Intravenous Amiodarone for Incessant Tachyarrhythmias in Children

A Randomized, Double-Blind, Antiarrhythmic Drug Trial

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Background—Intravenous (IV) amiodarone has proven efficacy in adults. However, its use in children is based on limited retrospective data.

Methods and Results—A double-blind, randomized, multicenter, dose-response study of the safety and efficacy of IV amiodarone was conducted in 61 children (30 days to 14.9 years; median, 1.6 years). Children with incessant tachyarrhythmias (supraventricular arrhythmias [n=26], junctional ectopic tachycardia [JET, n=31], or ventricular arrhythmias [n=4]) were randomized to 1 of 3 dosing regimens (low, medium, or high: load plus 47-hour maintenance) with up to 5 open-label rescue doses. The primary efficacy end point was time to success. Of 229 patients screened, 61 were enrolled during 13 months by 27 of 48 centers in 7 countries. Median time to success was significantly related to dose (28.2, 2.6, and 2.1 hours for the low-, medium-, and high-dose groups, respectively; P=0.028). There was no significant association with dose for any arrhythmia subgroup, including JET, but the subgroups were too small for an accurate assessment. Adverse events (AEs) were common (87%), leading to withdrawal of 10 patients. There were 5 deaths in the 30-day follow-up period (2 possibly related to the study drug). Dose-related AEs included hypotension (36%), vomiting (20%), bradycardia (20%), atrioventricular block (15%) and nausea (10%).

Conclusions—In children, the overall efficacy of IV amiodarone, as measured by time to success, was dose related but not significantly for any arrhythmia subgroup. AEs were common and appeared to be dose related. Although efficacious for critically ill patients, the dose-related risks of IV amiodarone should be taken into account when treating children with incessant arrhythmias. Prospective, placebo-controlled trials would be helpful in assessing antiarrhythmic drug efficacy in children, because their results may differ from retrospective series and adult studies. (Circulation. 2005;112:3470-3477.)

Key Words: arrhythmia ■ atrioventricular node ■ drugs ■ heart defects, congenital ■ pediatrics

Intravenous (IV) amiodarone hydrochloride (HCl) has proven efficacy for the treatment of a variety of ventricular and supraventricular arrhythmias (VAs and SVAs) in adults.1-14 The available data in the literature for children, from a total of ∼65 patients, suggest that the drug is reasonably safe and effective for a variety of VAs and SVAs, including postoperative junctional ectopic tachycardia (JET).1,7-9 However, all prior studies have been unblinded and uncontrolled, leaving the possibility of bias. Furthermore, despite the fact that the commercially available preparation of IV amiodarone (Cordarone, Wyeth Pharmaceuticals) is known to cause significant hypotension in animals13 and adult humans,4 most of the studies in children have reported minimal hypotensive side effects.1,5-9 Consequently, this study was designed to address the efficacy and safety of amiodarone IV in a clinical trial. Because the available uncontrolled reports on amiodarone IV have noted far greater benefit than risk, investigators believed it was unethical to include a placebo in the trial. Given this limitation, this study was designed as a double-blind, dose-response trial without a placebo group. The primary objective of this study was to compare the efficacy...
and safety of 3 dose regimens of IV amiodarone in patients 30 days to 16 years old with critical arrhythmias.

Methods

The study was a randomized, multicenter, double-blind, parallel-group, dose-response, safety, efficacy, and pharmacokinetic (PK) study of 61 children aged 30 days through 16 years. A total of 48 centers from the United States, South America, and South Africa (Appendix in the Data Supplement) participated in the study. Human studies review groups at each participating center approved the study. Written, informed consent was obtained from the parent or legal guardian of each subject, and where appropriate, written assent was obtained from the study participant. The study design, including the selection of the patient population and dose regimens, was as outlined in a written request from the US Food and Drug Administration (FDA).

Inclusion and Exclusion Criteria

Patients aged 30 days through 16 years with ECG documentation of any incessant SVA and/or VA or with JET if the junctional rate was ≥50th percentile of heart rate for age were eligible for the study. “Incessant” was defined as persistent tachyarrhythmia with no intervals of sinus rhythm ≥30 seconds in the 30 minutes before administration of blinded drug therapy. Weight limits were 2 to 75 kg inclusive. Exclusion criteria included (1) use of amiodarone in the prior 3 months, (2) conditions or other drug use known to have important interactions with amiodarone, (3) imminent death, and (4) intentional hypothermia to ≤35°C to treat the arrhythmia ≤3 hours before study drug initiation. Concomitant antiarrhythmic drug administration was allowed, so long as the other agent(s) remained at a constant delivery rate for the 1-hour periods before and after study drug initiation and subsequently remained constant or decreased.

Study Drug

Patients were allocated to receive 1 of 3 blinded dose regimens of IV amiodarone for 48 hours in equally divided groups (Figure 1). The randomization was stratified by arrhythmia diagnosis (VA, SVA, or JET). Drug dosages were based on the prior literature with a 1, 5, and 10 mg/kg load during the first hour plus a 2, 5, and 10 mg · kg⁻¹ · d⁻¹ maintenance dose during the subsequent 47 hours for low-, medium-, and high-dose groups, respectively. All loading regimens occurred during the first study hour in 4 infusions given every 15 minutes over 10 minutes. Because of concerns about amiodarone causing plastic to leach from the IV tubing at low drug administration rates, all maintenance administration was given as a series of equally divided boluses, each infused every 2 hours over 10 minutes. Thus, the maximum bolus dose was 0.83 mg/kg, comparable to the doses used currently when amiodarone is administered by a clinician at the bedside. Drug concentrations were varied accordingly to maintain blinding. Up to 5 open-label rescue doses of 1 mg/kg could be administered beginning at minute 70 of the study, at the discretion of the investigator.

The low-dose loading regimen of 1 mg/kg was administered as a single dose of 1 mg/kg given over the first 10 minutes of the load, followed by 3 placebo infusions, whereas the medium- and high-dose loading regimens were divided into 4 equal doses over the first study hour. Investigators were encouraged to administer rescue boluses only when clinically necessary and to allow the patient to remain in the study through the 47-hour maintenance phase, regardless of drug effect, so long as safety was not compromised. Transient hypotension could be treated as needed clinically and the patient could still remain in the study so long as the study drug administration followed the protocol.

AE/Safety Monitoring

All patients who received at least 1 dose of the study drug were monitored for 30 days for adverse events (AEs) and safety. Safety blood samples drawn before and periodically during the study included electrolytes, a complete blood count, and thyroid, renal, and liver profiles. Heart rate, ECG, and blood pressure changes were monitored during drug administration for AEs. Hypotension and bradycardia during loading were also classified according to whether or not they had potential clinical significance, defined as a systolic blood pressure fall of ≥20 mm Hg, a diastolic blood pressure fall of ≥10 mm Hg, and a heart rate fall to ≤50th percentile for age.

PK Evaluation

PK studies were performed at US sites only. Blood samples (0.5 mL) for assessment of amiodarone HCl and desethylamiodarone (DEA) levels were to be taken from all patients during the loading phase and from patients who had not received any open-label amiodarone (rescue or outside the study protocol) during the maintenance and washout phases of the study. Loading-phase samples were drawn before administration of the first study drug bolus and immediately (1) at completion of the first bolus (10 minutes), (2) before administration of the final bolus (45 minutes), (3) at completion of the final bolus (55 minutes), and (4) before initiation of the maintenance infusion (120 minutes). Maintenance-phase samples were drawn immediately (1) before dosing at 8 and 24 hours, (2) before the last maintenance phase, and (3) before initiation of any open-label amiodarone. Washout-phase samples were drawn (1) immediately after the last study drug dose and (2) at trough levels at 2 hours (±15 minutes), 4 hours (±30 minutes), 8 hours (±60 minutes), 24 hours (±3 hours), 72 hours (±10 hours), 7 days (±1 day), 15 days (±2 days), and 30 days (±4 days).

Data Analysis

Efficacy

Analysis for the intention-to-treat (ITT) population, which included all randomly assigned patients (n=61) who had received at least 1 loading dose of the study medication, is presented in this report. Individual patients were considered to have a protocol success at the time they either (1) returned to sustained “sinus” rhythm for ≥10 minutes or (2) for JET patients, had a reduction in heart rate to ≤180 bpm and the heart rate was 20% lower than baseline for ≥10 minutes, both without any 30-second period of arrhythmia.

The study had 2 primary end points. One was the traditional time to success for the ITT population. It was anticipated that the use of rescue boluses would confound assessment of the dose response by reducing the differences in the actual administered dose; thus, a composite end point combining the time to success with the time-to-rescue-bolus was also defined as a primary end point.

Secondary end points included that proportion of patients who had arrhythmia termination, at least 1 rescue bolus, recurrent arrhythmia after initial success, or arrhythmia recurrence requiring rehospitalization, and the number of rescue boluses.

Pharmacokinetics

Concentrations of amiodarone and DEA were used to characterize the PK profile for the 3 dose regimens. For all patients with PK data,
the following parameters were estimated: (1) Peak and trough concentrations ($C_{\text{max}}$ and $C_{\text{min}}$) during the loading phase, (2) average concentrations ($C_{\text{avg}}$) during the maintenance phase according to the areas under the concentration-time curves from an 8-hour time point to the last sampling point $t$ during maintenance administration (AUC$_{\text{t}}$) divided by the interval of 8 hours to $t$. These parameters were also assessed for any dose effect. For patients who did not receive a rescue bolus and were not switched over to open-label amiodarone at the end of study drug treatment, the terminal disposition PK characteristics were assessed by (1) the rate constant ($\lambda$) obtained from a monoexponential regression of the last 4 concentration points and (2) the half-life ($t_{1/2}$), calculated as $t_{1/2} = \ln(2)/\lambda$.

Amiodarone clearance and its possible association with age were also assessed.

### Statistical Considerations

By assuming a proportional-hazards model with 30% and 80% treatment successes in the low- and high-dose groups, respectively, and 20 patients per group, we found that the study had $\sim \text{80\%}$ power to detect a statistically significant dose-related trend ($\alpha=0.05$, 2 side; hazard ratios of $\sim 1.9$ and 4.5, respectively). For the time to success and other time-related end points, the distributions of these times were estimated by Kaplan-Meier methods.\textsuperscript{5} Dose response was analyzed by a proportional-hazards model\textsuperscript{6–10} with loading dose as the independent variable and arrhythmia type as a stratification variable and an interaction term to assess differential dose effect by arrhythmia subtype. Tests for trends on categorical variables were done with Cochran-Mantel-Haenszel tests\textsuperscript{3} and on continuous variables with a general linear model. The effect of arrhythmia type (SVA and JET only) on the dose response for time to success was also assessed with the proportional-hazards model. A separate evaluation was not done for the VA group because it contained only 4 patients. Unless specified otherwise, data are reported as mean±SD. For all evaluations, a probability value of $<0.05$ was considered statistically significant. All calculations were done with SAS software (SAS Institute, Inc; SAS/STAT User’s Guide, version 8).

### Results

#### Subjects and Enrollment

A total of 221 patients were screened by 48 participating centers, resulting in randomization of 61 patients from 27 centers during a period of 13 months, yielding an enrollment rate of just under 0.1 patients per center per month. Screen failures occurred for a variety of reasons, including young age and an unstable medical condition requiring immediate treatment. Just over half of the randomized patients had an arrhythmia diagnosis of JET, whereas 42% had an SVA and 4 patients had a VA. The study population had a broad range of ages and weights (Table 1).

Of the 61 patients, 36 completed the 48-hour blinded phase, and 25 were withdrawn from the blinded phase for the following reasons: 10 because of AEs, 10 for lack of efficacy after receiving at least 1 rescue bolus, and 5 at the discretion of the investigator or sponsor. Of the 41 patients who met the primary end point, 20 patients did not have a documented, continuous 10-minute ECG rhythm strip. These patients had conversions verified through a shorter ECG strip and/or physician and chart confirmation of the 10-minute rhythm, which was thought to be diagnostically adequate in every case, despite not meeting the exact criteria in the original protocol.

#### Concurrent Cardiac Disease

The majority of patients (n=43, 71%) had concurrent cardiac disease contributing to their arrhythmias (Table 2). Congenital heart disease, cardiomyopathy, and preexcitation were the most frequent associated cardiac conditions. Furthermore, in

### Table 1. Demographic and Baseline Characteristics by Dose Regimen

<table>
<thead>
<tr>
<th>Characteristic Variable</th>
<th>Low (n=19)</th>
<th>Medium (n=20)</th>
<th>High (n=22)</th>
<th>Total (N=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JET</td>
<td>9 (47.4)</td>
<td>10 (50.0)</td>
<td>12 (54.5)</td>
<td>31 (50.8)</td>
</tr>
<tr>
<td>SVA</td>
<td>9 (47.4)</td>
<td>9 (45.0)</td>
<td>8 (36.4)</td>
<td>26 (42.6)</td>
</tr>
<tr>
<td>VA</td>
<td>1 (5.3)</td>
<td>1 (5.0)</td>
<td>2 (9.1)</td>
<td>4 (6.6)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>4.3±5.1</td>
<td>3.9±4.6</td>
<td>4.1±4.8</td>
<td>4.1±4.7</td>
</tr>
<tr>
<td>Median</td>
<td>1.7</td>
<td>1.5</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Minimum–maximum</td>
<td>0.2–13.8</td>
<td>0.1–14.9</td>
<td>0.1–13.9</td>
<td>0.1–14.9</td>
</tr>
<tr>
<td>Weight, kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>18.3±17.1</td>
<td>16.7±17.5</td>
<td>16.0±14.7</td>
<td>16.9±16.2</td>
</tr>
<tr>
<td>Median</td>
<td>10.8</td>
<td>10.3</td>
<td>9.2</td>
<td>10.2</td>
</tr>
<tr>
<td>Minimum–maximum</td>
<td>4.0–62.2</td>
<td>3.1–75.0</td>
<td>3.4–51.9</td>
<td>3.1–75.0</td>
</tr>
<tr>
<td>Total dose during blinded phase, mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>6.2±2.9</td>
<td>14.2±4.3</td>
<td>24.9±9.4</td>
<td>15.6±10.0</td>
</tr>
<tr>
<td>Minimum–maximum</td>
<td>0.50–10.08</td>
<td>5.42–20.08</td>
<td>7.50–34.92</td>
<td>0.50–34.92</td>
</tr>
<tr>
<td>Geographic location, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>8 (42.1)</td>
<td>12 (60.0)</td>
<td>12 (54.5)</td>
<td>32 (52.5)</td>
</tr>
<tr>
<td>Non-US</td>
<td>11 (57.9)</td>
<td>8 (40.0)</td>
<td>10 (45.5)</td>
<td>29 (47.5)</td>
</tr>
</tbody>
</table>

Abbreviations are as defined in text.
37 patients (61%), the qualifying arrhythmia occurred in the immediate postoperative period after congenital heart surgery, including 28 of 31 patients with JET (90%).

Concomitant Medications
All patients were receiving at least 1 concomitant medication, with most receiving >1, reflecting the severity of the patients’ conditions. The most common concomitant medications were dopamine (49%), furosemide (48%), digoxin (43%), milrinone (33%), captopril (21%), dobutamine (20%), and epinephrine (16%).

Treatment Compliance
A total of 3 patients were administered the incorrect dose of study drug. Two patients received an overdose of study drug (123% and 106%) based on incorrect body weight measurements, and 1 patient was underdosed by 50% as a result of a drug administration error.

Efficacy Evaluation
Primary End Point
Time to Success
The median time to success for the low-, medium-, and high-dose groups was 28.2, 2.6, and 2.1 hours, respectively, with a statistically significant dose relation such that a higher dose was associated with a shorter time to success (hazard ratio = 1.103; 95% confidence interval, 1.011 to 1.205; P = 0.028; Figure 2). Early responders were seen during and just after the loading phase in all 3 dose groups, with the largest frequency of response occurring in the medium- and high-dose groups, and a very low response rate in the low-dose group. This early difference among groups was maintained throughout the remainder of the study; however, as rescue boluses and maintenance therapy were given, responses in the low-dose group narrowed the difference among the groups during the first 30 study hours. A total of 20 patients did not reach this efficacy end point, 13 because of early withdrawal and 7 who completed the 48-hour study period without efficacy.

Composite-Rank End Point
This composite end point was not statistically significant (P = 0.231) for the overall group and was thought not to be clinically relevant to the analysis. Consequently, for brevity, it is not discussed further in this report.

Secondary End Points
Outcome Status
Outcome status is presented in Table 3. At the completion of the study, there were fewer successes in the low-dose group (47%) relative to the medium- (80%) and high- (73%) dose groups, but there was no statistically significant trend. At the end of the loading dose, there appeared to be increased success in the high-dose group (41%) compared with the medium- and low-dose groups (25% and 16%, respectively; P = 0.083), but the difference did not reach statistical significance. In general, the numbers of premature withdrawals were comparable among the 3 groups (5, 3, and 5 in the low-, medium-, and high-dose groups, respectively).

Table 2: Concurrent Cardiac Disease by Arrhythmia Type

<table>
<thead>
<tr>
<th>Arrhythmia</th>
<th>Congenital Heart Disease</th>
<th>Cardiomyopathy</th>
<th>Preexcitation</th>
<th>Postsurgical</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>43</td>
<td>7</td>
<td>4</td>
<td>37</td>
<td>12</td>
</tr>
<tr>
<td>JET</td>
<td>28</td>
<td>0</td>
<td>0</td>
<td>28</td>
<td>3</td>
</tr>
<tr>
<td>SVA</td>
<td>13</td>
<td>4</td>
<td>3</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>VA</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations are as defined in text. Patients may have had >1 concurrent cardiac disease.

Table 3: Efficacy and Patient Status by Dose Group

<table>
<thead>
<tr>
<th>Results</th>
<th>Low (n=19)</th>
<th>Medium (n=20)</th>
<th>High (n=22)</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful at 70 minutes, n (%)</td>
<td>3 (15.8)</td>
<td>5 (25.0)</td>
<td>9 (40.9)</td>
<td>0.083</td>
</tr>
<tr>
<td>Successful at end of study, n (%)</td>
<td>9 (47.4)</td>
<td>16 (80)</td>
<td>16 (72.7)</td>
<td>0.155</td>
</tr>
<tr>
<td>Completed 48 hours without success, n</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>Premature withdrawal for AE, n</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>...</td>
</tr>
<tr>
<td>Withdrawal for lack of efficacy, n</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>...</td>
</tr>
<tr>
<td>Withdrawal, investigator discretion, n</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>...</td>
</tr>
</tbody>
</table>

Abbreviations are as defined in text.
Rescue Bolus and Recurrence Related End Points

There was no dose-response relation (Table 4) for the administration of rescue boluses. The percentage of arrhythmia-free hours during the total blinded phase increased with dose, nearly reaching significance \( (P = 0.053) \). This finding is consistent with the shorter time to success at higher doses, because the earlier successes should have yielded a longer arrhythmia-free period. No patient was rehospitalized for arrhythmia recurrence during the 30-day follow-up period.

Arrhythmia Subtypes Analysis: JET and SVA

There was no significant interaction between arrhythmia type and dose response (Figure 3 and Table 5; \( P = 0.862 \)), suggesting that the dose response in both SVA and JET was similar to the overall group response. However, when the 2 subgroups were analyzed independently, no significant dose response could be demonstrated for either SVA or JET (Figure 3). Interestingly, in all dose groups, the JET patients had a high rate of success during the blinded portion of the study, ranging from 67% (low dose) to 83% (high dose) (Table 5). Alternatively, for SVA, the conversion rates were more scattered, ranging from 33% (low dose) to 89% (medium dose), again with no clear relation to dose for the conversion rate or time to success (Table 5).

Safety Evaluation

Total exposure to amiodarone during the blinded phase of the study (study drug plus open-label IV rescue boluses) ranged from 6 to 25 mg/kg (Table 1). AEs (Table 6 and Table 7) occurred in 87% of patients, ranging between 80% and 91% for the 3 dose groups. A wide variety of AEs from multiple organ systems was reported. The number of AEs in each group was too small for an accurate statistical analysis; however, only 5 AEs appeared to be both dose related and occurred in \( > 1 \) patient: Hypotension (36.1%), vomiting (19.7%), bradycardia (19.7%), atrioventricular block (14.8%), and nausea (9.8%) (Table 6). Most of these events occurred within 4 hours, when there was the clearest separation of dose and success among the groups.

A total of 24 patients (39.3%) reported at least 1 significant AE during the study, but only hypotension, bradycardia, and atrioventricular block appeared to be both dose related and occurred in \( > 1 \) patient (Table 6). The rate of clinically significant changes in heart rate and blood pressure during loading, as defined in Methods, appeared to be dose related (Table 7). A total of 10 patients were withdrawn for significant safety issues: 4 for hypotension, 5 for bradycardia, and 3 for atrioventricular block. These withdrawals appeared to be dose related, occurring in 1, 4, and 5 patients from the low-, medium-, and high-dose groups, respectively. There were no dose-related changes in any of the laboratory parameters, including hepatic (alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase), thyroid (reverse triiodothyroxine, triiodothyroxine, thyroxine, thyroid-stimulating hormone), and renal (creatinine, blood urea

![Figure 3. Time to success for arrhythmia subgroups of JET and SVA. No interaction of subgroup and dose was present \( (P = 0.862) \). Abbreviations are as defined in text.](http://circ.ahajournals.org/)

<table>
<thead>
<tr>
<th>TABLE 4. Other Secondary End Points by Dose Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results</td>
</tr>
<tr>
<td>Dose Group</td>
</tr>
<tr>
<td>Rescue bolus related</td>
</tr>
<tr>
<td>Bolus required, n (%)</td>
</tr>
<tr>
<td>No. of boluses*</td>
</tr>
<tr>
<td>Recurrence related</td>
</tr>
<tr>
<td>Recurrent arrhythmias during blinded phase, n (%)</td>
</tr>
<tr>
<td>Blinded phase arrhythmia-free hours (proportion of 48 hours, %)</td>
</tr>
<tr>
<td>Hospitalization for arrhythmias during 30-d follow-up, n</td>
</tr>
</tbody>
</table>

*Average includes zero for patients not receiving a bolus.
nitr bearing the any time on through 30 days. Of the 20 patients who underwent peripheral IV study drug administration, 5 (25%) developed phlebitis.

**Deaths**

There were 5 deaths during the 30-day follow-up period. All of the deaths were considered by the investigators to be unrelated to the study protocol or medication; however, 2 of the deaths (1 in the medium-dose and 1 in the high-dose group) occurred within 24 hours of significant, hypotensive AEs that, in review of the data, could have been related to study drug and may have contributed to the patients’ subsequent death.

**Pharmacokinetics**

The PK evaluation was planned for patients enrolled in the United States only (n=32) or Canada (n=0). Of the 32 patients, 3 were excluded for acquisition or technical issues. Four of the remaining 29 patients completed PK sampling for the loading-dose, maintenance, and washout phases. The remaining 25 patients all had loading-phase data, whereas a few had maintenance data and none had washout data.

There was a dose-related increase in Cmax, Cavg, and the area under the curve, which, when normalized for dose, demonstrated no significant effect of dose on PK properties (Figure 4). The maximum concentration during loading occurred at 10±0 minutes for the low dose and 50±14 minutes for both the medium and high doses. Although samples were available for only a few patients who completed the maintenance phase, it was clear that there was a rapid drop in amiodarone concentrations (Figure 5) and a slow increase in DEA trough levels (not shown) soon after the loading-dose and initiation of the reduced dose for maintenance. In fact, amiodarone concentrations during the maintenance phase were consistently <1 μg/mL for even the high-dose protocol. For the 3 patients with complete washout-phase data, the amiodarone t1/2 values were 9.3, 6.9, and 11.4 days (Figure 6, right). Finally, there was a strong trend toward an increase in dose-normalized Cavg with age (P=0.06, Figure 6, left), suggesting a decrease in clearance of the drug from the plasma with age.

**Discussion**

This study is the first randomized, double-blind, therapeutic trial of an antiarrhythmic drug performed in a pediatric population. There were a number of important findings. First, IV amiodarone had a significant dose response for pediatric patients with a variety of critical arrhythmias, with a shorter time to success for the 2 higher-dose groups (5 and 10 mg/kg) than the low-dose group (1 mg/kg). However, possibly because of small sample size, this study could not demonstrate an independent dose response for the arrhythmia subtypes of SVA or JET, despite the very strong indications from uncontrolled studies in the literature that IV amiodarone is efficacious for the treatment of JET.1-4,10-20 Finally, though efficacious, there was a high rate of clinically significant AEs that appeared to be dose related, including hypotension, bradycardia, and atrioventricular block. Taken together, the results strongly support the use of randomized trials (preferably placebo controlled) to assess the efficacy and safety of pharmacological agents used in pediatric patients with significant heart disease.

On the basis of a variety of randomized, controlled trials, IV amiodarone has been shown to have a favorable risk-benefit profile,7 leading to its approval by the FDA for adults with stable but critical arrhythmias, as well as in the setting of...
a cardiac arrest.21,22 Although no randomized trials have been performed in the pediatric population, a number of uncontrolled studies have been performed, suggesting a similar risk-benefit profile to that in adults. Totaling ≈65 patients, these studies have reported overall rates for complete or “partial” efficacy of ≈86% and for JET of ≈95%. Furthermore, in doses similar to the medium- and high-dose groups in this study, AEs were reported to be uncommon, with hypotension (defined variably) in only ≈10% of the patients across all studies and few other side effects. One of the studies was performed prospectively and protocol driven, but no study included comparison therapies, blinded or unblinded. Based largely on these reports, IV amiodarone has become the treatment of choice for many children with critical arrhythmias and most cases of postoperative JET. Furthermore, IV amiodarone has now been added to the Pediatric Advanced Life Support protocols for conversion of resistant ventricular arrhythmias, despite the lack of any studies investigating its role in such a setting. Importantly, although the prospective, blinded data from this study do support the use of amiodarone for critical arrhythmias, they also suggest that prior case series of IV amiodarone use in the pediatric population have overestimated its safety and efficacy.

### Effect of Arrhythmia Subtype

The fact that there was no significant interaction between arrhythmia subtype and the dose response for time to success suggests that the dose responses for SVA and JET were similar to those for the group as a whole. However, when the subgroups were analyzed independently, no statistical dose response could be demonstrated for either SVA or JET by any end point, possibly because of small sample size. Evaluation of the outcomes in Table 5 and the time to success curves in Figure 3, provides several insights. Most JET patients eventually reached a success end point, regardless of dose. Importantly, however, for the JET patients, the number of rescue boluses in the 3 dose groups was not different (2.0, 2.6, and 1.9 for the low-, medium-, and high-dose groups, respectively). Together, these data suggest that IV amiodarone has at most a weak dose effect for JET. It is also possible that a dose effect was overwhelmed by a high rate of spontaneous resolution or that the doses administered were all too low. Further studies based on a more extensive analysis of the JET patients in this study may be helpful to clarify these findings.

### Pharmacokinetics

The PK properties of amiodarone IV were generally similar to those in adults,21,22 demonstrating no effect of dose on the PK properties during the loading phase and a rapid fall in plasma concentrations after the load. However, there were a few differences from adult studies in the PK properties found in this study that are internally consistent. There was a trend toward an increase in $C_{avg}$ with age ($P=0.061$) that suggests a decrease in clearance of the drug from plasma with increasing age. There was also a $t_{1/2}$ of 6.9 to 11.4 days, which is not as long as that reported in adults. Neither of these findings is clear enough to recommend age-based changes in

**Figure 5.** Concentration of amiodarone on a logarithmic scale during the first 24 hours of the protocol for all 3 dose levels. Note how concentration falls rapidly regardless of dose.

**Figure 6.** Dose-normalized $C_{avg}$ vs age (left) and washout-phase levels for the subjects who had such data (right). Abbreviations are as defined in text.

| TABLE 7. Potentially Significant Blood Pressure and Heart Rate Changes During the Load |
|-----------------------------------------------|------------------|------------------|------------------|------------------|
|                                               | Low Dose (n=19)  | Medium Dose (n=20) | High Dose (n=22) | Total (N=61)     |
| SBP decrease ≥20 mm Hg, n (%)                 | 2 (10.5)         | 4 (20.0)          | 9 (40.9)         | 15 (24.6)        |
| DBP decrease ≥10 mm Hg, n (%)                 | 5 (26.3)         | 8 (40.0)          | 12 (54.5)        | 25 (41.0)        |
| Heart rate ≤50th percentile for age, n (%)    | 2 (10.5)         | 5 (25.0)          | 6 (27.3)         | 13 (21.3)        |

SBP and DBP indicate systolic and diastolic blood pressure, respectively. Abbreviations are as defined in text.
drug administration at this time, but they do provide a basis for further study.

Limitations and Barriers to Study Performance
This study was as remarkable for its completion as for its outcome. The barriers to performing the study were substantial. Most important was the very small number of pediatric patients who met the stringent entrance criteria for study enrollment, leading to the use of 48 centers to enroll 61 patients. In addition, the pediatric arrhythmia specialists designing and performing this study thought it unethical to include a placebo group on the basis of existing uncontrolled studies. The inclusion criteria required that all patients had critical arrhythmias. Investigators, study coordinators, and investigational pharmacists had to be available at all times. Furthermore, the study drug required 20 to 40 minutes to prepare, which, coupled with the consent process, represented a recruitment barrier in these critically ill patients. AEs were common in these patients, and in fact, 5 died during the study. Virtually all of the barriers to successful completion of the study discussed also represent limitations for data interpretation. The most important one is the lack of a placebo group. Despite these limitations, the results did demonstrate that relying solely on the results of retrospective studies or prospective studies in adults for evaluating therapeutic options in children is inherently flawed.

Conclusions
IV amiodarone was shown to have a dose response for the treatment of a variety of critical supraventricular and ventricular arrhythmias in a pediatric population. The lowest dose of amiodarone used in this study (1 mg/kg) was not particularly effective, suggesting that a higher dose should be used. Efficacy could not be demonstrated in this small population for any arrhythmia subgroup independently, including JET, despite the strong indications in the literature of its efficacy for JET. Serious AEs were common. Hypotension, bradycardia, and atioventricular block were all dose related and clinically significant. The results indicate that IV amiodarone may be both less effective and less safe than suggested in prior retrospective studies. Thus, IV amiodarone should be used with caution when treating children with critical arrhythmias. Finally, given the limitations of interpreting this study, based in part on the lack of a placebo control group, it can be concluded that whenever possible, a placebo control should be used to best evaluate the safety and efficacy of antiarrhythmic agents in the pediatric population.

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Disclosure
Dr Saul was a consultant for Wyeth-Ayerst during the design, performance, and analysis of the study. Drs Graepel and Wang and S.W. Burriss and P. Cargo were all employees of Wyeth-Ayerst during the study. Dr Koskelo was an employee of Quintiles, a clinical research organization responsible for study performance at centers outside the United States.

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Intravenous Amiodarone for Incessant Tachyarrhythmias in Children: A Randomized, Double-Blind, Antiarrhythmic Drug Trial

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