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A multicentre, double-blind randomized crossover comparative study on the efficacy and safety of dofetilide vs sotalol in patients with inducible sustained ventricular tachycardia and ischaemic heart disease

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Background Antiarrhythmic drugs are still used for the treatment of ventricular tachyarrhythmias, in combination with implantable cardioverter-defibrillators or without them.

Aim of the study In a double-blind randomized crossover design, the short- and long-term efficacy and safety of oral dofetilide or oral sotalol were compared in 135 patients with ischaemic heart disease and inducible sustained ventricular tachycardia.

Methods The inducibility of ventricular tachycardia was determined by programmed electrophysiological stimulation at baseline. Patients were then blindly randomized to receive either oral dofetilide 500 μg twice daily or oral sotalol 160 mg twice daily, for 3 to 5 days. Suppression of inducible ventricular tachycardia on the drug was then assessed by programmed electrophysiological stimulation. After a wash-out period of at least 2·5 days, the patients received the alternative treatment for 3 to 5 days. Suppression of inducible ventricular tachycardia on the alternate drug was again determined by programmed electrophysiological stimulation. Selection of long-term treatment was allocated blindly according to programmed electrophysiological stimulation results.

Results During the acute phase, 128 patients received both dofetilide and sotalol. Sixty-seven patients were responders to either drug. Forty-six patients (35·9%) were responders to dofetilide compared with 43 (33·6%) to sotalol (P=ns). Only 23 patients responded to both dofetilide and sotalol. Adverse events, deemed to be treatment related, were seen in 2·3% of patients receiving dofetilide and 8·6% of patients receiving sotalol (P=0·016). Three patients on dofetilide had torsade de pointes. Two patients receiving sotalol died during the acute phase (one was arrhythmic death, and the other was due to heart failure). During the long-term phase, two of 42 patients (4·8%) receiving dofetilide and three of 27 patients (11·1%) receiving sotalol withdrew from treatment due to lack of efficacy. Overall, during the long-term phase, 23·8% of the patients receiving dofetilide and 37·0% of the patients receiving sotalol, withdrew from treatment with a similar pattern of withdrawals for the two drugs.

Conclusion Dofetilide was as efficacious as sotalol in preventing the induction of sustained ventricular tachycardia. There was no concordance in the response rate in two-thirds of the patients. Dofetilide was significantly better tolerated during the acute phase than sotalol. Both dofetilide and sotalol were well tolerated during the long term with no statistically significant difference in the adverse events.
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Introduction

With the exception of amiodarone, electrophysiological testing has been frequently used to guide selection of the most appropriate drugs in the treatment of patients with sustained ventricular tachyarrhythmias[1–3]. The basis of this approach is that antiarrhythmic drugs that effectively suppress inducible ventricular tachyarrhythmias are associated with a better outcome than drugs in which inducibility persists[2].

AVID[4], a prospective, randomized trial, has had an impact on the management of sustained ventricular tachyarrhythmias. The study found that, among survivors of ventricular fibrillation or in patients with sustained ventricular tachycardia causing severe symptoms, the implantable cardioverter-defibrillator is superior to amiodarone or sotalol in increasing overall survival. In subsequent analysis, the benefit conferred by device therapy was not confirmed for the subgroup of patients with well-preserved left ventricular ejection fraction[5,6], and the same finding was confirmed by a recent meta-analysis of implantable cardioverter-defibrillator secondary prevention trials[7]. In patients with well-preserved left ventricular ejection fraction, prospective studies with larger patient numbers are needed to compare drugs and cardioverter-defibrillators[6,7]. In clinical practice, there is still a need for antiarrhythmic drug treatment in the management of ventricular tachyarrhythmias. This need includes the prevention of ventricular tachycardia recurrences in patients with well-tolerated sustained ventricular tachycardia or with symptomatic non-syncopal sustained ventricular tachycardias and left ventricular ejection fraction >40% (two categories of patients not included in AVID) or for reducing ventricular tachycardia recurrences in patients who already have an implantable cardioverter-defibrillator. Moreover, although the implantable cardioverter-defibrillator has a favourable profile in terms of cost-effectiveness when appropriate indications are followed[8,9], its cost has limited widespread diffusion of this non-pharmacological treatment in some countries, especially in eastern Europe[10].

The ESVEM study is still the only study to use an electrophysiologically guided strategy to compare the efficacy and safety of alternative antiarrhythmic drug therapy in patients with ventricular tachyarrhythmias[3,11]. The efficacy of different class III antiarrhythmic agents in patients with ventricular tachyarrhythmias in particular has not been determined by a randomized crossover study using electrophysiologically guided treatment.

Dofetilide is a selective potassium channel blocker[12] recently approved for the treatment of atrial fibrillation and effective for treating and preventing a broad range of supraventricular and ventricular tachyarrhythmias[13–15]. Pre-clinical studies have shown that dofetilide produces marked increases in the effective refractory period and action potential duration without affecting the fast inward current[16]. In addition, it suppresses ventricular tachycardia[14] and reduces energy requirements for ventricular defibrillation[17].

Dofetilide has been shown to be effective in preventing the induction of sustained ventricular tachycardia in approximately 30% to 40% of cases[14]. Sotalol has been extensively employed for ventricular tachycardia prophylaxis[11,18,19]. However, in addition to its class III antiarrhythmic activity, it has also beta-blocking properties that some patients cannot tolerate.

The aims of this study were to compare, in a double-blind randomized crossover design, the short- and long-term efficacy and safety of oral dofetilide and oral sotalol in patients with ischaemic heart disease and sustained ventricular tachycardia induced by programmed electrophysiological stimulation.

Methods

Patients

Eligible patients were males and females of non-childbearing potential with evidence of ischaemic heart disease and sustained ventricular tachycardia (defined as ventricular tachycardia lasting >30 s or <30 s but requiring emergency cardioversion) which could be induced by programmed electrophysiological stimulation in a drug-free state. Patients had to be 18 years of age or older and had to provide written informed consent prior to entering the study.

Exclusion criteria included: unstable severe congestive heart failure (NYHA class IV); myocardial infarction, evidence of recent myocardial infarction, unstable angina pectoris or survival from sudden cardiac death during the 3 weeks prior to the study; bradycardia (<50 beats . min^{-1}); a history of polymorphic ventricular tachycardia secondary to treatment with antiarrhythmic drugs; a malfunctioning pacemaker; systolic hypotension (80 mmHg) or diastolic hypertension (>110 mmHg); prolonged QTc interval (>440 ms) in the drug-free state and in the absence of pre-excitation or bundle branch block; major haematological (aplastic anaemia or agranulocytosis), hepatic or renal (serum creatinine >300 μmol . l^{-1}, creatinine clearance <40 ml . min^{-1}) disease; hypo- or hyperkalaemia (<3·6 mmol . l^{-1} or >5·5 mmol . l^{-1}); and hypo- or hypermagnesaemia (<0·6 mmol . l^{-1} or >1·25 mmol . l^{-1}). In addition, patients were excluded if they had received any medication or therapy known to be associated with torsade de pointes during the period corresponding to five half-lives prior to commencement of the study or if they had received amiodarone within the previous 3 months. Patients who were already treated with sotalol for ventricular tachycardia were also excluded. Patients were excluded if they had a contraindication to beta-blockers, were receiving cimetidine which could not be changed to another appropriate therapy, had participated in any other studies involving investigational drugs within 1 month prior to entry into this study, or had evidence of drug or alcohol abuse.

PES protocol

S_1S_1 + Extrastimuli	RV Apex	RV OT
550 + S_2	Stage 1	Stage 9
550 + S_2S_3	Stage 2	Stage 10
400 + S_2	Stage 3	Stage 11
400 + S_2S_3	Stage 4	Stage 12
330 + S_2	Stage 5	Stage 13
330 + S_2S_3	Stage 6	Stage 14
550 + $S_2S_3S_4$	Stage 7	Stage 15
400 + $S_2S_3S_4$	Stage 8	Stage 16

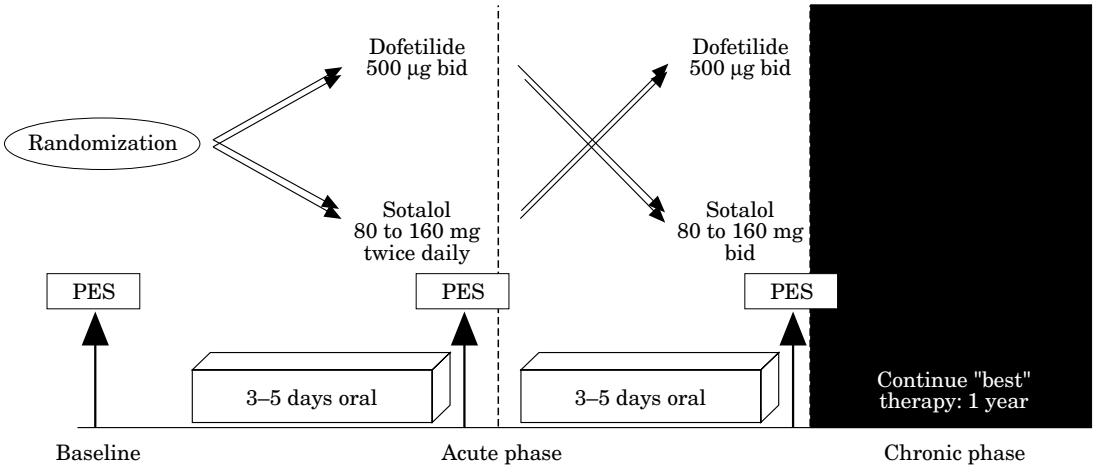

Figure 1 **Flow chart of the study protocol, including the acute and chronic phase. In the upper left the multistaged study protocol for programmed electrophysiological stimulation (PES) is shown. RV = right ventricular; OT = outflow tract.**

Study design

This was a double-blind study of dofetilide and sotalol comprising an acute crossover phase followed by a long-term phase of 12 months. Figure 1 depicts the study design.

A screening evaluation, consisting of a full clinical examination, blood pressure measurement, 12-lead resting ECG, 24-h Holter monitoring; assessment of left ventricular ejection fraction, and blood and urine sampling for haematological and biochemical parameters, was performed no more than 15 days prior to study entry.

Programmed electrophysiological stimulation was performed at baseline and following the last dose of dofetilide or sotalol in the acute phase of the study. Prior to programmed electrophysiological stimulation, the RR interval, QRS duration and QT interval were determined during sinus rhythm. The ventricular diastolic pacing threshold was determined and the ventricular effective refractory period was measured after a ventricular drive cycle of eight beats at a cycle length of 400 ms. Stimulation of ventricular tachycardia was then attempted. Three drive cycle lengths (S_1S_1) of 550, 400 and 330 ms were used (eight beats each) followed by one, two or three extrastimuli (S_2,S_3,S_4). Programmed electrophysiological stimulation was performed at two sites: the apex and outflow tract of the right ventricle. Only patients with sustained ventricular tachycardia induced by programmed electrophysiological stimulation at baseline in a drug free state were included in the study. The stage at which ventricular tachycardia was induced was classified from 1 to 16 depending on the ventricular drive cycle length, the number of extrastimuli and the location of stimulation, as shown in Fig. 1.

In the acute phase, random allocation to one of the two treatments was based on a computer generated pseudo-random code using the method of random permuted blocks. According to this randomization, in the acute phase the patients received blindly either oral dofetilide 500 µg twice daily or oral sotalol 80 mg twice daily (first day only) followed by oral sotalol 160 mg twice daily, for 3 to 5 days (the drugs were administered as similar capsules). Following this, the programmed electrophysiological stimulation protocol was repeated in an attempt to induce ventricular tachycardia. Patients were considered drug responders if sustained ventricular tachycardia could not be induced by similar or less intense stimulation than originally used. After a washout period of at least 2·5 days, patients received the alternative treatment for 3 to 5 days, following which, programmed electrophysiological stimulation was again repeated to determine the patient's response to the second drug. Blood samples were intermittently collected for dofetilide plasma concentration throughout the acute phase. If side-effects, spontaneous ventricular

tachycardia, deterioration of cardiac function, or clinical evidence of treatment failure, developed, the investigator could stop the drug and, if appropriate, cross the patient over to the second treatment. However, the investigators were requested to terminate the study if proarrhythmia was reported.

Long-term treatment was based on the patient's responses during the acute phase. Patients who responded to both drugs were continued on either drug at the investigator's discretion (blind evaluation). Patients who responded to only one of the two drugs were continued on the drug to which they responded and patients who responded to neither drug were withdrawn from the study. If a patient who had responded to both drugs during the acute phase was not tolerating or not responding to treatment during the long-term phase, then the investigator could change treatment for that patient to the alternate therapy. Any such change of therapy was carried out under hospital supervision and close monitoring of the patient. Investigators remained blind with regard to drugs in all the study phases. Patients were evaluated 1, 3, 6, 9 and 12 months after the start of long-term treatment. At each visit, interim history was recorded, a clinical cardiovascular examination was performed, ECG and blood pressure measurements were obtained, blood samples were collected for dofetilide plasma concentrations, and safety were monitored by recording adverse events. A 24-h Holter recording was obtained at the 3- and 9-month visits and blood and urine samples were analysed for haematological and biochemical parameters at the 1-, 6- and 12-month visits.

Safety assessments

All observed or volunteered adverse events, irrespective of causal relationship to study treatment, were recorded. The patients were withdrawn from the study if any of the following events occurred: (1) proarrhythmic events, defined as torsade de pointes, new ventricular fibrillation, ventricular tachycardia resistant to cardioversion, new sustained ventricular tachycardia (>30 s at a rate of >100 min^{-1}) provided no ventricular rhythm longer than a triplet had previously been documented off drugs, development of sustained (>75 min) supraventricular tachycardia at a rate >120 min^{-1} (or atrial fibrillation or flutter at any rate) in a patient in whom these rhythms had never previously been documented or suspected on clinical grounds, supraventricular tachycardia (with the exception of atrial fibrillation) which had previously been terminated with pacing and/or intravenous atrioventricular blockers and in whom these agents were no longer effective ('incessant supraventricular tachycardia'), or sudden cardiac death; (2) excessive prolongation of the QTc interval (>550 ms); (3) failure of treatment (e.g. recurrence of sustained ventricular tachycardia or ventricular fibrillation); (4) intolerable adverse events (as judged by the patient) or events considered unacceptable by the investigator; (5) deterioration of cardiac function; (6) creatinine clearance <40 $ml.min^{-1}$; (7) insufficient patient compliance; (8) patients' refusal to continue the study; or (9) any clinical reason assessed by the investigator to warrant withdrawal.

The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki, 1989 and approved by the local ethics committees for each centre involved in the study.

Statistical analysis

It was anticipated that 40% of patients would respond to both dofetilide and sotalol treatment. Based on this, 130 patients would be sufficient to detect a 20% change in the response rate between treatments at the 5% significance level with 80% power. The sample size of 130 patients also allowed detection of an increase from 10% to 25% in the number of patients reporting adverse events in the acute phase at the 5% level of significance with 80% power[20].

It was anticipated that 52 patients (26 patients on each treatment) would enter the long-term phase of the study. This sample size was sufficient to detect a difference in withdrawal rates (due to adverse events or lack of efficacy) of 6% on dofetilide compared with 42% on sotalol[13] at the 5% level of significance and with 80% power.

The primary efficacy end-point for this study was the proportion of patients responding to treatment during the acute phase. These data were recorded at the end of each period in the acute phase of this study. A patient was classified as a non-responder to treatment if ventricular tachycardia occurred spontaneously or was induced as a result of the programmed electrophysiological stimulation. To be included in the intention-to-treat analysis, a patient had to have at least one dose of study treatment in both periods of the acute phase. For the purpose of the intention-to-treat analysis, all patients with missing data for treatment response, but who had taken treatment during that period, were coded as non-responders. A further analysis performed to be supportive of the intention-to-treat analysis excluded those patients that had no data recorded for treatment response for one or other periods. The proportion of patients responding to treatment was presented descriptively and analysed using a log-linear model in SAS (SAS Institute Inc.). The effects formally tested were direct by period interaction, homogeneity of the odds ratio across countries, treatment (Prescott's test) and period, using likelihood ratio tests. The proportion of patients responding to treatment was estimated for each treatment group, and a 95% confidence interval (CI) for the difference between dofetilide and sotalol was calculated. Secondary efficacy end-points were changes in ventricular effective refractory period during the acute phase and the incidence of decreased left ventricular function, change in NYHA classification, and the incidence of symptoms associated with ventricular tachycardia during the chronic phase.

Table 1 Clinical characteristics of patient population (135 patients)

	Randomized to dofetilide as first drug and then crossed to sotalol	Randomized to sotalol as first drug and then crossed to dofetilide
Number of patients	69	66
Mean age (range) (years)	63 (37–79)	63 (39–79)
Male/female	57/12	63/3
Previous myocardial infarction	66	61
Q wave	59	50
Non-Q wave	7	11
NYHA class		
I	26	32
II	39	31
III	4	3
Left ventricular ejection fraction (%) (mean ± SE)	40 ± 2	41 ± 2
Left ventricular aneurysm	25	23
Previous pacemaker implant	2	1
Previous cardioverter-defibrillator implant	6	6

The primary safety end-point for this study was the proportion of patients reporting at least one treatment-emergent adverse event (including objective events) during the acute phase. The analysis of adverse events was performed using SAS (SAS Institute Inc.)[21]. The effects formally tested were treatment (Prescott's test)[22] and period, using likelihood ratio tests under a log-linear model. The direct by period interaction and homogeneity of odds ratios across countries was not determined, as there were too few events in each cell. Treatment-related and treatment-emergent adverse events were analysed in a similar manner. Another primary safety end-point was the time to withdrawal (all causality, treatment-emergent) from the chronic phase. Survival functions were estimated for time to withdrawal for reasons categorized as 'all-causality' during the long-term phase, for each treatment group. This analysis was performed using the LIFETEST procedure in SAS (SAS Institute Inc.). Due to the non-randomized nature of the treatment administered during the long-term phase of this study, the comparison of the dofetilide and sotalol estimated survivor functions was not formally tested. Secondary safety end-points for this study were: the proportion of patients reporting at least one treatment-emergent, treatment-related adverse event during the acute phase, and patient withdrawal due to lack of efficacy during the chronic phase.

Results

Clinical characteristics of the patients

A total of 138 patients were screened and 135 were randomized to receive treatment. Patient demographics are listed in Table 1.

The patient population was also characterized by five different clinical settings: aborted sudden death (nine patients), clinical sustained ventricular tachycardia (95 patients among which 54 had haemodynamically tolerated ventricular tachycardia at a mean rate of 180 ± 33 beats . min^{-1} [range 115–250] and 41 had ventricular tachycardia that was at a mean rate of 216 ± 46 beats . min^{-1} not tolerated haemodynamically [range 140–352]), unexplained syncopoea (15 patients), non-sustained ventricular tachycardia (six patients), or ischaemic heart disease with inducible sustained ventricular tachycardia (10 patients). Overall, 73 patients had previously received antiarrhythmic treatments for preventing ventricular tachyarrhythmias (mean anti-arrhythmic drug trials=$1{\cdot}7 \pm 1{\cdot}1$, range 1–6).

Results of acute phase treatment

During the acute phase, which was double-blind, randomized and crossover, 132 patients received dofetilide 500 μg twice daily and 131 received sotalol 160 mg twice daily (the initial first dose was 80 mg twice daily for the first day). Seven patients (four dofetilide and three sotalol) had incomplete acute phase data and were excluded from the intention-to-treat analysis. Table 2 summarizes the main electrophysiological data at baseline and during treatment with dofetilide and sotalol.

During the acute phase of the study, 46 of the 128 patients (35·9%) who received dofetilide responded to treatment compared with 43 of the 128 patients (33·6%) who received sotalol (P=ns). The number of responders was independent of the order of drugs and was constant among the different countries. Among 67 responders, 23 patients (34·3%) responded to both dofetilide and sotalol treatment, 23 patients (34%) only responded to dofetilide treatment and 21 patients (31%) only responded to sotalol treatment (Fig. 2).

During the acute phase, dofetilide, was discontinued in eight patients and sotalol was discontinued in seven

Table 2 Main electrophysiological data (values in ms) at baseline and during treatment with dofetilide and sotalol (third day of treatment)

	Baseline	Change from baseline		Difference[1]	95% CI for difference	*P* value
		Dofetilide	Sotalol			
VERP	230·9	23·5	32·2	− 8·5	(− 15·2, − 1·8)	0·0134
RR	859·8	18·7	218·2	− 199·9	(− 246·1, − 153·7)	0·0001
QRS	100·85	1·11	1·75	− 0·53	(− 3·21, − 2·15)	0·6944
QT	395·8	42·5	59·3	− 16·7	(− 29·6, − 3·7)	0·0131
QTc	425·3	39·6	14·8	25·2	(13·1,37·3)	0·0001

[1]Difference of least squares means estimated from mode.
VERP=ventricular effective refractory period.

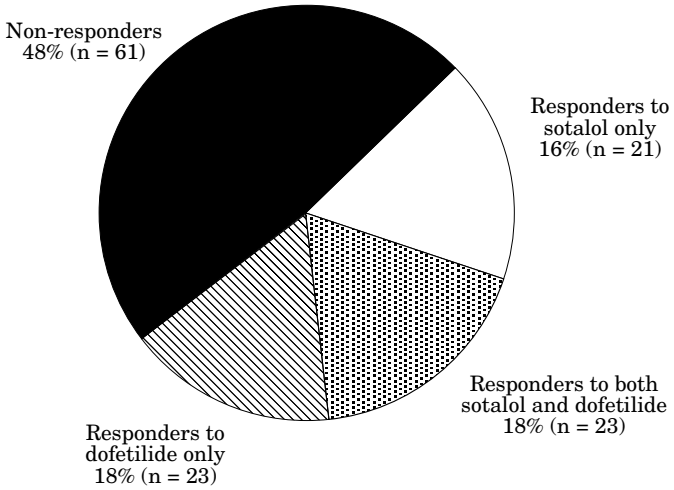

Figure 2 **Results of acute phase treatment, based on response to programmed electrophysiological stimulation.**

patients. Ten (four dofetilide and six sotalol) of these discontinuations were drug- related. One patient in each group was discontinued for lack of efficacy. Three patients receiving dofetilide developed torsade de pointes. Two patients receiving sotalol died. Sotalol was discontinued in one patient each for dizziness, syncope, and a combination of asthma and leg oedema. During the acute phase, 11 of the 128 patients (8·6%) who received dofetilide experienced at least one all-causality adverse event compared with 25 of the 128 patients (19·5%) who received sotalol (P=0·002; CI 0·173–0·043). These adverse events were deemed to be treatment related in three (2·3%) patients receiving dofetilide and 11 (8·6%) patients receiving sotalol (P=0·016). Excluding objective test findings, in the acute phase adverse events were reported with a lower prevalence for dofetilide (seven patients; 5%) compared with sotalol (23 patients; 18%). Dizziness (one patient; 0·8%) was the only drug related adverse event reported by patients receiving dofetilide. Dizziness was also the most common adverse event reported by the patients during treatment with sotalol (five patients; 3·8%). Additional adverse events reported by patients receiving sotalol were: severe asthaenia, nausea, headache, hypotension, heart failure and peripheral oedema. As previously noted, sotalol treatment was discontinued in three patients secondary to reported symptoms.

Results of long-term treatment

Sixty-seven patients entered the long-term phase. The long-term treatment drugs were allocated blindly according to the electrophysiological results (see Method section above). Thus 41 received dofetilide and 26 received sotalol. During the long-term treatment, 20 patients, 10 receiving dofetilide (23·8%) and 10 receiving sotalol (37·0%), withdrew from treatment. The pattern of withdrawals was similar for both dofetilide and sotalol (Fig. 3). Eight discontinuations (four dofetilide and four sotalol) were considered to be treatment-related. The reasons for withdrawal in the patients receiving dofetilide were lack of efficacy in two patients, sustained ventricular tachycardia in one patient, and syncope, nausea, vomiting and diarrhoea in one patient. Three of the four treatment-related sotalol withdrawals were for lack of efficacy and the remaining patient died. Treatment was temporarily

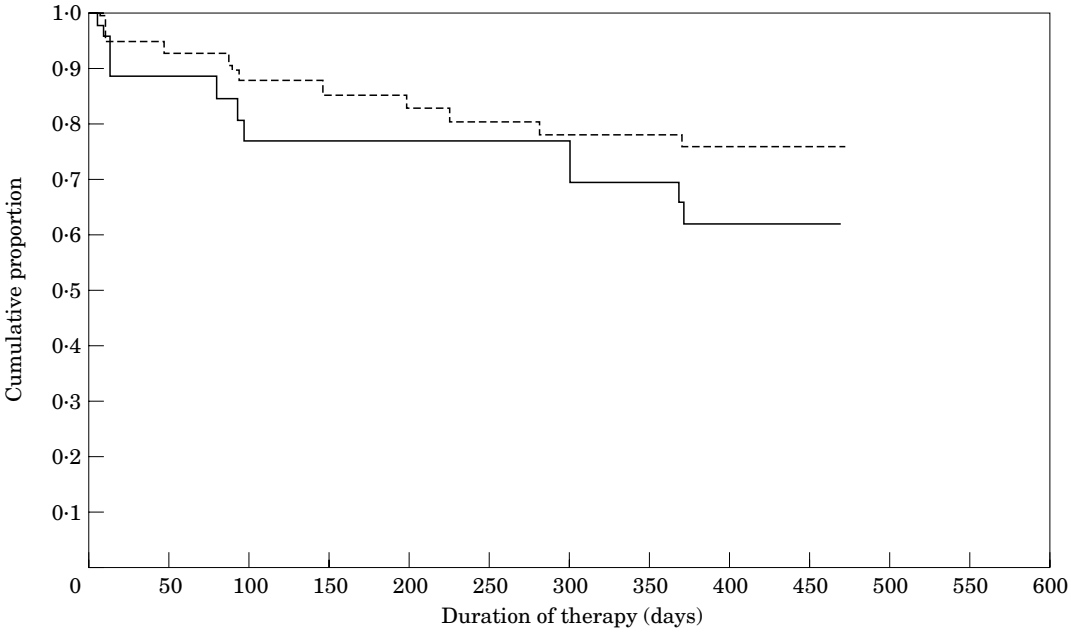

Figure 3 **Results of long-term treatment in 67 patients (41 treated with dofetilide and 26 with sotalol) entering the chronic phase. The curves depict the pattern of withdrawals for each drug (no statistically significant difference). - - - =dofetilide 500 µg twice daily; ——=sotalol 160 mg twice daily.**

stopped or reduced for nausea, vomiting and a respiratory tract infection in the dofetilide group and/or ventricular tachycardia, dizziness, a respiratory tract infection and a decrease in renal function in the sotalol group.

In the long-term treatment phase, adverse events were reported by 27 out of 42 patients (64·3%) treated with dofetilide versus 18 out of 27 (66·7%) treated with sotalol (P=ns). These events comprised mild headache, dizziness, dyspepsia, nausea and vomiting.

Proarrhythmic effects and deaths

Ten patients (six dofetilide; four sotalol) in the acute phase and four patients (two dofetilide; two sotalol) in the long-term phase had proarrhythmic events.

In the acute phase, three patients had torsade de pointes during treatment with dofetilide. A female patient (left ventricular ejection fraction=48%) developed QT interval prolongation to 570 ms 75 min after her first dose of dofetilide. Torsade de pointes occurred shortly thereafter and was terminated by four shocks from her implanted cardioverter-defibrillator and intravenous $MgSO_4$. A male patient (left ventricular ejection fraction=40%) developed ventricular tachycardia on the second day of the washout period having previously received sotalol. This episode was terminated by the patient's implanted cardioverter-defibrillator. On the third and fourth day of dofetilide therapy, recurrent episodes of monomorphic and polymorphic ventricular tachycardia developed and dofetilide was discontinued. Review of the ECG data determined that one of the episodes of polymorphic ventricular tachycardia was torsade de pointes. Another female patient (left ventricular ejection fraction=50%) developed QTc prolongation to 602 ms on the second day of dofetilide therapy, following which, dofetilide was discontinued. The following day an episode of torsade de pointes occurred. This episode was successfully treated with intravenous $MgSO_4$. In addition, during dofetilide treatment in the acute phase, one patient (left ventricular ejection fraction=23%) had a new sustained ventricular tachycardia, one patient (left ventricular ejection fraction=30%) had a new ventricular fibrillation during programmed electrophysiological stimulation, and one patient (left ventricular ejection fraction=20%) had a polymorphic ventricular tachycardia.

During sotalol treatment in the acute phase, three patients developed new sustained ventricular tachycardia, one of whom also developed new ventricular fibrillation, and one patient (left ventricular ejection fraction=57%) had syncope which was thought to be potentially arrhythmic in origin.

During long-term treatment, two patients receiving dofetilide and one receiving sotalol had new sustained ventricular tachycardia. Another patient (left ventricular ejection fraction=20%) receiving sotalol had a presumed arrhythmic death on day 12 of treatment.

Overall four deaths were observed: two were arrhythmic deaths and two were due to heart failure. One arrhythmic death occurred following four episodes of ventricular fibrillation on day 2 of sotalol therapy in a patient with a left ventricular ejection fraction of 28%. Sotalol was discontinued and intravenous amiodarone started but the patient developed progressive

bradycardia and cardiogenic shock and died later that day. The other arrhythmic death occurred suddenly at home on day 12 of sotalol treatment, as previously described. One of the deaths due to heart failure occurred during the acute phase. This patient (left ventricular ejection fraction 25%) developed ventricular tachycardia on the fifth day of sotalol therapy. She was successfully treated with a DC cardioverter but developed progressive left ventricular failure with hypotension and peripheral oedema and died 2 days later. The other death due to heart failure occurred in a patient with a left ventricular ejection fraction of 24% who had a myocardial infarction on day 279 of dofetilide therapy and died 1 week later from cardiogenic shock.

Discussion

The current study is a crossover study comparing two different class III antiarrhythmic agents, thus allowing a within-patient comparison of drug efficacy in the acute phase, as judged by the ability to suppress ventricular tachycardia inducibility at programmed electrophysiological stimulation. Moreover, contrary to other studies (Table 3), it was based on a relatively homogeneous population of patients, all of whom had ischaemic heart disease. Seventy per cent of the patient population of this study were the cases with sustained ventricular tachycardia, with a low prevalence (7%) of patients with aborted sudden death. This patient population is, therefore, quite different from the population enrolled in other studies dealing with ICD treatment[4,–6,26,28] or exclusively with patients with aborted sudden death[1] or dealing with primary prevention of sudden death in coronary artery disease patients at high risk[24,27]. Thus, the clinical profile of the patients enrolled in this study is similar to that of patients enrolled in the studies by Steinbeck *et al.*[2], by Haverkamp *et al.*[19] and in the ESVEM study[3,11]. For patients with sustained ventricular tachycardia without arrhythmia-induced haemodynamic impairment, treatment with antiarrhythmic agents guided by programmed electrophysiological stimulation or with empiric amiodarone are still the most frequent treatment strategies. No prospective controlled study has examined the role of implantable cardioverter-defibrillators in this subset of patients. Moreover, recent analysis of AVID[6] and CIDS[5] studies showed that in patients with life-threatening ventricular tachyarrhythmias and relatively well-preserved left ventricular ejection fraction (>35%), survival with cardioverter-defibrillators may not differ from that with amiodarone.

The results of this study demonstrate that dofetilide and sotalol have equal efficacy as determined by programmed electrophysiological stimulation but that dofetilide has a lower rate of adverse events with short-term therapy. This is a clinically relevant result because sotalol was the most effective drug in ESVEM[11] (35% acute efficacy, similar to that in the present study) and did not differ from amiodarone in another study[23]. Sotalol, in its currently used racemic form, did not differ from placebo in a post-infarction mortality trial[29], while d-sotalol (a pure class 3 antiarrhythmic agent) had a worse effect on survival compared with the placebo in the SWORD study[30]. Dofetilide had a neutral effect on survival in the DIAMOND study[15]. Based on the findings of the present study, dofetilide may prove to be an alternative to sotalol treatment in ventricular tachyarrhythmias treatment, with comparable efficacy but better tolerability.

Two-thirds of the patients, in whom induction of ventricular tachycardia was suppressed by a study drug, responded to only one of the two class III antiarrhythmic agents. This finding may be interpreted in different ways: (1) dofetilide and sotalol may have a different effect on the same substrate due to their different electrophysiological properties and the effect on ventricular effective refractory period was different; (2) programmed electrophysiological stimulation results in terms of efficacy, based on the adopted criteria, may not be strictly reproducible, as supported by some papers in literature[31,32] or (3) the underlying substrate for ventricular tachycardia may differ and thus respond to different drugs. In any case, the clinical implications of this finding are important since the trial demonstrates that the probability of detecting a positive response during programmed electrophysiological stimulation is increased by testing a second class III antiarrhythmic agent. In the present study testing two drugs yielded to a 52% response rate. The results of Schoels *et al.*[33], although not based on a crossover design, are in agreement with these results since testing two drugs in sequence identified 70% of the responders, while the first drug identified only 50% of the responders.

Proarrhythmia

One of the most important issues in dealing with class III antiarrhythmic agents is the risk of proarrhythmia due to torsade de pointes. For sotalol, the risk of torsade de pointes is dose-dependent[18,34], In a study of 1363 patients, Hohnloser[18,34] found a 5·9% overall incidence of proarrhythmia. Unfortunately, sotalol's efficacy is also dose-dependent, creating an intriguing risk–benefit ratio problem. For sotalol, more than 50% of all proarrhythmic events occur during the first days of dosing but some proarrhythmic events only occur later in treatment[34]. In the current study, dofetilide demonstrated a similar pattern with all the torsade de pointes occurring during the first 3 days and six out of the eight episodes of proarrhythmia occurring during the acute phase of 3 to 5 days. Therefore, in-hospital initiation of dofetilide treatment is warranted.

In the present study of patients with ischaemic heart disease and inducible sustained ventricular tachycardia, the prevalence of torsade de pointes on dofetilide was 2%. In no case did death result from torsade de pointes (two out of three patients had a previously implanted

Table 3 Main studies on antiarrhythmic drug treatment in ventricular tachyarrhythmias

Study, reference, year	Number of patients	Aetiology	Patients' clinical profile				Number of patients previously tested with AA drugs	Basal EP for VT inducibility	Number of extrastimuli for EP testing
			Aborted sudden death	Sustained VT	Syncope	Non-sustained VT			
Amiodarone versus sotalol[23], 1989	59 R to amiodarone (30) or sotalol (29)	Prior MI in 64%	19%	66%	25%		100%	EP performed in 54%	n.a.
Steinbeck *et al.*[2], 1992	170: 61 inducible R to EP-guided AA Tx, 54 inducible R to metoprolol, 55 non-inducible R to metoprolol	CAD in 70%	29%	50%	21%		n.a.	EP performed in 100%: inducible ventricular tachycardia in 68%	1–2 extrastimuli
Kehoe *et al.*[24], 1993	473 with sotalol treatment guided by Holter or EP	Prior MI in 72%	38%	72%			100%	EP performed in 87%: inducible ventricular tachycardia in 65%	1–3 extrastimuli
CASCADE[1], 1993	128 R to amiodarone (113) or to conventional AA drugs (115)	CAD in 82%	100%				45%	EP performed in 80%: ventricular tachycardia/ VF inducible in 60%	1–3 extrastimuli
ESVEM[3,11], 1993	296 R to AA Tx. guided by EP (108) or by Holter (188)	Prior MI in 80%	19–25%	70–73%	5–8%		64%	EP performed in 100% at baseline with ventricular tachycardia inducible in all the pts.	1–3 extrastimuli
MADIT[25], 1996	196 R to ICD (95) or conventional Tx. (101)	CAD in 100%				100%	35–42%	EP performed in 100% at baseline with ventricular tachycardia inducible in all the pts. and not suppressed by i.v. procainamide	1–3 extrastimuli
Haverkamp *et al.*[19], 1997	396 submitted to EP-guided Tx. with oral sotalol	CAD in 72%	21%	76%	11%		n.a.	EP performed in 100% at baseline with ventricular tachycardia inducible in all the pts.	1–3 extrastimuli
AVID[4], 1997	1016 R to ICD (507) or AA Tx. (435 on amiodarone and 74 on sotalol)	CAD in 81%	45%	55%			15–16%	n.a.	n.a.
Pacifico *et al.*[26], 1999	302 with ICD R to sotalol (151) or placebo (151)	Prior MI in 66–73%	32–39%	61–68%			n.a.	n.a.	n.a.
MUSTT[27], 1999	704 R to EP-guided Tx. (351) or no AA Tx. (353)	CAD in 100%				100%	n.a.	EP performed in 100% at baseline with ventricular tachycardia inducible in all the pts.	1–3 extrastimuli
CIDS[5,28], 2000	659 R to ICD (328) or to amiodarone Tx (331)	CAD in 82–83%	45–50%	38–40%	12–15%		n.a.	EP performed in 63% with ventricular tachycardia/ VF inducible in 73% of pts.	n.a.
Present study	135 R to EP-guided Tx. with dofetilide or sotalol in a cross-over design	CAD in 100%, prior MI in 61–66%	7%	70%	11%	4%	54%	EP performed in 100% at baseline with ventricular tachycardia inducible in all the pts.	1–3 extrastimuli

AA=antiarrhythmic; EP=electrophysiological study; R=randomized; pts.=patients; ICD=implantable cardioverter defibrillator, Tx.=treatment; n.a.=not available; VT=ventricular tachycardia.

cardioverter-defibrillator). For safety, it is important to stress that all the cases of torsade de pointe started in the first 3 days of treatment. Therefore, continuous ECG monitoring in a hospital setting with intermittent determination of QT/QTc changes in the first days of treatment seems to be an appropriate way to initiate therapy.

Clinical implications

In the light of dofetilide's efficacy and safety in the present study and the lack of negative inotropic effects in previous studies[35,36], programmed electrophysiological stimulation-guided treatment with dofetilide appears to be advisable and useful in patients with ischaemic heart disease and ventricular tachycardia. The lower rate of withdrawals during long-term follow-up in dofetilide-treated patients compared with sotalol strongly supports the clinical usefulness of this new drug. The limitations of sotalol with regard to tolerability have also been stressed by other studies[26,37] where a high rate of sotalol discontinuations (33% at 1 year)[26] or cross-over to other treatments (27% within 3 months of treatment)[37] were found.

The management of sustained ventricular tachyarrhythmias has been affected by the results of a prospective randomized trial, AVID[4], demonstrating that, among survivors of ventricular fibrillation or in patients with sustained ventricular tachycardia causing severe symptoms, the implantable cardioverter-defibrillator is superior to amiodarone or sotalol for increasing overall survival. In subsequent analysis the benefit conferred by device therapy was not confirmed for the subgroup of patients with well-preserved left ventricular ejection fraction[5,6] and the same finding was confirmed by a recent meta-analysis of implantable cardioverter-defibrillator secondary prevention trials[7]. In patients with well-preserved left ventricular ejection fraction, prospective studies with larger patient numbers are needed to compare drugs and cardioverter-defibrillators[6,7].

In clinical practice, there is still a need for antiarrhythmic drug treatment in the management of ventricular tachyarrhythmias. This need includes the prevention of ventricular tachycardia recurrences in patients with well-tolerated sustained ventricular tachycardia or with symptomatic non-syncopal sustained ventricular tachycardias and left ventricular ejection fraction >40% (two categories of patients not included in AVID) or for reducing ventricular tachycardia recurrences in patients who already have an implantable cardioverter-defibrillator. In these subsets of patients, the lack of a negative inotropic effect[35,36] and the absence of significant increases in the defibrillation threshold[17] seem particularly appealing. Moreover, although the implantable cardioverter-defibrillator has a favourable profile in terms of cost-effectiveness when appropriate indications are followed[8,9], its cost has limited a widespread diffusion of this non-pharmacological treatment in some countries, especially in eastern Europe[10].

Although this study was not designed to evaluate the impact of antiarrhythmic drugs on mortality, it is noteworthy that in patients selected for long-term treatment on the basis of the response to programmed electrophysiological stimulation in the acute phase, the occurrence of arrhythmic death was low (only one arrhythmic death at 1 year, on treatment). When comparing outcomes after medical treatment in the current study with those in ESVEM[3,11] and AVID[4] studies, the incidence of death was found to be lower in this study than in either comparator. This may be related to a series of factors: (1) differences in patient population, (2) use of long-term treatment with antiarrhythmic agents only in responders to programmed electrophysiological stimulation (performed with up to three extrastimuli), (3) differences in the degree of underlying left ventricular dysfunction. In the literature, some papers[19,38] have stressed the limitations of programmed electrophysiological stimulation-guided treatment with sotalol in preventing sudden cardiac death at long-term. However, these studies were retrospective, and dealt with selected patients implanted with cardioverter-defibrillators[38] or with different underlying heart diseases[19]. More recently, sotalol proved effective in preventing death and device shocks in patients with implantable cardioverter-defibrillators[26], although this is a different field for drug evaluation[39].

Conclusions

After short-term treatment, dofetilide was as efficacious in preventing the induction of sustained ventricular tachycardia during programmed electrophysiological stimulation and had fewer adverse effects than sotalol. Although both dofetilide and sotalol were well tolerated during long-term treatment, with no significant difference in adverse events, dofetilide had a trend towards a lower likelihood of withdrawal. In view of the results of the present study, treatment with dofetilide guided by programmed electrophysiological stimulation appears to be a valid alternative to sotalol treatment in patients with ischaemic heart disease and ventricular tachycardia, with the advantage of better long-term tolerability.

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Appendix

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