Intravenous Amiodarone Used Alone or in Combination With Digoxin for Life-Threatening Supraventricular Tachyarrhythmia in Neonates and Small Infants

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Objectives: The purpose of this study was to report the efficacy of intravenous amiodarone alone or in combination with digoxin in neonates and small infants with life-threatening supraventricular tachyarrhythmia (SVT).

Methods: We retrospectively analyzed 9 neonates and small infants with life-threatening or resistant SVT who were treated with intravenous amiodarone alone or in combination with digoxin.

Results: This report consists of 8 patients with reentrant SVT and 1 with atrial flutter. On admission, 7 patients had a congestive heart failure and 3 of whom had cardiovascular collapse. Intravenous rapid bolus of adenosine caused a sustained sinus rhythm in 4 patients. These patients were given digoxin initially, but recurrence of persistent tachyarrhythmia necessitated the use of intravenous amiodarone in all these patients. Amiodarone was given initially to the other 4 patients in whom adenosine caused only temporary conversion to the sinus rhythm. It was effective in 2 patients. In the other 2, digoxin was added to therapy for tachycardia control. Amiodarone alone or in combination with digoxin effectively controlled reentrant SVT in all patients. This combined treatment caused ventricular rate control in patient with atrial flutter, and conversion to the stable sinus rhythm was achieved at approximately 8 months.

Conclusions: Intravenous amiodarone alone or in combination with digoxin was found to be safe and effective in controlling refractory and life-threatening SVT in neonates and small infants.

Key Words: amiodarone, arrhythmia, neonate, supraventricular tachycardia

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S upraventricular tachyarrhythmia (SVT) is the most common sustained arrhythmia in children.1,2 Most cases manifest within the first months of life.2–4 The presentation of SVT in this age group is frequently subtle, and recognition may be difficult.1,3,4 Because the symptoms are very nonspecific, they may be misinterpreted as sepsis or metabolic disease. Spontaneous resolution of these arrhythmias is common in a small infant, but some need long-term antiarrhythmic therapy.2,5,6

Amiodarone is an effective antiarrhythmic agent that was successfully used in children with refractory and life-threatening tachyarrhythmia.5,7–9 Amiodarone also has less negative inotropic effects, and it was suggested as the drug of choice in children with depressed myocardial function.7,9 Success rate of amiodarone in small infants and neonates with refractory arrhythmia may be low, and addition of other antiarrhythmic agents may be needed.3,5 During treatment, amiodarone-related adverse effects were less pronounced in children than adults.2,5 The aim of this study was to report the efficacy and safety of intravenous amiodarone alone or in combination with digoxin in neonates and small infants with refractory and life-threatening SVT.

METHODS

Neonates and small infants with life-threatening or resistant tachyarrhythmia who were treated with intravenous amiodarone between January 2005 and December 2007 were enrolled in this report. Patients were excluded from the study if tachyarrhythmia responded to intravenous bolus of adenosine and controlled with initial digoxin treatment. Arrhythmia was diagnosed by 12-lead electrocardiography (ECG). All patients also had a 12-lead ECG in a sinus rhythm to evaluate for the presence of ventricular preexcitation. A complete echocardiography was performed to evaluate cardiac anatomy and ventricular function. Thyroid and liver function tests were also studied in amiodarone-treated patients at the beginning of therapy and hospital discharge.

Treatment Protocol

All patients with SVT were given an intravenous rapid bolus of adenosine with a beginning dose of 150 µg/kg. If this dose was ineffective, adenosine was repeated with doses of 300 and 450 µg/kg. If adenosine caused permanent conversion to the sinus rhythm, digoxin was started initially with intravenous loading. Intravenous amiodarone was the initial antiarrhythmic agent in patients in whom intravenous adenosine caused only temporary conversion to the sinus rhythm.

Amiodarone Administration Protocol

Amiodarone was given with a loading dose of 5 mg/kg for 1 hour. It was followed with an intravenous maintenance dosage of 5 µg/kg per minute, and increased in 2.5 to 5 µg/kg per minute steps up to 30 µg/kg per minute until the arrhythmia was controlled or adverse effects occurred. If this therapy was ineffective in controlling arrhythmia, digoxin was added to the treatment. After the arrhythmia control, intravenous amiodarone was switched to oral treatment when the patients tolerated oral feeding. Time to arrhythmia control was defined as the time from the beginning of any drug to restoration of the sinus rhythm without any tachyarrhythmia episodes.

Outpatient Therapy and Follow-Up

Parents were informed about the signs and symptoms of tachycardia and heart rate monitoring. They encouraged to contact us when tachycardia recurred. Patients were discharged on a maintenance amiodarone dosage of 5 to 10 mg/kg per day. Seven patients were also given digoxin in addition to amiodarone therapy. Within the first month, amiodarone dosages were
decreased to 5 mg/kg per day in all patients. Serial outpatient evaluations were performed at 2-week to 3-month intervals, including physical examination, a 12-lead ECG, 24-hour Holter monitoring, and serum digoxin level in digoxin-given patients. Chest radiography and liver and thyroid function tests were done at 3- to 6-month intervals in patients on amiodarone treatment. The 24-hour Holter monitoring was also performed 1, 3, and 6 months after drug discontinuation.

RESULTS

Our report consists of 8 patients with reentrant SVT and 1 with atrial flutter (Table 1). Of the 8 patients with SVT, 3 had overt preexcitation in the resting 12-lead ECG. There were 5 boys, and the median age on admission was 15 days (range, 7 days to 3 months). All patients were admitted with nonspecific symptoms including dyspnea, tachypnea, poor feeding, paleness, and lethargy. The time interval between the onset of symptoms and the diagnosis of SVT ranged 1 to 4 days. On admission, 7 patients had congestive heart failure and 3 of whom had severe cardiovascular compromise that manifest cardiogenic shock. These 3 patients had metabolic acidosis and elevated transaminases, blood urea nitrogen, and cardiac troponin T levels. In addition to antiarrhythmic and inotropic treatment, these patients needed mechanical ventilatory support. Two patients had a hemodynamically insignificant congenital heart defect, 1 had secundum atrial septal defect, and 1 had a patent ductus arteriosus. In the patient with atrial flutter, a rhabdomyoma was seen in the right ventricular lateral free wall. This disappeared at approximately 6 months.

On admission, the tachyarrhythmia rates ranged between 246 and 300 beats per minute. Vagal maneuvers and ice application to the face were tried in 3 patients without any success. Intravenous rapid bolus of adenosine caused the sustained sinus rhythm in 4 patients. In the other 4, adenosine caused only a temporary cardioversion to the sinus rhythm lasting only a few seconds. The effective adenosine doses ranged from 150 to 450 μg/kg.

Amiodarone was the initial antiarrhythmic agent in 4 patients in whom intravenous bolus of adenosine caused only a temporary conversion to the sinus rhythm. It was effective in terminating the tachyarrhythmia in 2 patients. In the other 2, amiodarone dosages were increased to 30 μg/kg per minute, but it is not possible to control the tachyarrhythmia. These patients were given digoxin as the second antiarrhythmic agent.

In the other 4 patients, adenosine caused a permanent conversion to the sinus rhythm. These patients were given digoxin as the first antiarrhythmic drug. In all these patients, recurrence of persistent tachyarrhythmia within 2 to 4 hours necessitated the use of intravenous amiodarone as a second drug. With the combined treatment of digoxin and amiodarone, complete control of arrhythmia was achieved within 16 hours to 10 days.

In the patient with atrial flutter, amiodarone was initiated firstly. The patient continued to have tachyarrhythmia, and digoxin was added to the treatment. The combination of digoxin and intravenous amiodarone failed to control his tachyarrhythmia but slowed the heart rate and stabilized him hemodynamically. With this combined treatment, conversion to a stable sinus rhythm was achieved at approximately 8 months.

One patient died because of hemodynamic consequences of SVT. On admission, he had cardiovascular collapse and required cardiopulmonary resuscitation. He had both metabolic and respiratory acidosis. He was intubated, and mechanical ventilation was initiated. Intravenous inotropic agents were also administered. A rapid bolus of adenosine of 150 μg/kg caused temporary cardioversion to the sinus rhythm and the rhythm reverted to SVT again. Intravenous amiodarone was initiated with a loading dose of 5 mg/kg for 1 hour. At approximately 30 minutes of infusion, the tachycardia returned to a sinus rhythm. Amiodarone infusion was continued with a dosage of 5 μg/kg per minute. Despite the arrhythmia control, his clinical condition did not improve, and the patient died on the eighth hour of hospital admission.

After hospital discharge, none of the patient experienced tachyarrhythmia. The duration of the treatment in patients with reentrant SVT varied from 6 to 8 months. The patient with atrial flutter was given drug therapy for 1 year. None of the patients experienced further recurrence of tachyarrhythmia after withdrawal of therapy.

During intravenous amiodarone treatment, a decrease in blood pressure was observed in 1 patient. She needed intravenous inotropic treatment. A slight increase was seen in thyrotropin (TSH) levels in 2 patients. With continuation of the treatment, TSH levels returned to normal. Proarrhythmia or any other adverse effects did not occur that necessitated drug discontinuation.

**TABLE 1. Clinical Features and Therapy of the Patients**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/SEX</th>
<th>ECHO</th>
<th>Arrhythmia</th>
<th>Symptoms</th>
<th>Heart rate, beats per minute</th>
<th>AD Dose, μg/kg</th>
<th>Maximum AMIO Dosage, μg/kg per minute</th>
<th>Duration of IV AMIO</th>
<th>Therapy</th>
<th>Duration of Rhythm Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (A.G.)</td>
<td>12 d/M</td>
<td>Normal</td>
<td>SVT</td>
<td>Collapse (MV)</td>
<td>272</td>
<td>450</td>
<td>30</td>
<td>7 d</td>
<td>DIG + AMIO</td>
<td>48 h</td>
</tr>
<tr>
<td>2 (I.E.K.)</td>
<td>27 d/M</td>
<td>Normal</td>
<td>SVT</td>
<td>Collapse (MV)</td>
<td>300</td>
<td>150</td>
<td>5</td>
<td>Exitus</td>
<td>AMIO</td>
<td>30 min</td>
</tr>
<tr>
<td>3 (E.E.)</td>
<td>3 mo/F</td>
<td>Normal</td>
<td>SVT</td>
<td>Heart failure</td>
<td>268</td>
<td>150</td>
<td>20</td>
<td>13 d</td>
<td>DIG + AMIO</td>
<td>10 d</td>
</tr>
<tr>
<td>4 (S.A.)</td>
<td>23 d/F</td>
<td>Normal</td>
<td>SVT</td>
<td>Collapse (MV)</td>
<td>250</td>
<td>150</td>
<td>30</td>
<td>8 d</td>
<td>AMIO + DIG</td>
<td>3 d</td>
</tr>
<tr>
<td>5 (A.Y.)</td>
<td>7 d/M</td>
<td>PDA</td>
<td>SVT</td>
<td>Heart failure</td>
<td>256</td>
<td>150</td>
<td>30</td>
<td>12 d</td>
<td>AMIO + DIG</td>
<td>8 d</td>
</tr>
<tr>
<td>6 (E.C)</td>
<td>15 d/M</td>
<td>Normal</td>
<td>PDA</td>
<td>Ventricular mass</td>
<td>272</td>
<td>150</td>
<td>5</td>
<td>2 d</td>
<td>AMIO</td>
<td>6 h</td>
</tr>
<tr>
<td>7 (L.G.)</td>
<td>45 d/F</td>
<td>ASD</td>
<td>SVT</td>
<td>Palpitation</td>
<td>246</td>
<td>150</td>
<td>5</td>
<td>3 d</td>
<td>DIG + AMIO</td>
<td>16 h</td>
</tr>
<tr>
<td>8 (U.H.)</td>
<td>13 d/F</td>
<td>Normal</td>
<td>SVT</td>
<td>Heart failure</td>
<td>276</td>
<td>300</td>
<td>5</td>
<td>5 d</td>
<td>DIG + AMIO</td>
<td>24 h</td>
</tr>
<tr>
<td>9 (B.A.)</td>
<td>7 d/M</td>
<td>Ventricular mass</td>
<td>AFL</td>
<td>Heart failure</td>
<td>250</td>
<td>300</td>
<td>5</td>
<td>13 d</td>
<td>AMIO + DIG</td>
<td>8 mo</td>
</tr>
</tbody>
</table>

AD indicates adenosine; AFL, atrial flutter; AMIO, amiodarone; ASD, atrial septal defect; SVT, supraventricular tachycardia; d, day; DIG, digoxin; ECHO, echocardiography; F, female; h, hour; IV, intravenous; M, male; min, minute; mo, month; MV, mechanical ventilation; PDA, patent ductus arteriosus.
During the same study period, 8 additional patients within the same age group were seen to have SVT. Of these, 5 were referred from other hospitals for arrhythmia control. They were mildly symptomatic, and the tachyarrhythmia was easily controlled with digoxin. In the remaining 3 patients, SVT was recognized by change on the monitor in the pediatric ward. Tachyarrhythmia did not recur after termination of intravenous bolus of adenosine, and they were not given any long-term treatment.

**DISCUSSION**

This report consists of a group of neonates and small infants with difficultly controlled SVT. Eight patients had atrioventricular reentry as the underlying mechanism of tachyarrhythmia, and 1 had atrial flutter. All patients were admitted with nonspecific symptoms, and most had unstable hemodynamic conditions. Intravenous amiodarone alone or in combination with digoxin effectively controlled reentrant SVT in all patients. This combined treatment caused ventricular rate control in atrial flutter.

Supraventricular tachyarrhythmia is the most common sustained arrhythmia in neonates and small infants, and atrioventricular reentry is the most common underlying mechanism. The presentation of tachyarrhythmia in this age group is usually subtle and may include dyspnea, tachypnea, irritability, poor feeding, vomiting, and paleness. Because the symptoms are very nonspecific, they may be misinterpreted as sepsis or metabolic disease. The high heart rates during the long-standing tachyarrhythmia are not well tolerated by these patients. Depending on the age of the patients, the rate, and the duration of the tachyarrhythmia, they could also provoke cardiovascular collapse. All patients in our report were admitted with long-standing and fairly nonspecific symptoms. These long-standing tachyarrhythmia caused congestive heart failure in 7 patients. On admission, 3 patients had severe cardiovascular collapse and 1 patient died because of hemodynamic consequences of the tachyarrhythmia.

After restoration of the sinus rhythm, digoxin is usually initiated to these patients as the first antiarrhythmic agent, to prevent further attacks. The advantages of digoxin over other antiarrhythmic agents are lack of negative inotropic effect, easy monitoring of blood drug level, and a relatively rare proarrhythmic effect. Different alternative drugs to digoxin have been suggested as initial agents or as a second additional drug in case of failure of digoxin in controlling tachyarrhythmia. Amiodarone is a class III antiarrhythmic drug that has been successfully used in tachyarrhythmia that was refractory to other medical therapy. Different success rates have been reported with amiodarone treatment. Shuler et al reported a low success rate of amiodarone in neonates. They used amiodarone in neonates with reentrant SVT and had complete control only in 3 of 10 patients. Drago et al found that amiodarone alone was effective or partially effective in 56% of infants and children with tachyarrhythmia. The low success rate was attributed to the unsatisfactory response of reentrant SVT in infants. With the addition of propranolol, their success rate increased to 93%. In a large previous report, amiodarone alone or in combination with propranolol was used in 50 neonates and infants. Twenty-three of these patients had failed prior antiarrhythmic treatment. Amiodarone treatment controlled tachyarrhythmia in half of the patients, and an addition of propranolol had a complete success in the remaining of the patients. In our study, amiodarone was given to 4 patients as the first antiarrhythmic drug, and it was effective in controlling tachyarrhythmia in 2 patients. In the other 2, digoxin was added to amiodarone for tachyarrhythmia control. All 4 patients who were given digoxin initially needed amiodarone for tachycardia control. Amiodarone alone or combined with digoxin had complete success in all 8 patients with reentrant SVT.

There are concerns about the safety of intravenous amiodarone and the adverse effects of long-term treatment. When compared with adult patients, amiodarone-related adverse effects are less pronounced in pediatric age group. During intravenous amiodarone treatment, one of our patients developed hypotension, which necessitated intravenous inotropic treatment. A slight increase was also seen in the TSH level in 2 patients. With the continuation of the drug therapy, the TSH level returned to normal. No other adverse effects occurred that necessitated drug discontinuation.

In conclusion, control of persistent SVT may be difficult in neonates and small infants. Intravenous amiodarone alone or in combination with digoxin was found to be safe and effective therapy in controlling refractory and life-threatening SVT in neonates and small infants.

**REFERENCES**