Amiodarone is safe and highly effective therapy for supraventricular tachycardia in infants

Susan P. Etheridge, MD, Janet E. Craig, PNP, and Steven J. Compton, MD Salt Lake City, Utah

Background The clinical effectiveness of amiodarone must be weighed against the likelihood of adverse effects. Adverse effects are less common in children than in adults, yet there have been no large studies assessing the efficacy and safety of amiodarone in the first 9 months of life. We sought to assess the safety and efficacy of amiodarone as primary therapy for supraventricular tachycardia in infancy.

Methods We evaluated the clinical course of 50 consecutive infants and neonates (1.0 ± 1.5 months, 35 male) treated with amiodarone for supraventricular tachyarrhythmias between July 1994 and July 1999. At presentation, congenital heart disease, congestive heart failure, or ventricular dysfunction were present in 24%, 36%, and 44% of the infants, respectively. Infants received a 7- to 10-day load of amiodarone at either 10 or 20 mg/kg/d. If this failed to control the arrhythmia, oral propranolol (2 mg/kg/d) was added. Patients were followed up for 16.0 ± 13.0 months, and antiarrhythmic drugs were discontinued as tolerated.

Results Rhythm control was achieved in all patients. Of the 34 patients who have reached 1 year of age, 23 (68%) have remained free of arrhythmia, despite discontinuation of propranolol and amiodarone. Growth and development remained normal for age. Higher loading doses of amiodarone were associated with an increase in the corrected QT interval, but no proarrhythmia was seen. There were no side effects necessitating drug withdrawal.

Conclusions Amiodarone is an effective and safe therapy for tachycardia control in infancy. (Am Heart J 2001;141:105-10.)
at presentation and an ECG once sinus rhythm was established. Baseline serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum thyroxine (T4), and thyroid stimulating hormone (TSH) were obtained in all patients. A complete blood cell count was obtained at admission and the white blood cell count was normal for all patients. This test was not routinely obtained during follow-up and therefore these data are not included in this analysis. A reverse triiodothyronine (T3) was performed on some children during follow-up but these tests were not performed consistently and were not used for data analysis.

Amiodarone loading

Intravenous amiodarone (5 mg/kg over 1 hour) was used in 6 critically ill patients. These patients all had symptoms of congestive heart failure or shock resulting from supraventricular tachycardia. These patients had tachycardia that was either unresponsive to adenosine or cardioversion or had early recurrences after these therapies. All these patients were unresponsive to intravenous propranolol therapy. After intravenous loading, these patients were converted to maintenance therapy with oral amiodarone.

The remaining 44 patients were loaded with oral amiodarone. After initial stabilization, infants received a 7- to 10-day load of amiodarone at either 10 or 20 mg/kg/d (average 14 ± 5 mg/kg/d) in 2 divided doses. The loading dose was determined at the discretion of the treating physician. Infants with tachycardia that was more difficult to control tended to receive the higher loading dose. Oral amiodarone was given by mixing one half of a 200-mg tablet (Cordarone, Wyeth-Ayerst) with water and immediately administering an appropriate volume of this mixture. The unused portion of the liquid was discarded.

Oral propranolol (2 mg/kg/d in 3 divided doses) was added if sustained or symptomatic episodes of tachycardia persisted after completion of a 10-day amiodarone load. For the purposes of managing these patients, sustained tachycardia was defined as episodes lasting greater than 10 minutes and requiring an intervention for termination. All infants were monitored on telemetry for the loading period. All infants with decreased left ventricular function had a repeat echocardiography before discharge. Infants were discharged once they were clinically stable and had adequate tachycardia control for 3 days. Adequate tachycardia control was considered the absence of sustained and symptomatic tachycardia. Incessant forms of tachycardia such as MAT, PJRT, and AET were considered controlled if they had an average heart rate of <150 beats/min and were without signs or symptoms of congestive heart failure.

Outpatient therapy

Infants were discharged on a maintenance amiodarone dose of 5 to 10 mg/kg/d (mean dose 7 ± 2 mg/kg/d). Propranolol was discontinued at the physician’s discretion after a tachycardia-free interval (usually 2–7 months). Propranolol was the initial medication to be discontinued. Because it is administered three times daily, propranolol is more difficult to use than amiodarone. Additionally, parents were less compliant with propranolol for this reason. If there was no further tachycardia, amiodarone was discontinued at age 6 to 9 months on the basis of data that suggest that tachycardia is uncommon as children reach 1 year of age. A 24-hour Holter monitor was performed approximately 3 months after amiodarone was discontinued if clinical episode of tachycardia had not occurred.

Follow-up

Parents were instructed in the signs and symptoms of tachycardia and daily heart rate monitoring. They were encouraged to contact us if tachycardia recurred. The patients were followed up in the arrhythmia clinic at 2- to 12-week intervals. Physical examinations were performed with careful attention paid to possible systemic side effects. Follow-up 12-lead ECGs and 24-hour Holter monitors were undertaken to determine response to therapy. Corrected QT (QTc) intervals were noted on each 12-lead ECG. Thyroid and liver function tests were performed at 3- to 6-month intervals for the duration of amiodarone therapy. Routine chest radiographs were obtained in children requiring amiodarone therapy for 12 months or longer. Routine drug levels were not obtained.

Efficacy

The efficacy of amiodarone was assessed by tachycardia recurrence or persistence of any nonsinus tachycardia based on ECG and Holter monitor results.

Side effects

Height and weight measurements were obtained at each visit and compared with normal values. Cardiac toxicity was defined as worsening of arrhythmia or the new onset of significant bradycardia or atrioventricular block. Gastrointestinal toxicity was defined as poor feeding, intractable vomiting
occurring any time after the initiation of amiodarone, or an abnormal AST or ALT level. Neurologic toxicity was defined as increasing lethargy, tremor, motor disorder, or developmental delay occurring after initiation of amiodarone. Dermatologic toxicity was defined as skin discoloration or photosensitivity after initiation of amiodarone. Pulmonary toxicity was defined as tachypnea, hypoxemia, or abnormal lung findings on physical examination or chest radiography. Routine chest radiographs were obtained in patients where amiodarone therapy was required beyond the age of 1 year. Thyroid toxicity was defined as any T4 or TSH value outside age-specific norms with clinical symptoms. Ophthalmologic examinations were not performed because these abnormalities have not been described in infancy.14

Statistical analysis

The QT was corrected according to the formula of Bazett.19 All data are expressed as mean ± SD. Categorical data were compared with a Fisher exact test or a chi-square test. Continuous data were compared with the Student t test. A P value of <.05 was considered significant.

Results

Patient population

Between July 1994 and July 1999, amiodarone was used in 50 neonates and infants either alone (25 patients) or in combination with propranolol (25 patients) for the treatment of tachycardia. At presentation, the patients ranged in age from 1 day to 9 months with a mean age of 1.0 ± 1.5 months. Of this group, 23 (46%) patients had failed 1.3 ± 0.5 prior antiarrhythmic medications including intravenous procainamide, esmolol, diltiazem, and oral propranolol. The patients were 41 ± 67 days old at initiation of amiodarone therapy. Table I details additional patient demographic data.

Efficacy

Patients were monitored on telemetry for 8.0 ± 2.0 days. After the amiodarone load, 25 patients had no further episodes of tachycardia. The administration of amiodarone did not result in incessant tachycardia in any patient nor did the episodes of tachycardia increase in frequency after amiodarone. However, propranolol was added in the 25 patients with continued sustained tachycardia episodes after completion of a 10-day amiodarone load. There were no significant differences between these two patient groups in the incidence of congestive heart failure, associated congenital heart disease, tachycardia mechanism, or tachycardia rate. Patients receiving the more aggressive amiodarone loading dose (20 mg/kg/d, n = 19) were also more likely (P < .05) to require additional therapy with propranolol than were patients receiving the smaller loading dose (10 mg/kg/d, n = 31). This suggests that this group had tachycardia that was more difficult to control.

At discharge, all patients were asymptomatic and had normal ventricular function by echocardiogram. At discharge, 45 patients (90%) were in sinus rhythm without episodes of tachycardia, and 5 patients (AET n = 2, PJRT n = 1, MAT n = 1, AVRT n = 1) had occasional episodes of asymptomatic tachycardia. These 5 patients had mean heart rates <150 beats/min on the basis of telemetry and 24-hour Holter monitoring and no signs or symptoms of congestive heart failure. All 5 patients had normal ventricular function by echocardiogram. On the basis of history, 12-lead ECG, and 24-hour Holter monitoring, all patients were free of tachycardia within 3 months of discharge.

Side effects

There were no side effects necessitating drug withdrawal. Acute hypotension occurred in 2 patients during intravenous amiodarone infusion and resolved with volume administration. No proarrhythmic effects, acute toxicity, or significant conduction abnormalities were seen with intravenous amiodarone. Growth and development remained normal for age during oral amiodarone administration. Neither hemodynamic instability nor bradycardia (heart rate <60 beats/min) was noted, even in patients requiring both amiodarone and propranolol. No patient had neurologic, dermatologic, or pulmonary side effects during the follow-up period. Chest radiographs obtained in patients requiring amiodarone therapy beyond 1 year of age have remained normal. Table II details the baseline and maximum values for laboratory tests and QTc during follow-up. There were significant increases in AST, ALT, and TSH, but values remained within the normal range for age and no clinical effects were noted. There was no significant change in T4 levels.

### Table II. Results of baseline and follow-up testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>Maximum</th>
<th>Normal</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (U/L)</td>
<td>42 ± 16</td>
<td>48 ± 17</td>
<td>20-60</td>
<td>P &lt; .01</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>36 ± 27</td>
<td>42 ± 27</td>
<td>5-45</td>
<td>P &lt; .03</td>
</tr>
<tr>
<td>TSH (mIU/mL)</td>
<td>3.7 ± 2.5</td>
<td>4.2 ± 2.0</td>
<td>0.6-6.3</td>
<td>P &lt; .01</td>
</tr>
<tr>
<td>T4 (µg/dL)</td>
<td>12.8 ± 4.8</td>
<td>15.4 ± 12.0</td>
<td>8-16</td>
<td>NS</td>
</tr>
<tr>
<td>QTc (msec)</td>
<td>419 ± 67</td>
<td>462 ± 31</td>
<td>&lt;440</td>
<td>P &lt; .01</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SD. NS, Not significant; QTc, correct QT intervals.
The baseline QTc was 419 ± 67 msec and the maximal QTc on amiodarone was 462 ± 31 msec (P < .01). Additionally, 29 of 50 (58%) had a QTc > 440 msec at some time during therapy. The QTc increased during the loading phase and returned to normal during maintenance amiodarone therapy. Further QTc lengthening was not seen in the follow-up period. A prolongation of the QTc to > 440 msec was more likely (P < .005) in patients loaded with 20 mg/kg/d of amiodarone than patients loaded with 10 mg/kg/d. The loading dose was not adjusted on the basis of the results of the QT intervals. No patient had torsades de pointes. On the basis of 24-hour Holter monitoring, there was no bradycardia (heart rate < 60 beats/min), AV block, or pauses of more than 1.8 seconds.

Follow-up
The patients were followed up for 16.0 ± 13.0 months. A total of 34 patients have reached 1 year of age. Of these patients, 9 (26%) still require amiodarone because of recurrence of tachycardia with reduction of amiodarone and one patient requires both amiodarone and propranolol. Attempts to withdraw either medication resulted in tachycardia recurrence. The child with MAT underwent a successful radiofrequency catheter ablation at 2 years of age. In the remaining 23 (68%) patients more than 1 year old, amiodarone was successfully discontinued at 8.2 ± 3.6 months of age and propranolol discontinued at 6.7 ± 4.4 months.

Discussion
Previous pediatric studies of amiodarone have combined data from infants, older children, and adolescents. To our knowledge, this represents the largest study evaluating the safety and efficacy of amiodarone in infancy. In this series amiodarone alone or in combination with propranolol controlled tachycardia in all patients within 3 months of initiation of amiodarone therapy. Patients who received a higher loading dose of amiodarone were more likely to require propranolol for arrhythmia control but did not suffer clinical toxicity from the more aggressive dosing.

A few reports have suggested that infants have fewer drug-related side effects from amiodarone therapy. Although amiodarone use has been associated with keratopathy, thyroid abnormalities, skin changes, hepatitis, and pulmonary toxicity, most side effects develop only after prolonged therapy. Our experience demonstrates that short-term amiodarone use in neonates and infants is safe. There were no complications or side effects necessitating drug withdrawal. As seen in studies in adults, amiodarone did not exacerbate congestive heart failure in patients with ventricular dysfunction. In our series, control of tachycardia by amiodarone was associated with resolution of tachycardia-induced heart failure signs and symptoms. All patients had normal ventricular function at discharge.

Despite careful monitoring for systemic complications, the infants in our series appeared to be remarkably tolerant of amiodarone. We noted 2 infants with hypotension during intravenous administration of amiodarone, consistent with earlier reports in other pediatric series. Although we noted increased QTc intervals during drug loading, this effect usually normalized and never worsened during maintenance therapy and was not associated with torsades de pointes. Although there was an increase in the ALT, AST, and TSH levels, we did not observe clinical abnormalities in thyroid or liver function. This suggests that infrequent testing may be sufficient in infants receiving a limited course of therapy. In this population we currently perform routine screening liver and thyroid testing every 6 months.

Although pulmonary fibrosis is seen in approximately 3% of adult patients treated with amiodarone for 1 year and 5% treated for 2 years, it is even rarer in children. There are case reports of pulmonary toxicity in infants receiving both oral and intravenous amiodarone. We did not observe pulmonary toxicity in our patients, possibly because we did not routinely obtain chest radiographs in children treated for < 1 year. No respiratory symptoms occurred in our patients.

The tolerance of amiodarone by infants in this study was much better than in the experience with adult patients on amiodarone. Even with low-dose amiodarone, adverse effects were seen in approximately 4% of adults and discontinuation rates approach 25%. Two large, placebo-controlled studies of amiodarone in patients after myocardial infarction, the European Myocardial Infarction Amiodarone Trial and the Canadian Myocardial Infarction Amiodarone Trial noted similar rates of adverse effects and drug discontinuation. A meta-analysis of randomized low-dose amiodarone trials suggests that adverse pulmonary and thyroid effects are seen in approximately 2% and 4% of patients, respectively.

The use of amiodarone as primary therapy has been limited by the need for hospitalization during oral loading. In our 50 patients rhythm monitoring revealed no proarrhythmic effects or conduction abnormality during the loading period or during follow-up. Thus, once tachycardia is suppressed, outpatient completion of the load may be a reasonable approach to some patients. Our experience in these 50 infants would support this approach in selected patients. Since evaluation of these data we have shortened the routine hospital amiodarone-loading period to about 2 to 3 days unless a longer period is needed to achieve adequate tachycardia control.

The optimal choice of long-term pharmacologic treat-
ment of tachycardia in infants is controversial. Conventional medications such as digoxin or β-blocking agents are often used first. Digoxin is problematic because of questionable efficacy, delay in effect, and the possibility of increasing anterograde conduction in patients with Wolff-Parkinson-White syndrome. Identification of an effective medical strategy is crucial for it may obviate or delay the need for catheter intervention in infants and small children where the risks of the procedure are greater.

Many infants with supraventricular tachycardia have long quiescent periods after the first year of life, even in the absence of antiarrhythmic drugs. Thus antiarrhythmic medications may often be safely discontinued after the first year. A short-term course of amiodarone will provide excellent tachycardia control yet avoids the adverse effects that are typically seen only after several years of therapy. The smaller group of patients with refractory arrhythmias may require a longer course of drugs as a bridge to ablation.

This study did not provide a comparison group treated with other antiarrhythmic agents or treated with propranolol alone. In a previous study we found that propranolol was effective in only 55% of infants in whom it was used as a single agent for the treatment of supraventricular tachycardia. Therapy with digoxin, propranolol, or both has been reported to be effective in 64% and nadolol in 75% of children with supraventricular tachycardia. However, 38% of patients treated with nadolol had symptoms necessitating a medication change. Flecaïnide has been reported to control or partially control tachycardia in 84% of patients. Although side effects were uncommon, a proarrhythmic effect necessitating drug withdrawal was seen in 5 patients with Wolff-Parkinson-White syndrome. Propafenone was similarly efficacious, resulting in tachycardia control in 83% to 93% of children, and again proarrhythmic effects were seen. We report similar efficacy with the use of amiodarone alone or in combination with propranolol, but no proarrhythmic effects were seen in our patients. Additional limitations of this study include the lack of surveillance ophthalmologic and pulmonary screening in our patients. No definite symptoms or signs were observed, but routine ophthalmologic testing was not performed and chest radiographs not obtained unless therapy was needed for more than 1 year.

We found that amiodarone alone or in combination with propranolol controlled tachycardia in all infants. There were no side effects requiring drug withdrawal. No rhythm disturbances were seen during drug loading, suggesting that outpatient loading may be safe once tachycardia is suppressed. We conclude that amiodarone is an effective and safe therapy for tachycardia in infancy.

References


