

Intravenous Sotalol - Reintroducing a Forgotten Agent to The Electrophysiology Therapeutic Arsenal

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Abstract

Sotalol is a racemic mixture possessing beta-blocker and class III anti arrhythmic properties. Approved by US food and drug administration (FDA) since 2009 based on its bioequivalence with oral sotalol, clinicians are less familiar with the potential uses of the intravenous form despite its re-launch in United States in 2015. Available literature suggests that intravenous sotalol in recommended doses can be safely administered in adult and pediatric population achieving rapid reliable therapeutic plasma concentration and without additional proarrhythmic effects when compared to its oral form as well as other antiarrhythmic medications. Intravenous sotalol may have potential uses as an alternative agent for highly symptomatic atrial fibrillation post cardiac surgery as well as in life threatening ventricular arrhythmias. As with its oral form, judicious use with close attention to QTc and renal function is warranted. Further studies are needed to better understand the safety, efficacy and different dosing regimens of parenteral sotalol in adults and children.

Introduction

Sotalol is a racemic mixture that has beta blockade (conferred by the l enantiomer) and potassium channel blockade (conferred by the d enantiomer) properties. Recognized initially for its anti-anginal and anti-hypertensive properties as a non-cardioselective beta-blocker, sotalol became known for its anti-arrhythmic effects in the 1980s. While oral sotalol is commonly utilized to maintain sinus rhythm in patients with Atrial Fibrillation (AF), Atrial Flutter (AFL) and to suppress life threatening ventricular arrhythmias (VA), its intravenous formulation is less commonly used. The US Food and Drug Administration (FDA) approved intravenous sotalol originally in 2009 based on its bioequivalence to oral sotalol; however, the drug was not available in the USA until it was re-launched in 2015. The intravenous formulation has potential as an additional rapid onset medication to treat both supraventricular and ventricular arrhythmias particularly in an emergency setting. [1]

Electrophysiology and Mechanism of Action

The Class II electrophysiological effects of sotalol are manifested as an increase in sinus cycle length, decreased AV nodal conduction and increased refractoriness. Sotalol also exhibits class III antiarrhythmic effects through I_{Kr} blockade resulting in prolongation of atrial and ventricular monophasic action potentials, and effective refractory

Key Words

Intravenous sotalol, Sotalol hydrochloride, Refractory ventricular arrhythmia, Atrial fibrillation, Post operative atrial arrhythmia, QT prolongation.

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periods in atria, ventricle, and accessory pathways.

The beta-blocker effect of oral sotalol is non-cardioselective, half maximal at 80mg/day dose and maximal at a dose of 320-640 mg/day. Compared to some other beta-blockers= sotalol does not have a partial agonist or membrane stabilizing activity. While studies have suggested that sotalol manifests its anti-arrhythmic and QT prolonging properties only with doses in excess of 160 mg, Somberg et al noted significant QT prolongation after administration of a single low dose of sotalol. [2]

Effect of sotalol therapy has been studied in both acute onset and persistent AF. Infusion at a dose of 1.5 mg/kg decreased the energy requirement for transvenous as well as transthoracic cardioversion to restore sinus rhythm. In a study of 18 patients with persistent AF, Lai et al reported a mean decrease in transthoracic cardioversion energy of 50 J. Sotalol infusion significantly increased the mean A-A (atrial local electrogram) intervals during AF in the patients needing lower energy for cardioversion. [4] Another study found the effect to be more evident in acute AF patients using transvenous atrial defibrillation as opposed to chronic AF. [5] Slowing of atrial rate and increase in R-R interval was observed in both studies.

D-sotalol has also been shown to lower defibrillation energy (DFT) for ventricular fibrillation up to 32 ± 27% with a statistically significant increase in ventricular effective refractory period and decrease in the incidence of hemodynamically significant and sustained ventricular arrhythmias. [6],[7] This effect was studied in comparison to amiodarone in the OPTIC trial where 94 patients were randomized to receive amiodarone, beta-blockers and/or sotalol therapy. While a 1.29 J statistically significant rise in DFT was observed in the amiodarone arm when compared to a slight decrease in DFT with beta-blockers and sotalol group, the overall effect was deemed clinically insignificant. [8]

Hemodynamic Effects of intravenous Sotalol in Humans

Intravenous sotalol causes a significant decrease in heart rate and cardiac output with little or no effect on mean stroke volume, right atrial and pulmonary capillary wedge pressure. These effects, evident within the first 10-15 minutes of the infusion, are seen in both healthy subjects and in patients with heart disease, at rest, with exercise and even at low doses. Thumala et al reported a significant decrease in HR, cardiac index and LV dp/dt at rest in patients with structural heart disease but with an increase in LVEDP and systemic vascular resistance.^{[9],[10]}

Pharmacology, Safety & Dosing

Sotalol hydrochloride injection is FDA approved in the United States for life-threatening ventricular arrhythmias and maintenance of sinus rhythm in highly symptomatic, refractory AF or AFL. The principles applicable to oral sotalol in terms of safety are valid for intravenous sotalol administration as well. Per FDA labeling, intravenous sotalol is to be administered as a diluted infusion slowly over 5 hours.

Pharmacokinetics of Intravenous Sotalol

The bioavailability of oral sotalol is around 93% with peak plasma concentrations observed in 2.5-4 hours. It is not bound to plasma proteins and is excreted unchanged by the kidneys with an elimination half-life of 12-16 hours. In comparison, intravenous sotalol reaches therapeutic levels within minutes and the corresponding dose is slightly less than oral dose ([Table 1]).

Table 1: Dose Conversion between Oral and Intravenous Sotalol

Oral Sotalol	Intravenous Sotalol
80 mg	75 mg (5 mL)
120 mg	112.5 mg (7.5 mL)
160 mg	150 mg (10 mL)

The maximum concentration (C_{max}) of 75mg of intravenous sotalol is similar to an orally administered dose of 80mg when infused over 5 hours. The recommended infusion rate is based on evidence showing a large overshoot of maximum serum concentration with rapid administration and high risk of QT prolongation.^[11]

Pharmacodynamic Effects of intravenous Sotalol

The beta-blocker effect is similar in both oral and intravenous sotalol and can be evaluated by decrease in HR and change in RR interval on EKG. The effect is most evident within the first half hour of drug administration, peaks at 1 hour and reaches a plateau thereafter. Further increase in RR interval may be counter acted by a reflex sympathetic activation in response to a fall in BP. The changes in RR interval are highly dose dependent and are evident at lower than anti-arrhythmic doses.^[11]

In a bioequivalence study comparing oral and intravenous sotalol in 15 healthy volunteers, a strong correlation was found between serum sotalol concentration and QT prolongation with risk of Torsade de pointes (TdP) increasing when QTc exceeded 500 msec. QTc prolongation with intravenous administration occurs within 0.5 hours of infusion, reaches a maximum value at 2 hours, and shows a linear correlation with sotalol blood level.^{[11],[12]}

Gender Differences in Response to Sotalol Therapy

Females are more likely to have drug induced excessive QTc prolongation and have a 2-3 times higher risk of developing TdP with intravenous sotalol as compared to males. The disparity in cardiac repolarization has been studied in females aged 18-45 years

by Somberg et al. The mechanisms underlying this gender disparity is not completely understood but the fact that pre-pubertal males and females have no difference in QTc intervals points to some role for gonadal steroids. Therefore, close QTc monitoring is essential in females during intravenous sotalol use.^[15]

Sotalol Therapy during Pregnancy and Lactation

Sotalol is classified as a category B drug with available human safety data. It does cross the placental barrier but in animal studies there was no increased incidence of congenital anomalies.^[1] O'Hare et al studied 6 healthy pregnant female volunteers between 32-36 weeks of gestation and up to 6 weeks post partum receiving 100 mg intravenous and 400 mg oral sotalol. The study showed altered pharmacokinetics of sotalol in antenatal patients with similar oral bioavailability, rapid plasma clearance (6.6 hours versus 9.3 hours in post natal period) and no change in volume of distribution.^[13] Although data is inconclusive there is still suggestion that sotalol can be potentially teratogenic and hence, is not often the first choice in pregnant females. Close fetal monitoring is necessary when used. It is readily secreted in breast milk and infant may ingest as much as 20% of the maternal dose. Breast-feeding decision while on therapy should be made taking into account the importance of the drug to the mother and monitoring the baby for signs of toxicity.^{[1],[14]}

Safety Profile, Proarrhythmic Effects & Adverse Reactions

Intravenous sotalol should be initiated in a monitored clinical setting with available resuscitation equipment. QT intervals, serum potassium and magnesium need to be checked periodically. Creatinine clearance should be calculated to establish dosing interval. It is generally recommended not to initiate sotalol therapy with baseline QTc more than 450 msec (Use JT >330 msec for QRS duration > 100 msec).

Contraindications to therapy include severe sinus bradycardia, sick sinus syndrome, second or third degree AV block unless functional pacemaker in place, congenital long QT syndrome, cardiogenic shock, uncontrolled heart failure, creatinine clearance <40 ml/min, serum potassium <4 meq/L, bronchospastic conditions or known hypersensitivity to sotalol.^[16]

Proarrhythmia from oral sotalol is seen in 2-4% of patients. The estimated risk is similar or lower with intravenous sotalol. Interestingly, a meta-analysis of 962 patients, with the majority having underlying heart disease, showed the risk of TdP with intravenous sotalol to be <1%. Tissue accumulation has been postulated as a possible explanation for TdP with chronic oral therapy, which is not seen with short-term intravenous use. Alternative explanations for this low incidence of TdP in this study include administration during tachycardia in the acute setting and resultant shortened QT, possible reverse use-dependence, and heterogeneity in dosing and infusion duration.^[17]

Hypotension is the most commonly reported side effect after intravenous sotalol, particularly when given in the early post-cardiac surgery setting. It is also of clinical significance in patients with VT with or without concomitant use of lidocaine. The incidence is lower in comparison to amiodarone and similar in groups randomized to lidocaine or sotalol.^{[1],[17],[20]} Bradycardia, AV block and heart failure are also reported, especially in patients with low ejection fraction. Non-cardiac adverse effects from intravenous sotalol include non-specific gastrointestinal or neurological (headache, dizziness, malaise) complaints but the incidence is significantly lower than amiodarone. Non-allergic bronchospasm from beta-blocker properties of sotalol

are reported in 1.8-2.4% cases. [1],[20]

FDA Approved Clinical Indications for Intravenous Sotalol

The current FDA approved indications for intravenous sotalol are: As a substitution for oral formulation in patients. It can be particularly useful in the post-operative and critically ill patient group when reduced intestinal permeability and gastrointestinal absorption is insufficient to reach effective serum concentrations.

To prolong time in sinus rhythm and prevent atrial fibrillation/atrial flutter recurrence in highly symptomatic patients.

For the treatment of life threatening ventricular arrhythmia provided they are not associated with QT prolongation and TdP.

For the treatment of supraventricular and ventricular arrhythmia in pediatric population. [16]

IV Sotalol: Is there a potential role for another intravenous antiarrhythmic agent in 2016? ([Table 2])

Post-Cardiac Surgery Atrial Arrhythmias

Atrial arrhythmias are common following cardiac surgery. These arrhythmias not only increase patient morbidity but also present a therapeutic challenge in terms of rate and rhythm control. Beta-blockers are first line therapy (class IA recommendation) followed by amiodarone (class IIA) and sotalol (class IIB) in perioperative period. [18] Randomized controlled trials have shown sotalol to be more effective than placebo in treating post-operative supraventricular tachycardia. Two clinical trials have shown a non-significant difference between sotalol and amiodarone in preventing post-operative AF. Sotalol was more effective than beta-blockers in reducing the incidence of AF in cardiac surgery patients. The combination of magnesium and sotalol had an augmented significant

Table 2: Potential Clinical Applications of Intravenous Sotalol

Clinical Applications of Intravenous Sotalol
Treatment of AF in post cardiac surgery patients (conversion rates similar to intravenous amiodarone with shorter loading time for Class III effects and shorter elimination half life upon withdrawal)
Prevention of early recurrence of atrial fibrillation post cardioversion and maintenance of SR
Potential use for reducing hospital time for sotalol initiation but further studies are needed
Life threatening ventricular tachycardia as an alternative agent to intravenous amiodarone or procainamide
Post congenital heart surgery in pediatric population
Pediatric supraventricular and ventricular tachycardia

reduction in postoperative AF. [19],[20]

Intravenous sotalol may indeed prove to be useful for rate and rhythm control of atrial arrhythmias in post-cardiac surgery patients without contraindication to beta-blockers. The exact time for initiation of therapy remains a concern although it has shown similar efficacy before and after surgery. Hemodynamically significant hypotension and difficulty in maintaining sinus rhythm due to interaction with anesthesia (beta-blocker properties) are major issues when loaded before surgery. Given its advantage over amiodarone in terms of short duration of action as well as short loading time to achieve steady state, intravenous sotalol may prove to be a reliable alternative agent. [19]

Available data supports the cost-effectiveness of using intravenous sotalol, showing reduction in hospital stay by 0.5 days. Further studies are needed to provide definitive information in terms of benefit gained. [19]

Restoration and Maintenance of Sinus Rhythm in Atrial Fibrillation and Atrial Flutter

Sotalol has similar efficacy compared to class IA and IC anti-

arrhythmics as well as amiodarone in conversion from AF to normal sinus rhythm. [20],[21] Thomas et al showed poor overall reversion rate in patients randomized to receive sotalol, amiodarone or digoxin but overall superior ventricular rate control (less than 100 beats per minute) with sotalol and amiodarone at 6 and 12 hours in comparison to digoxin. In the same study, patients receiving amiodarone infusion were more likely to have adverse reactions including hypotension. No additional benefit and increased risk of adverse effects were observed with higher doses of class III agents. [22] In another study of 120 patients with new onset AF randomized to digoxin, sotalol or amiodarone, a definite benefit was observed with amiodarone and sotalol in terms of reduction in time to reversion to normal sinus rhythm and ventricular rate control with minimal side effects. [23]

Analyzing pooled data from randomized studies, Somberg et al. reported similar conversion rates to NSR using either amiodarone or sotalol in new onset AF with the lowest success rates in persistent AF. Although patients on amiodarone reported more adverse reactions,

Table 3: Recommendations for Use of Intravenous Class III Anti Arrhythmic Drugs in ACLS Guidelines

	IV Sotalol	IV Amiodarone	IV Ibutilide
Dosing	1.0-1.5 mg/kg over 5-30 minutes	1000 mg over first 24 hours: Initial Load: 150 mg in 100 mL infused over 10 min; followed by 1mg/min for 6 hours; followed by 0.5 mg/min thereafter	Patients weighing ≥60 kg: 1 mg over 10 minutes. Patient weighing <60 kg: 0.1 mL/kg (0.01 mg/kg) over 10 minutes. A second 10-min infusion may be administered if arrhythmia does not terminate after first infusion.
Indications	Refractory VT/VF	Refractory VT/VF	QT prolongation and Torsades de pointes
Major Warnings	QT prolongation and Torsades de Pointes	Boxed Warning for hypotension; bradycardia and AV block; hepatic injury, Pulmonary toxicity.	0.625

those treated with sotalol had higher risk of AF recurrence. [20]

Only intravenous Ibutilide (given as 1-2 mg doses over 10 minutes) has been shown to be more effective than intravenous sotalol in converting AF/AFL to NSR. Similar conversion rate was observed for Dofetilide for AFL. The risk of sustained TdP with Ibutilide was around 2% when higher doses were used. [24]

In-Hospital Initiation of Sotalol for Atrial Fibrillation

Intravenous sotalol, offers significant flexibility in dosing compared to oral sotalol. It reaches therapeutic levels quicker and offers easier dose titration based on QTc and clinical response. These properties could be potentially useful in hospital initiation of sotalol and to facilitate transition to oral sotalol.

Further studies are needed and are being planned to look at dosing and duration for intravenous sotalol administered as a loading dose to initiate oral sotalol therapy in adult patients with AF.

Intravenous sotalol in prevention of early recurrence of atrial fibrillation after cardioversion

Early recurrence of atrial fibrillation (ERAF) is known to occur in 13-36% of the patients after electrical cardioversion. Repeat cardioversion without pharmacologic support is successful only in 10% of these patients. Atrial premature beats with shorter coupling interval and greater prematurity as well as sinus node suppression and bradycardia (long-short sequence) induced dispersion of

refractoriness in atrial myocardium are postulated mechanisms. With the exception of profoundly bradycardiac patients, intravenous sotalol has been shown to suppress ERAF in up to 80% of patients. Sotalol confers benefits in these cases with its beta-blocking as well as anti-arrhythmic properties.^[25]

Ventricular Arrhythmias

Intravenous sotalol is approved for life threatening ventricular arrhythmias with the initial dose being 75mg infused over 5 hours once or twice daily depending on renal clearance. Doses may be titrated to therapeutic effect while monitoring hemodynamic parameters and QTc interval. Intravenous Sotalol rapidly increased ventricular effective refractory period and acutely terminated sustained VT in 69% as opposed to 18% given Lidocaine. It has been shown to be similar to Nifekalant and Dofetilide in suppressing inducible VT. While the SWORD trial with d-sotalol (no beta blocker effect) showed increased mortality in acute myocardial infarction, later studies suggest that racemic sotalol is effective and safe in ischemic cardiomyopathy and can be used in post infarction patients without added risk.^{[16],[26],[27]}

Although amiodarone and sodium channel blockers remain the drugs of choice for treating VT, the availability of intravenous sotalol may provide an effective substitute particularly in young patients with structurally normal hearts. Studies have shown that the risk of TdP may be comparatively lower with intravenous dosing provided it is injected slowly and in the absence of significant renal dysfunction, hypomagnesemia or hypokalemia.

The acute advantage gained by terminating VA can be transitioned over to sustained response with continued oral therapy. In a prospective multicenter trial, Sotalol significantly reduced VT/VF seen in patients with implantable cardioverter defibrillators but the rate of discontinuation of the medication because of side effects remained high (35%).^[28]

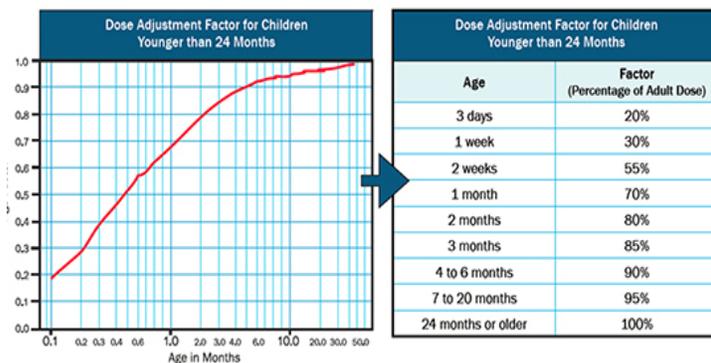


Figure 1: Recommended Dose Adjustment for Intravenous Sotalol in Pediatric Patients

Utility in Arrhythmia therapy for Children

Sotalol is not the preferred first line of treatment in pediatric population due to lack of supporting evidence and safety concerns. It is however, used as a second line agent for incessant and refractory supraventricular and ventricular tachycardia in neonates, infants and children. High dose sotalol therapy (150 mg/m²) was shown to be safe and efficacious in achieving partial or complete suppression of SVT (including atrial tachycardia, AV reentrant tachycardia and junctional ectopic tachycardia) in 90% of the patients between ages of 7 to 728 days. No proarrhythmic effect or significant QTc prolongation requiring alteration of therapy was observed.^[28]

Similar results have been reported with intravenous sotalol with success rate of arrhythmia termination ranging from 60-70%. QT prolongation requiring treatment alteration, TdP, bradycardia, and AV block occurred only at very high doses (210 mg/m²). Intravenous sotalol may therefore be acceptable for use in children with resistant tachycardias, when initiated in hospital setting with doses normalized to body surface area ([Figure 1]).^{[1],[16]}

Conclusion

Intravenous sotalol may provide a new therapeutic option to US physicians for effective treatment of supraventricular and ventricular arrhythmias in the pediatric and adult population particularly those with preserved ejection fraction and renal function. Moreover, by delivering a dose-dependent serum concentration independent of absorption and bioavailability, intravenous sotalol shortens time to reach therapeutically effective levels and could allow seamless transition to oral sotalol. As with its oral form, judicious use with close attention to QTc and renal function is warranted and further studies are needed to better understand the safety, efficacy and different dosing regimens for intravenous sotalol in adults and children.

Conflict Of Interests

None.

Disclosure

SAB-No relevant disclosures.

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