Comparison of sotalol with amiodarone for long-term treatment of spontaneous sustained ventricular tachyarrhythmia based on coronary artery disease

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Aim To compare the efficacy of sotalol versus amiodarone for long-term treatment of ventricular tachyarrhythmias.

Methods Patients (n=75) with spontaneous, sustained ventricular tachyarrhythmias secondary to remote myocardial infarction were studied. After intravenous electrophysiological testing, both sotalol and amiodarone were predicted to be ineffective in 50 (67%) patients. Five patients were excluded. Forty-five patients were randomized to receive sotalol (n=22) or amiodarone (n=23) for maintenance therapy. The primary outcome variable was the time to first recurrence of sustained ventricular tachyarrhythmia.

Results At 36 months, 75% of those allocated sotalol remained free of ventricular tachyarrhythmia compared with 38% of those allocated amiodarone (P=0.05). On multivariate analysis the risk of recurrence of ventricular tachyarrhythmia for patients on amiodarone was 5.9 times higher (P=0.008) than that for patients on sotalol.

Conclusion Sotalol is superior to amiodarone for long-term treatment of ventricular tachyarrhythmia secondary to coronary artery disease when both drugs have been predicted to be ineffective at intravenous electrophysiological testing. Randomized trials in larger numbers of patients with ventricular tachyarrhythmia need to be performed comparing the two agents directly.

Key Words: Sotalol, amiodarone, ventricular tachyarrhythmia, ventricular tachycardia, coronary artery disease.

See page 321 for the Editorial comment on this article

Introduction

Class III antiarrhythmic agents have become popular for treatment of ventricular tachyarrhythmias[1]. Amiodarone and sotalol are the two most commonly used agents in this group[2,3]. Amiodarone is the antiarrhythmic agent most commonly used for treatment of refractory and potentially malignant ventricular arrhythmias[4]. Sotalol is being increasingly used as a first line agent in the management of ventricular arrhythmias because of the favourable pharmacokinetics of the agent[5].

However, the important question of the relative efficacy of sotalol vs amiodarone remains unanswered[5]. Only one study has made a direct randomized comparison between amiodarone and sotalol in patients with ventricular tachyarrhythmia[6]. This study showed no significant difference in prevention of arrhythmic death. However, the patient population was non-homogenous, with only 64% of patients having evidence of coronary artery disease. Electrophysiological studies to confirm inducibility of ventricular arrhythmia were not performed before randomization. It is therefore possible that some of these patients did not have inducible ventricular tachyarrhythmia. Patients without inducible ventricular tachyarrhythmia have a lower risk of recurrent ventricular tachyarrhythmia compared to patients with inducible ventricular tachyarrhythmia[7,8]. The duration of follow-up was only 12 months and the sample size was probably not large enough to demonstrate a significant difference in mortality between the two groups.

The purpose of our study was to compare the efficacy of sotalol and amiodarone in patients with documented spontaneous sustained ventricular tachyarrhythmia occurring late after myocardial infarction. The diagnosis of the clinical arrhythmia was confirmed by electrophysiological studies in all patients.


Methods

Study design

The protocol was approved by the research and ethics committee of the hospital. The study was conducted as part of a long running study evaluating the efficacy of intravenous drug testing in the electrophysiological laboratory for predicting long-term response to antiarrhythmic drugs in patients with ventricular tachyarrhythmias. The study was performed before automatic implantable defibrillators became freely available in Australia. The recruitment period was between October 1986 and February 1991. During the study period our belief was that intravenous drug testing might be useful in predicting the long-term efficacy of an antiarrhythmic agent. Our policy at that time (which subsequently has been discontinued) was to perform intravenous drug testing at electrophysiological studies in all patients with inducible ventricular tachyarrhythmia. Patients in whom an antiarrhythmic drug was predicted to be effective were treated with that antiarrhythmic agent and followed up. We were unsure about the optimum treatment for patients in whom both sotalol and amiodarone were predicted to be ineffective at electrophysiological studies. We were aware that in some of these patients the antiarrhythmic agent might still prove to be effective in the long term. This would be especially true for amiodarone in which intravenous drug testing might be assessing its Class I action while the long-term efficacy might be due to its Class III action. To determine the best mode of treatment for patients in whom both sotalol and amiodarone were predicted to be ineffective at electrophysiological studies, we included them in a randomized trial of long-term treatment with sotalol vs amiodarone.

The primary outcome variable was the time to first episode of spontaneous sustained ventricular tachyarrhythmia. The nature of recurrences was established from electrocardiograms, written records and by interview of witnesses and attending physicians. Arrhythmic death was defined as instantaneous (<5 min), unexpected death occurring without preceding symptoms of ischaemia, death due to documented ventricular tachyarrhythmia or unwitnessed and unexpected death. Cardiac mortality was defined as death due to any cardiac cause.

All patients were followed up for a maximum period of 36 months, withdrawal from the study, or until their first recurrence of ventricular tachyarrhythmia, whichever was earlier.

Patients

Entry criteria for this study were: (1) documented spontaneous sustained ventricular tachyarrhythmia not related to acute ischaemia, electrolyte imbalance or drug toxicity; (2) ventricular tachyarrhythmia inducible with programmed ventricular stimulation; (3) age ≤ 75 years; (4) angiographically documented significant (>50% stenosis) coronary artery disease; (5) both sotalol and amiodarone predicted to be ineffective at intravenous testing in the electrophysiological laboratory; (6) informed consent. Exclusion criteria were: (1) occurrence of ventricular tachyarrhythmia during previous treatment with oral amiodarone or sotalol; (2) marked ventricular decompensation following intravenous administration of amiodarone or sotalol.

Electrophysiological study

All antiarrhythmic medications were ceased for one week before baseline electrophysiological studies. Amiodarone was ceased for at least 6 weeks prior to electrophysiological studies. The study was performed in the fasting state after premedication with 10 mg oral diazepam. At the baseline study two quadrupolar and one tripolar 6 F electrode catheters were introduced percutaneously through a femoral vein under fluoroscopic guidance and positioned at the high right atrium, right ventricular apex and His bundle region, respectively. At subsequent electrophysiological studies to assess antiarrhythmic drugs, a single 6 F quadrupolar catheter was inserted and positioned at the right ventricular apex. Programmed stimulation was performed using a WP Instruments stimulator delivering rectangular pulses 2 ms in duration.

Stimulation protocol

A fixed protocol of programmed stimulation was used with the number of extrastimuli as the only variable. This protocol has been described in detail previously and its reproducibility documented. A drive train of eight ventricular paced beats was used with a cycle length as close as possible to 600 ms. Current intensity was the conventional twice diastolic threshold. The right ventricular apex was the site of ventricular stimulation. Each extrastimulus was delivered at an initial coupling interval of 300 ms and then decremented in 10 ms steps until ventricular refractoriness. Each extrastimulus coupling interval was delivered three times before decrementing. When ventricular refractoriness was reached, that extrastimulus was placed 10 ms later than the ventricular effective refractory period and an additional extrastimulus was added at an interval of 300 ms, and decremented in the manner described above. A maximum of four extrastimuli were used for induction of ventricular tachycardia in the baseline state. The value of four extrastimuli during programmed ventricular stimulation is now well established. The end-point of stimulation was induction of a sustained ventricular tachyarrhythmia lasting <10 s.

Drug testing

Electrophysiological study for intravenous drug testing was conducted on a different day to the baseline study.
Only one drug (sotalol or amiodarone) was tested on a particular day. Sotalol was always tested first. There was an interval of at least 7 days between sotalol and amiodarone testing. Each patient was tested on both drugs even if the first drug test was predicted to be ineffective. Before drug administration ventricular tachycardia was induced once using the protocol outlined above. After the arrhythmia had been terminated for 10 min, sotalol or amiodarone was administered intravenously. Sotalol was administered at a dose of 1·5 mg per kg body weight intravenously over 20 min. Amiodarone was administered at a dose of 10 mg per kg intravenously over 10 min. After drug administration, programmed ventricular stimulation was performed again starting at the beginning of the protocol described earlier. A maximum of seven extrastimuli were allowed for induction of ventricular tachyarrhythmia following drug administration. The drug was considered antiarrhythmic if ventricular tachyarrhythmia was induced with ≥ two extrastimuli more than that required to induce ventricular tachyarrhythmia off medication during the same study. Thus, if a patient who had ventricular tachyarrhythmia inducible with three extrastimuli at the baseline drug-free state, was found to have ventricular tachyarrhythmia inducible only with five extrastimuli after the intravenous drug, it was predicted that the drug is antiarrhythmic. The drug was considered to be not antiarrhythmic if ventricular tachyarrhythmia was induced with ≤ one extrastimulus compared to that required to induce ventricular tachyarrhythmia off medication during the same study. The intravenous drug testing protocol was being used at the time of this study as part of an evaluation of the efficacy of intravenous drug testing at electrophysiological studies in patients with ventricular tachyarrhythmia. We used up to seven extrastimuli after the drug to determine whether the increase in the number of extrastimuli after a drug would predict long-term antiarrhythmic efficacy of the drug. This aspect of the study, assessing the usefulness of intravenous drug testing at electrophysiological studies, is beyond the scope of this paper.

**Selection of patients, randomisation and long term antiarrhythmic treatment**

Between October 1986 and February 1991, 118 patients with documented spontaneous sustained ventricular tachyarrhythmia, significant coronary artery disease and age ≤ 75 years were referred to us for electrophysiological studies. Two patients refused consent for inclusion in the intravenous drug testing trial and one patient was not capable of giving consent. Ventricular tachyarrhythmia was not inducible in 32 patients at programmed ventricular stimulation. Three patients died in hospital before intravenous drug testing and three patients underwent surgical treatment for ventricular tachycardia. Two patients underwent intravenous drug testing with an agent other than sotalol or amiodarone. Thus in total 43 patients were excluded.

The remaining 75 patients underwent intravenous drug testing of sotalol and amiodarone for ventricular tachyarrhythmia at electrophysiological studies. In 50 (67%) patients neither sotalol nor amiodarone were predicted to be antiarrhythmic (Fig. 1). Sotalol alone was predicted to be effective in 22 (29%) patients, amiodarone alone in two (3%) and both sotalol and amiodarone in one (1%). These patients were treated with the appropriate antiarrhythmic agent and were not included in this study. In addition, a total of five patients were excluded because of a previous occurrence of ventricular tachyarrhythmia on oral amiodarone or sotalol (n=3), ventricular decompensation following intravenous sotalol (n=1) or protocol violation (n=1).

The remaining 45 patients in whom no drug had been predicted effective at intravenous electrophysiological testing were randomized to either sotalol or amiodarone. Twenty-two patients were allocated sotalol and 23 amiodarone for long-term treatment. Sotalol was prescribed at a dose of 160 mg b.i.d. orally. Amiodarone was given at a loading dose of 800 mg orally per day for 1 week followed by a maintenance dose of 400 mg per day orally.

**Sample size estimates and termination of trial**

At the time of commencement of this study there were no definite data on the relative efficacy of sotalol and amiodarone in patients with documented sustained ventricular tachyarrhythmia based on coronary artery disease to allow a reasonably accurate estimate of sample size. DiCarlo et al. reported a ventricular tachyarrhythmia recurrence rate of 39% after a mean of 7·3 months of therapy in patients treated with amiodarone. Senges et al. reported a recurrence rate of 11% at 16 months in patients with sustained ventricular tachycardia treated with sotalol. We predicted the recurrence rate on amiodarone at 36 months to be 50%. If treatment with sotalol resulted in a recurrence rate of 20% at 36 months, a sample size of 38 patients per arm would be required for a power of 80% for detection of a statistically significant difference between the two treatment arms (two-sided test, 5% significance level).

Implantable defibrillators with antitachycardia pacing capability became available in our hospital in August 1990. In February 1991 we felt that it was likely that implantable defibrillators with antitachycardia pacing capability would prove more effective for long-term treatment of ventricular tachyarrhythmia than drugs predicted to be ineffective at electrophysiological studies.
We therefore performed a preliminary analysis which revealed that sotalol was statistically significantly superior to amiodarone ($P=0.05$). We could therefore be sure that sotalol was equal to or better than amiodarone. The only point of continuing the study would have been to prove conclusively that amiodarone was worse than sotalol. Knowing that a significant proportion of those end-points would lead to death of our patients, we decided to terminate recruitment at that time.

**Statistical analyses**

The results were analysed using an intention-to-treat analysis. The statistical software package was SPSS\textsuperscript{16}. Baseline characteristics were compared using t-tests or chi-squared tests as appropriate. Covariates considered as potential independent predictors of ventricular tachyarrhythmia were therapy (sotalol or amiodarone), left ventricular ejection fraction ($\leq 30\%$ or $\geq 30\%$), number of diseased coronary arteries ($\leq 2$ or $>2$), type of presenting arrhythmia (ventricular tachycardia or ventricular fibrillation), history of cardiac arrest with spontaneous episodes, left ventricular end-diastolic pressure ($\leq 12$ or $>12$), number of extra-stimuli required to induce ventricular tachyarrhythmia, change in number of extra-stimuli required to induce ventricular tachyarrhythmia after intravenous antiarrhythmic medication compared to number of extra-stimuli required to induce ventricular tachyarrhythmia in the baseline state, and cycle length of induced ventricular tachyarrhythmia ($\leq 350$ ms or $>350$ ms). Multivariate Cox proportional hazards models were fitted to the data in the intention-to-treat analysis. Multivariate Poisson regression was used to analyse the patient–month data in the actual treatment received analysis. An exhaustive search procedure was used to identify the best-fitting models under an intention-to-treat or actual treatment-received analyses. Kaplan–Meier survival curves were used to illustrate the proportion remaining free from ventricular tachyarrhythmia in each therapy group.
Results

Patient characteristics

The characteristics of the patients in the two groups are shown in Table 1. The amiodarone group were slightly older but had better left ventricular function than those allocated sotalol. Overall the two groups were well balanced.

Intention-to-treat analysis

Recurrence of ventricular tachyarrhythmia

Kaplan–Meier estimates of the percentage of patients free from ventricular tachyarrhythmia (VT/VF) at various time points are shown in Fig. 2. There was greater recurrence of ventricular tachyarrhythmia in the amiodarone-allocated group than in the sotalol-allocated group. The difference was statistically significant ($P=0.05$). Three (13%) patients allocated amiodarone had recurrence of fatal ventricular tachyarrhythmia, compared to one (5%) allocated sotalol (Table 2). One (4%) patient in both groups died from a cause other than ventricular tachyarrhythmia.

Univariate analysis

The only variables significantly associated with recurrence of ventricular tachyarrhythmia were antiarrhythmic drug given, number of diseased coronary arteries and ventricular tachyarrhythmia cycle length. The univariate hazard ratios associated with each of these variables are set out in Table 3. The instantaneous risk of ventricular tachyarrhythmia for patients on amiodarone was 3.2 times higher ($P=0.03$) than that for patients on sotalol.

Multivariate analysis

The best fitting multivariate model obtained by an exhaustive search is presented in Table 4. Antiarrhythmic therapy, number of diseased coronary arteries and ventricular tachyarrhythmia cycle length were the covariates that were independent predictors of ventricular tachyarrhythmia. The hazard ratio of each were adjusted for the effects of the other two independent predictors of arrhythmia recurrence. Treatment with amiodarone was associated with a 5.9 times higher risk of ventricular tachyarrhythmia recurrence than treatment with sotalol ($P=0.008$) after adjusting for the effects of age, number of diseased coronary arteries and ventricular tachyarrhythmia cycle length.

Table 1 Patient characteristics (mean ± SD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sotalol</th>
<th>Amiodarone</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>22</td>
<td>23</td>
<td>—</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58 ± 10</td>
<td>64 ± 7</td>
<td>0.02</td>
</tr>
<tr>
<td>Males (%)</td>
<td>19 (86%)</td>
<td>19 (83%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>20 (91%)</td>
<td>16 (70%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Cardiac arrest before treatment</td>
<td>8 (36%)</td>
<td>6 (26%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Presented with ventricular tachycardia</td>
<td>20 (91%)</td>
<td>21 (91%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Presented with ventricular fibrillation</td>
<td>2 (9%)</td>
<td>2 (9%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Three vessel coronary artery disease</td>
<td>3 (14%)</td>
<td>6 (26%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>21 ± 9</td>
<td>15 ± 8</td>
<td>0.04</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure &gt;20 mm Hg</td>
<td>10 (45%)</td>
<td>5 (22%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>29 ± 12</td>
<td>34 ± 12</td>
<td>0.12</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt;30%</td>
<td>15 (68%)</td>
<td>9 (39%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Number of extra-stimuli</td>
<td>2.7 ± 0.8</td>
<td>2.3 ± 0.6</td>
<td>0.1</td>
</tr>
<tr>
<td>CL of induced ventricular tachycardia (ms)</td>
<td>286 ± 61</td>
<td>287 ± 65</td>
<td>0.9</td>
</tr>
<tr>
<td>CL of induced ventricular tachycardia &gt;350 ms</td>
<td>4 (18%)</td>
<td>4 (17%)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Number of extra-stimuli=Number of extra-stimuli required to induce ventricular tachyarrhythmia in the baseline state; CL=cycle length.

![Figure 2](image_url)  
Kaplan–Meier survival curves of freedom from recurrence of ventricular tachyarrhythmia based on an intention-to-treat analysis. The number of at-risk patients at each time point are given at the top: ——=sotalol (Sot); —=amiodarone (Amio); VT/VF=ventricular tachyarrhythmia.
Cross-overs due to intolerance of oral therapy

One patient randomized to sotalol died before oral therapy was commenced (Fig. 1). Six (29%) of the remaining 21 patients allocated to the sotalol group crossed over to the amiodarone group because of side effects. Four (17%) of the 23 patients in the amiodarone group crossed over to the sotalol group because of side effects. This resulted in sample sizes of 19 on sotalol and 25 on amiodarone on a treatment-received basis. Half the patients who developed major side effects with sotalol did so with 0·3 month. The median time to major side effects in the amiodarone group was 3·5 months (Table 5). The side effects observed with sotalol were dyspnoea, dizziness and hypotension, lethargy, and impotence. Side effects associated with amiodarone included malaise, rash, headache, flushes and dyspnoea due to pulmonary fibrosis.

Actual treatment analysis

The results of the actual treatment analysis are summarized in Table 2. One patient who was allocated sotalol died of ventricular tachycardia in hospital before sotalol therapy could be commenced. This patient was excluded from the sotalol treatment received group. None of the patients who crossed over to the other treatment arm died or had recurrence of ventricular tachyarrhythmia. The results of the actual treatment analysis (univariate and multivariate) were essentially the same as intention to treat analysis and hence are not described in detail here.

Discussion

Our study found that sotalol is probably superior to amiodarone for prevention of recurrences of ventricular
tachyarrhythmia in patients with coronary artery disease and inducible ventricular tachyarrhythmia. This outcome might appear surprising to many, but we feel is consistent with what has been published previously regarding the efficacy of each agent. Because of the limited sample size and because patients were screened with intravenous drug testing before randomization the study by no means has established the superior efficacy of sotalol over amiodarone, but merely has demonstrated the need for randomized trials with larger sample sizes comparing the two agents directly.

**Efficacy of sotalol and amiodarone in preventing recurrence of ventricular tachyarrhythmia**

In our study the percentage of patients free from ventricular tachyarrhythmia on sotalol was 86% at 12 months. This is comparable to the 80% arrhythmia-free survival at 12 months in the ESVEM trial[17]. This is also comparable to a non-randomized study of sotalol in which ventricular tachyarrhythmia was prevented in 76% at 12 months[18]. In our study amiodarone prevented ventricular tachyarrhythmia recurrence in 69% at 12 months, and in 43% at 36 months. This is consistent with the arrhythmia-free survival found by Strasberg et al. at 36 months of 40% in patients with inducible ventricular tachyarrhythmia on oral amiodarone[19]. This is also comparable to some non-randomized studies of amiodarone in which ventricular tachyarrhythmia was prevented in 74%–76% at 7–10 months and in 59% at 3 years[12,20,21].

The CASCADE Study compared the efficacy of amiodarone to conventional therapy for long-term treatment of survivors of out-of-hospital ventricular fibrillation not associated with a Q-wave myocardial infarction[22]. The study group was non-homogenous with 82% having coronary artery disease and 18% having no coronary artery disease. Amiodarone-treated patients who had inducible sustained ventricular tachyarrhythmias at baseline electrophysiology study in the CASCADE study had an 82% survival free of cardiac death and sustained ventricular arrhythmias at 2 years. In our study, the survival free of ventricular tachyarrhythmia on amiodarone at 2 years was 50%. The difference in the outcome with amiodarone between the CASCADE study and our study can be explained by the differences in prognosis between patients who present with ventricular fibrillation versus ventricular tachycardia[23,24]. Patients with ventricular tachycardia have higher recurrence rates of ventricular tachyarrhythmia and poorer long-term prognosis than patients with ventricular fibrillation. In our study, 91% of the patients on amiodarone had ventricular tachycardia on presentation compared to the CASCADE trial where all patients had ventricular fibrillation.

**Efficacy of sotalol and amiodarone in preventing death from ventricular tachyarrhythmia**

We found that fatal recurrences of ventricular tachyarrhythmia occurred in 13% of patients treated with amiodarone and in 5% of patients treated with sotalol over a 3 year follow-up.

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**Table 4** Intention to treat analysis: Best fitting multivariate proportional hazards model (exhaustive search) for arrhythmia recurrence

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value taken</th>
<th>Hazard ratio* (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years</td>
<td>0-94</td>
<td>(0-88, 1-0)</td>
<td>0-05</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td>1</td>
<td>5-9</td>
<td>0-008</td>
</tr>
<tr>
<td>Amiodarone</td>
<td></td>
<td>(1-6, 22-2)</td>
<td></td>
</tr>
<tr>
<td>Number of diseased coronary arteries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2</td>
<td>6-9</td>
<td>(1-8, 26-3)</td>
<td>0-005</td>
</tr>
<tr>
<td>Ventricular tachyarrhythm cycle length</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤350 ms</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;350 ms</td>
<td>15-6</td>
<td>(3-8, 64-6)</td>
<td>&lt;0-001</td>
</tr>
</tbody>
</table>

*Each hazard ratio shown here is adjusted for the effects of the other independent predictors in this best fitting model.

**Table 5** Crossovers due to adverse reactions on oral therapy

<table>
<thead>
<tr>
<th></th>
<th>Sotalol</th>
<th>Amiodarone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients initially allocated (Intention-to-treat allocation)</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>Number of patients who subsequently crossed over to the other group</td>
<td>6 (27%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>Early crossover (≤2 days)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Late crossover (&gt;2 days)</td>
<td>3 (14%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>Median time at which cross over took place</td>
<td>0-3 months</td>
<td>3-5 months</td>
</tr>
</tbody>
</table>
Our mortality rate on amiodarone is consistent with other studies\(^{[12,19–21,25]}\). In these studies, death from ventricular tachyarrhythmia occurred in 12–23% at 1–3 years. Arrhythmic mortality on amiodarone in our study is higher than in the recently published EMIAT and CAMIAT trials\(^{[26,27]}\). These trials demonstrated that amiodarone decreased the incidence of arrhythmic mortality compared to placebo in patients with left ventricular ejection fraction ≤40% or with frequent ventricular premature depolarizations, respectively, following a recent myocardial infarction. However, there was no apparent benefit on all-cause mortality. Arrhythmic death and resuscitated cardiac arrest on amiodarone was 5.7% and 2.5% compared to 8.2% and 5.2% on placebo in EMIAT and CAMIAT trials, respectively. However, the patients in both the EMIAT and CAMIAT trials generally had a better outcome than patients included in our trial because patients with documented sustained ventricular tachyarrhythmia were excluded from both these trials.

It is likely that amiodarone is less effective in controlling ventricular tachyarrhythmia in patients with coronary artery disease than in patients without coronary artery disease\(^{[28,29]}\). That might explain the poor outcome of patients treated with amiodarone in our study. In the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure, amiodarone did not reduce the incidence of sudden death or prolong survival among patients with heart failure, except for a trend toward reduced mortality among those with non-ischaemic cardiomyopathy\(^{[30]}\). Seventy two percent of patients who received amiodarone in this trial had ischaemic heart disease. At 2 years the rate of sudden death was 15% in the amiodarone group and 19% in the placebo group. Nicklas et al. reported similar findings\(^{[31]}\). In a double-blind, placebo-controlled trial of low dose amiodarone in patients with severe heart failure and asymptomatic frequent ventricular ectopy they found that amiodarone caused no improvement in mortality or decrease in the incidence of sudden death. Amiodarone seemed to have less effect in patients with ischaemic heart disease than in patients with non-ischaemic cardiomyopathies. At 1 year, the overall mortality rate among patients with ischaemic heart disease was 34% for those receiving amiodarone and 19% for those receiving placebo. The 1-year overall mortality among patients with non-ischaemic cardiomyopathies was 24% vs 27% in those receiving amiodarone and placebo respectively. In the GESICA trial, amiodarone had a beneficial effect on sudden death as well as total mortality\(^{[32]}\). The beneficial effect of amiodarone in this trial could be due to the relatively low proportion of patients with previous myocardial infarction included in this trial. Only 39.6% of patients treated with amiodarone had previous myocardial infarction. Incidence of sudden death in the amiodarone-treated group was 12.3% compared to 15.2% in the placebo group.

The outcome of patients treated with sotalol in our trial is consistent with other clinical trials. A death rate of 4% has been reported with sotalol when used to treat patients with sustained ventricular tachyarrhythmia at a mean follow up of 346 days\(^{[18]}\). In the ESVEM study mortality from arrhythmia in patients treated with sotalol was 15% at 3 years\(^{[17]}\).

It is not clear whether it is the beta-blocking effect or the class III effect that is important for sotalol. In the SWORD Trial, d-sotalol resulted in more arrhythmic deaths than placebo in patients with left ventricular ejection fraction ≤40% and either a recent (6–42 days) myocardial infarction or symptomatic heart failure with a remote (>42 days) myocardial infarction\(^{[13,34]}\). Antz et al. suggested from their randomized study that metoprolol (16 patients) is as effective as dl-sotalol (18 patients) in patients with documented sustained ventricular tachycardia\(^{[35]}\). During a 2-year follow-up there was no difference in the incidence of arrhythmia recurrence, sudden death, or total mortality between the two groups. The study was limited by the small number of patients. Prophylactic beta-adrenergic blockade has been shown to reduce the incidence of sudden death by 18–35% in survivors of acute myocardial infarction who have not had spontaneous ventricular tachyarrhythmia before therapy\(^{[36]}\). It is possible that the combination of the beta-blocking and class III effects are important for sotalol’s antiarrhythmic efficacy.

Two trials have compared amiodarone to pure beta-blockers (metoprolol or propranolol) and reported that amiodarone is superior to beta-blockers in suppressing ventricular ectopic beats on Holter monitoring\(^{[37,38]}\). However, it is becoming increasingly apparent that suppression of ventricular ectopic beats on Holter monitoring does not correlate with a beneficial effect on the recurrence of spontaneous sustained ventricular tachyarrhythmia\(^{[30,31,39]}\).

**Poor tolerance of sotalol and amiodarone**

Side effects caused discontinuation of sotalol in 27% and of amiodarone in 17% of our patients. Adverse effects caused withdrawal of sotalol in 7%–22% of patients in other studies\(^{[18,40,41]}\). Amiodarone induced adverse effects requiring withdrawal of therapy in 32%–35% of patients in other studies\(^{[42,43]}\). Even though sotalol increases resting left ventricular ejection fraction it may worsen cardiac failure by preventing increase of cardiac output on exercise\(^{[15,40,44,45]}\). In our study, three (14%) patients developed significant left ventricular decompensation soon after starting sotalol. In our study as well as others, side effects were manifested early during sotalol therapy, generally in the first few days\(^{[15,45]}\). In contrast, side effects occurred at a median time of 3.5 months with amiodarone. Other investigators also have reported frequent side effects during chronic therapy with amiodarone\(^{[13,22,46,47]}\).

**Impaired left ventricular function**

Left ventricular ejection fractions of less than 30% in patients with ventricular tachycardia are associated with
higher cardiac mortality than a left ventricular ejection fraction of \( >30\% \)\(^{48,49}\). In our study, the mean left ventricular ejection fraction was \( 31\% \), typical of previous studies of patients with ventricular tachyarrhythmia secondary to old myocardial infarction\(^{19,50}\). Impaired left ventricular function without clinical cardiac failure was not a contraindication to treatment with sotalol in the majority of patients in our study and others\(^{60}\).

Intravenous drug testing prior to randomization

Intravenous testing was used to assess the efficacy of sotalol and amiodarone prior to randomization. Even though intravenous testing might be expected to predict the long-term efficacy of sotalol, it may not accurately reflect the long-term efficacy of oral amiodarone because of the well known delay in the onset of antiarrhythmic effects of amiodarone\(^{51–53}\). It is possible that some of the patients included in the study in whom amiodarone was predicted ineffective at intravenous testing could have been predicted effective at electrophysiological testing after chronic oral amiodarone\(^{51,52}\). If that were true, there may be a bias in favour of amiodarone in our study since the patients in whom sotalol was predicted to be effective were excluded. However, our findings showed a poorer outcome for patients treated with amiodarone.

Conclusions

Sotalol was superior to amiodarone for long-term treatment of ventricular tachyarrhythmia secondary to coronary artery disease in patients in whom both sotalol and amiodarone were predicted to be ineffective on intravenous electrophysiological testing. Side effects are common with both sotalol and amiodarone and better antiarrhythmic drugs need to be developed. Sotalol manifests major side effects early, facilitating introduction of alternate therapy while patients are still in the hospital. Adverse effects with amiodarone occur later during therapy. Our study has not conclusively proven that sotalol is superior to amiodarone in all patients with ventricular tachyarrhythmia and coronary artery disease, but has demonstrated the need for randomised studies in larger numbers of patients comparing the two agents directly.

Clinical implications

Recently the results of the AVID trial have suggested that implantable defibrillators are superior to antiarrhythmic agents in a subgroup of patients with ventricular tachyarrhythmia\(^{56}\). The study was conducted in patients who had been resuscitated from near-fatal ventricular fibrillation or who had undergone cardioversion from sustained ventricular tachycardia. Patients with ventricular tachycardia also had either syncope or other serious cardiac symptoms, along with a left ventricular ejection fraction of \( 0.40 \) or less. It is likely that from now on implantable defibrillators would be used as primary therapy in this subgroup of patients with ventricular tachyarrhythmia\(^{57}\). The main role of antiarrhythmic agents in such patients with ventricular tachyarrhythmias would be as supplementary therapy in patients who already have implantable defibrillators. Sotalol and amiodarone are the two agents most suitable for this purpose. There is a pressing need for a randomized trial comparing these two agents directly in patients with ventricular tachyarrhythmia who already have an implantable defibrillator. The question whether sotalol or amiodarone is superior is also important in patients with ventricular tachyarrhythmia who are not suitable for treatment with an implantable defibrillator. Until such a trial is conducted, it would be reasonable to consider sotalol preferable to amiodarone because of the

Study limitations

Our study randomized a relatively small number of subjects. Because of the small sample size, we had to use arrhythmia recurrence as our primary end-point instead of the more reliable total mortality\(^{54}\).

Our data suggested that sotalol was superior to amiodarone in the patients included in this study. At worst, sotalol may have an equivalent efficacy to amiodarone. It is unlikely that amiodarone is superior to sotalol. Although this may come as a surprise to many, our results are generally comparable to previous non-randomized studies of these two drugs. The loading dose of amiodarone that we used in our trial (800 mg per day for one week) is less than that used in some other trials\(^{19,25}\). However, the outcome with amiodarone was similar in these studies compared to ours. In the AVID trial, the trial protocol recommended a loading dose of 800 to 1600 mg/day, with a minimal in-hospital loading of 5-6 g\(^{55}\). It is not clear whether a higher loading dose of amiodarone would significantly improve the antiarrhythmic efficacy without increasing the possibility of unwanted side effects.

Patients who were intolerant of the allocated antiarrhythmic drug (17–29\%) crossed over to the other group. This indicates the poor tolerance of both drugs by patients and probably mirrors common clinical practice with these agents. To compensate for this cross-over we performed both an intention-to-treat analysis as well as an actual treatment received analysis. The results were similar with both types of analysis.

The strength of our study is that the study population was homogenous. All patients had spontaneous sustained ventricular tachyarrhythmia secondary to coronary artery disease and had reliably inducible ventricular tachyarrhythmia in the electrophysiology laboratory.
relative efficacy of sotalol shown in this trial and the relative toxicity of amiodarone.

References


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