Amiodarone Therapy for Drug-Refractory Fetal Tachycardia

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Background—Fetal tachycardia complicated by ventricular dysfunction and hydrops fetalis carries a significant risk of morbidity and mortality. Transplacental digoxin is effective therapy in a small percentage, but there is no consensus with regard to antiarrhythmic treatment if digoxin fails. This study evaluates the safety, efficacy, and outcome of amiodarone therapy for digoxin-refractory fetal tachycardia with heart failure.

Methods and Results—Fetuses with incessant tachycardia and either hydrops fetalis (n=24) or ventricular dysfunction (n=2) for whom digoxin monotherapy and secondary antiarrhythmic agents (n=13) were not effective were treated transplacentally with a loading dose of oral amiodarone for 2 to 7 days, followed by daily maintenance therapy for <1 to 15 weeks. Digoxin therapy was continued throughout gestation. Newborns were studied by transesophageal pacing or ECG monitoring to determine the mechanism of tachycardia. Three fetuses were delivered urgently in tachycardia during amiodarone loading, and 3 required additional antiarrhythmic agents for sustained cardioversion. Amiodarone or amiodarone combinations converted 14 of 15 (93%) with reentrant supraventricular tachycardia, 2 of 2 with ventricular or junctional ectopic tachycardia, and 3 of 9 (33%) with atrial flutter. Amiodarone-related adverse effects were transient in 5 infants and 8 mothers. Mean gestational age at delivery was 37 weeks, with 100% survival.

Conclusions—Orally administered amiodarone is safe and effective treatment for drug-refractory fetal tachycardia, specifically reentrant supraventricular tachycardia, junctional ectopic, or ventricular tachycardia, even when accompanied by hydrops fetalis or ventricular dysfunction. (Circulation. 2004;109:375-379.)

Key Words: tachycardia • atrial flutter • antiarrhythmia agents • fetus • amiodarone

Successful in utero cardioversion of sustained fetal tachycardia complicated by hydrops fetalis has improved to 60% to 85% with transplacental antiarrhythmic therapy,1-4 yet many centers with large series of patients have reported fetal and neonatal mortality as high as 8% to 30%.2-7 Potential contributing factors for high mortality include failure to achieve cardioversion with subsequent progression of hydrops fetalis, multiple interventional procedures, premature delivery, and possible proarrhythmia. Digoxin is the most common first-line antiarrhythmic agent for fetal tachycardia.1-8 If digoxin fails, there is no consensus on the most effective and safest secondary agent for tachycardia conversion. The present study reports our experience using amiodarone, a highly effective antiarrhythmic agent in children,9 for the treatment of drug-refractory tachycardia in the fetus with hydrops or myocardial dysfunction.

Methods

Between August 1990 and July 2002 at 5 Chicago-area hospitals (25 patients) and Utrecht, the Netherlands (1 patient), 26 fetuses (16 male, 10 female) under 36 weeks of gestation received amiodarone therapy using a uniform protocol for treatment of tachycardia. This represented all fetuses with hydrops for whom previous therapy had failed in 5 Chicago Hospitals in which, after 1991, amiodarone was used predominantly as second-line rather than third-line therapy; and in Utrecht (University Hospital), after publication of their sotalol experience in 2000, amiodarone was used for drug-refractory tachycardia. Some patients were referred to the Chicago hospitals after failure of second-line agents at other centers. No fetuses treated with amiodarone were excluded from this analysis. In all cases, both maternal and fetal records were reviewed. Twenty-four fetuses had hydrops fetalis, and 2 had ventricular dysfunction without hydrops. Ventricular dysfunction was identified when right or left ventricular shortening fraction measured <20% by echocardiogram, with atrioventricular (AV) valve regurgitation. Tachycardia was sustained for >12 hours without conversion or with only brief spontaneous conversions in all. Fetal tachycardia was defined as a fetal heart rate

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>200 bpm (either atrial or ventricular) and/or heart rate pattern or AV conduction pattern inconsistent with sinus rhythm (junctional tachycardia). The fetal tachycardia mechanism was diagnosed by standard echocardiographic and Doppler techniques, confirmed by ECG and transesophageal pacing (TEP) in the neonatal period. For 24 of 26 fetuses, digoxin therapy had failed (9 transplacental, 15 transplacental plus direct intramuscular digoxin), 1 fetus received only amiodarone (because of AV dissociation in tachycardia), and 1 sotalol-refractory fetus received digoxin after amiodarone initiation. Thirteen had been treated unsuccessfully with multiple antiarrhythmic medications, including verapamil in 5, quinidine in 5, flecainide in 4, and sotalol in 2.

During continuous inpatient cardiac telemetry and after informed consent, mothers were given oral loading doses of amiodarone 1800 to 2400 mg/d for 2 to 7 days, with single doses not exceeding 800 mg. This loading protocol was based on rapid oral loading protocols used at the time of initiation of the study for adult patients. Before amiodarone loading, the digoxin dose was decreased by 50%, and all other antiarrhythmic agents were discontinued. Serum chemistries and thyroid functions were serially monitored in mothers and later in infants. Maternal ECGs (daily during loading and regularly during follow-up) were used to assess cardiac effects of the drug. Amiodarone levels were not obtained routinely because they have not, in follow-up, been used at the time of initiation of the study for adult patients. Inpatient treatment continued until the fetus was predominantly in sinus rhythm and hydrops was resolving. The maintenance dose of amiodarone was selected to provide continued gradual loading with 800 mg/d for 1 week (if the tachycardia persisted) or decreased to the lowest effective dose necessary to sustain sinus rhythm, usually 200 to 400 mg/d. Criteria for transition from loading to maintenance included 1 or more of the following: (1) 7 days of loading at 1800 to 2400 mg/d, (2) conversion of fetal tachycardia >50% of the day, or (3) side effects (bradycardia, AV block, etc). Chronic amiodarone treatment was continued until hydrops resolved and tachycardia was quiescent for at least 3 weeks. Complete termination of amiodarone was achieved in some cases without reintiation of fetal tachycardia. Digoxin was continued until delivery. Patients were seen as outpatients weekly prenatally and at 1, 6, and 24 weeks postpartum.

A second antiarrhythmic agent was given after 8 to 15 days of amiodarone in 3 patients because of persistent fetal tachycardia and unresolved hydrops. Combined regimens included amiodarone/verapamil in 2 (verapamil to a maximum of 120 mg every 8 hours) and amiodarone/flecainide in 1 (flecainide to a maximum of 100 mg every 8 hours). Fetuses were delivered before sustained cardioversion or term gestation if there were maternal indications or fetal cardiac dysfunction with progression of hydrops. Eight fetuses were delivered at 30 to 37 weeks of gestation; 3 in tachycardia during amiodarone loading [progressive fetal ventricular dysfunction (n=1), premature rupture of membranes (n=1), or maternal toxemia (n=1)] and 5 in sinus rhythm during amiodarone maintenance [non reassuring heart rate variability patterns (n=1), premature rupture of membranes (n=3), or persistent ascites/foramen ovale stenosis (n=1)]. After delivery, antiarrhythmic therapy was withheld unless tachycardia recurred. Twenty-two of 26 infants underwent a TEP procedure2,13,14,15 within 1 week of delivery to determine the mechanism of tachycardia,14 assess residual amiodarone effect, and guide neonatal antiarrhythmic management. In 4 patients, Holter and telemetry monitoring was sufficient for mechanism assessment. Student’s t tests were used to determine differences in gestations at presentation or delivery (unpaired), and paired t tests were used to assess changes in ECG intervals in the mothers.

### Results

#### Fetal Tachycardia Presentation

Characteristics of fetal tachycardia at presentation are shown in Table 1. For fetuses having multiple mechanisms, the primary mechanism is listed in Table 1. Specific breakdown of mechanisms is listed in the section on neonatal ECG findings. Gestational ages at presentation did not differ with tachycardia mechanism.

#### Response to Therapy

Drug efficacy is outlined in Table 2 for the 26 fetuses. Treatments listed were amiodarone and digoxin; amiodarone alone; or amiodarone, digoxin, and a third agent. Mean time to conversion was 6 days (range, 2 to 21 days). Two patterns of conversion were observed during fetal tachycardia. The most common was a gradual decline in tachycardia rate before termination. In 2 fetuses, an abrupt and permanent conversion occurred within 3 days without significant rate decline. Mean cumulative amiodarone dose at load end (7 days) was 12.3 g (range, 8.4 to 16.8 g). The duration of in utero therapy ranged from 1 to 15 weeks (mean, 34 days). Amiodarone was discontinued for quiescent tachycardia (n=9) an average of 4 weeks before delivery. Recurrence of fetal tachycardia occurred in 1 patient 3 weeks after discontinuation. One fetus treated with amiodarone did not convert until digoxin was added to the regimen. Mean time to resolution of hydrops was 11 days (range, 2 to 56 days).

#### Indications for and Mode of Delivery

All fetuses and infants survived. Prematurity (<37 weeks gestation) was 31%. Mean gestation for those on maintenance treatment during in utero therapy was 34 weeks (range, 31 to 39 weeks). Mean birth weight was 1920 g (range, 1400 to 2375 g). Mean age at delivery was 37 weeks (range, 23 to 42 weeks). Atrial rates, bpm

<table>
<thead>
<tr>
<th>Condition</th>
<th>AVRT</th>
<th>AF</th>
<th>VT</th>
<th>JET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>214–316</td>
<td>130–260</td>
<td>240–250</td>
<td>135–180</td>
</tr>
<tr>
<td>Mean</td>
<td>262</td>
<td>183</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Mean age at presentation, wk</td>
<td>29</td>
<td>27</td>
<td>31</td>
<td>23</td>
</tr>
<tr>
<td>Ventricular rates, bpm</td>
<td>214–316</td>
<td>130–260</td>
<td>240–250</td>
<td>135–180</td>
</tr>
<tr>
<td>Atrial rates, bpm</td>
<td>262</td>
<td>378</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Range</td>
<td>214–316</td>
<td>260–500</td>
<td>130 sinus/450 AF</td>
<td>130–155</td>
</tr>
</tbody>
</table>

AVRT indicates atrioventricular reciprocating tachycardia; AF, atrial flutter; VT, ventricular tachycardia; and JET, junctional ectopic tachycardia.

#### TABLE 2. Response to Digoxin and Oral Amiodarone Therapy or Amiodarone Combinations

<table>
<thead>
<tr>
<th></th>
<th>AVRT</th>
<th>AF</th>
<th>VT</th>
<th>JET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivered during amio loading</td>
<td>1/15</td>
<td>2/9</td>
<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td>Conversion: Amio + dig or amio alone</td>
<td>11/15 (73%)</td>
<td>3/9 (33%)</td>
<td>1/1 (100%)</td>
<td>1/1 (100%)</td>
</tr>
<tr>
<td>Conversion: Amio + dig + verapamil or flecainide</td>
<td>3/15 (20%)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Total converting with treatment</td>
<td>14/15 (93%)</td>
<td>3/9 (33%)</td>
<td>1/1 (100%)</td>
<td>1/1 (100%)</td>
</tr>
</tbody>
</table>

Values are n/total n treated (% success). Amio indicates amiodarone; dig, digoxin. Other abbreviations as in Table 1.
amiodarone was 37 weeks (range, 30 to 41 weeks) and for those delivered prematurely, 35 weeks (range, 33 to 37.5 weeks). There were no differences in the gestational ages at delivery between fetuses with supraventricular tachycardia (SVT) or atrial flutter (39 versus 37 weeks, respectively, \( P=0.5 \)). The cesarean section rate in premature fetuses was 100%, and in the term group, 16%. Mean birth weight was 3.2 kg (range, 1.6 to 4.0 kg).

### Maternal and Fetal Adverse Side Effects

Side effects related or potentially related to amiodarone are summarized in Table 3. Side effects serious enough to withdraw amiodarone were encountered in 1 mother with a photosensitivity dermatitis and thrombocytopenia (minimum platelet count, 55,000). One mother with normal thyroid function during the treatment period developed hypothyroidism 6 months postpartum requiring thyroid supplementation. In limited cases in which amiodarone serum levels were obtained, low or low-therapeutic values were noted. Thyroid functions derived from cord blood at delivery were normal in all except 5 infants. These 5 had a mean TSH of 26 IU, all except 5 infants. These 5 had a mean TSH of 26 IU.

#### Maternal and Neonatal ECG/Rhythm Characteristics and Side Effects With Digoxin and Oral Amiodarone or Amiodarone Combinations

<table>
<thead>
<tr>
<th>Maternal</th>
<th>Pre</th>
<th>Load</th>
<th>Maintenance</th>
<th>Neonatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECGs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>83±10</td>
<td>74±11*</td>
<td>75±10*</td>
<td>139±27</td>
</tr>
<tr>
<td>PR, ms</td>
<td>146±19</td>
<td>162±25*</td>
<td>168±15*</td>
<td>127±28</td>
</tr>
<tr>
<td>QRS, ms</td>
<td>81 ±6</td>
<td>88±10*</td>
<td>93±11*</td>
<td>65±13</td>
</tr>
<tr>
<td>QTc, ms</td>
<td>419±19</td>
<td>429±27</td>
<td>436±31</td>
<td>412±28</td>
</tr>
<tr>
<td>WPW</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>2</td>
</tr>
<tr>
<td>RAE/BAE</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>14</td>
</tr>
<tr>
<td>ST depression</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>4</td>
</tr>
<tr>
<td>Rhythm findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>First-degree AVB</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Mobitz I second-degree AVB</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>QTc prolongation &gt;500 ms</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin rash/thrombocytopenia</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

AVB indicates atrioventricular block; Load, amiodarone loading phase; Maintenance, amiodarone maintenance phase; ms, milliseconds; Pre, before amiodarone initiation; RAE/BAE, right or biatrial enlargement; and WPW, Wolff-Parkinson-White before excitation.

*\( P<0.05 \) vs pretreatment ECG.

### Neonatal Electrophysiological Findings

Mechanisms of tachycardia were because of accessory AV connections with manifest Wolff-Parkinson-White syndrome in 2, concealed accessory connections in 13, atrial flutter with concealed accessory AV connections in 2, atrial flutter alone in 7, junctional ectopic tachycardia in 1, and ventricular tachycardia with intermittent AV block and atrial flutter in 1. Two fetuses with atrial flutter in utero were noninducible at TEP and had no clinical tachycardia. Postnatal antiarrhythmic therapy was given to 19 of 26 infants on the basis of clinical recurrence (13 patients) or TEP findings (6 patients). In 11 of
19, the regimen ultimately included reinitiation of amiodarone.

Discussion
In this study, 14 of 15 fetuses in heart failure secondary to SVT and 2 of 2 with ventricular or junctional tachycardia converted to sustained sinus rhythm when treated with amiodarone or combination regimens including amiodarone. All 26 fetuses were delivered alive, with no serious sequelae of prematurity. Side effects of amiodarone were transient and precluded continued administration in only 1 of 26 mothers. These results support the use of amiodarone for the hydropic fetus with reentrant SVT refractory to transcplacental and direct intramuscular digoxin. Amiodarone successfully treated fetal SVT even when multiple other antiarrhythmic agents had failed.

Amiodarone Efficacy and Safety
Although direct comparison with other studies conducted at different institutions and over differing time periods is not possible, some review of published experience with fetal tachycardia management is warranted. Several agents have been suggested as first- or second-line therapy for fetal tachycardia with hydrops, but no agent has been shown to be consistently effective and safe. Few agents have been used in combinations other than with digoxin. Two antiarrhythmic agents currently thought to be highly successful in fetal cardioversion have significant associated mortality rates under certain circumstances. Sotalol, a class III agent with β-blocker activity, converted 40% to 60% of hydropic fetuses with SVT, but with a 25% to 30% mortality.4,7 Similarly, flecainide has a 60% to 85% efficacy but up to 18.5% mortality for refractory fetal tachycardia associated with hydrops.2,3,15-17 Jouannic et al18 reported sudden death in 1 fetus with mild ascites and normal ventricular function within 12 hours of initiation of flecainide and another with hemodynamic deterioration necessitating delivery. Oudijk et al4 also reported similar sudden demise shortly after initiation or dose increase for sotalol. These experiences directly contrast with the present study, in which all hydropic fetuses survived. Although ECG effects were noted postnataally, profound bradycarrhythmias necessitating emergent delivery or severe conduction defects, such as reported with flecainide,17 were not noted.

Amiodarone has been shown in many pediatric studies9,19-22 and in anecdotal accounts in the fetus18,23-26 to be highly efficacious when other drugs have failed. Crossover efficacy for amiodarone for reentrant SVT was seen in this series and has been reported in other fetal studies for both flecainide and sotalol response failures.18,25,26 Some investigators have advocated partial SVT control when slowing of the rate results in a triphasic venous flow pattern.15 However, in this series, progression of hydrops fetalis in the setting of partial control necessitated alternative effective drug therapy with amiodarone.

Other Management Strategies
Enhancing Conversion
In addition to the selection of amiodarone treatment, other factors may have contributed to fetal survival. An intramuscular rather than intracordal route of direct fetal digoxin administration was used.27 The authors have reported more rapid conversion of SVT with intramuscular digoxin administration than with maternal administration alone in the hydropic fetus.27 Cardiac arrest and negative inotropic effects with intracordal administration of drugs have been reported previously, including with amiodarone,3 as has death caused by cord injury.28 Finally, a third agent in addition to amiodarone and digoxin was used for cardioversion in 3 patients with SVT rather than accepting partial control or very premature delivery.

Pharmacodynamics
The transplacental transfer characteristics of amiodarone in the fetus have been controversial.29-31 Limited transplacental transfer has been reported. The antiarrhythmic action of amiodarone and its active metabolites is complex and does not lend itself to easy analysis because of its delayed accumulation and tissue deposition. This study suggests that oral maternal administration of amiodarone results in a fetal heart rate effect presumably as a result of transplacental transfer of amiodarone and its active metabolites. Acute risk to the fetus was reduced compared with direct intracordal administration. Similarly, risk of maternal and fetal hypotension from maternal intravenous amiodarone administration was also avoided. Time to conversion with oral amiodarone was similar in this study to that reported for sotalol and flecainide.3,15

Side Effects
Prolonged fetal exposure to amiodarone has been reported to cause biochemical and rare clinical hypothyroidism and possible fetal growth retardation.29-32 Because it was used for <15 weeks, the maternal and fetal exposure to amiodarone was shorter than with previous reports. Transient biochemical hypothyroidism was detected in 5 infants, but only 1, who received chronic postnatal amiodarone therapy, required treatment. One mother developed hypothyroidism 6 months postpartum; however, it is unlikely that this was caused by amiodarone treatment.

It is difficult to compare ECG results in this study with results from previous series of antiarrhythmic therapy, because detailed maternal and neonatal ECG findings associated with in utero tachycardia treatment in larger series of patients have not been published. Some mild increase in conduction intervals and reduction in rate were noted with amiodarone. In anecdotal accounts and in our experience, rare instances of right bundle-branch block (maternal, neonatal, or both) and marked QT prolongation have been observed with flecainide (Reference 17 and Cuneo, personal communication). These marked ECG changes were not observed in this series. In a review of amiodarone treatment during pregnancy, Widerhorn et al13 reported sinus bradycardia in 3% of neonates and prolonged QT interval in 9%, but these fetuses had been exposed throughout pregnancy.

Efficacy of Amiodarone for Atrial Flutter
Although safe and efficacious for the treatment of SVT and ventricular and junctional tachycardia, amiodarone was
poorly effective in terminating atrial flutter. Oudijk et al4 have demonstrated 80% conversion with sotalol, or sotalol and digoxin, with no mortality in the atrial flutter group. Flack et al20 reported conversion of atrial flutter using amiodarone given by triple-route administration (intracardial, intraperitoneal, and transplacental) in 1 fetus with sotalol-refractory atrial flutter; however, transplacental administration alone did not seem sufficient.

Limitations of the Study
Limitations of this study include its long duration, necessitating retrospective chart analysis, and the involvement of multiple institutions. Because of the rarity of drug-refractory fetal tachycardia with hydrops fetalis, no single institution is likely to accumulate large numbers of patients. Direct comparisons with other studies are of limited value when they represent care over different time periods.

In summary, fetal tachycardia complicated by hydrops or ventricular dysfunction can be treated safely and effectively in utero even in drug-refractory cases. Assessment of the mechanism of fetal tachycardia, perhaps facilitated by the newer techniques of magnetocardiography34 and tissue velocity imaging,35 may help in choice of medication. Amiodarone seems to have low associated fetal mortality and excellent efficacy for treatment of SVT, junctional tachycardia, and ventricular tachycardia in the hydropic fetus. Its administration should be monitored by a team of clinical specialists with experience in arrhythmia management and familiarity with the side effect profile of amiodarone.

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References
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