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REVIEW

The Use of Intravenous Sotalol in Cardiac Arrhythmias

Rahul Samanta, MBBS, MRCP, FRACP [a,b], Aravinda Thiagalingam, PhD, FRACP [a,b], Christian Turner, FRACP [c], Dhanunjaya J. Lakkireddy, MD [d], Pramesh Kovoor, MBBS, PhD, FRACP [a,b*]

[a]Department of Cardiology, Westmead Hospital, Sydney, NSW, Australia
[b]The University of Sydney, Sydney, NSW, Australia
[c]Children's Hospital, Sydney, NSW, Australia
[d]University of Kansas Hospital, Kansas City, KS, USA

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Sotalol is a non-selective beta-adrenergic blocking agent without intrinsic sympathomimetic activity. It has the additional unique property of producing pronounced prolongation of the cardiac action potential duration. Sotalol therapy has been indicated for the management of supraventricular arrhythmias, refractory life threatening ventricular arrhythmias and atrial fibrillation/flutter. Until recently, sotalol was only available in the oral form, however, it was approved for intravenous administration by the US Food & Drug Administration (FDA). The current recommendations are for sotalol 75–150 mg to be administered intravenously over 5 hours. This rate of administration does not reflect the majority of the research that has been performed with regards to intravenous sotalol. Also, the safety of intravenous bolus dosing of 100 mg over 1 and 5 minutes has previously been demonstrated. The antiarrhythmic action of sotalol depends on its ability to prolong refractoriness in the nodal and extra nodal tissue. Hence, by giving a lower dose over a long duration, patients may not necessarily benefit from its anti-arrhythmic potential. The purpose of this article is to review the research that has been conducted with regards to dosage and safety of intravenous sotalol, its electrophysiological effects and finally the spectrum of arrhythmias in which it has been used to date.

Keywords Sotalol • Arrhythmias • Ventricular arrhythmias • Anti arrhythmics

Background and History

Sotalol is a non-selective beta-adrenergic blocking agent without intrinsic sympathomimetic activity. It has the additional unique property of producing pronounced prolongation of the cardiac action potential duration [1] which becomes manifest on the electrocardiogram (ECG) by a prolonged QT interval [2]. The unique actions of sotalol were first described by Singh et al. in isolated rabbit atrial and ventricular muscle [3]. Sotalol therapy has been indicated for the management of ventricular and supraventricular arrhythmias, refractory life threatening ventricular arrhythmias and atrial fibrillation/flutter [2]. In addition to this, it has also been used to prevent inappropriate shocks in patients with implantable cardioverter defibrillators and management of postoperative atrial fibrillation (AF) in patients undergoing cardiovascular surgery. However, until recently, a parenteral formulation of sotalol was unavailable. Hence, sotalol therapy was not an option for patients who were unable to take oral therapy. This problem was addressed in 2010 when the use of intravenous sotalol was approved by the US Food & Drug Administration (FDA) [2].

The recommended dose was 75 to 150 mg infused over 5 hours once or twice daily depending on the renal function.

*Corresponding author at: Department of Cardiology, Westmead Hospital, PO Box 533, Wentworthville, NSW 2145, Australia. Tel.: +61-2-9845-6030, Fax: +61-2-9845-8323., Email: pramesh.kovoor@sydney.edu.au

This dosing schedule was, however, not in agreement with some of the previous research that has been conducted. The purpose of this article is to review the research that has been done specifically with regards to intravenous sotalol. Based on this review, recommendations could be made for a safe and effective dosing schedule for intravenous sotalol and to describe further potential indications.

IV Sotalol Dosing and Administration/Current FDA Recommendations

The FDA indications for intravenous sotalol include substitution for oral therapy in patients who are unable to take oral sotalol, maintenance of normal sinus rhythm in patients who have symptomatic atrial fibrillation/flutter and are currently in sinus rhythm and treatment of documented life threatening ventricular arrhythmias [2] (Figure 1).

The recommendations for intravenous (IV) dosing have been made based on the corresponding oral dose [2].

Prior to administration, a baseline ECG should be performed along with serum potassium, magnesium levels and the creatinine clearance should be calculated. Sotalol should not be administered in patients with QT interval > 450 ms (JT > 330 ms if QRS > 100 ms) [4]. The dosing schedule should be adjusted according to the creatinine clearance. Twice and once daily dosing is recommended for creatinine clearance of greater than 60 and 40–60 mls/min respectively. Sotalol is not recommended if the creatinine clearance is less than 40 mls/min.

The recommended starting dose for intravenous sotalol, is 75 mg over 5 hours once or twice daily again depending on the creatinine clearance. This dose can be titrated up to 112.5 mg over 5 hours. For ventricular arrhythmias the recommended starting dose is the same and this can be increased by 75 mg/day every 3 days. Oral doses as high as 240–320 mg have been used which would correspond to an IV dosage of 225–300 mg. The most effective dose for prevention of AF was 120 mg od or bd (corresponding to 112.5 mg IV). However, doses as high as 160 mg od or bd (150 mg IV) have been used.

Intravenous sotalol has also been recommended for treatment of wide complex tachycardias in the 2015 American Heart Association (AHA) guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care [5].

Paediatric Dosing

For children 2 years and above initiation at 30 mg/m^2 three times a day (equivalent to 160 mg oral daily dose for adults) was recommended by the manufacturer [4]. Subsequent titration to 60 mg/m^2 (360 mg total adult daily dose) should be performed according to blood pressure, QT interval and clinical response. For children younger than 20 months the dosage should be reduced by a factor which depends mainly upon age.

Replacement of Oral With Intravenous Sotalol

The adjustment for the intravenous dosage assumes on average a 94% bioavailability of oral sotalol [2]. Based on the

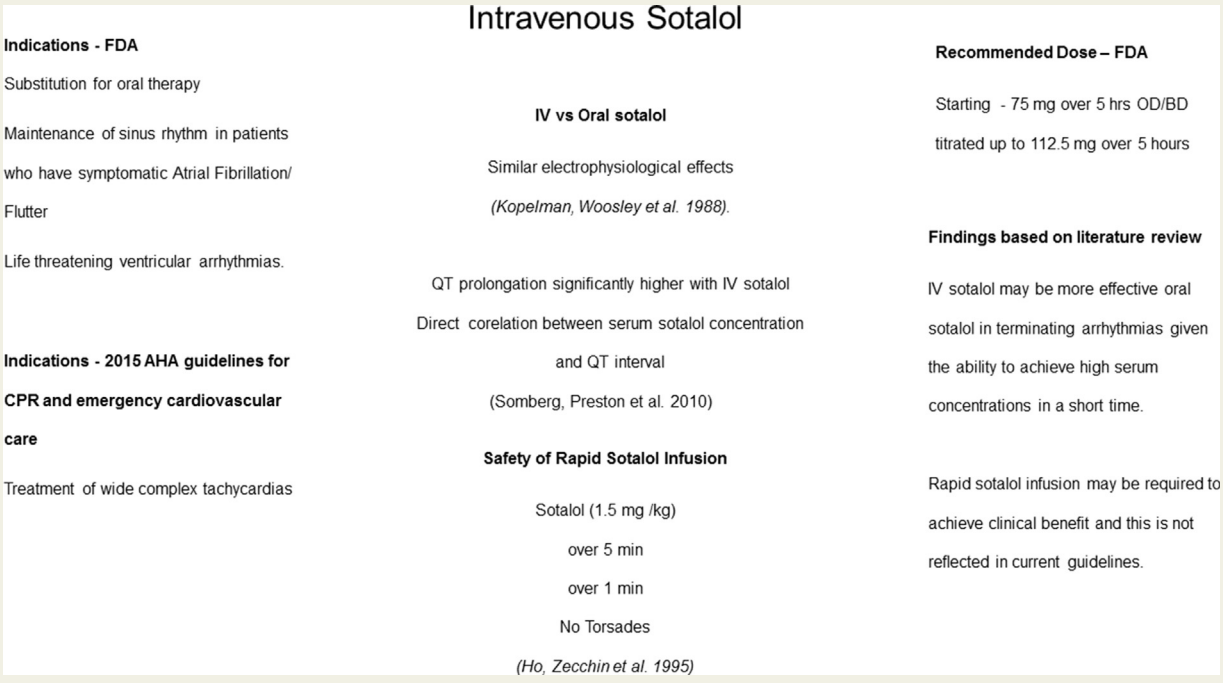

Figure 1 Current guideline based dosing and indications for intravenous sotalol and potential additional indications along with rationale for rapid IV infusion.

known linear pharmacokinetics of sotalol, it has been recommended that 80 mg and 160 mg oral dose can be replaced with 75 mg and 150 mg intravenous dose respectively. Rapid intravenous administration leads to high serum concentrations. The degree of QT prolongation is directly proportional to the serum levels of sotalol [6]. Hence, this may potentially result in an increased risk of torsades de pointes [2]. Despite the increase in QT interval with rapid intravenous administration, the incidence of torsades de pointes is rare [7].

Somberg et al. performed a study to determine the dose of intravenous sotalol that would produce effects similar to oral sotalol [2]. Fifteen volunteers were given intravenous (75 mg over 2.5 hr) and oral sotalol (80 mg). Significant QTc prolongation occurred both after oral and intravenous administration starting at 0.5 hours and peaking at 2 hours. There was more prolongation with IV administration than after oral sotalol. Higher doses or a more rapid/bolus administration were not assessed in this study.

Intravenous sotalol resulted in higher C_{max} in comparison to oral sotalol [2]. Further to this, simulation studies demonstrated that with increasing the length of infusions to 3, 4, and 5 hours, the C_{max} changed to 128%, 113%, and 102% of the oral C_{max}. Area under curve (AUC) did not differ according to the duration of the infusion. On the other hand, bolus administration of 75 mg of sotalol over 5, 10 and 20 minutes resulted in a significantly high (more than double) C_{max} in comparison to 80 mg of oral sotalol. Hence the recommendation was made for a 5-hour infusion to duplicate the C_{max} of oral administration [2]. In the same study, the maximum beta blocking effect was noted at lower doses (1 hr/30 mg) in comparison to the dose required for maximum QT prolongation (2 hrs/60 mg).

Use of Rapid Intravenous Sotalol Infusion

The safety of a rapid sotalol infusion has been previously demonstrated by Ho et al. [7] (Table 1). In 109 patients with spontaneous and inducible VT, sotalol (1.5 mg/kg) was administered over 5 minutes in 57 and over 1 minute in 52 patients during sinus rhythm. After commencement of the 5-minute infusion, a rapid increase in the Right Ventricular Effective Refractory Period (RVERP) was noted from a baseline of 231 ± 17 ms, reaching a plateau of 268 ± 23 ms at 10 minutes. Following the 1-minute injection, RVERP increased almost immediately from a baseline of 237 ± 25 ms to reach a plateau of 271 ± 31 ms at 5 minutes. Significant hypotension was noted in two patients (one in each group); both responded to volume replacement. Significantly, torsades was not noted in this study.

Electrophysiology of Sotalol

Sotalol is the only beta blocking drug that causes delayed myocardial repolarisation after acute administration [3]. The class III action of sotalol was first demonstrated by Singh et al. [3] In their study on isolated atrial and ventricular muscle, sotalol greatly prolonged the duration of action potential. Sotalol had no effect on the initial phase and had exerted its action on the plateau phase [8]. In addition to this, sotalol was found to prolong the Q-Tc interval of the electrocardiogram in anaesthetised guinea pigs. The authors concluded that this effect contributed to the anti-arrhythmic activity of sotalol. One postulated mechanism by which this occurs is through specific blockade of the rapidly activated component of the delayed rectifier potassium current [9].

Electrophysiology of Intravenous Sotalol

In agreement with the previous animal studies Edwardsen et al. [10] demonstrated that sotalol given in an intravenous dose of 100 mg, produced a consistent increase in the ventricular repolarisation time. Echt et al. compared the effects of intravenous propranolol and sotalol in 17 patients [11]. Sotalol, but not propranolol, demonstrated prolongation of

Table 1 **Dosing of Intravenous Sotalol.**

Author	No. of Subjects	Dose	Duration	QT Prolongation	Comments
Somberg et al.	15 healthy volunteers	Sotalol given both 75 mg IV and 80 mg PO	2.5 hrs (IV)	QT prolongation at 2 hrs was significantly more in IV vs oral and this correlated with higher serum sotalol concentration.	Administration of the infusion over 5 hours resulted in equivalent Cmax when compared to oral dose. No torsades.
Ho et al.	109	1.5 mg/kg	5 min (57 patients) 1 min (52 patients)	RVERP 268 ± 23 from 231 ± 25 at baseline after 10 min RVERP 271 ± 31 from 237 ± 25 at 5 min	No hypotension or torsades despite the presence of left ventricular dysfunction.

Abbreviations: RVERP, right ventricular effective refractory period.

the right atrial and right ventricular monophaslc action potential at 90% repolarisation. The duration of prolongation was dependent on plasma sotalol concentration. In addition to this, several investigators have performed detailed studies assessing the electrophysiological effects of intravenous sotalol. The findings from these studies have been shown in Table 2. The studies demonstrated increase in sinus cycle length, sinus node recovery time (excluding one study where there was no significant effect [12]), AH interval, atrioventricular (AV) effective refractory period, AV functional refractory period, right atrial effective refractory period and right ventricular effective refractory period [12–14]. Certain electrophysiologic changes induced by intravenous sotalol were in common with other beta blockers including propanolol, atenolol and metoprolol. These effects included prolongation of sinus cycle length, sinus node recovery time, AH interval, AV effective refractory period and AV functional refractory period [14]. The prolongation of the right atrial and the ventricular effective refractory period has been attributed to the class three action of sotalol [13]. Thus, the electrophysiologic changes produced by sotalol are present in all cardiac tissues, including the accessory conduction pathways.

Comparison Between Electrophysiological Effects of IV and Oral Sotalol

Kopelman et al. compared the effect of IV and oral sotalol in patients with coronary artery disease and ventricular tachycardia (VT) [15]. Intravenous (1.5 mg/kg over 30 mins followed by an infusion of 0.008 mg/kg) and oral sotalol (160 mg bd for 12 hrs, followed by an adjusted dose according to efficacy/side effects) caused significant increases in sinus cycle length, AH interval, Wenckebach cycle length and atrioventricular node relative and functional refractory periods compared with the baseline drug-free state. There was no statistically significant difference between oral and intravenous sotalol when comparing these parameters. Also, both intravenous and oral sotalol caused significant prolongation of QT interval, atrial effective refractory period and right ventricular effective refractory period compared with baseline. No differences were noted between intravenous and oral sotalol in this regard. Both intravenous and oral sotalol significantly increased the VT cycle length and prevented induction of sustained VT in a similar percentage

Table 2 Electrophysiological Effects of Intravenous Sotalol.

Author	Ward et al.	Edvardsson	Echt et al.	Nathan et al.	Touboul et al.	Touboul et al.	Kunze et al.	
Year	1979	et al. 1980	1982		1984	1987	1987	
No. of Patients	10	8	17	24	12	14	17	
Infusion protocol	0.4 mg/kg	100 mg	0.30 or 0.60 mg/kg	0.40 mg/kg	0.6 mg/kg in 5 minutes	0.6 mg/kg in 5 minutes	1.5 mg/kg in 15 minutes	
SCL	↑			↑	↑			
SNRT	↑			↑	–			
SA	–			↑				
AH	↑			↑	↑	↑	↑	
HV	–			–	–	–	–	
QRS					–			
QT			↑	↑	↑			
QTc				–				
JT					↑			
AVERP	↑				↑	↑	↑	
AVRRP						↑		
AVFRP	↑				↑	↑	↑	
RRPHP						↑	↑	
ERPRA	↑		↑		↑	↑	↑	↑
ERPRV	↑	↑	↑		↑	↑	↑	–↑
APAG					↑		↑	↑
APRG					↑		↑	↑

Abbreviations;: SCL, sinus cycle length; SNRT, sinus node recovery time; AVERP, atrioventricular effective refractory period; AVRRP, atrioventricular relative refractory period; AVFRP, atrioventricular functional refractory period; RRPHP, relative refractory period His Purkinje system; ERPRA, effective refractory period right atrium; ERPRV, effective refractory period right ventricle; APAG, accessory pathway antegrade effective refractory period; APRG, accessory pathway retrograde effective refractory period. ↑ – increase, – no change.

of patients (intravenous sotalol 2 of 9, 22%, oral sotalol 2 of 11, 18%).

The significantly higher serum concentrations achieved with rapid infusion of intravenous sotalol were not achieved with oral administration [2]. Hence theoretically IV sotalol may have more potential to terminate arrhythmias in comparison to oral.

Intravenous Sotalol and Individual Arrhythmias

Pharmacological Cardioversion of Atrial Fibrillation

Early studies looking at the effect of intravenous sotalol in cardioverting acute AF resulted in a variable success rate from 0 to 47% [10]. These studies, however, used relatively small doses of intravenous sotalol varying from 10 to 60 mg. In a study involving 41 patients with recent onset AF and normal LV function administration of 40 mg sotalol intravenously resulted in cardioversion in 54% of the patients [16]. In a trial involving 93 patients Sung et al. assessed the safety and efficacy of sotalol to terminate AF (48 patients) and to compare two doses of sotalol (1 mg/kg and 1.5 mg/kg over 10 minutes). There was no difference between the two doses of sotalol [17]. In another study 40–100 mg of sotalol when administered intravenously in eight patients with chronic atrial fibrillation resulted in cardioversion in only one patient [10].

The use of sotalol following cardiovascular surgery was investigated in a randomised trial involving 40 patients with coronary artery bypass graft (CABG) and atrial fibrillation or flutter. Campbell et al. compared the efficacy and side effects of intravenous sotalol with digoxin/disopyramide [1]. Although there was no difference in number of patients reverting to sinus rhythm in each group, patients receiving sotalol had a significantly shorter time to reversion.

Intravenous sotalol has not been recommended for pharmacological cardioversion of atrial fibrillation in the recent AHA guidelines [18]. Both flecainide [19] and ibutilide [20] have been shown to be more efficacious than sotalol in this regard.

Reisinger et al. compared the safety and efficacy of intravenous flecainide and sotalol in a trial involving 106 haemodynamically stable patients with atrial fibrillation [19]. Compared to sotalol, flecainide was more efficacious at converting to sinus rhythm (52 vs 23%, $p = 0.003$) (Table 3). Adverse effects were similar in both. A single episode of torsades de pointes in conjunction with acute congestive heart failure developed after infusion of sotalol in a patient with reduced left ventricular function.

A trial involving 308 patients in 43 European centres compared the efficacy and safety of ibutilide with that of dl-sotalol (1 mg ibutilide, 2 mg ibutilide and 1.5 mg/kg dl-sotalol) in terminating chronic atrial fibrillation or flutter [20] (Table 3). Both drugs were found to be more effective against atrial flutter than against atrial fibrillation. The investigators demonstrated that ibutilide was superior to dl-sotalol for treating atrial flutter (70% and 56% *v* 19%). The high dose of ibutilide was more effective for treating atrial fibrillation than dl-sotalol (44% *v* 11%) and the lower dose of ibutilide (44% *v* 20%, $p < 0.01$). With sotalol bradycardia was noted in 6.5% and hypotension in 3.7% patients. With ibutilide two (0.9%) who received the higher dose developed polymorphic ventricular tachycardia. One of them required direct current cardioversion.

Efficacy of Electrical Cardioversion Following Intravenous Sotalol

There has also been evidence that sotalol may have an influence on the atrial defibrillation threshold. In a study involving 25 patients with chronic and 13 patients with acute AF undergoing transvenous defibrillation sotalol when given intravenously at 1.5 mg/kg over 15 minutes resulted in a reduction in the atrial defibrillation threshold [21]. When administered as a 1.5 mg/kg infusion in 18 patients with persistent AF, sotalol was found to reduce the atrial defibrillation energy requirement by increasing atrial refractoriness [22].

The current FDA recommendations for sotalol with regards to AF are for maintenance of sinus rhythm in patients with paroxysmal AF who are currently in sinus rhythm [2]. This is based on the data pertaining to oral sotalol. The initial trials with regards to termination of acute AF showed variable success rates (summarised in Table 3). This could be explained by variable dosage and infusion rates. Given the ability to reduce the atrial defibrillation threshold, it is possible that sotalol may be used as an adjunct to direct current (DC) cardioversion in patients with AF, however more research would be needed to establish the use of sotalol in this role.

Supraventricular Tachycardias

Atrio Ventricular Nodal Reentrant Tachycardia

There have been limited studies assessing the effect of sotalol on AV Nodal Reentry tachycardia (AVNRT). Rizos et al. [23] compared the effect of IV sotalol (1.5 mg/kg) vs metoprolol (0.15 mg/kg) each administered as a single dose over 15 minutes in 17 patients with recurrent paroxysmal supraventricular tachycardia (SVT). Sotalol was more effective than metoprolol in preventing induction of sustained SVT (59% w vs 17:26%) ($p < 0.05$). The site of action of sotalol was either the anterograde limb or the retrograde limb. There was an increase in the anterograde effective refractory period of the slow and fast AV nodal pathway. Sung et al. assessed the effect of two doses (1 mg/kg and 1.5 mg/kg over 10 min) of intravenous sotalol in 93 patients out of whom 45 had Supra ventricular tachycardia (SVT) [17]. In the SVT group, conversion to sinus rhythm occurred in 14% who received placebo compared to 67% of sotalol group regardless of the dosage ($p < 0.05$).

Table 3 Intravenous Sotalol in Cardioversion for Atrial Fibrillation.

Author	Patient No/Design	Sotalol Dose	Comparison	Result/Comments
AF				
Peters et al. 1998	41/prospective	40 mg IV	NA	Cardioversion occurred in 22(54%) of patients with recent onset AF.
Sung et al. 1995	93/multi centre, randomised, double blind placebo-controlled trial	1 mg/kg and 1.5 mg/kg	Placebo	There was no difference between the two doses of sotalol and placebo in that successful cardioversion occurred in 2 (14%) of 9 of those who received placebo, 2 (11%) of 14 who received 1.0 mg/kg sotalol, and 2 (13%) of 11 who received 1.5 mg/kg sotalol.
Campbell et al. 1985	40/randomised	1 mg/kg bolus intravenously followed by 0.2 mg/kg intravenously over 12 hrs	Digoxin/disopyramide	Post bypass patients with AF receiving sotalol had a significantly shorter time to reversion (58.8 min) vs 187.7 min with digoxin/disopyramide
Reisinger et al. 1998	106/prospective, randomised, single-blind, multicentre trial	1.5 mg/kg	Flecainide	Compared to sotalol, flecainide was more efficacious at converting to sinus rhythm (52 vs 23%, p – 0.003).
Vos et al. 1998	308 patients	100 mg	Ibulitide 1 mg and 2 mg	Ibutilide was superior to dl-sotalol for treating atrial flutter (70% and 56%*v* 19%) for ibulitude 2 mg, 1 mg and sotalol respectively.
IV Sotalol as an aid to DC cardioversion				
Lau et al. 1997	25	1.5 mg/kg over 15 minutes	NA	Sotalol administration resulted in reduction of acute defibrillation threshold.
Lai et al. 2000	18	1.5 mg/kg	NA	Sotalol was found to reduce the atrial defibrillation energy requirement by increasing atrial refractoriness.

Abbreviation: AF, atrial fibrillation.

Given the availability of intravenous adenosine, the use of intravenous sotalol in this context would be limited, unless the tachycardia is recurrent, in which case IV sotalol with its longer efficacy might have a role.

Atrio Ventricular Reentrant Tachycardia

The effect of intravenous sotalol on accessory pathway conduction has been assessed by several investigators [13,23–26]. The results of these studies have been summarised in Table 4. Although limited in number of patients and with various dosage regimens, overall, the above studies demonstrate the ability of intravenous sotalol to modify the functional properties of anomalous AV pathways. These properties have not been demonstrated with other beta blockers and form a basis of the anti-arrhythmic action of sotalol in accessory pathway conduction. The mechanism of termination of tachycardia, however, seems to be a result of slowed conduction in the AV node. The increase in the effective refractory period of the accessory pathway following sotalol administration suggests that this agent can slow the ventricular response in the atrial tachyarrhythmias including AF with rapid antegrade conduction via the accessory pathway. One advantage with regards to sotalol would be its longer half-life (10–20 hrs) in comparison to adenosine (10 sec), hence theoretically providing a reduced short-term risk of recurrence of the arrhythmia.

Ventricular Arrhythmias

Non Ischaemic Ventricular Tachycardia

Senges et al. [27] studied the effect of intravenous sotalol (1.5 mg/kg) on 18 patients with a history of sustained ventricular tachycardia (n = 15) and ventricular fibrillation (n = 3) not related to acute myocardial infarction. They used programmed electrical stimulation to assess the effect of sotalol. The spontaneously occurring arrhythmia could be reproducibly initiated in 15 of the 18 patients. The study demonstrated that 67% (12 of 18) of patients they studied were noninducible with sotalol treatment. In this study, however, stimulation protocol was rather nonaggressive, including using only two extra stimuli (Table 5).

In another study involving 37 patients with refractory recurrent ventricular tachycardia/fibrillation (VT/VF) not related to previous myocardial infarction [28], 33 patients with inducible VT/VF underwent electrophysiological

Table 4 Intravenous Sotalol in Atrioventricular Reentrant Tachycardia.

Author	Patient No/ Design	Sotalol Dose	Comparison	Result/Comments
Nathan et al. 1982	13/ Prospective	0.4 mg/kg over 15 to 30 minutes	NA	Accessory pathway refractoriness increased in both the antegrade and retrograde direction. In 12 patients sotalol was given during AVRT and this resulted in termination in 5.
Bennet et al. 1982	15/ Prospective	1.5 mg/kg over 5 minutes	NA	Intravenous sotalol prolonged the effective refractory periods of the ventricles and accessory pathways and reduced the ventricular response to atrial fibrillation in the patients with Wolff-Parkinson-White syndrome
Touboul et al. 1987	14/ Prospective	0.6 mg/kg sotalol over 5 minutes	NA	Sotalol resulted in significant increase in the retrograde effective refractory period of the anomalous pathway. There was a tendency towards increased refractoriness during antegrade AP conduction. Sotalol prevented the initiation of sustained re-entry. In most cases this was the result of the development of AV nodal block.
Kunze et al. 1987	17/ Prospective	1.5 mg/kg over 15 minutes	NA	SVT inducible in 15 patients after treatment with sotalol. In 10 patients this was non-sustained and terminated spontaneously.
Rizos et al. 1984	17/ Prospective	(1.5 mg/kg)	Metoprolol (0.15 mg/kg)	Sotalol prevented the induction of tachycardia in 10 compared to 4 for metoprolol (p 0.05).

Abbreviations: AVRT, atrio ventricular reentry tachycardia; SVT, supraventricular tachycardia.

testing and programmed electrical stimulation with double extra stimuli during ventricular pacing. Intravenous sotalol (1.5 mg/kg over 5–10 mins) prevented reinduction of VT/VF in 15 patients (45.5%). In patients where inducibility was not supressed there was slowing of the VT, CL increasing from 256 ± 65 to 306 ± 77 msec.

Ventricular Arrhythmias Associated With Coronary Artery Disease

Suppression of Reinduction of Ventricular Tachycardia

In a retrospective study involving 138 patients (117 of whom had coronary artery disease) intravenous sotalol prevented induction of VT/VF in 45% of the patients compared to 39% with amiodarone (non-significant) and 15 to 22% with other class 1 agents [29]. A prospective multicentre study compared IV sotalol to IV procainamide using a VT induction protocol with three extra stimuli. Sotalol prevented VT/VF in 35% patients compared to only 22% by procainamide. This difference was, however, not statistically significant [29].

In a double-blind parallel clinical study involving 110 patients (80% with coronary artery disease) with documented VT and undergoing programmed extra stimuli (PES), sotalol was shown to prevent inducibility of VT/VF to a greater extent than procainamide (30% vs 20%) [30]. Triple extra stimuli were used in the PES protocol during ventricular pacing. Lengthening of the refractory period was associated with prevention of VT/VF induced by PES. In addition to this, there was a strong correlation between the baseline VT cycle length and response to sotalol. Patients with baseline VT CL $\leq$ 270 ms were three times more likely to respond to sotalol. Also, a strong correlation was noted between the change in right VERP values and response to sotalol. Most responders had right ventricular effective refractory period (VERP) of at least 290–300 msec at basic CL of 600 ms.

Termination of Ventricular Tachycardia With Intravenous Sotalol

In a double blinded trial involving 33 patients (28 with previous acute myocardial infarction (AMI)) Ho et al. demonstrated that sotalol was significantly more effective than lignocaine when analysed on an intention-to-treat basis (69% vs 18%; 95% confidence interval for absolute difference of 51%, 22–80%, p = 0.03) in terminating ventricular tachycardia. One patient in each group was noted to become hypotensive after administration of the drug and required cardioversion which was successful. One death was noted in each group.

The efficacy of sotalol versus lignocaine was compared in a trial involving 129 patients with out-of-hospital cardiac arrest refractory to multiple shocks [31]. There was no significant difference between the two groups. Given the inclusion criteria of ventricular fibrillation which was refractory to $\geq$4 shocks, the outcome was poor in both groups. In this regard sotalol was similar to amiodarone. In a trial involving 3026 patients with out-of-hospital cardiac arrest due to initial shock refractory VF or pulseless electrical activity neither amiodarone nor lignocaine resulted in significantly higher rate of survival or neurological recovery when compared to placebo [32].

Table 5 Intravenous Sotalol in Ventricular Arrhythmias.

Author	Patient No/Design	Sotalol Dose	Comparison	Result/Comments
Ischaemic VT/VF				
Nademanee et al. 1990	138 Retrospective	1.5 mg/kg	Amiodarone	Sotalol equivalent to amiodarone in prevention of VT/VF Induction in patients with clinical sustained VT.
Nademanee et al. 1990	153 Prospective multi centre	Plasma level 2.14 ± 0.40 μg/ml	Procainamide	Sotalol prevented VT/VF induction in 35% patients vs 22 patients with procainamide (not significant).
Singh et al. 1995	110 Double-blind parallel	1.5 mg/kg loading and 0.5 mg/kg maintenance	Procainamide	Sotalol was shown to prevent inducibility of VT/VF to a greater extent than procainamide (30% vs 20%)
Ho et al. 1994	33 Double blinded	100 mg IV over 5 mins	Lignocaine	Sotalol was significantly more effective than lignocaine in termination of spontaneous VT which did not result in cardiac arrest.
Kovoor et al. 2005	129	100 mg	Lignocaine	In patients with out-of-hospital cardiac arrest there was no significant difference between sotalol and lignocaine in survival to hospital admission (12% vs 23%p = 0.09) and survival to hospital discharge (3% vs 7%, p = 0.33).
Non-Ischaemic VT				
Senges et al. 1984	18	1.5 mg/kg	NA	In patients with history of sustained ventricular tachycardia (n = 15) and ventricular fibrillation (n = 3) not related to acute myocardial infarction, 67% (12 of 18) of patients were non-inducible with sotalol treatment.
Nademanee et al. 1985	33	1.5 mg/kg	NA	In 33 patients with refractory recurrent VT/VF, sotalol prevented reinduction of VT/VF in 15 patients (45.5%). In 9 of the 18 patients where sotalol did not prevent re induction, the induced VT was non-sustained.

Abbreviations: VT, ventricular tachycardia; VF, ventricular fibrillation.

With regards to ventricular arrhythmias, sotalol seems to be more effective than class 1 agents and at least as effective as amiodarone. The termination or prevention of re-induction of ventricular arrhythmias may be explained by the short term prolongation of the VERP after administration of intravenous sotalol [27]. The increase in VERP that has been reported is variable from no significant changes [14] to a significant prolongation [10,23,27,29]. The difference in prolongation can be explained by the lower dose of sotalol (0.4 mg/kg) in the former study. Hence, giving a lower dose or one that does not result in prolongation of RVERP may not be effective in terminating the arrhythmia. Notably the abovementioned trials (summarised in Table 4) have used relatively high doses (1.5 mg/kg) administered over a short time (5–10 mins). The current FDA recommendations are hence not supported by evidence as far as ventricular arrhythmias are concerned. No incidence of torsades was documented in any of these trials.

Paediatric Use

To our knowledge, only one study assessed the use of intravenous sotalol in the paediatric population. Intravenous sotalol (5 mg/kg) was used in a study involving 19 children (mean age 2 years) with incessant tachycardia [33]. Successful reversion to sinus rhythm occurred in 7/9 patients with AVNRT, 4/6 with atrial tachycardia, 2/3 with atrial flutter and one patient with idiopathic VT. Obvious QTc prolongation occurred in two patients (486–500 ms) however, no episodes of torsade was detected. Unfortunately, the dose specifications lacked any detailed description and the duration of the infusion was not documented in this study.

Conclusion

The fact that intravenous sotalol has now been approved by the FDA enables its use in those who are unable to take the oral formulation. The dosage schedule, however, is not in keeping with majority of the previous published data. Although rapid intravenous administration may lead to some QT prolongation, the safety and efficacy of rapid intravenous bolus doses have been demonstrated. The anti-arrhythmic effect of sotalol in AVRT occurs by virtue of its effect on the accessory pathway ERP although termination of AVRT usually occurs in the AV node. Sotalol, however, can slow the antegrade conduction via the accessory pathway and may be useful in patients with AF and Wolff–Parkinson–White (WPW) syndrome. Intravenous sotalol is not as effective as flecainide and ibutilide in pharmacological cardioversion of atrial fibrillation and this is reflected in the current guidelines [18]. It may, however, be used as an aid to DCCV for atrial fibrillation by reducing the defibrillation threshold. The effectiveness of sotalol, with regards to ventricular arrhythmias, depends on its effect on the ventricular effective refractory period. Hence, by giving lower doses over longer duration intravenously the effect on RVERP and hence its ability to terminate tachyarhythmias might be compromised. Intravenous sotalol is more effective than IV lignocaine in terminating ventricular tachycardia not causing cardiac arrest. Revision of the current FDA guidelines should be considered to enable rapid intravenous administration in a variety of clinical situations where efficacy and safety of intravenous sotalol have been demonstrated.

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