 54 patients died of pulmonary toxicity, although 3 of the 5 deaths were not clearly or solely pneumonitis.

Although pulmonary toxicity seemed to be associated with a high daily dosage regimen (greater than or equal to 600 mg/day) and with chronic treatment (greater than or equal to 6 months), the European data indicated that pneumonitis also developed with lower doses (less than or equal to 400 mg/day).

Considerably higher rates of pulmonary toxicity have been reported by others, 4-7% by Heger, Fogoros, Peter and McGovern (all 1983), 13% in the Mason survey, 15% by Magro, 6% by Porterfield, and 11% by Anastasiou-Nana. Diffusion capacity abnormalities may be more common still and many prove a means of early diagnosis. Patients clearly should be monitored closely for this complication as it has proved fatal in roughly 10% of cases.

Amiodarone frequently induced minor changes in liver function tests, and rarely (less than 0.5%) did the hepatic ADR require termination of treatment. Published reports of severe toxic reactions do exist, however, although this appears to be rare.

Changes in thyroid function tests frequently occurred among patients on amiodarone (elevated serum T_4 and reverse T_3 and decrease in serum T_3), but less than 2% of the patients in the Detailed Study developed any clinical thyroid disorder (hypo- and hyperthyroidism) and less than 0.5% of patients in the Detailed Study and Global Survey required discontinuation of amiodarone. A recent report, however, described hypothyroidism in 8% of patients, hyperthyroidism in 2.5%

In summary, the ADR associated with amiodarone were frequent and varied. Although they were tolerated by these populations with life-threatening arrhythmias and proved reversible with dosage adjustment or discontinuation, they appear to represent a significant degree of unpleasantness. The serious, life-threatening ADR encountered were aggravation of the arrhythmia (as often as 5%, probably no worse than alternative agents) and pulmonary toxicity.

VIII ADVISORY COMMITTEE REVIEW

On June 19, 1984, the Cardiovascular and Renal Drug Advisory Committee unanimously recommended approval of amiodarone for use in patients with life-threatening cardiac arrhythmias that do not respond to conventional therapy.

IX LABELING

A copy of the labeling is attached.

APPENDIX I

Summary of Pharmacokinetic/
Pharmacodynamic Studies from the Literature

SUMMARY OF PHARMACOKINETIC/PHARMACODYNAMIC STUDIES WITH AMIODARONE

Investigator	Design (subjects/dose)	Assay	Results
2) Andreasen, et al Eur J Clin Pharmacol 19 293, 1981	N=7 patients Two-way crossover A 400 mg i v over 2 min and Cordarone 400 mg single oral dose 2-4 day washout between dosing	HPLC (limit of sensi tivity 0.1 mg/l)	<p>(Mean \pm SD)</p> <p>Single dose</p> <p>Oral 7.3 ± 2.9 hrs $\frac{i v}{i v}$</p> <p>T_{max}</p> <p>Bioavailability $43\% \pm 19\%$</p> <p>V_d 400 l</p> <p>Large intersubject variability</p> <hr/> <p>$t_{1/2}$ elimination 13.7 days (after 100 mg tid N 1)</p> <p>Multiple dosing - 200 mg q8h</p> <p>Trough levels 0.44 - 1.70 mg/l after 1 wk 0.75- 2.84 mg/ after one month</p> <p>After i v dose no unchanged A found in urine Urinary I_2 excretion was 5% of the oral dose</p> <p>Quantitative protein binding could not be determined by equilibrium dialysis, but was characterized as strong</p> <p>High concentration in bile (N=1) suggests enterohepatic circulation</p> <p>RBC conc of A = 60% of plasma conc</p>

A-Amiodarone

 T_{max} = time to peak plasma conc $t_{1/2}$ = half-life V_d = vol of distribution

AUC = area under the plasma concr time curve

HPLC = high pressure liquid chromatography

SUMMARY OF PHARMACOKINETIC/PHARMACODYNAMIC STUDIES WITH AMIODARONE

Investigator	Design (subjects/dose)	Assay	Results				
3) Bonati, et al N Engl J Med 308 906 1983	5 renal patients undergoing hemodialysis were compared to 5 normal volunteers after receiving a single i.v. bolus of A 150 mg	HPLC	<p>Elim $t_{1/2}$ mean + S.D. (hrs)</p> <table border="0"> <tr> <td>normal subjects</td> <td>renal patients</td> </tr> <tr> <td>6.1 ± 1.7</td> <td>5.6 ± 2.3</td> </tr> </table> <p>No amiodarone in dialysis fluid or dialyzer membrane</p> <p>Conclusion: Patients with renal failure have no changes in amiodarone elimination when compared to normal volunteers. Amiodarone is not dialyzable.</p>	normal subjects	renal patients	6.1 ± 1.7	5.6 ± 2.3
normal subjects	renal patients						
6.1 ± 1.7	5.6 ± 2.3						
4)a) Boppana et al Clin Pharmacol Ther 33 209, 1983	64 patients 12 with supra-ventricular arrhythmias (SVT)	HPLC limit of sensitivity of 0.1 mg/l	29 patients reported 36 side effects. A mean steady-state plasma concentration of A was 3.1 ± 1.2 mg/l (N=26) in patients with side effects vs 2.3 ± 1.3 mg/l (N=38) for those free of side effects.				
b) Rotmensch, et al PACE 6 1327 1983	52 with ventricular arrhythmias (VT)		11/52 patients (92%) had no recurrence of SVT at plasma concentrations of 1.5 ± 0.6 mg/l for DA.				
c) Rotmensch et al J Am Coll Cardiol 1 630, 1983			45/52 patients (87%) had no recurrence of VT at plasma levels of 2.5 ± 1.1 mg/l for A and 1.5 ± 0.6 mg/l for DA.				

A = Amiodarone

DA = Desethylamiodarone

HPLC = high pressure liquid chromatography

SUMMARY OF PHARMACOKINETIC/PHARMACODYNAMIC STUDIES WITH AMIODARONE

Investigator	Design (subjects/dose)	Assay	Results
5) Broekhuysen et al Arch Int Pharma codyn and Ther 177 340, 1969	a) 41 patients total A oral & i v single dose of 100 mg or 150 mg	Measured radio-labeled ¹³¹ I-amiodarone	- Slow & irregular absorption - Low plasma conc = 1 to 2 mg/l (for 300 mg/day) - Bioavailability 50% (in rats)
	b) A, 100 mg tid po for 7 days		- Urinary elimination at 24 hrs only 0.6 to 1.5% of dose
	c) A, 300 to 600 mg/day po for 1 mo to 4 yrs (N=16)		30 days after chronic dosing only 16 to 34% of total dose eliminated - ¹²⁵ I equilibrium reached after chronic dosing 2 grams of ¹²⁵ I retained
6) Canada, et al Curr Ther Res Clin Exp 30 968 1981	N=8 pts - Single dose 800 mg A po N=12 pts - Multiple oral doses A 200-800 mg/ day for an average of 16.4 weeks	HPLC (limit of sensitivity 0.05 µg/l)	Single Dos (Mean ± SEM) $C_{max} = 1.70 \pm 0.35 \text{ mg/l}$ $T_p = 5.2 \pm 0.6 \text{ hr}$ Slow absorption C_{max} is unrelated to dose intersubject variability Steady state (Mean ± SEM) $C_{ss} = 1.57 \pm 0.10 \text{ mg/l}$ for dose of 2.9 to 11.7 mg/kg/day Steady-state concentration correlated well with daily dose ($r = 0.72$ p less than 0.05) Total clearance = $1.40 \pm 0.3 \text{ ml/min}$

A = Amiodarone

 C_{max} = peak plasma conc C_{ss} = steady-state plasma conc

HPLC = high pressure liquid chromatography

SUMMARY OF PHP PHARMACOKINETIC/PHARMACODYNAMIC STUDIES WITH AMIODARONE

Investigator	Design (subjects/dose)	Assay	Results
7) Candelpergher, et al G Ital Cardiol 12 79 1982	Gravid female during last 3 months of pregnancy received A, 200 mg/day	HPLC (limit of sensitivity 0.02 mg/l)	Limited transplacental transfer cord blood A = 25% & DA = 50% of maternal levels Infant had some ECG changes and bradycardia
8) Debbas, et al Eur J Clin Invest 13 123, 1983	1) Ten patient, not on amiodarone 2) Twenty patients on A, 200 mg/day for greater than 3 mos 3) Ten patients on A, 400 mg/day for 5 out of 7 days for greater than 3 mos Measured plasma and tissue concentrations of drug	HPLC for tissue and plasma levels	Good correlation between 1) myocardial concentration and dose ($r_2 = 0.90$) 2) myocardial and plasma levels ($r_2 = 0.93$) 3) dose and plasma levels ($r_2 = 0.95$) 4) No difference between atrial and ventricular tissue levels (p greater than 0.05)
9) Debbas, et al Proc Br Cardiac Soc p 297 1983	Nine patients on A, 200 to 400 mg/day for at least 3 mos QT_C prolongation vs tissue and plasma levels were evaluated	HPLC for tissue and plasma levels	1) Significant lengthening of QT_C after A from 454 ± 34 msec to 533 ± 61 msec (p less than 0.01) 2) Good correlation between plasma levels and myocardial levels ($r_2 = 0.85$) 3) Good correlation between percentage increase in QT_C with myocardial ($r_2 = 0.93$) and plasma ($r_2 = 0.84$) levels

A = Amiodarone

DA = Desethylamiodarone

HPLC = high pressure liquid chromatography

SUMMARY OF PHARMACOKINETIC/PHARMACODYNAMIC STUDIES WITH AMIODARONE

Investigator	Design (subjects/dose)	Assay	Results
10) Fraser, et al (unpublished report)	Two patients taking amiodarone for greater than 18 mos, 400 to 600 mg/day	Nerve conduction studies HPLC	Two patients developed severe sensory neuropathy and one patient had sensory symptoms with objective evidence of peripheral neuropathy after 18, 19 and 30 months of treatment with A All patients had high serum concentrations especially of DA (mean = 3 mg/l). Sural nerve biopsy showed concentrations 80 times greater than in plasma (187 mg/kg wet weight) compared to a mean of 43 mg/kg wet weight in patients without clinical evidence of neuropathy <u>Conclusion</u> Neuropathy is an effect of long-term treatment with A associated with high concentrations of A and DA. It is more common in older patients
11) Gobbato et al Int J Clin Pharm Res 2:279 1982	2 patients single oral dose of A, 600 mg had bile collected during surgery 5 patients had saliva levels measured 1 patient, chronic oral dosing, A 200 mg/day had breast milk levels measured	HPLC (limit of sensitivity of 0.1 mg/l)	- Salivary levels of A 7-fold less than plasma - Bile A conc, 10 to 30-fold greater than plasma - Breast milk A conc about the same as plasma DA levels 2 fold greater than A levels in breast milk

A = Amiodarone

DA = Desethylamiodarone

HPLC = high pressure liquid chromatography

SUMMARY OF PHARMACOKINETIC/PHARMACODYNAMIC STUDIES WITH AMIODARONE

Investigator	Design (subjects/dose)	Assay	Results
12) Graboys et al Am Heart J 106 873, 1983	121 patients with refractory atrial tachycardias - 600- 1200 mg/day (loading) for 5-7 days - 200 600 mg/day (maintenance)	HPLC (limit of sensitivity 0.05 mg/l)	Dose (mg) N Plasma Conc (mg/l) 200 65 1.8 400 49 2.2 600 7 3.4 Patients with AF had plasma conc from 0.5 to 6.0 mg/l (mean 2.0 mg/l) and those with SVT 0.9 to 4.4 mg/l (mean 1.9 mg/l)
13) Haffajee et al Circulation 64 263 1981 abstract	Single dose, 800 mg, A p.o. (N=9) Chronic dosing	HPLC (limit of sensitivity 0.05 mg/l)	Bioavailability approximately 50% Single dose C _{max} of A = 2.8 - 7.7 mg/l Steady state conc (C _{ss}) of A = 0.7 - 2.6 mg/l achieved in (N=55) 2-4 weeks after dosing Efficacy achieved at 1 to 2 mg/l t _{1/2} of elimination = 13.60 days (N=3) <u>Conclusion</u> - Monitoring of A levels is useful in management of patients

A = Amiodarone

C_{max} = peak plasma conct_{1/2} = half-life

HPLC = high pressure liquid chromatography

AF = atrial fibrillation

SVT = supraventricular tachycardia

SUMMARY OF PHARMACOKINETIC/PHARMACODYNAMIC STUDIES WITH AMIODARONE

Investigator	Design (subjects/dose)	Assay	Results
			<u>Atrial Tachycardia Patients</u>
14) Haffajee, et al Circulation 67 1347, 1983	122 patients treated with A for 1.5 - 53 mos (mean 9.3 mos) for atrial and ventricular tachycardias (VT)	HPLC	<p>41 of 48 patients with atrial fib-flutter (85%) responded on mean maintenance doses of 349 ± 122 mg/day (mean duration of 10 mos). Non-responders had similar doses of 460 ± 135 mg/day.</p> <p>Serum concentrations were the same 1.5 ± 0.6 vs 1.7 ± 0.7 mg/l for responders vs non-responders, respectively. Four patients relapsed when serum levels fell below 0.1 mg/l.</p>
			<u>Ventricular Tachycardia Patients</u>
			<p>Four patients with PES-inducible atrial fib-flutter could not be induced when serum levels were greater than 1.0 mg/l. 38 of 50 patients with VT responded (76%) on a mean dose of 371 ± 145 mg/day following 8 days to 4 weeks of high oral loading. Non-responders had a mean maintenance dose of 500 ± 175 mg/day.</p> <p>Serum levels of A were similar for both responders (1.8 ± 0.7 mg/l) and non-responders (1.9 ± 0.7 mg/l). Serum levels below 1.0 mg/l caused recurrence of arrhythmia in 3 responders.</p> <p>Side effects increased when serum levels were greater than or equal 2.5 mg/l.</p>

A = Amiodarone

HPLC = high pressure liquid chromatography

SUMMARY OF PHARMACOKINETIC/PHARMACODYNAMIC STUDIES WITH AMIODARONE

Investigator	Design (subjects/dose)	Assay	Results	
15) Harris et al Circulation 64 263 1981 abstract	70 patients A, 200 to 1200 mg/day p o	HPLC (limit of sensitivity 0.1 mg/l)	A Steady state concentrations (mg/l) t _{1/2} elim (days)	DA 0.2 - 5.2 0.3 - 4.7 52 60
			<p><u>Conclusion</u> Good correlation between dose and plasma levels, poor correlation between efficacy (increased PR and RR intervals) and plasma levels. Good correlation between side effects and plasma levels.</p>	
16) Harris, et al Postgrad Med J 59 42, 1983 abstract	2 patients with chronic renal failure, one on peritoneal dialysis, A, 800 mg/day po for 1 week then 200 mg/day one on hemodialysis, A 400 mg/day p o for one month 10 patients with normal renal function	HPLC (limit of sensitivity of 5 ug/l)	Renal patients - A & DA concentrations were within normal range for dose and did not fluctuate during dialysis. Dialysate had no drug detected. Rat'io DA/A 0.1. Same ratio as seen in patients with normal renal function. In 10 additional patients - urinary concentrations of A & DA very low	
			<p><u>Conclusion</u> Since renal route is not important for elimination of drug A is a good drug to use in the renally impaired.</p>	

A = Amiodarone
DA = Desethylamiodarone
t_{1/2} = half-life
HPLC = high pressure liquid chromatography

SUMMARY OF PHARMACOKINETIC/PHARMACODYNAMIC STUDIES WITH AMIODARONE

Investigator	Design (subjects/dose)	Assay	Results
17) Harris et al Circulation 67 45, 1983	140 patients retrospective review of side effects A = 100 to 1200 mg/day (mean = 360 mg/day for up to 2 years)	HPLC (limit of sensitivity of 0.1 to 0.005 mg/l)	<ul style="list-style-type: none"> - Drug levels correlated well with dose - Side effects which were dose related liver enzyme abnormalities - Side effects which were dose and duration-related corneal micro deposits facial pigmentation - Side effects unrelated to dose thyroid abnormalities peripheral neuropathy - Unknown relationship pulmonary fibrosis? <p>However all side effects except myxedema resolved upon discontinuation of therapy</p>

A = Amiodarone
DA = Desethylamiodarone
HPLC = high pressure liquid chromatography

SUMMARY OF PHARMACOKINETIC/PHARMACODYNAMIC STUDIES WITH AMIODARONE

Investigator	Design (subjects/dose)	Assay	Result									
18) Heger, et al	Measured plasma & red cell hemolysate (RCH) levels of A & DA	HPLC	A = 3.0 mg/l DA = 2.43 mg/l									
a) Circulation 66 223 1982 abstract	55 patients receiving mean oral A dose of 444 mg/day for at least 1 month											
b) Am Heart J 106 931, 1983	Loading doses administered were 800 or 1600 mg/day for 15 days in 14 patients with VT or VF											
		plasma (N=55)	A = 1.58 mg/l DA = 3.65 mg/l									
		RCH (N=28)	Of 28 patients receiving similar doses, adverse effects (ADR) occurred in 9 patients. 19 patients were free of side effects.									
		RCH conc	<table border="0"> <tr> <td></td> <td>9 pts with ADR</td> <td>19 pts free of ADR</td> </tr> <tr> <td>A</td> <td>= 2.65 mg/l</td> <td>A = 0.78 mg/l</td> </tr> <tr> <td>DA</td> <td>= 6.55 mg/l</td> <td>DA = 2.28 mg/l</td> </tr> </table>		9 pts with ADR	19 pts free of ADR	A	= 2.65 mg/l	A = 0.78 mg/l	DA	= 6.55 mg/l	DA = 2.28 mg/l
	9 pts with ADR	19 pts free of ADR										
A	= 2.65 mg/l	A = 0.78 mg/l										
DA	= 6.55 mg/l	DA = 2.28 mg/l										
		<u>Conclusion</u>	Concentrations of A & DA in RCH may represent intracellular or membrane-bound drug and may be marker for ADR.									
			There was a direct relationship between the size of the daily loading dose (800 or 1600 mg) and plasma conc. DA was less present during initial days of therapy.									

A = Amiodarone
 DA = Desethylamiodarone
 HPLC = high pressure liquid chromatography
 VT = ventricular tachycardia
 VF = ventricular fibrillation

SUMMARY OF PHARMACOKINETIC/PHARMACODYNAMIC STUDIES WITH AMIODARONE

Investigator	Design (subjects/dose)	Assay	Results
19) Holt, et al Proc Int Symposium Sydney 1982	A, 200 mg/day (N=101) A 400 mg/day (N=75) & A 600 mg/day (N=18) chronic oral dosing	HPLC (limit of sensitivity 0.1 mg/l to 5 ug/l)	Good linearity between dose and plasma concentrations in the range of 200 to 600 mg/day Mean ratio across all doses of DA/A = 1.08 ± 0.33 (SD) during chronic treatment (Storey et al Ther Drug Monitoring 4:385 (1982) has used this ratio of DA/A as a guide to drug compliance)
20) a) Holt et al J Am Coll Cardiol 1:630 1983 b) Adams et al Symposium Br Cardiol Soc 25 1982 abstract	Tissue from 3 patients during surgery & autopsy patients	HPLC (limit of sensitivity of 0.1 mg/kg wet weight with 100 mg tissue sample)	Except for fat tissue concentrations of DA were greater than A Ratio of A/DA for fat = 4.8 plasma = 0.82 other tissue = 0.28 Drug accumulation was greatest in fat, liver, lung and spleen
21) Holt, et al Proc Int Symposium, Sydney 1982	4 patients with facial pigmentation biopsy of affected & non- affected skin	HPLC (limit of sensitivity of 0.1 mg/kg wet weight)	Ten-fold higher concentrations of DA & A in affected skin (DA greater than A)

A = Amiodarone
DA = desethylamiodarone

SUMMARY OF PHARMACOKINETIC/PHARMACODYNAMIC STUDIES WITH AMIODARONE

Investigator	Design (subjects/dose)	Assay	Results
22) Holt, et al Proc Int Symposium Sydney 1982	15 patients had salivary levels measured protein binding determined	HPLC (limit of sensitivity of 5 ug/l)	- *Free salivary levels (mean \pm SD) of drug were 2.42 \pm 2.43 mg/l - Strongly protein bound (exact % was difficult to determine)
23) Holt et al Am Heart J 106 840, 1983	Six healthy volunteers 3-way crossover, single 400 mg dose of A 1) Cordarone [®] (oral formulation used in Europe and USA) 2) Cordarone X [®] (oral formulation used UK) 3) i v formulation	HPLC (limit of sensitivity 5 ug/l)	Oral Bioavailability Absorption time Incomplete absorption across GI mucosa rather than first-pass metabolism probably accounts for low bio availability Mean \pm SD Cordarone [®] Cordarone X [®] 0.35 \pm 0.09 0.35 \pm 0.13 6.5 \pm 0.6 hrs 5.7 \pm 1.0 hrs i v Mean-total clearance of A 8.61 \pm 1.88 l/h elimination t _{1/2} of A 24.6 \pm 11.7 days (biphasic elimination) Mean-blood/plasma ratio at 2.5 mg/l of A 0.73 \pm 0.06 Metabolite (DA) had similar elimination t _{1/2} suggesting formation rate-limited kinetics

A = Amiodarone
DA = Desethylamiodarone
t_{1/2} = half-life
HPLC = high pressure liquid chromatography

SUMMARY OF PHARMACOKINETIC/PHARMACODYNAMIC STUDIES WITH AMIODARONE

Investigator	Design /subjects/dose)	Assay	Results
24) Holt et al Am Heart J 106 840 1983	8 patients chronic oral dosing with A (more than 8 months)	HPLC (limit of sensitivity of 5 ug/ml)	initial decline by half in blood levels over 2.5 to 10 days post-drug (N=4) - rebound at approximately 20 days (N 4) elim $t_{1/2}$ (days) mean - SD for A 52.6 ± 2.4 (range 26-107 days) and for DA 61.2 ± 31.1 (range 20-118 days) (N=8) In patient with $t_{1/2}$ of 10 days antiarrhythmic effect continued for 18 weeks <u>Conclusion</u> biphasic elimination after chronic dosing
25) Holt et al J Clin Pharm Ther 35 247 1984 abstract	27 patients treated with chronic A for at least 3 mo 17 patients receiving chronic antidepressant therapy 22 patients suffering from acute drug overdose 20 normal volunteers	HPLC, RIA for rT_3 (reverse T_3)	rT_3 increased in patients treated with A however these overlapped with levels of rT_3 in patients not under amiodarone treatment There was no significant difference between patients mean rT_3 who were controlled or not controlled for their arrhythmia during dose titration with A

A = Amiodarone

DA = Desethylamiodarone

 $t_{1/2}$ = half-life rT_3 = reverse T_3

HPLC = high pressure liquid chromatography

RIA = radioimmune assay

SUMMARY OF PHARMACOKINETIC/PHARMACODYNAMIC STUDIES WITH AMIODARONE

Investigator	Design (subjects/dose)	Assay	Results		
			Single oral dose 1400-1800 mg (N=6)	(Mean + SD) Multiple dosing 800-1800 mg/day 2-8 wks (N=12)	Multiple dosing 600-1000 mg maintenance 2-8 wks (N=4)
26) Kannan et al Clin Pharmacol Ther 31:438, 1982	a) Single oral dose A, 1400-1800 mg/day, (N=6)	HPLC (limit of sensitivity 0.05 ug/ml)	Age = 59 ± 12 yrs Wt = 87 ± 24 kg Dose = 1600 ± 163 mg C _{max} = 6.9 ± 4.2 mg/l	Age = 67 ± 5 yrs Wt = 97 ± 4 kg Dose = 750 ± 165 mg	By 6 wks ratio of metabolite to A = 850%
	b) Repeated oral dosing, 1-8 wks (N=12)		T _{max} = 4.9 ± 1.2 hr 1/2 a t = 2.5 ± 0.9 hr 1/20 = 7.2 ± 5.0 hr		C _{ss} loading = 3.84 ± 2.92 mg/l C _{ss} maintenance = 1.08 ± 0.11 mg/l Duration of maint = 39 ± 13 days t _{1/2d} = 29 ± 19 days
	c) A 5 mg/kg single i.v. dose (N=1)				
<u>Conclusion</u> Monitoring of A levels is not useful in therapeutic management of patients					

A=AmiodaroneC_{ss} = steady-state plasma concC_{max} = peak plasma concT_{max} = time to peak plasma conct_{1/2} = half-life

HPLC = high pressure liqu'd chromatography

SUMMARY OF PHARMACOKINETIC/PHARMACODYNAMIC STUDIES WITH AMIODARONE

Investigator	Design (subjects/dose)	Assay	Results
27) Lelloz et al J Pharm Pharmacol 36 366, 1984	In vitro protein binding	Filtration of 125I-amiodarone - equilibrium dialysis	Amiodarone is strongly and highly bound (96%) by albumin and B-lipoprotein. It does not interfere with binding of digoxin or warfarin. Reduced binding of 125 A to albumin was caused by quinidine, amitriptyline, cefazolin and palmitate.
28) McKenna, et al Am J Cardiol 51 1231, 1983	Gravid female - last month of pregnancy received A, 400 mg/ day	HPLC (limit of sensitivity of 5 ug/l)	Limited transplacental transfer of drug (cord blood 0.15 and 25% of maternal levels for A and DA, respectively). Infant Apgar = 9 Breast milk - high and variable concentrations (A greater than DA). These levels increased 2 to 9 weeks post partum.
29) Mostow, et al Circulation 66 223, 1982 abstract	Correlation of plasma conc of A with control of PVC's, paired ventric- ular complexes (VE's), & ventricular tachy- cardia (VT)	HPLC	Significant reduction in VT and VE when plasma A concentrations greater than 1.5 mg/l

A = Amiodarone

DA = Desethylamiodarone

HPLC = high pressure liquid chromatography

SUMMARY OF PHARMACOKINETIC/PHARMACODYNAMIC STUDIES WITH AMTODARONE

Investigator	Design (subjects dose)	Assay	Results
30) Pitcher et al Lancet 1 597, 1983	Gravid female - last month of pregnancy received A	HPLC (limit of sensitivity of 5 µg/l)	Limited transplacental transfer - cord blood A = 10% and DA = 2% of maternal level. Breast milk concentration on 2nd and 3rd day post partum - A = 0.5 to 1.8 mg/l - DA = 0.4 to 1.8 mg/l
31) Riva et al J Cardiovasc Pharmacol 4 264, 1982	a) Single oral dose of A 400 mg, 3 normal vol and 3 patients b) Single i v dose of A, 3 normal vol - 150 mg and 3 patients - 5 mg/kg c) Multiple dose of A, p o 200 mg/day, 3 patients	HPLC	i v Biexponential elimination with a prominent distribution phase Volume of distribution = 9.26-21.05 l/kg V _c = 0.98-2.33 l/kg (large volume of distribution & low V _c inter tissue distribution) elim t _{1/2} = 11.6 to 20.7 hrs (underestimated) p o Bioavailability - 22-86% T _{max} = 2-10 hr C _{ss} trough = 0.038-0.305 mg/l Conclusion Kinetics of normal subjects and patients are similar

A = Amlodarone

DA = Desethylamodarone

C_{ss} = steady-state plasma concT_{max} = time to peak plasma conct_{1/2} = half-life

HPLC = high pressure liquid chromatography

SUMMARY OF PHARMACOKINETIC/PHARMACODYNAMIC STUDIES WITH AMIODARONE

Investigator	Design (subjects/dose)	Assay	Results
32) Staubli et al Eur J Clin Pharmacol 24 485 1983	Seventeen patients on long term amiodarone 5 mg/kg/day maintenance dose (2.1 to 9.3 mg/kg) for 150 to 880 days	HPLC for amiodarone Redox reaction for measurement of in- organic iodide and organic iodine	Steady state plasma concentrations of A ranged from 0.65 to 5.7 $\mu\text{mol/l}$ (0.44 to 3.88 mg/l) for a 3 to 9 mg/kg dose. At steady state serum levels were directly proportional to dose. 5 mg/kg had average level of A of 2.5 $\mu\text{mol/l}$ (1.7 mg/l). The elimination $t_{1/2}$ ranged from 21 to 78 days for A (mean 41±19 days). For NA1 (nonamiodarone iodine) the $t_{1/2}$ ranged from 24 to 160 days (mean 64±43 days). Control of arrhythmia was satisfactory in 12 patients with serum levels greater than 1.5 $\mu\text{mol/l}$ (1.0 mg/l). Side effects occurred at A levels greater than 4.0 $\mu\text{mol/l}$ (2.8 mg/l). Thyroid abnormalities were unrelated to dose.
33) Studer et al Symposium Zurich 1979	Six healthy vol A 400 mg single oral dose 10 patients chronic dosing with A	Unlabeled I_2 - measured (inorganic and organic iodine)	- Maximum resorption occurred in 3 to 7 hrs Organic & inorganic I_2 levels still increased after 56 days post-single dose - $t_{1/2}$ elim of A = 14 hrs - $t_{1/2}$ elim of I_2 = 39 hrs excretion via bile not urine - during chronic dosing I_2 uptake excretion

A=Amiodarone
 $t_{1/2}$ = half-life

HPLC = high pressure liquid chromatography

APPENDIX II

Additional U S Data (Dr Douglas Zipes)

ADDITIONAL U S DATA

Introduction

Dr Douglas Zipes, Professor of Medicine at the Indiana University School of Medicine, Indianapolis, studied the effects of amiodarone in the treatment of cardiac arrhythmias

Study Design

Patients with severe, recurrent cardiac arrhythmias were evaluated at baseline (pre-amiodarone phase) with continuous electrocardiographic monitoring, electrophysiology study and an exercise test. Amiodarone was administered in initial loading doses of 800-1600 mg/day. The patients were evaluated after 2 to 4 weeks and depending on the response, the dose of amiodarone was lowered to 400-600 mg/day, a second antiarrhythmic agent was added to the treatment, or amiodarone treatment was discontinued. Refer to Table II 1 for the Study Schema

Demographic Profile

A total of 230 patients (181 males, 49 females, age 56 ± 12 years) with ventricular tachyarrhythmias were studied for a mean (\pm SD) period of 19 ± 14 months. These patients were treated for ventricular fibrillation (VF=64), sustained ventricular tachycardia (VT=114) or nonsustained ventricular tachycardia (VT=52). The duration of arrhythmia ranged from 1-156 months (mean 16 months)

The underlying cardiac diseases included

- ischemic heart disease - 156
- cardiomyopathy - 43
- primary electrical disease - 12
- valvular heart disease - 10
- mitral valve prolapse - 9
- congenital heart disease - 1

Prior to amiodarone, patients received an average of 4 (range 2-17) antiarrhythmic drugs per patient. The reason for failure of the prior antiarrhythmic medication was the recurrence of VT and VF in the majority of patients. One hundred twenty-two patients had electrical cardioversion

The mean (\pm SD) left ventricular ejection fraction of the patients studied was 0.33 ± 0.14 . According to the New York Heart Association criteria, the functional classifications were as follows:

<u>Class</u>	<u>number of patients</u>
I	34
II	127
III	63
IV	6

Some of the patients described in this study are also included in the series of 50 consecutive patients used in each of the 5 centers included in the NDA.

Results

During a follow-up of 19 ± 14 months (mean \pm SD), 140 of 230 patients (61%) continued amiodarone treatment to the end of the observation period. Amiodarone was withdrawn in 90 patients due to the following reasons:

	<u>N</u>
Sudden cardiac death	22
Recurrent ventricular tachycardia	23
Death from heart failure	22
Noncardiac adverse effects	20
Other effects	3

Thus, of 207 patients in whom outcome could be assessed, 44 died and 23 had recurrent VT. Depending on preference, this could be described as a mortality of 21%, a failure rate (SD + recurrent VT) of 22% or a failure rate (all death and recurrent VT) of 32%.

Electrophysiologic studies were carried out in 129 patients. Amiodarone produced significant prolongation of SCL, AH interval, HV interval, and induced VT cycle length. It prevented VT induction in 19 of 129 patients (15%), these patients subsequently had no recurrence of VT. In the remaining 110 patients VT was inducible. However, in 83 of 110 patients (75%), VT did not recur. Therefore, long-term amiodarone treatment (23 + 3 months) was continued in these 102 (19 plus 83) patients. The results are summarized in Table II 2.

In addition, effects of amiodarone were studied in 74 patients with supraventricular tachyarrhythmia (SVT). Fifty-six of 74 patients had atrial fibrillation and 18 were treated for paroxysmal SVT (including WPW). Amiodarone was withdrawn in 3 patients due to side effects and one patient died. Amiodarone was judged effective in those patients who were either tolerant to therapy, had no symptomatic recurrence, had no arrhythmia on ECG or had marked reduction in frequency and duration of episodes. Amiodarone was effective in 60 of 74 patients and ineffective in 10, therapy was discontinued in 3 patients because of side effects and one patient died. For a summary of amiodarone response in SVT patients, refer to Table II 3.

One or more adverse effects occurred in 152 of 230 patients during amiodarone therapy. The cardiac adverse effects included aggravation of VT-VF, bradyarrhythmia requiring permanent pacing, bundle branch block and aggravation of heart failure (refer to Table II 4). Nausea/ anorexia/weight loss were the most frequent noncardiac adverse effects followed by tremor, skin discoloration, ataxia, visual "halos" and photosensitivity (Table II 5). Eight of 230 patients (3.5%) developed pulmonary toxicity and 13 patients (5.7%) had skin discoloration (for details refer to Table II 6).

A total of 30 of the 230 patients (13%) discontinued therapy because of adverse effects.

From this study, the following conclusions were drawn:

- Amiodarone is an effective antiarrhythmic agent in the treatment of refractory VT-VF.
- Amiodarone produces significant electrophysiologic effects on sinus node, AV node, His-Purkinje system and the ventricle.
- Failure to prevent VT induction on electrophysiology study does not preclude a favorable response with long-term treatment, but successful suppression of inducibility presages a highly favorable outcome.
- At the dosages of amiodarone employed, the risk of significant adverse effects warrants careful surveillance during treatment.

TABLE II 1 STUDY SCHEMA

Control (baseline)

Continuous ECG
Electrophysiology Study
Exercise Test

Amiodarone Treatment
(Loading dose 800-1600 mg/day)

2-4 weeks

Evaluation of Amiodarone
Treatment

Amiodarone Treatment
Continued (Outpatient)
(Maintenance dose 400-600 mg/day)

Addition of Second
Antiarrhythmic Agent

Amiodarone Treatment
Discontinued

TABLE II 2 RESULTS OF ELECTROPHYSIOLOGIC (EP) STUDY
TO INDUCE VENTRICULAR TACHYCARDIA

129 pts

Control	111 pts Control EP Study	18 pts No control EP Study	
Amiodarone EP Study	19 pts No VT induced	110 pts VT induced	
Long Term Treatment	19 pts + 83 pts No recurrent VT (23 + 3 mo)	25 pts Recurrent VT (11 + 2 mo)	2 pts Amiodarone Discontinued

TABLE II 3 RESPONSE TO AMIODARONE IN PATIENTS
 WITH SUPRAVENTRICULAR TACHYARRHYTHMIA

<u>Arrhythmia</u>	<u>N</u>	<u>Effective**</u>	<u>Ineffective</u>	<u>Terminating Side Effects*</u>	<u>Patient Death</u>
Atrial Fibrillation	56	46	6	3	1
Paroxysmal SVT (incl WPW)	18	14	4	0	0

**Amiodarone was considered effective in those patients who were either tolerant to therapy and had no symptomatic recurrence, had no arrhythmia on ECG, or had marked reduction in frequency and duration of episodes

*Side effects requiring amiodarone withdrawal were nausea/fatigue (1), weakness (1) and goiter (1)

TABLE II 4 CARDIAC ADVERSE EFFECTS

	<u>No. of episodes</u>
Aggravation of VT-VF*	10
Bradycardia requiring permanent pacing	4
Bundle branch block	2
Aggravation of heart failure	1

*Nine patients developed aggravation of VT-VF during amiodarone treatment as follows

<u>Pre-Treatment Arrhythmia</u>	<u>Number Patients</u>		<u>Arrhythmia during Amiodarone</u>
VF			polymorphic VT
VT(s)	6	5	incessant VT
VT(ns)	2	3	VF

VT(s) = ventricular tachycardia (sustained)
 VT(ns) = ventricular tachycardia (non sustained)

TABLE II.5 NON-CARDIAC ADVERSE EFFECTS

	<u>No. of Occurrences</u>		<u>No. of Occurrences</u>
Nausea, anorexia, weight loss	62	Impotence	7
Tremor	28	Insomnia	6
Blue skin discoloration	26	Constipation	5
Ataxic gait	20	Hypothyroidism	4
Visual "halos"	19	Dermatitis	3
Photosensitivity	11	Purpura	2
Pulmonary toxicity	9	Hepatitis	1
Headache	7	Hypertthyroidism	1
No. of patients with greater than or equal to 1 adverse effect			- 152 patients
No. of patients who discontinued treatment due to ADR			- 30 patients

TABLE 11.6 SELECTED ADVERSE EFFECTS
PULMONARY ADVERSE EFFECTS
(N=8)

Total amiodarone dosage (g) - range	112 - 396
mean \pm SD	151.6 \pm 134.4
Duration of treatment (months) - range	2 weeks - 30
mean \pm SD	9.4 \pm 9.8
Plasma amiodarone concentration* (ug/ml)	2.30 & 3.40
Amiodarone lung concentration (ug/g)	734

*N=2

SKIN DISCOLORATION
(N=13)

Total amiodarone dosage (g) - range	204 - 1056
mean \pm SD	465 \pm 214
Duration of treatment (months) - range	17 - 45
mean \pm SD	30.6 \pm 8.8
Plasma amiodarone concentration* (ug/ml)	1.90 - 4.00
mean \pm SD	2.96 \pm 0.96

*N=0

APPENDIX III

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List of References

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