Clinical Pharmacokinetics and Efficacy of Amiodarone for Refractory Tachyarrhythmias


SUMMARY Using a high-pressure liquid chromatographic assay, we measured serum amiodarone concentrations serially in 122 patients treated with amiodarone for 1.5-53 months (mean 9.3 months) for control of refractory symptomatic atrial or symptomatic and life-threatening ventricular tachyarrhythmias. The atrial tachyarrhythmias were successfully controlled in 45 of 54 patients (83%) during a mean follow-up of 10.0 months. In the ventricular tachyarrhythmia group, which included 22 survivors of sudden cardiac death, 38 of 50 patients (76%) responded to amiodarone during a mean follow-up of 10.9 months. Although the mean serum amiodarone concentration did not differ between responders and nonresponders, eight responders relapsed when their serum concentration fell below 1.0 mg/l. Side effects resulted in withdrawal of amiodarone in only 10 of 122 patients (9%) despite a 30% overall incidence of side effects. Central nervous system and gastrointestinal side effects became more frequent with serum concentrations > 2.5 mg/l, although only central nervous system side effects achieved statistical significance.

Absorption and disposition kinetics of a single oral 800-mg dose of amiodarone were studied in eight patients. Serum values were measured for 24 hours in five patients during maintenance therapy, and elimination kinetics after long-term therapy were evaluated in three patients. The tissue concentration of amiodarone was determined in two patients who died during long-term amiodarone therapy and an attempt was made in 14 patients to correlate serum concentrations with daily dosages during maintenance therapy. The pharmacokinetics of oral amiodarone support the practice of using high loading dosages until arrhythmia suppression or apparent steady state is achieved (usually 2-4 weeks), followed by low-dose maintenance therapy (200-600 mg once a day) for treatment of symptomatic atrial and ventricular tachyarrhythmias.

AMIODARONE has been progressively recognized as a remarkably effective type III antiarrhythmic agent since its introduction in 1967.1-9 It was first introduced as an antianginal drug because of its coronary and systemic vasodilator properties10 and was later found to be an effective antiarrhythmic agent. Rosenbaum et al.2,3 demonstrated the clinical efficacy of amiodarone for a wide variety of cardiac arrhythmias, including those complicating the Wolff-Parkinson-White syndrome. European and American investigators have confirmed amiodarone’s efficacy for arrhythmias refractory to conventional agents,3,9,12 However, oral dosing schedules are largely empiric, having evolved from early incomplete kinetic data in dogs and humans13 and cumulative clinical experience in humans.1,2,8,9

Whether amiodarone’s ineffectiveness in nonresponders is due to insufficient dosing or to lack of response has been difficult to assess because of inadequate pharmacokinetic data. Similarly, the relationship between side effects and clinically therapeutic dosages and serum amiodarone concentrations has not been established. Andreasen et al.14 and researchers in our laboratory15-17 have established similar high-pressure liquid chromatographic (HPLC) assays for amiodarone and have attempted to delineate the pharmacokinetics of amiodarone in patients. We have described apparent steady-state kinetics18 and attempted to correlate maintenance serum amiodarone concentrations with clinical effectiveness of amiodarone for a variety of symptomatic atrial and ventricular tachyarrhythmias, including fatal ventricular tachycardia/fibrillation (survivors of sudden cardiac death) refractory to conventional and also to some investigational antiarrhythmic agents. In this report we relate our clinical and pharmacokinetic experience with oral amiodarone.

Materials and Methods

Subjects

We studied 122 patients (78 males and 44 females), 54 with symptomatic atrial and 68 with ventricular tachyarrhythmias, including life-threatening ventricular tachycardia (VT) refractory to conventional antiarrhythmic agents (table 1). Digoxin was continued in 29 patients (10 in the atrial group). During long-term amiodarone therapy (range 1.5-53 months, mean 9.3 months), antiarrhythmic agents were taken concomitantly by five patients (quinidine in three, disopyramide in one and mexiletine in one). The patients were 22-93 years old (mean 56.2 years). No patient was excluded from the study based on renal, hepatic or cardiac function. In the atrial group, the underlying diagnoses were idiopathic atrial arrhythmias in 15 patients, sick sinus syndrome in 11, valvular heart disease in 12, coronary artery disease in 10, and hypertensive heart disease in two. Forty-six of 68 patients in the ventricular group had coronary artery disease and previous myocardial infarction and 43 (63%) had evidence of left ventricular failure.

Criteria for Amiodarone Therapy

Atrial Tachyarrhythmia Group

All 54 patients in the atrial tachyarrhythmia group had had extensive trials with conventional antiarrhyth-
mic agents (quinidine, procaïnamide, disopyramide, digoxin and propranolol) for control of atrial tachyarhythmias. Forty-eight had recurrent or incessant symptomatic atrial fibrillation-flutter (A fibr-flutter) and six had symptomatic paroxysmal supraventricular tachycardia (SVT). All 54 patients had received one to five drugs (mean 3.4) alone or in combination before receiving amiodarone. The patients had had atrial tachyarrhythmias for 21–48 months (mean 38 months).

### Ventricular Tachyarrhythmia Group

The VT group consisted of 68 patients, 50 with symptomatic, sustained VT and 23 with unsustained VT. A ventricular tachyarrhythmia lasting five to 12 beats was defined as unsustained VT; a tachyarrhythmia lasting 12 beats or longer was considered sustained VT. Twenty-two patients (32%) survived at least one episode of sudden cardiac death. Quinidine, procaïnamide, disopyramide, propranolol, tocainide and mexiletine were used alone and in combination in standard dosages with therapeutic blood levels before amiodarone. Each patient had one to six (mean 3.5) drug trials before receiving amiodarone. All 50 patients with sustained VT had at least one documented recurrence of VT while taking the previously tried antiarrhythmic agents. Each patient had nine to 18 episodes of clinical VT (mean 7.8 episodes) and had had recurrent refractory VT for 8 days to 7 months (mean 36 days) before being considered for amiodarone. The efficacy of these agents was judged by symptoms, continuous in-hospital ECG monitoring, 24-hour ambulatory ECG monitoring and hospital admissions for recurrence of VT or sudden cardiac death.

### Programmed Cardiac Stimulation

Twenty-four patients underwent programmed cardiac stimulation (PCS) before and after at least 4 weeks of high-dose amiodarone loading. The PCS protocols were similar to those described by Ruskin et al. A digital programmed stimulator (Medtronic 5325) was used to deliver 1.8-msec electrical impulse at about twice the diastolic threshold. The PCS protocols involved inserting single (A<sub>V</sub>) extrastimuli during sinus rhythm and atrial pacing (A<sub>V</sub>, A<sub>1</sub>) at cycle lengths of 600 or 500 msec, and atrial (A<sub>V</sub>, A<sub>1</sub>) pacing at incremental rates until atrioventricular (AV) Wenckebach was reached. Then, atrial overdrive pacing up to 800 beats/min was performed for 2 minutes at each rate. This was followed by inserting single and double (V<sub>1</sub>, V<sub>2</sub>) premature ventricular extrastimuli during sinus rhythm, right ventricular apex and right ventricular outflow pacing (V<sub>1</sub>, V<sub>2</sub>) with basic drive cycle lengths of 600 or 500 and 400 msec and, when necessary, left ventricular pacing. Next, incremental ventricular overdrive pacing to a cycle length of 300 msec was performed. The protocol was completed by ventricular burst pacing at 225, 250, 275 and 300 beats/min for 5–10-beat bursts or until limited by the ventricular refractory period.

### Drug Administration

Initially, patients were given an oral loading dose of 800 mg of amiodarone a day for 2–4 weeks until arrhythmia suppression was achieved. Thereafter, the maintenance dose was gradually reduced to 200–600 mg/day in all patients. After the development of our HPLC assay, we used the maintenance serum amiodarone concentration to monitor and modify the dosing schedules for all the patients. Because relapses in the non-life-threatening tachyarrhythmias occurred when the serum amiodarone concentrations fell to 1.0 mg/l or less, we attempted to maintain the serum amiodarone concentration above this level, especially in patients with life-threatening VT. Once the single-dose absorption-distribution kinetics became available, we increased the initial loading dosage to 800 mg twice daily in the VT group, in whom we wished to achieve arrhythmia control as early as possible. In the atrial arrhythmia group, loading dosages were 800–1200 mg/day. The maintenance amiodarone dosage was 200–600 mg/day (mean 380 ± 125 mg/day) in the atrial tachyarrhythmia group and 200–800 mg/day (mean 394 ± 140 mg/day) in the VT group.

### Pharmacokinetics and Amiodarone Assay

An HPLC assay for amiodarone, modified from Broekhuysen et al., was developed at this institution and has been described in detail. The assay is sensitive to 0.05 mg/l and does not detect separate metabolites.

Maintenance (apparent steady-state) serum amiodarone concentrations were determined after the first month of high-dose loading and every 3 months thereafter in all 122 patients at least 4 hours after the ingestion of amiodarone. Serum concentrations were also determined if significant side effects intervened. We tried to correlate both therapeutic effectiveness and the development of side effects with the maintenance serum amiodarone concentration in all patients receiving...
long-term oral amiodarone therapy. In addition, absorption, distribution and elimination kinetics were studied in smaller subgroups of the study population as follows:

Absorption and disposition kinetics were studied in eight patients after a single oral 800 mg dose of amiodarone followed by frequent blood sampling in the 24 hours after administration. Urine was collected in four patients throughout this sampling period for measurement of urinary amiodarone clearance.

In five patients, after high-dose amiodarone loading for 8 days to 4 weeks (mean 17 days), multiple blood samples throughout a 24-hour period for serum amiodarone concentrations were obtained during maintenance therapy for determination of serum amiodarone concentrations. Three patients took 200, 400 and 600 mg of amiodarone, respectively, as a single daily dose, and two took amiodarone 200 mg twice daily and 200 mg three times daily, respectively.

Elimination kinetics were studied in three patients in whom amiodarone was discontinued after long-term oral therapy for 4, 5 and 7 months, respectively.

Human tissues were analyzed for amiodarone content (µg/g tissue) in two patients who died during long-term oral amiodarone therapy (5 and 15 months, respectively).

Safety Evaluation

All patients had baseline chest x-ray, ECG, 24-hour ambulatory monitoring (for at least two 24-hour periods), ANA, T₄, T₃, TSH, complete blood count, electrolytes, Chem 12 screening, urinalysis and complete ophthalmologic examination before initiation of amiodarone therapy. During the first year of amiodarone therapy these investigations were repeated every 3 months except for chest x-ray and ANA, which were repeated at 6-month intervals, and 24-hour ambulatory monitoring, which was obtained at least yearly and usually more frequently.

Efficacy Assessment

For analysis of efficacy, patients were considered to be responders or nonresponders. Patients were considered a nonresponder if their arrhythmias could not be controlled clinically after 4 weeks of high-dose oral amiodarone, if there was clinical or symptomatic recurrence of VT/A fibrillation during long-term therapy or if VT/A fibrillation was still present on 24-hour ambulatory ECG monitoring. When VT was inducible by PCS during maintenance amiodarone, the results were noted, but the patient was classified as a responder or nonresponder by the clinical criteria described. In the unsustained VT group, a nonresponder was a patient in whom there was persistence of clinical palpitations and < 80% decrease in ventricular ectopic activity.

Side Effects

After commencing amiodarone therapy, all patients were examined and interviewed at 1 month and every 3 months thereafter, or sooner if indicated. Subjective side effects were spontaneously reported by patients, and all patients were routinely questioned for side effects referable to all organ systems.

Results

Pharmacokinetics

Absorption Kinetics of a Single 800-mg Dose

The serum amiodarone concentrations after an 800-mg dose of amiodarone in eight patients is shown in figure 1. There was wide interpatient variability in serum concentrations and a delayed appearance of amiodarone in the serum (mean lag time 1.44 hours), a mean absorption half-life of 1.62 hours, and a tₘₐₓ (time taken to achieve maximum serum concentration of the drug) of 5.2 ± 0.6 hours. The interpatient variability in serum concentrations of amiodarone after a single 800-mg dose did not correlate well with the mg/kg dose. The maximal serum concentration (Cₘₐₓ) ranged from 0.6–3.2 mg/l (mean 1.7 mg/l). The disposition or disappearance of amiodarone from the serum in all eight patients after an 800-mg oral dose was relatively rapid; the mean disappearance half-life was 4.62 hours. No amiodarone or amiodarone-like sub-

![Figure 1. Absorption and disposition curves in eight patients after a single 800-mg oral dose of amiodarone.](http://circ.ahajournals.org/DownloadedFrom)
stances were detected in the urine for 24 hours after the dose. Dog studies in our laboratory and others have shown no fecal excretion of amiodarone after i.v. amiodarone. Thus, the short disappearance half-life after a single oral dose of amiodarone may represent a combination of predominant tissue uptake during circulation and negligible true elimination.

**Multiple Serum Amiodarone Samplings During Maintenance Therapy**

In five patients, multiple-serum amiodarone concentrations were measured over 24-hours during long-term maintenance amiodarone therapy. There was little variation in the serum amiodarone concentrations during the 24-hour period in relation to the time of drug ingestion (fig. 2). All five patients had received high-dose oral amiodarone (800–1600 mg/day) for 8 days to 4 weeks, and their maintenance dosage ranged from 200–600 mg/day in single and multiple daily doses.

**Elimination Kinetics After Long-term Amiodarone Therapy**

Elimination kinetics were studied in three patients in whom amiodarone was discontinued (two patients because of side effects and in the other because of inefficacy). These patients had been taking amiodarone for 7, 5 and 4 months, respectively. The elimination half-life of amiodarone in these patients was 30, 15 and 13 days, respectively. Amiodarone was detectable in serum for up to 6 months after its discontinuation in the patient who took amiodarone for 7 months.

**Human Tissue Content of Amiodarone During Long-term Therapy**

The tissue content of amiodarone in non-formalin-fixed organ specimens immediately after death revealed a high content of amiodarone in body fat (mesentery), fat-laden organs (bone marrow, liver, adrenals and pancreas) and lung tissue. There was relatively less amiodarone in heart muscle, though this was still 30 times more than in the plasma (table 2).

**Maintenance Serum Amiodarone Concentrations**

The maintenance serum amiodarone concentrations during long-term therapy were 0.4–3.3 mg/l (mean 1.7 mg/l) in the 122 patients. Immediately after prolonged high-dose oral loading, concentrations of up to 6.7 mg/l were recorded, especially early in the study. When this occurred the maintenance dose was reduced accordingly. In 14 patients after prolonged administration, depending on loading regimens, body size and, in particular, body fat, there was a reasonably good correlation between maintenance serum concentration and mg/kg dose of amiodarone (fig. 3) (r² = 0.72, p < 0.05; the equation of the best fit line by least-squares linear regression analysis was y = 0.912 + 0.099x).

**Arrhythmia Suppression (table 3, fig. 4)**

**Atrial Group**

Forty-one of the 48 A fib-flutter patients (85%) were long-term responders who were treated for 1.5–49 months (mean 10.1 months). In the seven nonresponders, treatment was discontinued after 1.5–23 months (mean 6.7 months). There was no significant difference in the maintenance dosages (mean 349 ± 122 vs 460 ± 135 mg/day) or maintenance serum amiodarone concentrations (mean 1.5 ± 0.6 vs 1.7 ± 0.7 mg/l) between the responders and nonresponders. However, four of the responders in the A fib-flutter

| TABLE 2. Postmortem Human Tissue Content of Amiodarone (µg/g tissue) |
|------------------------|------------------------|
|                        | Patient 1               | Patient 2               |
| Mesentery (fat)         | —                       | 385                     |
| Lung                   | 243                     | —                       |
| Bone marrow            | 157                     | 152                     |
| Adrenal                | 121                     | —                       |
| Liver                  | 111                     | 187                     |
| Pancreas               | 109                     | 145                     |
| Testes                 | 35                      | —                       |
| Spleen                 | 32                      | 98                      |
| Salivary               | 23                      | —                       |
| Thyroid                | 17                      | —                       |
| Brain                  | 6                       | —                       |
| Plasma                 | 0.6                     | 1.0                     |
group relapsed when their maintenance dosage was decreased and their serum amiodarone concentrations fell to 0.4, 0.5, 0.8, and 0.8 mg/l, respectively. All four responded once again when their serum amiodarone concentrations were raised above 1.0 mg/l.

Four of the six SVT patients were long-term responders who were treated for periods of 4–23 months (mean 9.8 months). The two nonresponders had recurrences at 9 and 23 months, respectively. The maintenance dosages in the four SVT responders was 400–600 mg/day (mean 500 mg/day) and their serum amiodarone concentrations were 1.4–2.8 mg/l (mean 2.0 mg/l), whereas the amiodarone dosages in the two nonresponders at the time of recurrence were 400 and 600 mg/day and the serum amiodarone concentrations were 1.8 and 3.2 mg/l, respectively.

Ventricular Group

Of the 50 patients with sustained VT (including 22 survivors of sudden cardiac death), there were 38 long-term responders (76%) who were treated for 1.5–53 months (mean 10.9 months) and 12 nonresponders who were treated for 1.5–15 months (mean 2.5 months). Thirteen of the 22 survivors (60%) of sudden cardiac death are long-term responders. There was no significant difference in the mean maintenance serum amiodarone concentrations between the 38 responders (1.8 ± 0.7 mg/l) and the 12 VT nonresponders (1.9 ± 0.7 mg/l). The nonresponders had a higher maintenance amiodarone dosage (range 400–800 mg/day, mean 500 ± 175 mg/day) than the VT responders (range 200–600 mg/day, mean 371 ± 145 mg/day).

In the 38 responders, consistent VT suppression occurred after 8 days to 4 weeks of high-dose oral amiodarone therapy. Thereafter, the dosage was gradually reduced in these responders in an attempt to maintain serum amiodarone concentrations greater than 1.0 mg/l. In the responder who developed pulmonary fibrosis, VT recurrence occurred 3 months after discontinuing amiodarone when his serum concentration was 0.5 mg/l.

In the unsustained VT group of 18 patients, there were 17 long-term responders who were treated for periods of 1.5–36 months (mean 8.9 months) and their maintenance serum amiodarone concentrations were 1.0–2.5 mg/l (mean 2.0 ± 0.6 mg/l). Three patients had a recurrence of ventricular ectopic activity or unsustained VT when their levels fell to 0.4, 0.5 and 1.0 mg/l, respectively. They became responders when their maintenance daily amiodarone dosages were increased, resulting in higher serum concentrations (fig. 4).

**Programmed Cardiac Stimulation**

The results of PCS and the arrhythmia response to amiodarone are shown in table 4. Sustained VT (> 12 beats) was inducible by PCS in 18 patients from the sustained VT group who were studied before amiodarone therapy and the remaining two patients had incessant VT. After at least 4 weeks of high-dose amiodarone therapy, sustained VT that was self-limiting or required termination was still inducible in 11 of 20 patients (55%). However, the cycle length of the VT in eight of 11 patients with inducible VT was longer with amiodarone (mean 292 ± 35 vs 376 ± 41 msec, p < 0.01). The serum amiodarone concentrations (1.8 vs 1.9 mg/l), QTc interval (0.47 vs 0.48 second) and prolongation of the effective refractory period of the right ventricle (38 ± 8 vs 41 ± 8 msec) did not differ between the inducible and noninducible VT patients during long-term amiodarone therapy. However, in the patients with sustained VT and frequent resting ventricular ectopic activity, there was > 80% suppression of ventricular ectopy and absence of VT by 24-hour ambulatory monitoring during long-term amiodarone therapy in both the inducible and noninducible groups. During a follow-up of 1.5–1.9 months (mean 6.8 months), three of 20 patients have had clinical recurrence of VT (two sudden cardiac death, one hemodynamically significant VT). All three patients had had inducible VT by PCS during maintenance amiodarone therapy, and their serum amiodarone concentrations were > 1.5 mg/l.

In four patients with PCS-inducible A fib-flutter before amiodarone, repeat PCS could not induce A fib/flutter during maintenance amiodarone when their serum concentrations were > 1.0 mg/l. These four patients have not had a clinical recurrence during 11–18 months of follow-up (mean 14.7 months).

**Side Effects**

The incidence and distribution of side effects during long-term amiodarone therapy are shown in table 5 and figure 5. Thirty-six of 122 patients (30%) reported at least one symptom or had an asymptomatic laboratory abnormality during amiodarone therapy. Most of these side effects were tolerable or could be minimized by decreasing the amiodarone dosage and serum concentration. The mean serum concentration (2.1 mg/l) when the side effect occurred did not significantly differ from the mean serum amiodarone concentration (1.8 mg/l) in the patients without side effects. However, in three patients with subjective visual disturbances and two with profound sinus node depression, these
side effects resolved when the daily amiodarone dosage was decreased and the serum concentration fell to < 2.0 mg/l. Amiodarone had to be discontinued in only 10 of 122 patients (9%) because of unacceptable side effects, which included refractory heart failure in two patients, pulmonary fibrosis in one patient, central nervous system side effects in four patients, and sun sensitivity in three patients.

Our initial experience suggested that serum amiodarone concentrations > 2.5 mg/l were associated with increased side effects. Thereafter, we attempted to maintain steady-state serum amiodarone concentrations < 2.5 mg/l. We retrospectively compared the frequency of side effects in 36 patients who at some point had serum amiodarone concentrations ≥ 2.5 mg/l with the frequency of side effects when their serum concentrations were < 2.5 mg/l (table 6). The incidence of gastrointestinal and central nervous system side effects was lower at serum concentrations < 2.5 mg/l, though only the central nervous system side effects decreased significantly (p < 0.05) in this small group. The overall frequency of long-term side effects did not change significantly when the serum amiodarone concentration was < 2.5 mg/l in these patients.

In the 33 patients also taking coumadin, a 30–50% potentiation of its effect necessitated a reduction in coumadin dosage and frequent prothrombin time checks. Although this interaction was unpredictable in onset, it occurred during chronic (steady-state) therapy. Asymptomatic biochemical abnormalities (thyroid and liver function tests) were noted in 20–25% of the patients during long-term therapy when their mean serum amiodarone concentrations were < 2.0 mg/l.

Almost all of the patients developed subcorneal infralens accumulations of amiodarone crystals and vortex-like amiodarone deposits in the corneal epithelium and stroma without objective visual acuity changes after 3 months of therapy. These deposits have gradually regressed in patients in whom amiodarone was discontinued.

Discussion

Amiodarone has several unique pharmacokinetic properties that remain to be fully defined. The acute single-dose absorption kinetics reveal a higher peak serum amiodarone concentration than that observed during long-term, lower-dose maintenance therapy. The disposition or disappearance of a single 800-mg dose of amiodarone is very rapid and there is no measurable amiodarone in the urine or feces after a single dose. Thus, the disappearance phase after a single dose of amiodarone probably represents predominant tissue uptake. Our postmortem studies corroborate these findings in that tissue concentrations of amiodarone were up to 300 times greater in most body tissues than in plasma. Fat and fat-laden organs contained the largest amounts of amiodarone, which suggests that amiodarone is lipophilic. Furthermore, after long-term administration, the terminal elimination half life is unusually long.

The metabolism of amiodarone has not been fully unraveled. However, the metabolite desethylamiodarone has recently been identified by Holt et al.22 using an HPLC assay similar to ours. There is no evidence that this metabolite consistently accumulates in body

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**Table 3. Arrhythmia Response to Amiodarone**

<table>
<thead>
<tr>
<th>Arrhythmia</th>
<th>No. of pts</th>
<th>No. of responders</th>
<th>Follow-up (months)</th>
<th>Maintenance dose (mg/day)</th>
<th>Maintenance serum amiodarone conc (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained ventricular tachycardia</td>
<td>50</td>
<td>38</td>
<td>1.5–53 (mean 10.9)</td>
<td>200–600</td>
<td>0.4–3.3</td>
</tr>
<tr>
<td>Unsustained VT and high-grade VEA</td>
<td>18</td>
<td>17</td>
<td>1.5–36 (mean 8.9)</td>
<td>200–600</td>
<td>1.0–2.5</td>
</tr>
<tr>
<td>Recurrent A fib-flutter</td>
<td>48</td>
<td>41</td>
<td>1.5–49 (mean 10.1)</td>
<td>200–600</td>
<td>0.5–3.0</td>
</tr>
<tr>
<td>Paroxysmal SVT</td>
<td>6</td>
<td>4</td>
<td>4–23 (mean 9.8)</td>
<td>400–600</td>
<td>1.4–2.8</td>
</tr>
</tbody>
</table>

Abbreviations: conc = concentration; VT = ventricular tachycardia; VEA = ventricular ectopic activity; SVT = supraventricular tachycardia; A fib-flutter = atrial fibrillation-flutter.
tissues or that it is pharmacologically active. During maintenance therapy, serum amiodarone concentrations are probably in equilibrium with the higher amounts of amiodarone found in body tissues. This may explain why the serum concentrations during long-term therapy fluctuate little compared with single-dose kinetics. Thus, the serum levels during chronic therapy may reflect tissue levels and therapeutic effect more accurately than they would during acute administration.

Our observations and those of Riva et al.19 suggest that it would take several months to achieve a steady state with a constant dose of 200–400 mg/day of amiodarone in the absence of a high-dose loading phase. Even with relatively high oral loading dosages, uniform, constant arrhythmia suppression was achieved in our responders only after 8 days to 4 weeks (mean 17 days) of therapy. These pharmacokinetic data and results from our laboratory and from Andreasen et al.14 substantiate the empiric use of current loading dosage schedules for amiodarone.

In this series, we used “apparent steady-state” serum amiodarone concentrations to titrate the maintenance dose prospectively. The retrospective analysis of the relationship between steady-state serum amiodarone concentrations, drug efficacy and side effects supports the use of steady-state serum concentrations for this purpose. As with other antiarrhythmic agents, there appear to be patients whose arrhythmias do not respond to amiodarone regardless of the maintenance dosage or steady-state serum concentration of the drug. Thus, in both ventricular and atrial groups, the nonresponders failed to achieve control of their tachyarrhythmias even when their amiodarone maintenance dosages and steady-state serum concentrations exceeded those of the responders. However, eight of the responders had recurrence of their arrhythmias when their steady-state serum amiodarone concentrations fell below 1.0 mg/l. In seven of these eight patients, the daily amiodarone dosage was increased and they became responders when their serum amiodarone concentrations exceeded 1.0 mg/l. We therefore feel that no patient should be considered a nonresponder unless a steady-state serum amiodarone concentration of > 1.0 mg/l has been achieved.

Because we attempted to maintain steady-state serum amiodarone concentrations at the lowest effective concentration, relatively few patients had serum amiodarone concentrations greater than 2.5 mg/l during long-term therapy. Among these patients who did have

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**Table 3. (Continued)**

<table>
<thead>
<tr>
<th>No. of non-responders</th>
<th>Follow-up (months)</th>
<th>Maintenance dose (mg/day)</th>
<th>Maintenance serum amiodarone conc (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>1.5–15 (mean 2.5)</td>
<td>400–800 (mean 500 ± 175)</td>
<td>1.1–2.8 (mean 1.9 ± 0.7)</td>
</tr>
<tr>
<td>1</td>
<td>11</td>
<td>400</td>
<td>1.5</td>
</tr>
<tr>
<td>7</td>
<td>1.5–23 (mean 6.7)</td>
<td>200–600 (mean 460 ± 135)</td>
<td>0.5–3.3 (mean 1.7 ± 0.7)</td>
</tr>
<tr>
<td>2</td>
<td>9 and 23 months</td>
<td>400 and 600</td>
<td>1.8 and 3.2</td>
</tr>
</tbody>
</table>

**Figure 5.** Incidence of side effects in relation to long-term serum amiodarone concentration. n = the number of maintenance serum amiodarone concentration determinations. Each patient had multiple determinations at different times. If a patient had more than one determination in a given serum range, that patient was counted only once for that range. If a patient had determinations falling in more than one range, that patient is counted once in each range.

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**Table 4. Patient Characteristics and Arrhythmia Response in the 24 Patients Undergoing Programmed Cardiac Stimulation During Amiodarone Therapy**

<table>
<thead>
<tr>
<th>Before amiodarone</th>
<th>No. of pts with PCS-inducible tachyarrhythmia</th>
<th>No. of pts with incessant tachyarrhythmia</th>
<th>Duration of amiodarone therapy before repeat PCS (weeks)</th>
<th>Serum amiodarone concentrations during repeat PCS (mg/l)</th>
<th>Arrhythmia inducible at PCS while on amiodarone</th>
<th>Clinical recurrence of arrhythmia</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained VT</td>
<td>18</td>
<td>2</td>
<td>4–34 (mean 9.4)</td>
<td>1.5–2.3 (mean 1.9 ± 0.4)</td>
<td>11</td>
<td>3*</td>
<td>1.5–19 (mean 6.8)</td>
</tr>
<tr>
<td>Recurrent A fib-flutter</td>
<td>4</td>
<td>0</td>
<td>5–10 (mean 6.4)</td>
<td>1.2–2.8 (mean 1.8 ± 0.7)</td>
<td>0</td>
<td>0</td>
<td>11–18 (mean 14.7)</td>
</tr>
</tbody>
</table>

*VT was inducible at PCS and recurrences occurred at 1.5, 3 and 7 months after start of amiodarone therapy.

Abbreviations: VT = ventricular tachycardia; A fib-flutter = atrial fibrillation-flutter; PCS = programmed cardiac stimulation.
TABLE 5. Side Effects During Long-term Amiodarone Therapy

<table>
<thead>
<tr>
<th>Side effect</th>
<th>No. of pts</th>
<th>Serum amiodarone concentrations (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS (tremors, paraesthesiae, nightmares, ataxia)</td>
<td>22/122 (19%)</td>
<td>10 pts: &gt;2.5 (mean 3.5) 12 pts: 0.5–2.5 (mean 1.7)</td>
</tr>
<tr>
<td>Sun sensitivity</td>
<td>24/122 (20%)</td>
<td>0.8–2.8 (mean 1.7)</td>
</tr>
<tr>
<td>Profound sinus node depression</td>
<td>3/122 (3%)</td>
<td>2.4, 2.5 and 2.6</td>
</tr>
<tr>
<td>Subjective visual disturbance</td>
<td>3/122 (3%)</td>
<td>3.7, 3.9 and 4.3</td>
</tr>
<tr>
<td>Clinical hyperthyroidism</td>
<td>2/122 (2%)</td>
<td>4.8, 1.4</td>
</tr>
<tr>
<td>Clinical hypothyroidism</td>
<td>1/122 (1%)</td>
<td>1.4</td>
</tr>
<tr>
<td>Gastrointestinal side effects (constipation, anorexia, nausea, etc.)</td>
<td>18/122 (15%)</td>
<td>7 pts: 0.8–1.8 (mean 1.3) 11 pts: 2.1–4.4 (mean 2.8)</td>
</tr>
<tr>
<td>Abnormal liver function tests (SGOT, alkaline elevations &lt; 2 × normal)</td>
<td>26/122 (21%)</td>
<td>0.5–3.3 (mean 1.7)</td>
</tr>
<tr>
<td>Worsening of congestive heart failure</td>
<td>3/122 (2%)</td>
<td>1.4, 1.6 and 1.8</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>1/122 (1%)</td>
<td>1.5</td>
</tr>
<tr>
<td>Total no. of pts experiencing side effects</td>
<td>36/122 (30%)</td>
<td>0.8–4.4 (mean 2.1)</td>
</tr>
</tbody>
</table>

Abbreviation: CNS = central nervous system.

serum concentrations exceeding 2.5 mg/l, the incidence of side effects tended to decrease as their serum concentrations decreased below 2.5 mg/l, but this change was only significant in regard to central nervous system side effects. The overall incidence of side effects and the incidence of life-threatening side effects (pulmonary fibrosis, sinus arrest, exacerbation of ventricular tachycardia, aplastic anemia) were considerably less than those described in the recent reports. The patients in these reports were similar to ours but received higher maintenance amiodarone dosages for extended periods. Presumably, these patients also had higher serum amiodarone levels than our patients. We therefore believe that steady-state serum amiodarone concentrations of 1.0–2.5 mg/l minimize the incidence of serious side effects without sacrificing therapeutic efficacy.

The clinical usefulness of measuring serum amiodarone concentrations is analogous to that of serum digoxin concentrations in that the serum concentration of the drug may be used to guide chronic dosing, to determine which patients are nonresponders to adequate serum concentrations, to confirm drug compliance and to confirm the clinical impression of drug excess. Whereas serum and tissue amiodarone concentrations during maintenance therapy are not precisely predictable based upon our present knowledge of the pharmacokinetics, the steady-state serum drug concentrations serve as an approximation of the patient's absorption and disposition of amiodarone. When the drug appears to be ineffective, the HPLC assay can establish whether the patient has achieved a 'minimal' therapeutic steady-state serum concentration. When toxicity is suspected, the steady-state serum amiodarone concentration can indicate whether the patient is receiving a dosage in excess of that needed for a therapeutic effect.

PCS studies in our patients with atrial tachyarrhythmias predicted our clinical results. However, inducibility of ventricular tachycardia by PCS during amiodarone therapy was not a perfect predictor of subsequent clinical relapse in our VT patients, as has been reported in other series.26, 27 Our patients in whom VT was not inducible by PCS during amiodarone therapy, however, have all done well. We feel that the specificity and sensitivity of PCS for predicting the outcome of amiodarone therapy for VT remain to be determined.

Our experience with long-term oral amiodarone therapy in 122 patients with refractory atrial and ventricular tachyarrhythmias confirms that amiodarone is a promising, highly effective antiarrhythmic agent. The pharmacokinetics of this unique drug have not been entirely clarified. Our results with an HPLC assay for serum amiodarone concentrations suggest that a rational approach to loading and maintenance dosages can minimize the incidence of serious side effects and prevent arrhythmia relapses in patients who respond to amiodarone.

### TABLE 6. Distribution of Side Effects in 36 Patients Who Had Maintenance Serum Amiodarone Concentrations Greater Than and Less Than 2.5 mg/l

<table>
<thead>
<tr>
<th>Side effect</th>
<th>&lt; 2.5 mg/l</th>
<th>≥ 2.5 mg/l</th>
<th>χ² (chi-square test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun sensitivity</td>
<td>11</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>CNS</td>
<td>3</td>
<td>11</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>GI</td>
<td>1</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>CHF</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Total no. of pts experiencing side effects</td>
<td>16</td>
<td>22</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: CNS = central nervous system (tremor, ataxia, paraesthesiae, headache, nightmares); GI = gastrointestinal (constipation, nausea, vomiting); CHF = congestive heart failure; Other = sinus node depression, subjective visual symptoms, hypo- and hyperthyroidism.
References

Clinical pharmacokinetics and efficacy of amiodarone for refractory tachyarrhythmias.
C I Haffajee, J C Love, A T Canada, L J Lesko, G Asdourian and J S Alpert

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