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Early Experience with Intravenous Sotalol in Children with and without Congenital Heart Disease

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Abstract

Background: Arrhythmias are common in the pediatric population. In patients unable to take oral medications or in need of acute therapy, options of intravenous (IV) anti-arrhythmics are limited. Recently IV sotalol has become readily available, but experience in children is limited.

Objective: To describe our initial experience with the use of IV sotalol in the pediatric population.

Methods: A retrospective study of all pediatric patients receiving IV sotalol was performed. Patient demographics, presence of congenital heart disease (CHD), arrhythmia type, efficacy of IV sotalol use and adverse effects were evaluated.

Results: A total of 47 patients (55% male and 51% with CHD) received IV sotalol at a median age 2.05 yrs (IQR 0.07–10.03 yrs), median weight 12.8 kg (IQR 3.8 – 34.2 kg), and 13 (28%) were acutely post-operative. Supraventricular arrhythmias, occurred in 40 (85%), and ventricular tachycardia (VT) in 7 (15%). Among 24 receiving IV sotalol for an active arrhythmia, acute termination was achieved in 21 (88%). Twenty three patients received IV sotalol as maintenance therapy due to recurrent arrhythmias and inability to take oral anti-arrhythmics; 19 (83%) were controlled on sotalol monotherapy. No patient required discontinuation of IV sotalol secondary to adverse effects, pro-arrhythmia, or QT prolongation.

Conclusions: IV sotalol is an effective antiarrhythmic option for pediatric patients and may be an excellent agent for acute termination of active arrhythmias. It was well tolerated with no patient requiring discontinuation secondary to adverse effects.

Keywords

Sotalol; arrhythmia; pediatrics; intravenous sotalol; supraventricular arrhythmia; ventricular arrhythmia

Introduction

Sotalol has been used safely and effectively in the management of pediatric arrhythmias, including supraventricular tachycardia (SVT) and ventricular tachycardia (VT)^{1–10}. Additionally, the efficacy of single dose oral sotalol for the conversion of active atrial arrhythmias in patients with congenital heart disease has been reported¹¹.

Recently, IV sotalol has become readily available and holds promise as an intravenous (IV) anti-arrhythmic, particularly as acute pharmacotherapy for arrhythmia termination. Studies in adults have shown that the use of IV sotalol has similar safety, pharmacokinetics and efficacy to oral sotalol^{12–14}. Preliminary pediatric studies have also shown that IV sotalol is predominantly safe and effective in children with supraventricular and ventricular arrhythmias. These studies are limited in number and scope. In particular, patients with congenital or structural heart disease, and/or depressed ventricular function (ejection fraction <50%) were excluded^{15,16}. Our study sought to describe our initial experience with IV sotalol in the pediatric population and include patients with congenital heart disease and depressed ventricular function.

Methods

An IRB approved retrospective study of all pediatric patients (<21 years of age) receiving IV sotalol at 2 pediatric institutions between April 2016 and December 2017 was performed. Inclusion criteria: all patients <21 years of age with and without congenital heart disease who received IV sotalol identified by the pharmacy administration database. No patient receiving IV sotalol was excluded. Patient demographics, presence of CHD, arrhythmia type, cardiac function, IV sotalol administration parameters, efficacy, and adverse effects were evaluated.

Severity of CHD was classified according to the 32nd Bethesda Conference Task Force 1¹⁷. Medical records, telemetry, electrocardiograms (ECG), echocardiograms, and Holter monitors were reviewed. QTc intervals prior to and following IV sotalol infusion were compared; all measurements were performed by a pediatric electrophysiologist. The most recent sinus ECG prior to IV sotalol administration was used for pre IV sotalol QTc calculation. Post IV sotalol QTc interval were obtained from the first sinus ECG following conversion in group 1 patients, and following 5 doses of IV sotalol in group 2 (see below for group designation). QTc intervals in patients with ventricular paced rhythm, pre-excitation or bundle branch block were performed but not included in the cohort's average QTc calculations.

Ventricular function was assessed by echocardiography from the most recent echocardiogram prior to IV sotalol administration. Ejection fraction (EF) was calculated

only in patients with systemic left ventricles. Ventricular function was classified according to the following: EF ≥55% normal, EF 41%–54% mildly depressed, 35–40% moderately depressed, and <35% severely depressed. For patients in whom an EF was not calculated, function was classified qualitatively by the interpreting echocardiography attending.

Physiologic data was also collected from the Sickbay platform. Sickbay (FDA K Number: K143304) is a clinical platform that stores bedside device data at native resolution for large-scale analysis. This data includes cardiac measurements (heart rate, blood pressure, telemetry, and cardiac monitor alarms), medication administration, and laboratory results. For the signals analyzed in this study data was collected every 2 seconds directly from the bedside monitors via Sickbay.

Patients were classified into two groups: Group 1 was the acute arrhythmia treatment group consisting of patients who received IV sotalol for acute termination of an active arrhythmia; group 2 was the maintenance infusion group consisting of patients who were unable to take oral medications and received IV sotalol as maintenance therapy for recurrent arrhythmias. Patients in group 1 received 1 mg/kg of IV sotalol (maximum dose of 80 mg) over 1 hour. Administration of IV bolus doses were performed in the ICU or emergency room setting under continuous telemetry monitoring. For patients with arrhythmia persistence following the initial IV sotalol bolus a second bolus (1 mg/kg) was given as soon as possible provided no adverse effects from sotalol were noted.

In group 2, IV sotalol was started at 80–90% of patients' prior daily oral maintenance dose of sotalol, or at 80–90% of the determined oral starting dose per the prescribing provider. The total daily dose was then divided and given every 8 hours or every 12 hours depending on the patient's age. Each individual maintenance IV sotalol infusion was given over 5 hours and performed in an ICU setting. In rare instances, IV sotalol infusion was reduced to 3 hours secondary to limited IV access and need to administer other medications. The maintenance dosage was chosen based on prior pharmacokinetic studies demonstrating approximately 90% bioavailability of oral sotalol, and similar peak levels between a 5-hour IV infusion and oral doses of sotalol¹². Patients had daily ECGs during the loading phase to monitor QTc and were on continuous telemetry. Arrhythmia control was defined as no arrhythmia recurrence on sotalol monotherapy (IV or oral) at the time of hospital discharge or at the conclusion of the study.

Sickbay was utilized to collect and compare heart rate and blood pressure measurements prior to and during the administration of IV sotalol. In group 1, heart rates and blood pressures during the 1 hour prior to sotalol administration were compared to the heart rates and blood pressures between 5 and 90 minutes following infusion onset. In group 2, heart rates and blood pressures during the 1 hour prior to the infusion were compared to the heart rates and blood pressures during the 5 hour infusion. Statistics for pre- and post-administration vital sign measurements were analyzed by a variety of quantitative and qualitative metrics. The mean heart rate and blood pressure for each patient was calculated for pre and post infusion. The mean difference per patient vital sign pre- and post-administration were then compared using the paired t-test. Histograms and empirical cumulative distribution function comparisons for each vital sign, were performed. Data in

histograms were depicted as normalized values with variance representing time spent at each value. Histograms were subsequently compared using the 2-sample Kolmogorov-Smirnov test.

Results

A total of 47 patients (55% male) received IV sotalol over the study period. Twenty four patients were in group 1 and received IV sotalol for acute termination of an arrhythmia, and 23 patients were in group 2 for maintenance therapy (Table 1). For the entire cohort, median age was 2.05 yrs (IQR 0.07–10.03 yrs), and median weight was 12.8 kg (IQR 3.8 – 34.2 kg). In total, 24 (51%) patients had CHD, and 1 (2%) had cardiac rhabdomyomas. Thirteen (28%) patients received IV sotalol in the acute post-operative setting. Surgeries performed included Fontan conversions, aortic arch surgeries, bidirectional Glenn, Blalock-Taussig-Thomas shunts, Norwood procedures, mitral valve replacement, arterial switch operation, cannulation for extracorporeal membrane oxygenation, and pulmonary homograft replacement. There was a wide variety of CHD (Supplemental Table 1). Moderate complexity CHD was present in 4 (17%) and severe complexity CHD in 20 (83%) (including 11 [46%] with single ventricle physiology). Ventricular function on the most recent echocardiogram prior to IV sotalol administration was normal in 31 (66%), mildly depressed in 5 (11%), and moderately depressed in 11 (23%), the median ejection fraction was 58% (IQR 40–64). Echocardiograms were performed on a median 1 day prior to the administration of IV sotalol (IQR 0,11). Supraventricular arrhythmias, including re-entrant supraventricular tachycardia (SVT), atrial flutter (AFL), focal atrial tachycardia (FAT), and atrial fibrillation (AFIB) occurred in 40 (85%), and ventricular tachycardia (VT) in 7 (15%). Overall, adverse effects were noted in 2 patients (4%), and are described below.

Group 1: Acute Arrhythmia Treatment Group

Among the 24 patients, in group 1, 9 (38%) had SVT, 9 (38%) had AFL, 3 (12%) had VT, 2 (8%) had FAT, and 1 (4%) had AFIB. In 21/24 (88%) patients, the administration of IV sotalol led to acute termination of the active arrhythmia (FIGURE 1). In 16 patients a single bolus over 1 hour resulted in termination. In the remaining 5 patients the initial bolus slowed the arrhythmia, and a second bolus (1 mg/kg) was required for arrhythmia termination. On average the second bolus was started 1.3 hours after the termination of the initial bolus. The 9 patients with re-entrant SVT had failed adenosine administration prior to receiving IV sotalol bolus. For the 6 patients receiving IV sotalol in the acute post-operative period, successful conversion occurred in 5 (83%). Post-operative arrhythmias treated included AFL 3, FAT 1, and VT 2. The one post-operative patient that did not convert to sinus had AFL.

In total, three patients did not convert to sinus rhythm: two had AFL (including the above mentioned post-operative patient) that was rate controlled with IV sotalol but subsequently required DC cardioversion; one patient in SVT had previously failed conversion with adenosine, did not break with a single IV sotalol bolus but converted to sinus rhythm with a second dose of adenosine following IV sotalol administration. Overall, the median time to conversion to sinus rhythm was 33 minutes (IQR 18–102). All patients that were converted to sinus remained in sinus rhythm.

Adverse effects were noted in 1 patient (4%). This patient was a 5 year old with normal cardiac anatomy and SVT who experienced hypotension (systolic blood pressure in the sixties) during sotalol administration. The infusion was paused, an IV fluid bolus was given and the sotalol infusion was subsequently completed. The patient was asymptomatic from his hypotension. No other adverse effects were noted during the IV bolus administration of sotalol.

Median post conversion QTc was 443 msec (IQR 429–451); the longest QTc post IV bolus was 490 msec. Median heart rates and blood pressure measurements before and during the administration of IV sotalol are noted in Table 2. Histograms as well as empirical cumulative distribution function for pre and post histograms are seen in Figure 2. Similar histograms will generate a greater degree of overlap between their corresponding distribution function graphs. Therefore, the more overlap there is between the distribution functions, the more similar the corresponding histograms. Following the administration of IV sotalol the median heart rate in the group as a whole decreased by approximately 25%. This decrease is attributed to arrhythmia termination / conversion to sinus as well as progression of AV block in AFL patients. There was no statistical significance in the per patient mean blood pressure difference pre or post infusion (Table 2). Following conversion to sinus rhythm 5 patients were transitioned to IV sotalol maintenance therapy, 12 to oral sotalol, and 3 to oral beta blocker. One patient had beta blocker added to their oral sotalol regimen, 1 was transitioned to IV beta-blocker, and 2 were not started on any chronic anti-arrhythmic medications.

Group 2: Maintenance Infusion Group

Twenty three patients were in group 2, and received IV sotalol as maintenance therapy for recurrent arrhythmias due to inability to take oral anti-arrhythmics. Arrhythmias in this group included SVT 9 (39%), AFL 3 (13%), FAT 6 (26%), AFIB 1 (4%) and VT 4 (17%). Median dose of maintenance IV sotalol infused was 120 mg/m²/day (IQR 103–123). In 19/23 (83%) arrhythmia control was achieved with sotalol monotherapy by the time of hospital discharge or conclusion of the study. For the remaining 4, 2 patients (1 FAT, 1 VT) required transition to other therapy due to incomplete efficacy, one patient (SVT) required the addition of propranolol to sotalol for complete control, and one patient (AFIB) was rate controlled.

Median heart rates and blood pressure measurements before and during IV sotalol administration are noted in Table 3. Histograms as well as empirical cumulative distribution function for pre and post histograms are displayed in Figure 3. There was no statistically significance in the per patient mean difference in heart rate or blood pressure during the administration of IV sotalol.

Adverse effects occurred in one patient (4%). This patient was an infant in the immediate post-operative period following a Norwood procedure with a Damus-Kaye-Stansel palliation. The patient had had recurrent re-entrant SVT and thus was started on sotalol 120 mg/m²/day IV for arrhythmia prophylaxis. The patient developed bradycardia and hypotension; the systolic blood pressure decreased from 55 mmHg to 45 mmHg during the first administration of sotalol. This occurred on post-operative day 0 after receiving an estimated 0.5 mg of sotalol (~3 mg/m², or 0.2 mg/kg) approximately 20 minutes into a 5

hour infusion. The infusion was held and restarted at a lower dose (60 mg/m²/day) once his bradycardia and hypotension had resolved. The lower dose was tolerated with no adverse effects. It is unclear if the bradycardia and hypotension were related to sotalol or to changing post-operative hemodynamics. Average QTc in group 2 patients prior to IV sotalol administration was 439 msec (STD 21.6) and at steady state following IV sotalol was 444 msec (STD 13.1). No patient required discontinuation of IV sotalol secondary to pro-arrhythmia, or QTc prolongation.

Discussion

There has been limited literature regarding the use of IV sotalol in the pediatric population^{15,16,18,19}. Our study adds to the limited data describing the safety and efficacy of IV sotalol in pediatric patients, and is the first to evaluate its use in the setting of CHD and/or depressed ventricular function. Overall, we found that IV sotalol was safe and effective in the treatment of supraventricular and ventricular arrhythmias in children with and without CHD and in the setting of depressed ventricular function.

In our study, IV sotalol had an excellent conversion rate of active arrhythmias. The median time to conversion with IV sotalol was 33 minutes, making IV sotalol an attractive option for the acute termination and treatment of patients with refractory arrhythmias. Of interest our time to conversion was significantly shorter when compared to a prior study by Li et al¹⁵ which described conversion times of up to 12 hours. It is unclear why the conversion times of our studies differed significantly. The administration of IV sotalol was similar in dosage 1–1.5 mg/kg, but differed in the speed of administration. In our study we administered sotalol over 1 hour while Li et al administered it over 10 minutes. One possible explanation includes differences in the management of arrhythmia persistence following initial IV sotalol bolus. Whereas Li et al immediately transitioned to propafenone (an oral medication with peak effect within 2–4 hours of administration²¹), 5 of our patients received a second IV bolus which resulted in arrhythmia termination. Differences in conversion times may also be attributed to differences in arrhythmia substrates between our two studies. Li reported a higher proportion of FAT patients (43% vs. 17% in our study); this group of patients also had the longest conversion times in their study (14 hours). Our overall conversion times more closely resemble the conversion times found by Rao et al when oral sotalol was administered to patients with CHD and FAT (average time 98 minutes) and intra atrial reentrant tachycardia (average time 145 minutes)¹¹.

In the setting of ventricular dysfunction, the use of certain anti-arrhythmic agents may be limited by their negative inotropic effects²². Despite its weak beta blocker activity, sotalol's effect on cardiac function is not as significant when compared to other beta blockers. Hemodynamic clinical studies of IV and oral sotalol have shown that sotalol's cumulative negative inotropic effects are less than anticipated for the degree of beta blockade achieved. The enhanced inotropy associated with its class III activity is thought to counterbalance the negative inotropy associated with its beta blocking effect²³. In clinical studies, exacerbation of heart failure has been uncommon occurring predominantly in patients with severely depressed cardiac function (EF <25%) and markedly dilated LV end diastolic volumes^{23–25}. Likewise in our study, when IV sotalol was utilized in several children with mildly and

moderately depressed ventricular function no deleterious hemodynamic sequelae resulted from sotalol's negative inotropic effects. Whether this also holds true for patients with severely depressed function is unknown since none of the patients in our cohort received IV sotalol in the presence of severely depressed function.

Overall, adverse effects were rare in our cohort occurring in only 4% of patients, and primarily manifested as transient bradycardia or relative hypotension. Even though our patients did not experience any pro-arrhythmic effects or torsade de pointes, the administration of sotalol (IV or oral) can predispose patients to developing significant arrhythmias. Therefore, due to both its potential hemodynamic and pro-arrhythmic effects, we continue to recommend that the administration of IV sotalol be performed in a setting that allows for close rhythm, heart rate, and blood pressure monitoring. ECGs should be performed during the loading period and the closely monitored. In our study, no patient required the discontinuation of sotalol due to QT prolongation.

Our study limitations are related to its retrospective nature. Primarily, our cohort demonstrates heterogeneity in both its arrhythmias and anatomical substrates and includes patients with and without CHD. As such, a larger sample size would be of significant benefit in characterizing the effect of IV sotalol on specific arrhythmia and anatomical substrates. Multicenter studies should also be performed to further expand upon the limited experience and assess the feasibility, safety and efficacy of IV sotalol across various practice settings. In addition because IV sotalol was administered at the discretion of the prescribing electrophysiologist, patient selection may have been limited by prescriber bias. Due to the retrospective format of our study, we are unable to determine if IV sotalol was withheld from any patient initially identified to receive sotalol.

CONCLUSION

Based on the findings of this study, IV sotalol was a safe and effective anti-arrhythmic option for pediatric patients when used for the acute termination of active arrhythmias and as maintenance therapy when necessary. Overall it was well tolerated, in patients with congenital heart disease and depressed ventricular function. It had excellent conversion rates in patients with acute arrhythmias and ought to be considered as a first line agent for acute conversion in patients with adenosine refractory SVT. Larger prospective studies are needed to further evaluate the efficacy and safety of sotalol in specific substrates and settings and to compare IV sotalol to other IV anti-arrhythmics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Acute Termination of Arrhythmias with IV Sotalol

Graphic illustration of arrhythmia response to IV sotalol in three patients with acute arrhythmias. Sotalol was administered over one hour. The green curve represents heart rate measurements in beats per minute. The purple line represents the duration of sotalol infusion. Figure 1a was obtained from a patient in IART. The decrease in heart rate shortly following sotalol administration exhibits a staircase pattern and corresponds to changes in atrioventricular conduction prior to conversion from IART to sinus rhythm. Note that arrhythmia termination occurs towards the end of sotalol infusion. Figure 1b was obtained

from a patient in reentrant SVT and demonstrates an abrupt decrease in heart rate with conversion from SVT to sinus rhythm early into sotalol administration. Figure 1c demonstrates the conversion of IART to sinus rhythm in a post-operative patient. The initial portion of the rhythm strip shows atrial flutter with variable AV node conduction. IART then terminates and converts to sinus rhythm with 1:1 conduction. IV = intravenous; IART= intra-atrial reentrant tachycardia; HR = heart rate. Figure 1a. Administration of IV Sotalol to a patient in IART Figure 1b. Administration of IV Sotalol to a patient in SVT Figure 1c. Conversion of IART with IV sotalol in a post-operative patient

Figure 2. Heart Rate and Blood Pressure before and during Sotalol Infusion in Group 1 Patients

Histograms and empirical cumulative distribution function comparisons of heart rate and blood pressure measurements for group 1 patients. The first row displays the histograms of heart rate and blood pressure measurements during the 1 hour prior to intravenous sotalol administration. The second row displays the histograms of heart rate and blood pressure measurement between 5 and 90 minutes following onset of sotalol administration. Histograms have been normalized for ease of visual comparison. The heights of the bars representing the percent of time spent at each value (y-axis). The x-axis represents the heart rate (beats per minute) or blood pressure values (mmHg). Counts for each vital sign are reported below each histogram. The third row displays the empirical cumulative distribution functions for their corresponding histograms in the first two rows. The more overlap there is between two empirical cumulative distribution functions, the more similar their corresponding histograms. NBP= non-invasive blood pressure, ABP = arterial line blood pressure, HR = heart rate, S= systolic, M= Mean, D= Diastolic

Figure 3. Heart Rate and Blood Pressure before and after Sotalol Infusion in Group 2 Patients
 Histograms and empirical cumulative distribution function comparisons of heart rate and blood pressure measurements for group 2 patients. The first row displays the histograms of heart rate and blood pressure measurements during the 1 hour prior to intravenous sotalol administration. The second row displays the histograms of heart rate and blood pressure measurements during the 5 hour infusion. Histograms have been normalized for ease of visual comparison. The height of the bars represent the percent of time spent at each value (y-axis). The x-axis represents the heart rate and blood pressure values. Counts for each vital sign are reported below each histogram. The third row displays the empirical cumulative distribution functions for their corresponding histograms in the first two rows. The more overlap there is between two empirical cumulative distribution functions, the more similar their corresponding histograms. NBP= non-invasive blood pressure, ABP = arterial line blood pressure, HR = heart rate, S= systolic M= Mean, D= Diastolic

Table 1.**Group Demographics**

	Group 1	Group 2
Total patients	24	23
Median Age yrs (IQR)	5.8 (1.4 –16.8)	0.37 (0.03 – 3.37)
% with Congenital Heart Disease	50% (n=12)	52% (n=12)
Immediate Post-operative period	25% (n=6)	30% (n=7)
Median Ejection Fraction % (IQR)	58% (40–65)	54% (43–61)
Supraventricular arrhythmias	88% (n=21)	83% (n=19)
Ventricular arrhythmias	12% (n=3)	17% (n=4)
Ventricular function	75% (n=18)	56% (n=13)
Normal	0% (n=0)	22% (n=5)
Mildly depressed	25% (n=6)	22% (n=5)
Moderately depressed		
Adverse effects	4% (n=1)	4% (n=1)

Group 1, Acute Arrhythmia Treatment Group. Group 2, Maintenance Infusion Group.

IQR indicates interquartile range (25th percentile, 75th percentile).

Table 2.

Comparison of Heart Rate and Blood Pressures before and during Sotalol Infusion in Group 1 Patients.

	HR	NBP S	NBP M	NMP D	ABP S	ABP M	ABP D
Pre infusion	158	94	69	55	74	58	45
Infusion	121	95	70	56	73	56	43
Mean Difference (95% CI)	37.7 (18.9, 56.4)	-1.2 (-6.4,4.1)	-1.1 (-4.7,2.4)	-0.6 (-3.8,2.7)	0.3 (-8.4,8.9)	2.1 (-3.3,7.5)	1.4 (-2.0,4.8)
Mean difference p-value	0.0004	0.644	0.504	0.728	0.946	0.389	0.357

Heart rate expressed as beats per minute. Blood pressure expressed as mmHg.

NBP = non-invasive blood pressure, ABP = arterial line blood pressure, HR = heart rate, S= systolic, M= Mean, D= Diastolic CI = confidence interval

Table 3.

Comparison of Heart Rate and Blood Pressures before and during Sotalol Infusion in Group 2 Patients.

	HR	NBP S	NBP M	NMP D	ABP S	ABP M	ABP D
Pre infusion	110	90	65	51	75	55	42
Infusion	109	91	66	52	77	56	43
Mean Difference (95% CI)	1.4 (-1.4,4.2)	-0.8 (-4.9,3.3)	-1.2 (-4.5,2.1)	-1.0 (-3.7,1.7)	-1.6 (-10.6,7.4)	-1.3 (-7.9,5.3)	-0.7 (-5.9,0.8)
Mean Difference p-value	0.311	0.679	0.442	0.459	0.708	0.670	0.761

Heart rate expressed as beats per minute. Blood pressure expressed as mmHg.

NBP= non-invasive blood pressure, ABP = arterial line blood pressure, HR = heart rate, S= systolic, M= Mean, D= Diastolic