Research Article

Interventional Cardiology

The safety and efficacy of sotalol in the management of acute atrial fibrillation: a retrospective case control study

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Objective: The European Society of Cardiology, American Heart Association and the American College of Cardiology guidelines on atrial fibrillation (AF) 2006 state that Sotalol should not be used in acute AF. We assessed the safety and efficacy of sotalol in acute AF when compared to other anti-arrhythmic drugs (ADD).

Methods: A single centre retrospective observational study on 300 patients admitted with acute AF over a 12 months period. Study drugs used were sotalol, amiodarone, flecainide, propafenone or disopyramide for rhythm control. Digoxin, beta blockers, verapamil, diltiazem were prescribed for rate control. Rates of cardioversion to sinus rhythm, readmission rates due to AF, all cause readmissions, mortality rates due to sudden cardiac death and all-cause mortality was recorded over a 2 year follow up period. For paired data, the Wilcoxon matched-pairs signed- ranks or paired t-test were used. For unpaired data, Fisher's exact test was used.

Results: 120 patients were discharged on sotalol. The mean total dose used was 169.2 mg daily. Cardioversion to sinus rhythm on discharge occurred in 68% in the rhythm control group versus 42% for rate control group ($p<0.001$). Sotalol had a significantly higher cardioversion rate regardless of the dose when compared to amiodarone ($p=0.036$) however, there were similar readmission rates for AF. Four patients died acutely in hospital, none were on sotalol. Compared to all drugs sotalol had the lowest mortality rates ($p=0.001$). Mortality rates were lower in patients who received the higher dose of sotalol; 7.4% for patients who received a total of 320 mg daily versus 11.8% in those who received 160 mg daily.

Conclusion: Sotalol is as safe and effective as other anti-arrhythmic drugs; in fact it was significantly more effective than amiodarone in this cohort. All AAD's demonstrated a significant improvement in cardioversion rates and a significantly lower mortality rate than rate controlling drugs.

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Atrial fibrillation (AF) is the most common cardiac arrhythmia and affects 1.5-2% of the population [1]. Over 6 million Europeans have AF and the prevalence is expected to double in the next 50 years [2].

AF is associated with increased risk of stroke, heart failure, impaired quality of life, reduced exercise tolerance, left ventricular systolic impairment and death. Subsequently there is significant cost implications associated [1,2]. Attempting to achieve sinus rhythm is therefore of importance.

Sotalol possesses a mixture of Vaughn-Williams class II and class III effects. The combination of rate and rhythm control properties may improve the chance of early restoration to sinus rhythm in patients who are in acute AF. This may limit the tendency towards electrical and structural remodelling seen in AF and improve the chance of long term rhythm control [3].

The use of sotalol for recent AF (less than 48 hours) is a class III indication and not recommended in the American College of Cardiology (ACC) American Heart Association (AHA) European Society of Cardiology (ESC) 2006 guidelines for AF [4]. However, it is important to note that a lack of clinical trials formed the basis of the guidelines.

In the 2012 ESC AF guidelines, sotalol can be used for AF if there is minimal or no structural heart disease [1]. In the ACC/AHA/ Heart Rhythm Society 2014 AF guidelines there is a class 1 indication for the use of sotalol for the maintenance of sinus rhythm [5]. However, the use of sotalol for acute AF has not been recognised.

Although sotalol does not carry guideline recommendations, it is generally understood that guidelines are only guides, and not a substitute for clinical judgement. Many patients with AF have contraindications to the class 1 medications, but may not be willing to accept the side effect profile associated with amiodarone. This retrospective trial is observational and is not intended to examine the reasons why sotalol was chosen, but rather to acknowledge that medications are often used off guideline recommendations and provide additional information for physicians who are trying to provide reasonable treatment for AF.

We sought to establish the efficacy and safety of oral sotalol as compared to other anti-arrhythmic drugs for acute AF in a district general hospital.

Methods

A retrospective analysis of 300 patients who were admitted with acute AF to a district general hospital between 1/1/2005-31/12/2005. Inclusion criteria included all patients considered to have primary AF. Exclusion criteria included patients who had acute AF requiring direct current cardioversion. Patients who had AF secondary to another cause such as sepsis, dehydration, alcohol, surgery, hyperthyroidism etc were also excluded.

Acute AF/recent onset AF was defined as AF of <48 hours duration [2] determined by the onset of patients symptoms. These patients were not known or documented to have AF previously. The type of drug administered was recorded i.e rate control or rhythm control. Rate control drugs included digoxin, beta-blockers, verapamil or diltiazem. Rhythm controlling agents prescribed included sotalol, amiodarone, flecanide, propafenone or disopyramide. Outcomes that were measured included all-cause mortality, cardiac death, readmission rates for AF, congestive cardiac failure and all cause readmissions over a 2 year follow up period. Rates of cardioversion to sinus rhythm on discharge were noted.

Statistical analyses

Following a test of statistical normality (Komolgrov-Smirnov test), data were expressed as mean with standard deviation (SD) or as median with inter-quartile range (IQR) for the normally distributed data and non-parametrically distributed data respectively. Comparisons between groups were analysed by 2-way repeated ANOVA or Kruskal–Wallis test, as appropriate. For paired data, the Wilcoxon matched-pairs signed-ranks or paired t-test were used. For unpaired data, Fisher's exact test was used. All analyses were performed using SPSS version 17.0. A p value of <0.05 was considered as statistically significant for all comparisons.

Results

Over the study period, 300 patients were admitted into the accident and emergency department with acute AF. drugs for each patient were documented (Table 1). One hundred and twenty patients received sotalol.

During admission 11 patients were treated with more than one drug. The maximum number of drugs used in any one patient was 3 agents. Twenty eight patients did not require any drug therapy as spontaneous cardioversion to sinus rhythm was achieved prior to arrival or whilst in the accident and emergency department. Patients who cardioverted to sinus rhythm prior to arrival to the accident and emergency department had an electrocardiogram performed by the paramedics initially confirming AF. Patients treated with sotalol received between 40 mg-160 mg twice daily orally, the majority (59 patients) receiving 80 mg twice daily orally.

The remaining patients died predominantly of non-cardiac causes. Mortality rates were lower in patients who received the higher dose of sotalol; 7.4% for patients who received 160 mg BD versus 11.8% in those who received 80 mg BD. However, this was not statistically significant. Compared to the rate control group, mortality rates were significantly lower in patients receiving an anti-arrhythmic drug; 29.8% versus 13.3% ($p < 0.001$) respectively. More specifically mortality rates were lower with sotalol when compared to all study drugs (Table 3).

Cardio version to sinus rhythm on discharge and 2 year follow up

Cardioversion to sinus rhythm on discharge

was achieved in 68% of patients receiving an anti-arrhythmic drug and 42% of patients receiving a rate limiting drug ($p < 0.001$). This remained significant regardless of the anti-arrhythmic drug used. All patients in the anti- arrhythmic arm received one drug on discharge. Patients in the rate control group received between 1-3 drugs.

At 2 year follow up, sotalol 80 mg BD had the highest cardioversion rates to sinus rhythm when compared to 40 mg BD and 120 mg BD; 78.0%, 67.6% and 70.4% respectively (Table 4).

Sotalol at any dose had a significantly higher cardioversion rate to sinus rhythm when compared to amiodarone (p=0.036) with a similar AF recurrence rate at 2 year follow up. Flecanide had the best cardioversion rate to sinus rhythm both on discharge and at 2 year follow up without any significant increase in complications.

Readmission rates

Overall readmission rates for recurrent AF was lower in patients treated with rate limiting drugs. Patients treated with sotalol or amiodarone had similar readmission rates for recurrence of AF over a 2 year period (26%).

Table 1: Discharge drugs for the 296 patients.

Drugs	Number of patients
Sotalol (40-160 mg BD)	120
Amiodarone	66
Flecainide	16
Other anti arrhythmic drugs	8
Rate Control medications	75
No Drug Therapy	28

Table 2: Causes of death and mortality rates over a 2 year follow up period.

Cause of death	Number of patients
Cerebrovascular event	11
Sudden death	6
Congestive cardiac failure	6
Acute coronary syndrome	4
Other	30
Death during first acute admission	4

Discussion

This study provides evidence for the safety and efficacy of sotalol in the pharmacological cardioversion of acute-onset/recent onset atrial fibrillation. The use of sotalol for recent AF is a class III indication and not recommended in the ACC/AHA/ESC 2006 guidelines for AF as it is thought to be harmful [4]. In our hospital there was an approved use for sotalol and was used in patients who did not have any contraindications, such as those with a history of heart disease and patients who had a prolonged QTc interval or risk factors predisposing to arrhythmia.

The class III recommendation for the use of sotalol in acute AF was based on 3 studies [6-8]. Furthermore, all but one of the studies comprised of study populations of less than 100 patients. The larger cohort of patients (>100) in our study has provided insight regarding the use of sotalol in acute AF with favourable outcomes.

In this study, sotalol doses ranged between 80 mg -320 mg daily with a mean total dose of 169.2 mg daily. When divided into individual dosage groups there was no significant differences in outcomes. However, the limited sample size in each dosage group diminished the power of the statistical test. Cumulatively there was no evidence of a significant difference in either efficacy or mortality for doses of 160 mg or less compared with doses of 240 mg per day.

Cardioversion to sinus rhythm on discharge and after a 2 year follow up period was best achieved with flecanide, followed by sotalol at any dose and then amiodarone; 84%, 72%, 56% respectively. In a meta-analysis of 46 trials flecanide and ibutalide had the best evidence for the cardioversion of AF to sinus rhythm. Sotalol was found to have negative efficacy for cardioversion to sinus rhythm [9]. Though sotalol does exhibit some Vaughan Williams class III antiarrhythmic behavior, these effects are usually manifested at higher doses (180 mg and above). Only 23% of our patients

Table 3: 2 year outcomes of patients treated with anti-arrhythmics versus rate limiting drugs.

	RHYTHM CONTROL ARM			RATE CONTROL ARM		
	Sotalol (120)	Amiodarone (66)	Other AAD (24)	Rate control (75)	No treatment (36)	
Age	68+/-8	69+/-9	61+/-8	69+/-8	68+/-6	
Deaths	13 (11%) p = 0.0004	11 (17%) p = 0.07	4 (17%) p= NS	23 (30%)	10 (28%)	
SCD	2 (1.7%)	2 (3.0%)	1 (4%)	3 (4.0%)	0	
All Cause Readmission	67 (56%)	39 (59%)	12 (50%)	50 (67%)	22 (61%)	
Readmission (AF)	31 (26%)	17 (26%)	5 (21%)	11 (15%)	7 (19%)	
Readmission (CCF)	3 (2.5%)	3 (4.5%)	0 (0.0%)	2 (3%)	2 (6%)	
Cardioversion to Sinus rhythm	86 (72%) p < 0.0001	37 (56%) p < 0.001	20 (83%) p < 0.0001	32 (44%)	15 (42%)	

TABLE 2: Comparison of rhythm and rate control strategies and outcomes. Data refers to n (%) or mean +/- SD as appropriate. All statistical comparisons in table are by Fishers exact test and are compared with the no AAD group (all rate control combined). SCD: Sudden Cardiac Death; AF: Atrial Fibrillation; CCF: Congestive Cardiac Failure.

Table 4: Cardioversion to sinus rhythm at 2 year follow up.

Drug and dosage	Number of patients	Cardioversion to sinus rhythm
Sotalol 80 mg daily	23/34	67.60%
Sotalol 160 mg daily	46/59	78%
Sotalol 240 mg daily	19/27	70.40%
Amiodarone	37/66	56%
Flecanide	14/16	88%
All other AAD	22/24	92%
Rate control drugs	32/75	42.70%

received the higher dose of sotalol.

In UK clinical practice, sotalol is often used at low doses (80–160 mg/day), at which it essentially acts in a similar manner to a class II beta adrenergic antagonist. The non-significant difference in the cardioversion rates between sotalol and amiodarone may well be due to the low dose of sotalol prescribed.

In another small study patients with acute AF were prescribed intravenous sotalol. There was no significant difference in cardioversion rates between intravenous sotalol and placebo [7] or between sotalol and amiodarone [10]. In these trials a single 1-1.5 mg/kg intravenous loading regime was prescribed as compared to the protracted oral regime in our study [7,10,11].

In 33 patients who received a maximum dose of sotalol 320 mg orally for acute AF the cardioversion rate to sinus rhythm was 52% compared to 86% taking quinidine. It is difficult to draw robust conclusions since there were a low number of patients that were recruited in this trial [12].

In our study there was no excess in mortality rates in patients who were prescribed sotalol. All-cause mortality and cardiovascular death rates were lower with sotalol when compared to patients treated with amiodarone or with rate limiting drugs. Previous studies have not highlighted areas of concern with regards to sotalol's safety [11-13].

The largest of the studies on sotalol included 103 patients in chronic AF/atrial flutter. Sotalol in this study was given intravenously, and no adverse outcome was observed despite rapid drug administration [11].

A small incidence of QTc prolongation without any adverse outcomes was seen when sotalol 320 mg was given orally for persistent AF [6]. In a further trial of 61 patients, receiving a maximum dose of sotalol 320 mg orally for acute AF, the discontinuation rate was 48% due to asymptomatic bradycardia or hypotension. Asymptomatic wide complex tachycardia was prevalent in 13% of patients [12].

When used as an antiarrhythmic agent, sotalol is often started at 80 mg twice daily for the first week, and thereafter titrated to 160 mg twice daily (or higher) after assessing the electrocardiogram for QT prolongation [10]. In our study patients were not prescribed sotalol if the QTc interval was prolonged or if there were electrolyte abnormalities which may have predisposed the patient to arrhythmia. Patients prescribed sotaolol subsequently had monitoring of their QTc interval by performing electrocardiograms during their follow up period. None of our patients had to discontinue sotalol due to QTc prolongation.

In a meta-analysis of 29 trials, sotalol and amiodarone were associated with adverse events and often required withdrawal [14]. In our study sotalol 40-160 mg BD was seen to be safe as there was no excess mortality.

Readmission rates for the recurrence of AF were 26% for patients prescribed sotalol. Recurrence of AF with sotalol has been reported as 24% [6]. There is strong evidence for the maintenance of sinus rhythm with sotalol. The majority of trials assessing the recurrence of AF are based on an ECG at follow up or by ambulatory ECG monitoring. There are no trials assessing readmission rates to hospital with AF on sotalol. In the amiodarone arm readmission for recurrence AF was also 26%. Amiodarone was found to be more effective at maintaining sinus rhythm at 1 year with a rate of >65% when compared to sotalol and other anti-arrhythmic drugs [14-17].

It is important to note that the majority of AF trials with sotalol recruited a low number of patients or were done in patients who did not have acute AF but mainly had persistent AF.

The most recent guidelines, both the ACC/AHA/HRS and the ESC guidelines on AF agree on the use of sotalol in patients without significant underlying heart disease (i.e., heart failure, coronary artery disease, or severe left ventricular hypertrophy) [1,5].

Sotalol is a viable anti-arrhythmic option for the restoration of sinus rhythm in patients in whoem flecainide and amiodarone are contraindicated. Amiodarone side effect profile includes photosensitivity, abnormalities in thyroid and liver function tests as well as pulmonary fibrosis. In patients who are prescribed warfarin for AF the internationalised normalised ratio maybe affected with the concomitant use of Amiodarone. Therefore in such circumstances sotalol is a potential option. Furthermore in patients who have ischaemic heart disease and AF the dual action of rate control and rhythm control with sotalol is advantageous. Amiodarone however, is preferred in patients with AF who have had a previous myocardial infarction and heart failure [4]. Our study therefore provides evidence for the superior efficacy of sotalol for the management of acute AF in more than 100 patients.

Conclusion

This study examined a real world use of sotalol in an off label use in the management of acute onset AF

and found it to be safe and effective. The combination of rate controlling properties with pharmacological cardioversion is attractive, especially in patients in whom flecanide and amiodarone is contraindicated. Sotalol demonstrated a significantly higher cardioversion rate on discharge and at 2 year follow up without an increase in mortality when compared to amiodarone and rate limiting drugs. Further studies in patients with acute atrial fibrillation are required to confirm our findings in a prospective manner and examine the optimum dosing regime.

Executive summary

- **Objective:** The European Society of Cardiology, American Heart Association and the American College of Cardiology guidelines on atrial fibrillation (AF) 2006 state that Sotalol should not be used in acute AF. We assessed the safety and efficacy of sotalol in acute AF when compared to other anti-arrhythmic drugs (ADD).
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- **Results:** 120 patients were discharged on sotalol. The mean total dose used was 169.2 mg daily. Cardioversion to sinus rhythm on discharge occurred in 68% in the rhythm control group versus 42% for rate control group ($p<0.001$). Sotalol had a significantly higher cardioversion rate regardless of the dose when compared to amiodarone ($p=0.036$) however, there were similar readmission rates for AF. Four patients died acutely in hospital, none were on sotalol. Compared to all drugs sotalol had the lowest mortality rates ($p=0.001$). Mortality rates were lower in patients who received the higher dose of sotalol; 7.4% for patients who received a total of 320 mg daily versus 11.8% in those who received 160 mg daily.
- **Conclusion:** Sotalol is as safe and effective as other anti-arrhythmic drugs; in fact it was significantly more effective than amiodarone in this cohort. All AAD's demonstrated a significant improvement in cardioversion rates and a significantly lower mortality rate than rate controlling drugs.
- The main presentations of these regular tachycardias are atrioventricular nodal re-entrant tachycardia and orthodromic atrioventricular reentrant tachycardia due to an accessory pathway.

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