Implementation of an Intravenous Sotalol Initiation Protocol: Implications for Feasibility, Safety, and Length of Stay

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Abstract

Introduction Oral sotalol initiation requires a multiple-day, inpatient admission to monitor for QT prolongation during loading. A one-day intravenous (IV) sotalol loading protocol was approved by the FDA in March 2020, but limited data on clinical use and administration currently exists. This study describes implementation of an IV sotalol protocol within an integrated health system, provides initial efficacy and safety outcomes, and examines length of stay compared to oral sotalol initiation. *Methods* IV sotalol was administered according to a pre-specified initiation protocol to adult patients with refractory atrial or ventricular arrhythmias. Baseline characteristics, safety and feasibility outcomes, and length of stay (LOS) were compared to patients receiving oral sotalol over a similar time period. *Results* From January 2021 to June 2022, a total of 29 patients (average age 66.0 ± 8.6 years, 27.6% women) underwent IV sotalol load and 20 patients (average age 60.4 ± 13.9 years, 65.0% women) underwent PO sotalol load. The load was successfully completed in 22/29 (75.9%) patients receiving IV sotalol and 20/20 (100%) of patients receiving oral sotalol, although 7/20 of the oral sotalol patients (35.0%) required dose reduction. Adverse events interrupting IV sotalol infusion included bradycardia (7 patients, 24.1%) and QT prolongation (3 patients, 10.3%). No patients receiving IV or oral sotalol developed sustained ventricular arrhythmias prior to discharge. LOS for patients completing IV load was 2.6 days shorter (mean 1.0 vs 3.6, $p < 0.001$) compared to LOS with oral load. *Conclusion* Intravenous sotalol loading has a safety profile that is similar to oral sotalol. It significantly shortens hospital LOS, potentially leading to large cost savings.

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Methods

IV sotalol was administered according to a pre-specified initiation protocol to adult patients with refractory atrial or ventricular arrhythmias. Baseline characteristics, safety and feasibility outcomes, and length of stay (LOS) were compared to patients receiving oral sotalol over a similar time period.

Results

From January 2021 to June 2022, a total of 29 patients (average age 66.0 $\pm$ 8.6 years, 27.6% women) underwent IV sotalol load and 20 patients (average age 60.4 $\pm$ 13.9 years, 65.0% women) underwent PO sotalol load. The load was successfully completed in 22/29 (75.9%) patients receiving IV sotalol and 20/20 (100%) of patients receiving oral sotalol, although 7/20 of the oral sotalol patients (35.0%) required dose reduction. Adverse events interrupting IV sotalol infusion included bradycardia (7 patients, 24.1%) and QT prolongation (3 patients, 10.3%). No patients receiving IV or oral sotalol developed sustained ventricular arrhythmias prior to discharge. LOS for patients completing IV load was 2.6 days shorter (mean 1.0 vs 3.6, $p < 0.001$) compared to LOS with oral load.

Conclusion

Intravenous sotalol loading has a safety profile that is similar to oral sotalol. It significantly shortens hospital LOS, potentially leading to large cost savings.

Keywords

Intravenous sotalol, atrial fibrillation, ventricular tachycardia, premature ventricular contractions, atrial flutter, quality improvement, antiarrhythmic drugs

Introduction

Atrial fibrillation (AF) is the most common rhythm disturbance, with lifetime risk estimates between 20-30% in the United States.[1]The disease is complex and often difficult to treat for clinicians. It represents a considerable cost burden with an estimated incremental cost of $26 billion in 2010.[2]Antiarrhythmic drugs (AAD) remain a cornerstone of therapy for management of atrial fibrillation (AF). The class III AAD sotalol has QT-prolonging effects that necessitate multiple days of inpatient hospitalization for observation during oral loading. This has been estimated to cost more than $10,000 per patient for a standard three-day admission, with the greatest proportion of cost coming from room and board.[3]The use of inpatient beds for these drug loads can also significantly impact hospital capacity to accept and manage other patients, given staffing and bed shortages.[4]

Intravenous (IV) sotalol was first approved for use by the FDA as a substitute for oral therapy in patients with supraventricular arrhythmias, life-threatening ventricular arrhythmias, and atrial fibrillation/flutter, but with recommendations for infusion over 5 hours.[5]In March 2020, the IV formulation of the drug received FDA approval for use in expedited loading of oral sotalol.[6]This approval was based on the Model-Informed Drug Development regulatory path, with simulated data showing that an initial one hour loading dose of IV sotalol followed by two oral doses in 24 hours reflected maximum QT prolongation over a one-day observation period.[7]The newly approved use case can reduce loading time by two days or more, with even greater reductions for those with impaired renal function. Despite the higher drug cost of IV sotalol, the anticipated reduction in hospital length of stay with intravenous sotalol is expected to lead to significant cost savings when compared to oral sotalol initiation.[3]

Thus far, available data supporting the use of one-day IV sotalol initiation has been limited to model-informed simulation data.[7] A single center experience with a one-day sotalol loading protocol for atrial arrhythmias has been briefly described, but there are no studies comparing IV versus oral sotalol load in a clinical context.[8]This study aims to describe implementation of a one-day IV sotalol initiation protocol for atrial and ventricular arrhythmias at a learning health system, and to provide initial feasibility and safety outcomes compared to oral sotalol initiation.

Methods

Patient Selection and Protocol Description

Administration of IV sotalol began in August 2021 using the protocol described in the Supplementary Appendix. Adult patients with a creatinine clearance (CrCl) greater than 30 mL/min and a primary indication of atrial or ventricular arrhythmias were included. Patients with bradycardia less than 60 bpm or corrected QT (QTc) interval greater than 450 ms were excluded, except in select cases with the approval and oversight of an attending cardiac electrophysiologist. Those with a paced QRS or bundle branch block were permitted a QTc interval up to 500 ms. Patients had their baseline electrolytes drawn and repleted, and a baseline electrocardiogram (ECG) was obtained. If they presented in a sustained atrial arrhythmia, cardioversion to sinus rhythm was performed prior to infusion. IV sotalol was then infused over 60 minutes with one-to-one nursing, frequent vital signs, and continuous cardiac telemetry. If the heart rate dropped below 60 bpm, the QT interval was used instead of the QTc interval for decision making. ECGs were obtained every 15 minutes during infusion. The infusion was stopped if the patient developed bradycardia less than 50 bpm or had prolongation of the QT/QTc interval to greater than 500 ms (550 ms for those with paced QRS or bundle branch block). After completion of infusion, patients were admitted to the inpatient telemetry unit for the remaining two oral doses, with subsequent ECGs 2-4 hours after each oral dose.

Patients undergoing oral sotalol initiation for atrial and ventricular arrhythmias from January 2021 to June 2022 were included for comparison with IV sotalol. Inclusion and exclusion criteria were identical. Oral doses were given based on standard prescribing regimens using CrCl, with ECGs similarly performed 2-4

hours after each dose of sotalol. Patients were required to be monitored for five oral doses before discharge. Patients with sustained atrial arrhythmias were cardioverted after the fifth oral dose of sotalol and monitored for an additional day after cardioversion. Those who experienced bradycardia less than 50 bpm or QT/QTc prolongation greater than 500 ms (550 ms for those with paced QRS or bundle branch block) either had their oral sotalol dose reduced or discontinued.

Demographics and Clinical Assessment

Patient demographics and clinical characteristics included age, sex, indication for sotalol initiation, CrCl, and left ventricular ejection fraction (LVEF). Patient clinical data was manually extracted via chart review. Heart rates and QT/QTc intervals by ECG were obtained every 15 minutes during sotalol infusion, and 2-4 hours after each oral sotalol dose. The QT interval was used for decision making when the heart rate was below 60 bpm. Abnormal QT/QTc intervals during sotalol loading were verified with manual calculation using the Bazett formula by the inpatient electrophysiology team. Heart rates and QT/QTc intervals were subsequently adjudicated by a study investigator.

Safety Endpoints and Outcome Measures

Outcomes related to sotalol dosing, changes in heart rate and QT/QTc interval in response to sotalol infusion and oral sotalol doses, and length of stay were assessed. Safety outcomes included the development of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF), bradycardia less than 50 bpm, and QT/QTc prolongation $>$ 500 ms (or 550 ms for those with paced QRS or bundle branch block). All events were determined by review of electronic medical records, with heart rates and QT/QTc intervals determined by evaluation of ECGs obtained during clinical care.

Statistical Analysis

Baseline characteristics and outcome comparisons between PO and IV sotalol initiation cohorts were performed using the student's t-test for non-categorical variables, and with the Chi-squared test for categorical variables. The one-sample Sign test was used to compare length of stay given the non-normal distribution.

Results

Demographics

Between January 1, 2021 and June 30, 2022, a total of 29 patients underwent intravenous sotalol initiation and 20 patients underwent oral sotalol initiation. Baseline demographics and clinical characteristics for both groups are reported in Table 1. The average age of the IV sotalol initiation group was 66.0 years and 27.6% were female. The primary indication for IV loading was 75.9% atrial arrhythmias and 24.1% ventricular arrhythmias. Average CrCl was 90.6 mL/min and average LVEF was 52.8%. For the PO sotalol initiation group, average age was 60.4 years and 65.0% were female. Primary indication for PO loading was 55.0% atrial arrhythmias and 45.0% ventricular arrhythmias. Average CrCl was 99.5 mL/min and average LVEF was 54.8%.

Clinical and Safety Outcomes

Changes in HR and QT/QTc interval over the course of IV sotalol initiation are described in Table 2. At the end of the 60-minute IV sotalol infusion, the mean QT/QTc interval had increased from baseline by 29.7 ms; at discharge after two additional oral doses, the QT/QTc interval had increased from baseline by 29.8 ms (Figure 1).

Of the 29 patients undergoing IV sotalol initiation, 7 had discontinuation of the infusion due to significant bradycardia (Table 3). 6 out of 7 of these patients were on AV nodal blocking agents (5 on metoprolol and 1 on diltiazem) that were not discontinued or dose reduced prior to the start of IV sotalol. Of the 7 patients who developed significant bradycardia, 3 also had prolongation of the QT interval that would have required discontinuation. A total of 22/29 patients (75.9%) underwent successful IV sotalol initiation. All patients undergoing PO sotalol initiation were able to complete their sotalol load, but 7 required dose

reductions due to bradycardia and/or QT prolongation. The two patients who required dose reduction due to bradycardia did not have their AV nodal blocking agents held prior to oral sotalol load. Four patients required cardioversion to sinus rhythm at the end of oral load. Average length of stay for the IV sotalol initiation group was 1 day compared to 3.6 days in the PO sotalol group ($p < 0.001$).

Discussion

In this study, IV sotalol was found to be a safe and well tolerated method of sotalol initiation for both atrial and ventricular arrhythmias. Almost 1 in 4 patients undergoing IV sotalol initiation had serious bradycardia, but 6/7 of them were on AV nodal blocking agents at the time of initiation. Discontinuing or dose reducing these agents prior to IV sotalol initiation may help to mitigate these effects. QT prolongation was noted only in the context of serious bradycardia in our IV sotalol cohort, with a rate of approximately 10% matching those found in other real-world data.[8] No patients undergoing oral sotalol initiation had the drug discontinued due to bradycardia or QT prolongation, but 35% of the patients had doses reduced to less efficacious doses.[9]No patients in either group had life threatening sustained ventricular arrhythmias during their hospitalization. Most notably, patients undergoing IV sotalol initiation had a significantly shorter hospital length of stay than patients undergoing oral sotalol initiation, with a mean difference of 2.6 days. Based on cost estimates done by Varela et al, this represents potential savings of more than $4000 per patient.[3]

Additional analysis was performed evaluating changes in the QT/QTc interval during IV sotalol infusion and after the first and second oral dose. The increase in the QT/QTc interval by the end of the intravenous infusion approximates that seen at discharge. These findings provide preliminary clinical corroboration for pharmacokinetics-pharmacodynamic models that simulate peak serum concentration of sotalol immediately after infusion.[7]Taken together, this suggests that discharge after infusion may be safe from a QT prolongation perspective. Efforts to decrease IV sotalol initiation time are already underway, with the DASH-AF study looking at discharge after IV infusion and a single oral sotalol dose currently enrolling patients.[10]

Study Limitations

Because of the small cohort size, conclusions about changes in the QT/QTc interval during and after infusion are tempered by large intra- and inter-patient variability in the QT/QTc interval. The PEAKS registry is a multi-center registry currently being established of patients receiving IV sotalol initiation that will further refine understanding of QT prolongation during and after infusion, with both clinical and pharmacokinetic-pharmacodynamic data.[11]This study's cohort also tended to be healthier, with overall preserved kidney function and low normal LVEF, and data may not be as generalizable to those with decreased renal clearance or more significantly depressed ejection fractions for whom sotalol can be more dangerous. There were also significantly more women in the PO sotalol load group, which may bias QT interval comparisons given the known differences in repolarization between genders.[12]Lastly, patients were only followed until discharge and longer-term safety outcomes are not available. These longer-term outcomes are presumed to be similar to patients loaded with oral sotalol.

Conclusion

The use of a one-day IV sotalol loading protocol for atrial and ventricular arrhythmias is safe and well tolerated. It reduces length of stay from an average of 3.6 days to 1 day compared to oral sotalol loading, which can translate into significant cost and resource savings. QT prolongation appears to be near its greatest immediately after sotalol infusion, which suggests discharge after infusion may be possible. Studies evaluating accelerated discharge after a single oral dose as well as an expanded multi-center registry of patients undergoing IV sotalol initiation are forthcoming.

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Table 1. Baseline demographics and clinical characteristics of patients receiving intravenous and oral sotalol initiation

	IV Sotalol	PO Sotalol	p-value
Patients (n)	29	20	-
Age (years)	66.0 ± 8.6	60.4 ± 13.9	0.087
Sex (n, % female)	8 (27.6%)	13 (65.0%)	0.009
Indication (n, %): - AF	17 (58.6%) 2 (6.9%) 3	11 (55.0%) 0 0 9 (45.0%)	0.168
- AFL	(10.3%) 7 (24.1%)		
- AT			
- PVC/VT			
CrCl (mL/min)	90.6 ± 24.1	99.5 ± 42.6	0.360
LVEF (%)	52.8 ± 12.0	54.8 ± 12.9	0.589

Abbreviations: IV, intravenous; AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; CrCl, creatinine clearance; LVEF, left ventricular ejection fraction; PVT/VT, premature ventricular contractions/ventricular tachycardia

Table 2. Changes in heart rate and QT/QTc interval during IV sotalol initiation

Patients completing initiation (n= 22)	Baseline (prior to receiving sotalol)	At end of intravenous sotalol infusion	At d
HR (mean ± SD)	71.2 ± 11.1	66.5 ± 13.8	61.8

QTc (mean ± SD)	456.9 ± 39.2	486.6 ± 35.1	486.7

Abbreviations: HR, heart rate

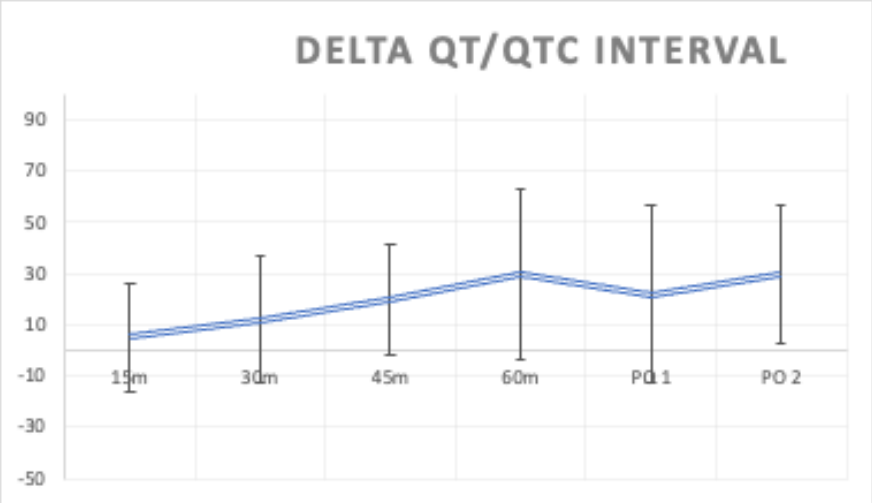

Figure 1. Mean change from baseline of the QT/QTc interval (ms) during IV sotalol initiation at 15 minutes, 30 minutes, 45 minutes, and 60 minutes into the infusion, as well as after the first and second oral dose. Error bars represent standard deviations.

Table 3. Clinical and safety outcomes during hospitalization for intravenous and oral sotalol initiation

	IV Sotalol	PO Sotalol	p-value
Bradycardia leading to drug discontinuation or dose reduction (n, %)	7 (24.1%)	2 (10.0%)	0.209
QT prolongation leading to drug discontinuation or dose reduction (n, %)	3 (10.3%)	6 (30.0%)	0.081
VT/VF	0	0	-
Average Length of Stay (mean, range)	1.0 (1 - 1)	3.6 (3 - 6)	< 0.001

Abbreviations: IV, intravenous; VT/VF, ventricular tachycardia/ventricular fibrillation