

Intravenous sotalol for conversion of atrial flutter in infants



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Introduction

Atrial flutter is an uncommon arrhythmia in the pediatric population but is well described in the perinatal period, in early infancy, and after cardiac surgery. It often occurs in the third trimester of pregnancy and in the early newborn period, usually within the first 2 days of life.¹ In infants without congenital heart disease (CHD) or ventricular dysfunction, the recurrence risk is low once flutter has been converted to sinus rhythm.² Strategies for medical cardioversion include digoxin, with perhaps a 33% conversion rate to sinus rhythm after loading.¹ There is a growing body of literature on the use of intravenous (IV) sotalol for various arrhythmias in children, raising the prospect of using IV sotalol as an acute pharmacotherapy for tachyarrhythmias, including medical cardioversion of atrial flutter in infants.^{3,4} Sotalol is a mixed isomer with both class II and III antiarrhythmic properties.⁵ Oral sotalol administration to the mother can treat fetal atrial flutter. It is also used to control other forms of supraventricular tachycardia (SVT) in infants and for several forms of intra-atrial reentry in older patients.⁶ In this case series, we describe a successful conversion of 3 infants with hemodynamically stable atrial flutter to sinus rhythm after a single dose of 2–2.5 mg/kg (30–40 mg/m²) of IV sotalol, given over 15–30 minutes, with no apparent adverse effects.

Case reports

Case 1

Case 1 involved a 1-day-old female subject, born at 34 weeks gestation via scheduled cesarean section for placenta previa. Pregnancy was uncomplicated, without noted arrhythmia. Her birth weight was 2.35 kg, length 46.5 cm, and Dubois-method body surface area (BSA) 0.17 m². She was found to be tachycardic on initial examination, and an electrocardiogram (ECG) showed narrow complex tachycardia at 200

beats per minute (bpm); the patient was hemodynamically stable. Adenosine was given, revealing rapid, typical atrial flutter with a cycle length of approximately 150 ms (Figure 1). An echocardiogram demonstrated normal cardiac structure and satisfactory function (in the context of tachycardia). Her creatinine was 0.55 mg/dL and creatinine clearance 37 mL/min/1.73 m². A single dose of IV sotalol (AltaThera, Chicago, IL) 5 mg (30 mg/m²; 2.1 mg/kg) was given over 15 minutes. Blood pressure and peripheral perfusion were stable during the infusion. The atrial flutter converted to sinus rhythm within 14 minutes without pause or bradycardia. There were no complications with the infusion. ECGs done after the infusion demonstrated normal sinus rhythm with no significant QT interval prolongation (baseline QTc was 430 ms and 435 ms within 48 hours after treatment). There was no recurrence of arrhythmia after a single dose.

Case 2

A 1-day-old male baby, infant of a diabetic mother, with a prenatal diagnosis of trisomy 21 was born at 37 weeks gestation. Birth weight was 3.1 kg, length 47 cm, and BSA 0.19 m². At 39 hours of life, he was noted to be tachycardic to approximately 200 bpm. ECG demonstrated atrial flutter with atrial cycle length approximately 150 ms and 2:1 and occasional 3:1 atrioventricular conduction. He was hemodynamically stable. An echocardiogram demonstrated structurally normal heart with persistent pulmonary hypertension and normal biventricular function. Baseline creatinine was 0.53 mg/dL and creatinine clearance 36.6 mL/min/1.73 m². IV sotalol 6 mg (30 mg/m²; 1.9 mg/kg) was infused over 15 minutes. Atrial flutter converted to sinus rhythm at 17 minutes (Figure 2). Blood pressure was stable during infusion, and there were no complications. Given the degree of pulmonary hypertension, there was a concern for increased risk of recurrence of atrial flutter. The patient was started on 4 mg (3.8 mg/kg/day, 57 mg/m²/day) oral sotalol every 8 hours for a total of 3 days for arrhythmia prophylaxis. Telemetry monitoring revealed no recurrence of atrial tachyarrhythmia or other concerns. Baseline QTc on ECG obtained before the onset of atrial flutter was 440 ms. Repeat ECG on sotalol demonstrated QTc of 452 ms. Oral sotalol was discontinued without recurrence of arrhythmia after 3 days.

KEYWORDS Intravenous sotalol; IV sotalol; Infantile atrial flutter; Neonatal atrial flutter; Atrial flutter
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KEY TEACHING POINTS

- In 3 infants with hemodynamically stable atrial flutter and normal ventricular function, a single dose of intravenous sotalol given over 15–30 minutes was effective in terminating atrial tachycardia within 30 minutes of administration.
- Baseline echocardiogram should be used to assess ventricular function before the administration of an intravenous beta-blocking agent.
- Acute pharmacotherapy for infantile atrial flutter avoids anesthesia or sedation required with direct current cardioversion or transesophageal pacing.
- QT prolongation is common with the administration of sotalol, and QTc should be carefully monitored.

Case 3

A 7-month-old female infant, delivered at 34 weeks gestation, underwent repair of congenital diaphragmatic hernia, coarctation of the aorta, and ventricular septal defect in the neonatal period, and had chronic pulmonary hypertension secondary to lung hypoplasia from diaphragmatic hernia. She developed narrow complex tachycardia to 240 bpm and ECG demonstrated atrial flutter with cycle length approximately 140 ms and 2:1 conduction. Baseline ECG (1 month prior to the episode) showed right bundle branch block with QTc of 370 ms. Her weight was 4.5 kg, length 57 cm, and BSA 0.27 m². She was hemodynamically stable. Echocardiogram showed normal ventricular systolic function. Baseline creatinine was 0.22 mg/dL and creatinine clearance >75 mL/min/1.73 m². She was given IV sotalol 10.8 mg (2.4 mg/kg; 40 mg/m²) over 30 minutes and converted to sinus rhythm during the administration of medication. She was placed on prophylactic enteral sotalol (2 mg/kg/day) for 10 days. This was then discontinued without tachyarrhythmia recurrence. QTc on sotalol was 442 ms (in the context of right bundle branch block), which was not significantly changed from baseline. There was no evidence of proarrhythmic effect.

Discussion

In this case series, we present 3 cases of hemodynamically stable atrial flutter: 2 newborns without CHD and an infant with repaired CHD. All were converted to sinus rhythm with IV sotalol. Various treatment options for atrial flutter in children are available, including synchronized direct current (DC) cardioversion, transesophageal pacing, and medical cardioversion. DC cardioversion using 0.5–1 J/kg has a high rate of success and low complication rate, but sometimes requires deep sedation or anesthesia.¹ Transesophageal atrial overdrive pacing can be done in neonates without

sedation or anesthesia; but for the rapid cycle lengths necessary to overdrive the tachycardia, it may be difficult to achieve adequate capture via a transesophageal electrode. Historically, digoxin has been the medication of choice for medical cardioversion of atrial flutter in children, but with limited success. Other antiarrhythmic medications have been used for refractory atrial flutter, including flecainide, amiodarone, propafenone, and quinidine.^{1,7,8}

Like the oral form of the drug, IV sotalol (AltaThera) is a mixed isomer of D- and L-sotalol. Both the D- and L-sotalol isomers have class III antiarrhythmic properties, while L-sotalol is responsible for the beta-blocking effect of the drug.⁵ Sotalol exhibits the property of reverse use dependence (ie, more prominent action potential prolongation at a lower heart rate).⁹ In one study evaluating the electrophysiologic effect of sotalol on the immature mammalian heart, sotalol was found to have more pronounced effects on the immature heart at the atrial level when compared with adult hearts.¹⁰ In a study evaluating the efficacy and safety of high-dose sotalol (median starting dose 142 mg/m²/day; median discharge dose 152 mg/m²/day) in newborns and infants with refractory supraventricular tachyarrhythmias, sotalol administration was not associated with torsades de pointes, incessant SVT, significant bradycardia, or atrioventricular node disturbances. It is notable that there was a mild increase in QTc after initiation of therapy and at the time of discharge, but no patients had QTc > 500 ms.¹¹

As IV sotalol became available in the United States for clinical use, a clinical protocol was devised for acute pharmacotherapy for atrial flutter in infants at Rady Children's Hospital San Diego. The protocol involves the use of IV sotalol for all hemodynamically stable infants with normal cardiac function, normal baseline QTc, and normal creatinine clearance for treatment of atrial flutter. A target dose of approximately 2 mg/kg (30–40 mg/m²) was selected as an initial dose, to be infused over 15–30 minutes in controlled settings in the Neonatal Intensive Care Unit with the cardiologist at the bedside during the administration of the first dose. It is important to note that age-related dosage reduction for children younger than the age of 2 years, as recommended by the manufacturer, was not performed in this case series.¹² An age-related adjustment was not made in our protocol, as only a single IV dose was anticipated. We hypothesized that targeting a slightly higher, but transient, peak serum level may improve acute efficacy for tachyarrhythmia conversion.

Eight months after this protocol was instituted, a retrospective chart review was performed to analyze all infants who received IV sotalol as sole therapy for atrial flutter. Three infants were identified. Exemption from human research requirements was confirmed with the Institutional Review Board. Authorization to publish anonymized results was obtained from the families of all 3 patients, satisfying requirements of our institutional privacy board.

This case series demonstrates successful conversion of 3 infants with atrial flutter to sinus rhythm after a single dose of IV sotalol, given over 15–30 minutes, with no apparent adverse effects. Conversion occurred within

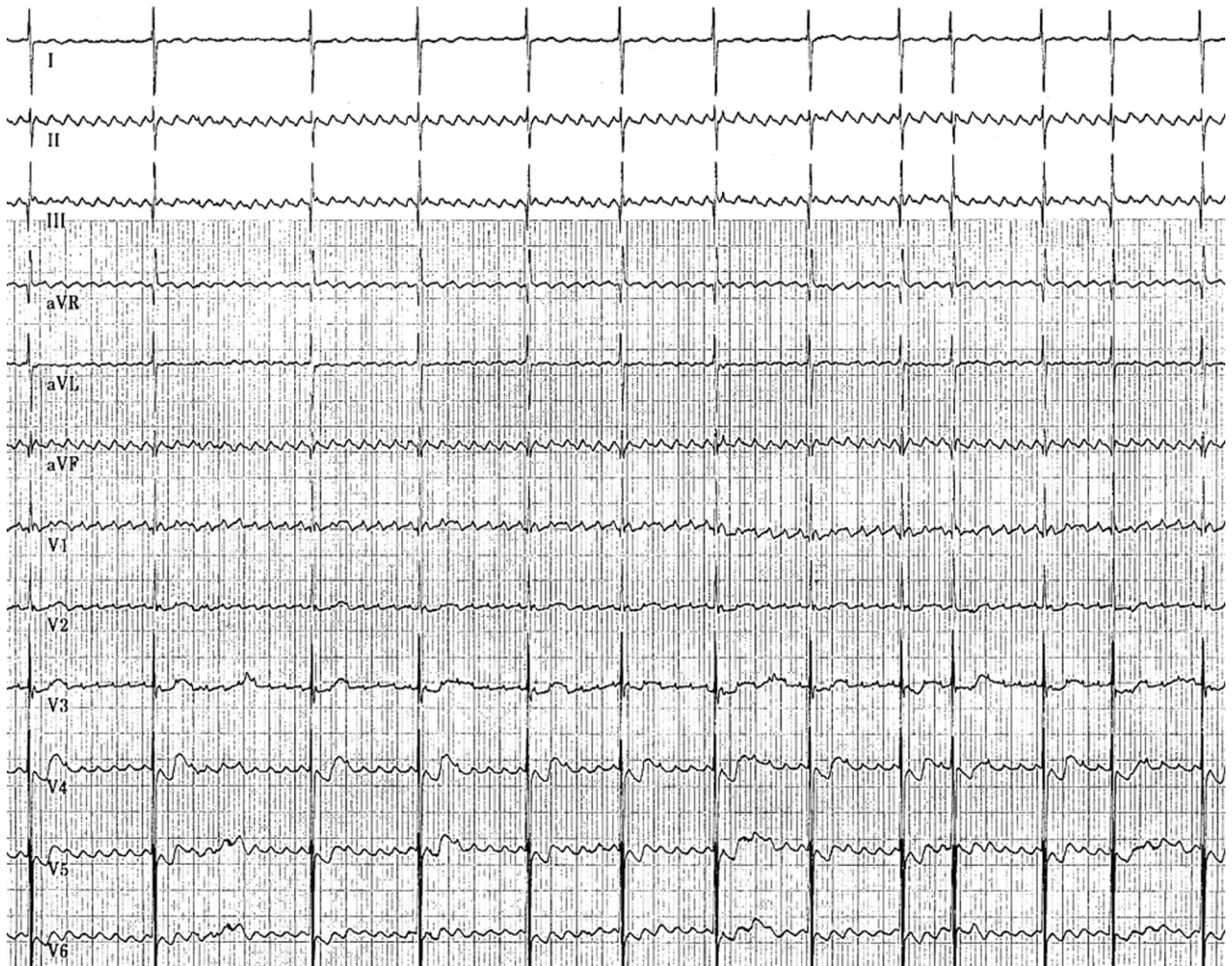


Figure 1 Case 1 electrocardiogram demonstrating rapid atrial flutter (after adenosine administration).

30 minutes of starting the infusion in all cases. All 3 patients had an echocardiogram demonstrating normal cardiac systolic function prior to administration of sotalol. There were no adverse events, proarrhythmia, pauses, or hypotension.

Li and colleagues⁴ reported the use of IV sotalol for treating incessant tachycardias in children. The authors initially reported dosing based on body weight (mg/kg) and later published dosing based on BSA for the same study population. In the original publication, the authors used 1 mg/kg given over 10 minutes as a loading dose, followed by 4.5 mg/kg/day as a maintenance dose. Among 83 patients in the study, 9 patients had atrial flutter. Out of these 9 patients, 4 (44%) converted to sinus rhythm within 1–24 hours using IV sotalol alone. The reported mean age for the atrial flutter group was 4.9 ± 7.8 years, with a range of 10 days to 10.5 years. It is unclear how many newborns or infants had atrial flutter, but the authors mentioned a 1-month-old infant who developed significant bradycardia after IV sotalol was given. In a follow-up publication, the authors reported the correlation between sotalol dosing based on body weight (mg/kg) vs BSA (mg/m^2). They concluded that sotalol dosing using the body weight method was lower than the BSA method

from infancy to young childhood (birth to 6 years), equal for older children (6–12 years), and higher for adolescents (12–18 years). It is important to mention that the reported BSA dosing calculation was based on the assumption that bioavailability of oral sotalol is approximately 95%, so they multiplied the dose by 0.95 for age adjustment for children younger than 2 years.¹³ Kim and colleagues³ reported 2 newborns with SVT who were treated with $30 \text{ mg}/\text{m}^2/\text{dose}$ IV sotalol, infused over 5 hours, using age correction factor. They demonstrated reversible QT prolongation after IV sotalol infusion.

These initial results are encouraging, suggesting that use of IV sotalol as a sole pharmacotherapy for infantile atrial flutter may be safe and efficacious and warrants further evaluation and investigation. Though none of the patients in this study experienced adverse effects, the small sample size is insufficient to exclude unusual or infrequent complications. Also, it would not be appropriate to generalize these data to other infantile and pediatric tachyarrhythmias without separately assessing these. Further, the use of IV sotalol in patients with depressed ventricular systolic function (including from tachyarrhythmia-induced cardiomyopathy)

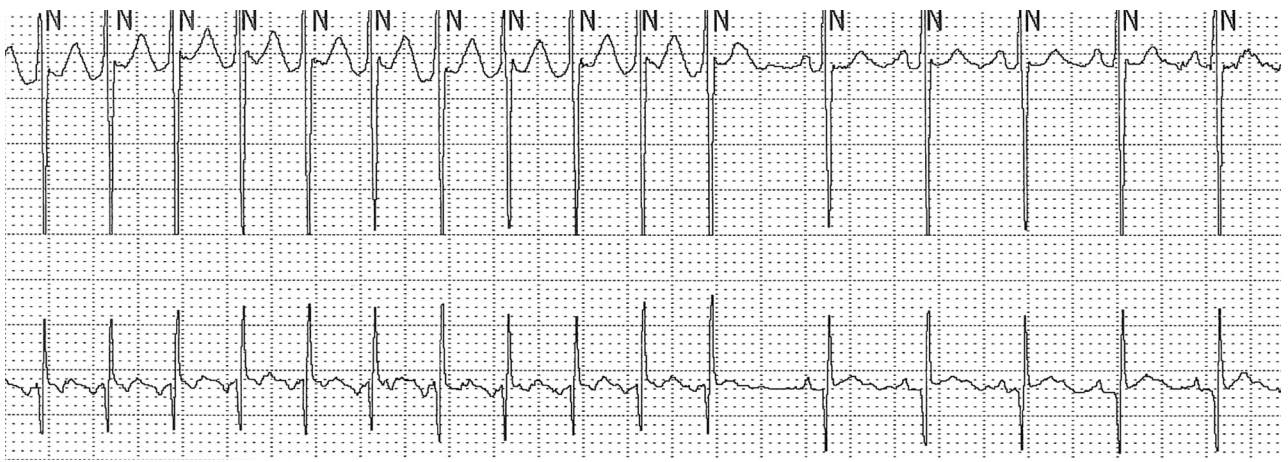


Figure 2 Conversion of atrial flutter to sinus rhythm with sotalol infusion.

was not assessed and warrants further investigation, including careful assessment of risks/benefits of IV sotalol in comparison to anesthesia risks for DC cardioversion, as well as other considerations.

Conclusion

In these 3 infants with atrial flutter and normal ventricular function, a single dose of IV sotalol (at a dose of approximately 2 mg/kg over 15–30 minutes) was safe and effective in terminating atrial flutter within 30 minutes of administration. IV sotalol is a promising initial therapy for atrial flutter in infants, thereby avoiding the need for sedation and anesthesia required for DC cardioversion or pacing. Further investigation is needed to more thoroughly assess the efficacy, safety, and cost-effectiveness of IV sotalol for treatment of infants with atrial flutter and other tachyarrhythmias.

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