Oral procainamide as pharmacological treatment of recurrent and refractory ventricular tachyarrhythmias: A single-center experience

Mauro Toniolo, MD,* Daniele Muser, MD,* Giulia Grilli, MD,*† Massimo Burelli, MD,*† Luca Rebellato, MD,* Elisabetta Daleffe, MD,* Domenico Facchin, MD,* Massimo Imazio, MD*

*From the *Cardiology Division, University Hospital S. Maria della Misericordia, Udine, Italy, and †Postgraduate School of Cardiovascular Sciences, University of Trieste, Trieste, Italy.*

BACKGROUND Antiarrhythmic therapy for recurrent ventricular arrhythmias in patients who have undergone catheter ablation, and in whom amiodarone and/or beta-blockers were ineffective or contraindicated, is a controversial issue.

OBJECTIVE The present study sought to evaluate the efficacy and tolerability of oral procainamide in patients with recurrent ventricular arrhythmias when the standard therapy strategy had failed.

METHODS All patients treated with procainamide for recurrent ventricular tachycardia (VT) or ventricular fibrillation (VF) in our institution between January 2010 and May 2019 were enrolled. The primary endpoint was the total number of implantable cardioverter-defibrillator (ICD) interventions after the beginning of procainamide therapy. Secondary endpoints were the total number of VTs and VFs recorded on the ICDs' controls and discontinuation of therapy. The events occurring during procainamide treatment were compared with a matched-duration period before the initiation of therapy with procainamide. Patients therefore served as self-controls.

RESULTS A total of 34 consecutive patients (32 male, 94.1%; mean age 74.4 ± 9.7 years) were included in the retrospective analysis. The mean time of procainamide treatment was 12.9 ± 13.7 months (median 9 [2–20] months). The mean dose of procainamide was 1207 ± 487 mg/day. Procainamide therapy significantly decreased ICD interventions (median 5 [0–22.5] vs 15.5 [3–32.25], $P < .05$). Procainamide also decreased the total number of VT/VF episodes (median 5.5 [0.75–30] vs 19 [7.5–30], $P < .05$). Only 3 patients (8.8%) presented severe side effects (dyspnea or hypotension), requiring discontinuation of therapy.

CONCLUSION Oral procainamide was associated with a significant decrease in ICD therapies and ventricular arrhythmias, showing an acceptable profile of tolerability.

KEYWORDS Antiarrhythmic drugs; Arrhythmias in heart failure; ICD therapies; Procainamide; Ventricular arrhythmias

(Heart Rhythm O2 2021;2:840–847) © 2021 Heart Rhythm Society. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

The antiarrhythmic treatment of recurrent ventricular tachyarrhythmias in patients who have undergone catheter ablation, and in whom amiodarone or beta-blocker treatment was ineffective or contraindicated, remains challenging and poorly defined. Most of these patients bear an implantable cardioverter-defibrillator (ICD), and repeated ICD interventions may occur, including electrical storm events. Frequent ICD discharges are associated with worse clinical outcomes and decreased quality of life,[1,2] while recurrent electrical storm events are a life-threatening condition. Antiarrhythmic drugs are usually the first-line treatment, followed by catheter ablation when indicated.[3,4] In case radiofrequency ablation is unfeasible, not readily available, or unsuccessful, and treatment with beta-blockers and amiodarone proves ineffective, procainamide might represent an alternative strategy for preventing the recurrence of ventricular tachyarrhythmias and ICD discharges. Procainamide is a class 1a antiarrhythmic agent whose primary mechanism is related to its antagonism of cardiac sodium channels delaying phase 0 of the cardiac cycle. Procainamide and its metabolite *N*-acetyl procainamide also exert potassium efflux channel–blocking effects, prolonging the QT interval. Procainamide is 75%–95% absorbed after oral administration. Approximately 50%–60% of the drug is excreted unchanged in the urine. Procainamide can reduce blood pressure by causing myocardial depression; it can also cause nausea, vomiting, diarrhea, and, on occasion, psychosis. It may be associated with drug-induced lupus erythematosus in as many as 30% of patients taking procainamide for 6 months or longer.[5] The present study

Address reprint requests and correspondence: Dr Mauro Toniolo, Cardiology Division, University Hospital S. Maria della Misericordia, Via Pozzuolo, 330, 33100 Udine, Italy. E-mail address: mautoniolo@libero.it.

2666-5018/© 2021 Heart Rhythm Society. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

https://doi.org/10.1016/j.hroo.2021.10.002

KEY FINDINGS

- This is the first report providing the efficacy and safety of oral procainamide in a setting of patients suffering from heart failure and recurrent ventricular tachyarrhythmias, bearing an implantable cardioverter defibrillator.
- This study gives a detailed description of characteristics and follow-up results of a pharmacological therapy with oral procainamide in 34 patients with ventricular arrhythmias refractory to other antiarrhythmic drugs and/or catheter ablation.
- This study aims to answer the question of management of patients with recurrent ventricular arrhythmias, where catheter ablation is not feasible and amiodarone is contraindicated.

sought to evaluate the efficacy and tolerability of procainamide in patients with recurrent ventricular arrhythmias when the standard therapy strategy has failed.

Methods

All consecutive patients treated with procainamide for recurrent ventricular tachycardia (VT) or ventricular fibrillation (VF) in our institution between January 2010 and May 2019 were included in our retrospective analysis. Patients' medical records, updated on routine follow-up visits, and ICD interrogation, if present, were analyzed. Every month, every patient was subjected to the following blood chemistry tests: white blood cells, hemoglobin, platelets count, creatinine, sodium, potassium, magnesium, gamma-glutamyl transferase, aspartate transaminase, alanine transaminase, and antinuclear antibody titers. Procainamide therapy was prescribed in the following categories of subjects: (1) in patients with a previous unsuccessful catheter ablation and in optimal medical therapy (including amiodarone, if feasible), when a redo ablation procedure was considered unfeasible; (2) in patients awaiting the procedure of catheter ablation (first or redo); (3) in patients unsuccessfully treated with optimal medical therapy or having contraindications to the standard medical therapy (including amiodarone) and considered unsuitable for ablation, or in patients who refused catheter ablation.

The demonstration of unsuccessful treatment with other antiarrhythmic drugs or their interruption because of the occurrence of side effects was mandatory before starting procainamide treatment. An attempt at amiodarone treatment was made for all but 3 patients, for whom it was not attempted owing to a past history of hyperthyroidism. Oral procainamide was available in the form of capsules of 250 mg (Byocoril®; Uriach Group [Spain]) and/or 300 mg (Procainamide Cloridrato; Farmacia Favero [Italy]). An electrocardiogram (ECG) was routinely performed 10 days after initiation of procainamide treatment and compared with a previous ECG.

Detection zones and arrhythmia therapy programming in patients with ICD were individualized. Two and 3 detection zones were programmed in 7 (21%) and 26 (79%) patients, respectively. The average VT-1 lower rate detection zone was 146 $\pm$ 9.1 beats per minute (bpm), the average VT-2 higher rate detection zone was 169.9 $\pm$ 18.3 bpm, and the average VF detection zone was 205.9 $\pm$ 26.4 bpm. The primary endpoint was the global burden of ventricular arrhythmias, including sustained VT/VF $\geq$30 seconds and nonsustained VT. Secondary endpoints were appropriate ICD therapies and procainamide discontinuation. An arrhythmic storm was defined as 3 or more episodes of sustained VT or VF occurring during a 24-hour period.

The events occurring during procainamide treatment were compared with a matched-duration period just before the start of procainamide therapy. In case of planned catheter ablation, we interrupted the follow-up the day before the ablation. All patients had already presented ventricular arrhythmias at the beginning of the follow-up period of analysis before the start of procainamide therapy.

Continuous variables were expressed as mean $\pm$ standard deviation when normally distributed or as median with interquartile range for non-normal distributions. Significance of differences was verified with paired Student *t* test or Wilcoxon rank sum paired test, as appropriate. The comparison of ventricular arrhythmias before and after procainamide therapy was made using Wilcoxon rank sum paired test, as data did not present a Gaussian distribution. The χ^2 test or Fisher exact test was used to compare categorical variables as appropriate. A Poisson log-linear model including exposure time as offset variable has been used to estimate incidence rate ratios of VT/VF, antitachycardia pacing (ATP), direct current (DC) shock, and ATP + DC shock. A 2-tailed probability value of $<.05$ was deemed significant. Statistical analyses were conducted using the SPSS software (SPSS v20; SPSS Inc, Chicago, IL).

Results

A total of 34 consecutive patients (32 male, 94.1%; mean age 74.4 $\pm$ 9.7 years) were included in this retrospective analysis. All patients but 1 had an ICD implanted.

The large difference between the numbers of men and women is probably due to the high presence of ischemic cardiomyopathy in our case series (73.5%).

In 19 patients (55.9%), a catheter ablation was performed before procainamide initiation: 8 of these 19 patients (42.1%) were submitted to an ablation immediately before procainamide initiation. Procainamide was started because of a suboptimal result of the ablation (eg, VT still inducible). On the contrary, 11 of these 19 patients (57.9%) had been submitted to a VT ablation a long time before, and they started oral procainamide for long-term relapses after many months free from arrhythmias (20.6 $\pm$ 23.3 months). In 10 patients (29%), a catheter ablation was performed after treatment initiation. In 3 patients (9%), 2 catheter ablations were

Table 1 Clinical characteristics of 34 patients

Characteristic	Result
Dilatative cardiomyopathy	29/34 (85.3%)
CAD	22/29 (75.9%)
Idiopathic	3/29 (10.3%)
Hypertrophic	1/29 (3.4%)
Alcoholic	1/29 (3.4%)
Myocarditis-related	1/29 (3.4%)
Valvulopathy-related	1/29 (3.4%)
Nondilatative cardiomyopathy	5/34 (14.7%)
CAD	3/5 (60%)
Idiopathic	1/5 (20%)
Valvulopathy-related (recurrent regurgitation after valve repair for prolapsed mitral valve disease)	1/5 (20%)
LVEF (%) (mean ± SD)	35% ± 11%
NYHA class: I/II/III/IV	7/24/2/1
ICD	33/34 (97%)
Single-chamber	5/33 (15.1%)
Dual-chamber	29/33 (87.9%)
Biventricular	11/33 (33.3%)
Pacemaker	1/34 (3%)
Prophylaxis	
Primary	8/33 (24.2%)
Secondary	25/33 (75.8%)
Comorbidities	
Hypertension	20/34 (58.8%)
Hyperlipidemia	16/34 (47.1%)
Diabetes	6/34 (17.6%)
Atrial fibrillation	20/34 (58.8%)
Chronic renal insufficiency	32/34 (94.1%)
CKD class: I/II/III/IV	2/14/11/5
COPD	9/34 (26.5%)
Thyroid disease	24/34 (70.6%)
Type of ventricular arrhythmia	
Monomorphic only	21/34 (61.7%)
Polymorphic VT or VF only	2/34 (5.9%)
Both monomorphic and polymorphic VT or VF	11/34 (32.4%)

CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SD = standard deviation; VF: ventricular fibrillation; VT = ventricular tachycardia.

Table 2 Pharmacological treatment before procainamide treatment (N = 34 patients)

Treatment	Result, n (%) patients
Beta-blockers	29/34 (85.3%)
Bisoprolol (mean dose 6.03 mg/day)	19/34 (55.9%)
Metoprolol (mean dose 200 mg/day)	2/34 (5.9%)
Carvedilol (mean dose 28.91 mg/day)	8/34 (23.5%)
Amiodarone alone (mean dose 196.78 mg/day)	29/34 (85.3%)
Sotalol alone (mean dose 200 mg/day)	2/34 (5.9%)
Amiodarone (200 mg/day) + mexiletine (600 mg/day)	2/34 (5.9%)
ACEi	19/34 (55.9%)
ARBs	6/34 (17.6%)
Sacubitril/valsartan	0
Aldosterone antagonist	14/34 (41.2%)
Furosemide	26/34 (76.5%)

ACEi = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers.

Table 3 Pharmacological treatment during procainamide treatment

Beta-blockers	29/34 (85.3%)
Bisoprolol (mean dose 6.30 mg/day)	22/34 (64.7%)
Metoprolol (mean dose 200 mg/day)	1/34 (2.9%)
Carvedilol (mean dose 25 mg/day)	6/34 (17.6%)
Amiodarone (mean dose 209.52 mg/day)	21/34 (61.8%)
Sotalol (mean dose 160 mg/day)	1/34 (2.9%)
Mexiletine	0
ACEi	15/34 (44.1%)
ARBs	7/34 (20.6%)
Sacubitril/valsartan	0
Aldosterone antagonist	14/34 (41.2%)
Furosemide	26/34 (76.5%)

Oral procainamide therapy was prescribed only for treatment of recurrent ventricular arrhythmias.

ACEi = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers.

Table 4 Electrocardiogram parameters before and after procainamide therapy

	Before procainamide	After procainamide	*P* value
Heart rate (beats/min)	67.6 ± 9.7	70.8 ± 9.3	.03
PR (ms)	182 ± 83.1	178.6 ±78.1	.54
QRS duration (ms)	153.1 ± 40.7	164.3 ±42.5	.08
QTc (ms)	458.3 ± 72.7	482.6 ± 49.4	.26
Tpeak – Tend (ms)	78.7 ± 18.6	83.4 ± 21.2	.07
P-wave duration (ms)	92.9 ± 38.5	96.6 ± 36.8	.12
Right bundle branch block	4 (11.8 %)	4 (11.8%)	1.0
Left bundle branch block	9 (26.5 %)	10 (29.4 %)	.78

Continuous variables are expressed as mean ± standard deviation. Categorical variables are expressed as absolute and percentage (in brackets).

performed, 1 before and the other after procainamide initiation. Overall, 26 out of 34 (77%) patients underwent catheter ablation.

All but 1 patient with severe chronic obstructive pulmonary disease was treated with beta-blockers with the maximal tolerable dose, and treatment was continued after procainamide was started. Before the beginning of the oral procainamide treatment, 9 patients (26.5%) underwent intravenous infusion of procainamide for an arrhythmic storm. The mean time of oral procainamide treatment was 12.9 ± 13.7 months (median 9 months; interquartile range: 2–20 months). The mean dose of procainamide was 1207 ± 487 mg/day. The starting dose of procainamide was 900 mg per day in all patients; the total daily dose was divided into 3 single doses; in 4 patients (12%) the dose was reduced to 600 mg per day and in 2 patients (6%) the dose was reduced to 750 mg per day during treatment because of slight drug intolerance: 3 patients experienced symptomatic hypotension (in 1 case with syncope), 1 patient had a worsening of dyspnea, 1 patient had gastrointestinal disorders, and in the remaining patient the dosage was reduced owing to worsening of renal function.

Table 5 Ventricular arrhythmias and ICD interventions before and after oral procainamide therapy

Ventricular arrhythmias and ICD interventions		Before procainamide	After procainamide	*P* value
VT/VF episodes	Mean ± SD	31.7 ± 65.5	16.25 ± 26.3	.015
	Median [IR]	19 [7.5-30]	5.5 [0.75-30]	
ICD interventions (ATP)	Mean ± SD	17.7 ± 20.6	13.1 ± 26.6	.077
	Median [IR]	14.5 [1.5-30]	3.5 [0-15]	
ICD interventions (shock)	Mean ± SD	3.9 ± 6	3.25 ± 7.9	.005
	Median [IR]	1.5 [1-5]	0 [0-1]	
ICD interventions (ATP + shock)	Mean ± SD	10.8 ± 16.6	8.2 ± 20.1	.024
	Median [IR]	15.5 [3-32.25]	5 [0-22.5]	

		Incidence rate		
	Incidence rate ratio (95% CI)	Before procainamide	After procainamide	*P* value
VT/VF episodes	0.48 (0.43–0.53)	2.46	1.19	<.001
ICD interventions (ATP)	0.7 (0.62–0.79)	1.37	0.96	<.001
ICD interventions (shock)	0.79 (0.61–1.01)	0.30	0.24	.06
ICD interventions (ATP + shock)	0.72 (0.64–0.80)	1.68	1.20	<.001

ATP = antitachycardia pacing; CI = confidence interval; ICD = implantable cardioverter-defibrillator; IR = interquartile range; SD = standard deviation; VF = ventricular fibrillation; VT = ventricular tachycardia.

In 1 patient (3%), the dose was increased to 1000 mg in order to achieve complete arrhythmic control; in 5 patients (15%), the dose was increased to 1200 mg; in 4 patients (11%), the dose was increased to 1500 mg; in 3 patients (9%), 2000 mg; and in 1 patient (3%), 2500 mg. Baseline clinical characteristics of the study group are presented in Table 1 and previous and concomitant pharmacological treatments in Tables 2 and 3. The ECG parameters show fairly notable QTc prolongation (Table 4), but in the only 2 patients with normal renal function, QTc moved from 450.5 ± 29 ms to 446 ± 46.7 ms, without prolongation.

The efficacy of procainamide treatment was evaluated by comparing the burden of ventricular arrhythmias and the number of appropriate ICD interventions during procainamide treatment with the same duration right before initiation of procainamide (Table 5). As Table 5 and Figures 1 and 2 show, the burden of ventricular arrhythmias, as well as the number of ICD interventions, significantly decreased after initiation of procainamide. In detail, the median of VT/VF episodes decreased from 19 (7.5–30) before procainamide therapy to 5.5 (0.75–30), $P < .05$, after procainamide treatment, and 10 patients were completely free from VT/VF episodes. Similarly, ICD interventions occurred in 33 patients before procainamide treatment and in 22 patients after procainamide, and the episodes of ICD therapies significantly decreased for DC shock (median 0 [0–1] vs 1.5 [1–5], $P < .05$) and for the combination of DC shock + ATP (median 5 [0–22.5] vs 15.5 [3–32.25], $P < .05$). We observed 21 arrhythmic storms before procainamide treatment vs 8 arrhythmic storms after procainamide treatment. Considering the relative incidence ratio (Table 5), a reduction of 52% in the VT/VF episodes and a reduction of 28% in the combination of DC shock + ATP were observed.

In the group of 15 patients who were not treated with catheter ablation before oral procainamide initiation, the results seemed to be similar for VT/VF episodes (median from 15 [10–30] to 10.5 [1.25–27.5], $P = .19$), for ATP (median from 14 [2–15] to 4 [1.25–13], $P = .35$), and for the combination of DC shock + ATP (median from 15 [3.5–22.5] to 5 [2–14], $P = .24$). The median of DC shock remained the same: 1 [0.5–6] before and 1 [0–1] after oral procainamide treatment. Procainamide tolerability without notable side effects was observed in 33 of 34 (97%) patients. In 1 patient, after several days, a worsening dyspnea determined the discontinuation of the therapy. In 2 other patients (6%), the therapy was discontinued after several months owing to severe hypotension. In 1 patient, we observed an elevation of antinuclear antibody titers, but because he was asymptomatic, this value did not cause a discontinuation or a dose reduction of oral procainamide. During the follow-up period, 15 patients (44%) died: 10 patients died owing to acute pulmonary edema/cardiogenic shock, 2 patients died owing to septic shock, 1 patient died owing to pulmonary embolism, 1 patient died owing to acute renal injury, and 1 patient died owing to pneumonitis. The mean time under procainamide therapy of patients who died was 5.9 ± 6.8 months. In our study population, amiodarone treatment was attempted in 31 (91%) patients, and it had to be discontinued in 10 (29%) of them because of severe drug-induced hyperthyroidism in 7 cases and pulmonary fibrosis in the remaining 3 cases. Eight more patients developed hyperthyroidism, but treatment was not discontinued, since they underwent thyroid radioiodine ablation. Other amiodarone-related side effects that did not require treatment discontinuation included hypothyroidism in 9 cases and a single case of keratopathy.

Discussion

The present study retrospectively investigated the efficacy and tolerability of procainamide in a sample of patients with recurrent ventricular arrhythmias (Figure 3) when the standard therapy strategy had failed. The main findings of

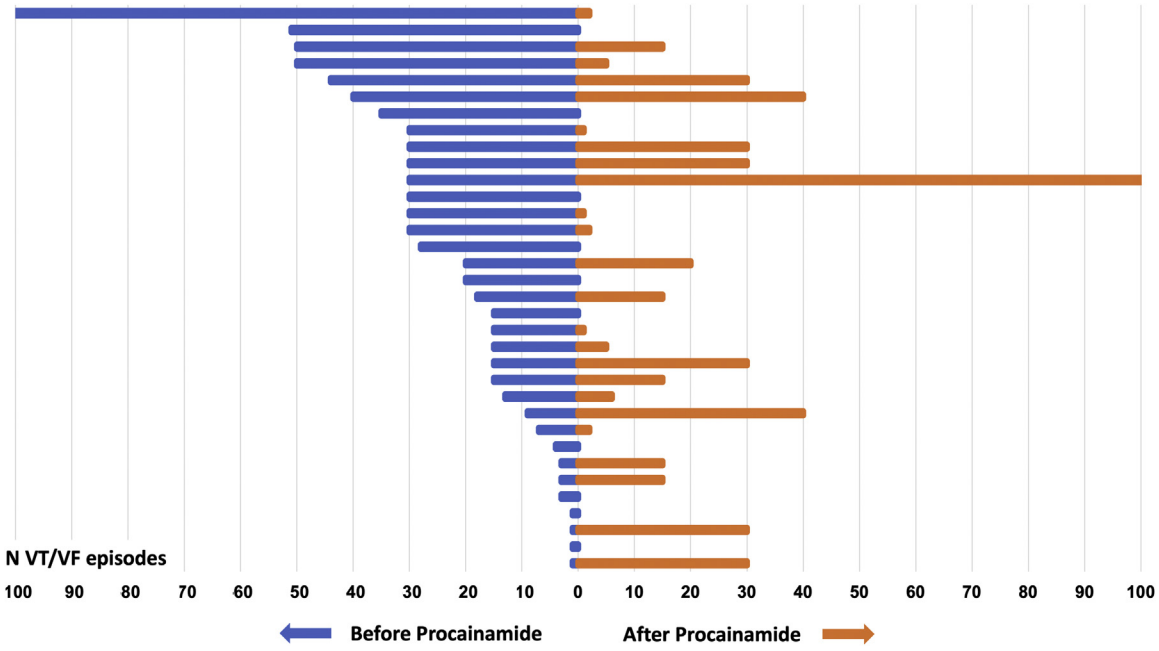

Figure 1 Plot showing the frequency (N) of ventricular tachycardia (VT)/ventricular fibrillation (VF) before (*blue lines*) and after (*orange lines*) procainamide administration. Each line represents an individual patient. Patients are arranged in ascending order according to arrhythmic episodes before therapy.

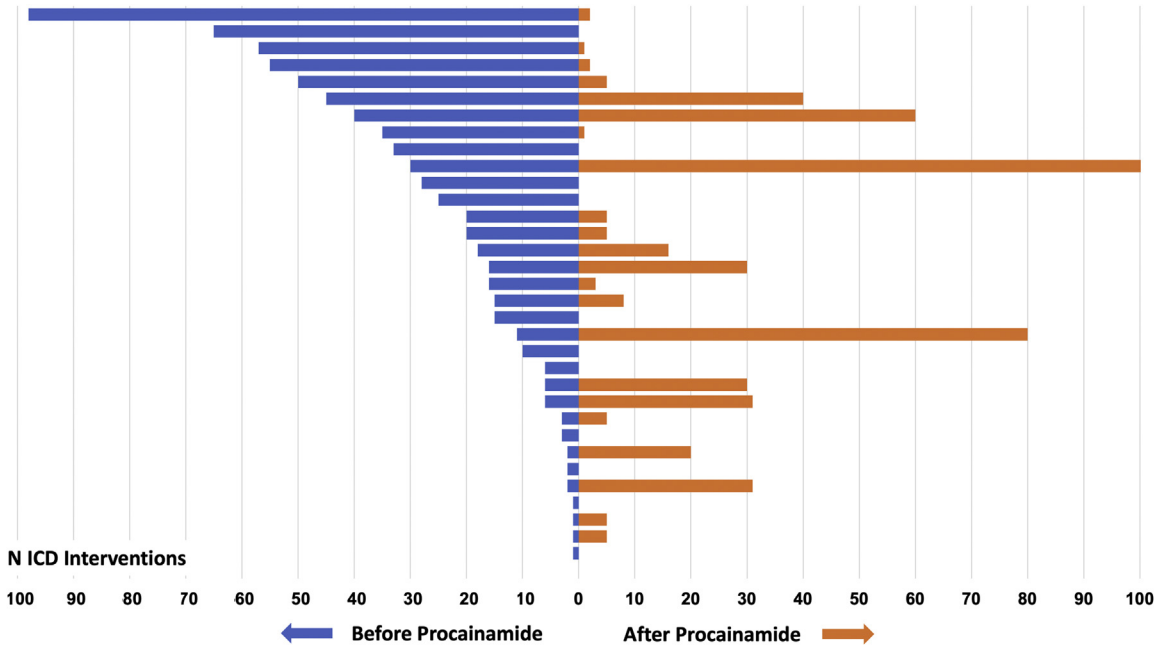

Figure 2 Plot showing the frequency (N) of implantable cardioverter-defibrillator (ICD) appropriate interventions before (*blue lines*) and after (*orange lines*) procainamide administration. Each line represents an individual patient. Patients are arranged in ascending order according to the number of episodes before therapy.

our study are as follows: (1) the procainamide therapy was associated with a reduction of ventricular arrhythmias and number of ICD interventions, in comparison with a matched period before initiation of therapy; and (2) procainamide showed an optimal degree of tolerability in our study population during the follow-up period.

Most clinical studies report a recurrence rate of ventricular arrhythmias of 20%–30% in ICD patients, resulting in even higher secondary prevention.[1,2] Antiarrhythmic drugs are usually prescribed long-term for the prevention of recurrences, and amiodarone commonly represents the first-line therapy. However, although amiodarone and sotalol have been clearly demonstrated to reduce recurrent ventricular arrhythmias,[6,7] they have been limited by tolerance and side effects.[8,9] As a matter of fact, long-term therapy with amiodarone is commonly associated with severe organ damage. It has been

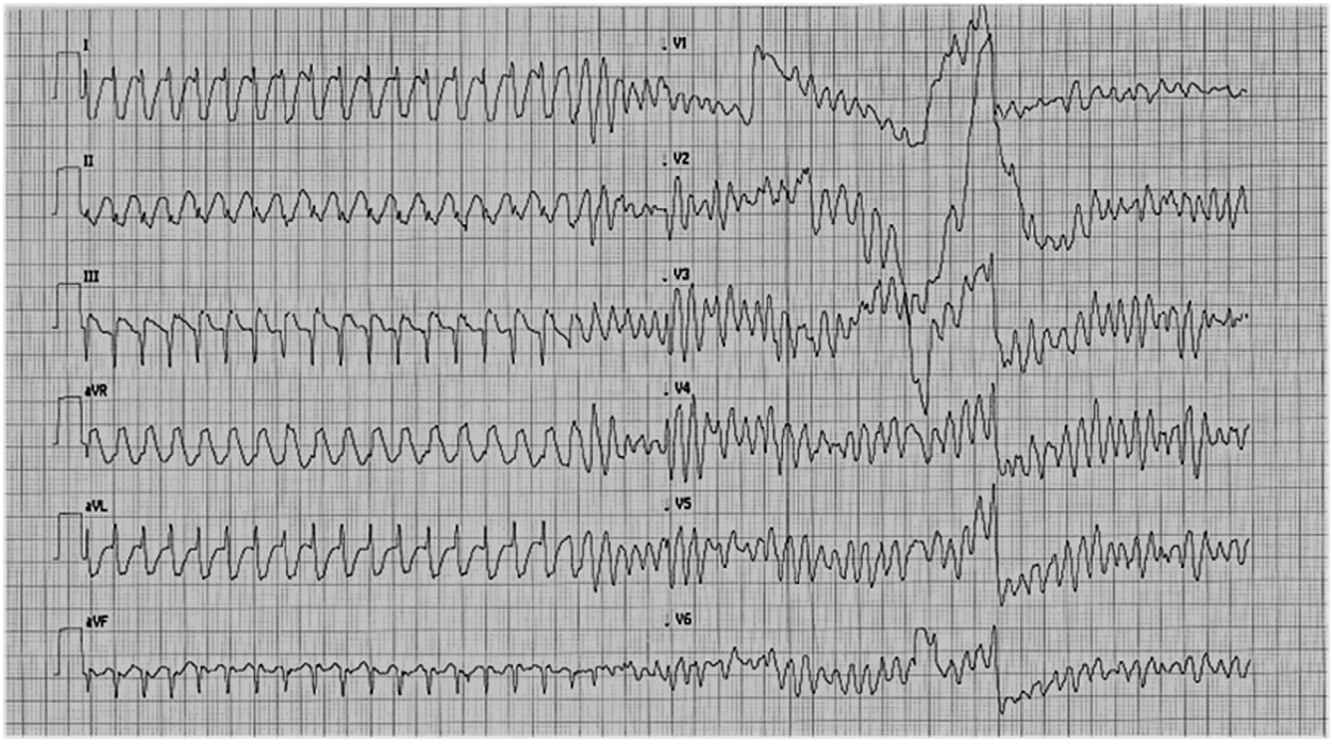

Figure 3 Twelve-lead electrocardiogram of ventricular tachycardia rapidly degenerating in ventricular fibrillation in a 76-year-old male patient with heart failure (ischemic etiology) and arrhythmic storm.

reported that almost 40% of patients treated with amiodarone discontinue medication after a median time of 21 months, mostly owing to thyroid, pulmonary, and gastrointestinal toxicity.[9] The Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) study showed that the combination of amiodarone with a beta-blocker was the most effective therapy for preventing ICD shocks compared with beta-blocker alone or sotalol.[10] The Cardiac Arrest in Seattle: Conventional versus Amiodarone Drug Evaluation (CASCADE) study reported that patients with an ICD who were receiving amiodarone had fewer appropriate shocks than those treated with class I antiarrhythmic drugs.[11] A meta-analysis found a concrete benefit of amiodarone in reducing the recurrence of ICD interventions; on the other hand, the impact of other class III antiarrhythmic drugs (sotalol, azimilide, dofetilide) was found to be less important, especially when beta-blockers were the control group.[12]

Data regarding the efficacy of procainamide in patients with heart failure, ICD, and refractory ventricular arrhythmias are limited. Its use expanded in the 1950s, but now it is only incidentally used. Recently, it was investigated for pharmacologic cardioversion of VT. In this field, procainamide is associated with fewer adverse cardiac events and is more effective for cardioversion compared to amiodarone.[13] Moreover, the PROCAMIO study compared, for the first time in a randomized design, intravenous procainamide and amiodarone for the treatment of acute episodes of sustained monomorphic VT: procainamide therapy was associated with fewer major cardiac adverse events and a higher proportion of tachycardia termination within 40 minutes.[14] On the contrary, there are only very old studies about the efficacy of oral procainamide. In the 1950s, it was shown to reduce or abolish ventricular arrhythmias in the acute setting in up to 90% of patients with ventricular premature depolarizations and 80% of patients with VT.[15–17] Some studies also evaluated the therapeutic antiarrhythmic plasma concentration range of procainamide, and they concluded that this value is very variable from one patient to another.[18,19] This could justify the large spectrum of dosages of procainamide also present in our case series. Procainamide, like most antiarrhythmic drugs, is known to reduce the systolic left ventricular function[20]: in our study, the patients' mortality rate during procainamide treatment was apparently higher than that in previous studies of patients with heart failure who had an ICD.[21] It is not clear whether procainamide may have contributed to the naturally occurring worsening of heart failure; however, this value could be more appropriately explained by the higher mortality rates of patients with a high ventricular arrhythmic burden,[22] such as the population of our study. In patients with sustained VTs, the response to intravenous procainamide does not reliably predict the response to oral procainamide[23]; for this reason, only 26.5% of our patients experienced intravenous infusion of procainamide before the beginning of oral administration.

The QTc prolongation in our patients after the beginning of oral procainamide therapy may be due to excessive

N-acetylprocainamide accumulation owing to chronic kidney disease. In fact, in the only 2 patients with normal renal function, QTc did not lengthen.

The current guidelines note that with the exception of beta-blockers (eg, metoprolol succinate, carvedilol), there is no evidence from randomized controlled trials that antiarrhythmic medications for ventricular arrhythmias improve survival when given for the primary or secondary prevention of sudden cardiac death. However, the use of these medications is essential in some patients to control arrhythmias and improve symptoms. The administration of intravenous procainamide in patients with hemodynamically stable VT can be useful to attempt to terminate VT (class IIa, level of evidence A).[4] Oral procainamide is included in a list of available drugs at a dose of 1000–4000 mg/day,[3] or 500–1250 mg every 6 hours,[4] but no specific recommendations are given about its use.[3,4] Catheter ablation is a fundamental tool for treating incessant VTs, electrical storm, and recurrent ICD shocks due to sustained VT (class I, level of evidence B).[3] In a VANISH trial substudy, catheter ablation provided greater relative benefit than escalation of antiarrhythmic drug therapy for patients who experienced recurrent VT, despite chronic oral amiodarone therapy, with the greatest effect on reduction of VT storms.[24] Catheter ablation is particularly effective in monomorphic scar-related VTs, when the ablation target is the isthmus of slow conduction within the VT reentry circuit.[25] In polymorphic VTs, it can be more difficult to find the ablation target[26]: in some patients, Purkinje fibers could be amenable to catheter ablation,[27] but in other patients catheter ablation could be infeasible. In our experience, catheter ablation was the first option for patients with recurrent monomorphic VT despite chronic oral amiodarone therapy. We introduced oral procainamide in patients with a previous failed ablation, as a bridge to catheter ablation, if the procedure was not feasible for anatomical reasons (eg, inaccessible location in the myocardium), or in patients who refused catheter ablation.

In this era when no new antiarrhythmic drugs have been developed for the treatment of ventricular arrhythmias in the field of heart failure, procainamide surely represents a valuable solution. Other possibilities could include quinidine, whose use is strongly limited by gastrointestinal intolerance,[28] and mexiletine, which initially appeared to be effective in acutely suppressing ventricular arrhythmias and reducing the risk of recurrence,[29] but in the following years its effectiveness has been questioned, especially in ventricular arrhythmias related to ischemic heart disease.[30] Moreover, the addition of mexiletine as part of the drug escalation strategy appeared ineffective in the VANISH trial.[31]

In many countries, patient access to oral procainamide could be critically endangered by a market withdrawal. We hope that the findings of this study will help scientific societies influence pharmaceutical and healthcare institutions to restore availability of this drug that is valuable in the care of arrhythmic patients.

Limitations

The most important limitation of this study is related to its retrospective and observational design without a control group. In addition, as all data were collected in a single center, the results should not be generalized. Another limitation is the relatively low number of patients included in the retrospective analysis. Moreover, the natural course of VT/VF events, reprogramming of ICD therapies and detection zones, correction of electrolyte derangements, and concomitant pharmacotherapy might have contributed to the apparent changes seen during and after procainamide therapy. For these reasons, this study should be viewed as an exploratory research and, as such, as a source of observations based on which to form new hypotheses.

Conclusion

The present study shows that medium- or long-term therapy with procainamide, in combination with amiodarone or alone, might be effective in improving the quality of life of patients with ICD and frequent ventricular arrhythmias and ICD shocks, regardless of the etiology of heart disease in a medium- or long-term setting. However, these findings would need larger, prospective, controlled, multicenter, and randomized trials to be confirmed.

Acknowledgments

The authors would like to thank the IRCAB Foundation (Udine, Italy) for its support in the statistical analysis of data.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosures

The authors have no conflicts to disclose.

Authorship

All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent

Informed consent was waived owing to the use of retrospective and de-identified data.

Ethics Statement

The research reported in this paper adhered to the CONSORT guidelines for the reporting of clinical trials and the guidelines set forth by the Helsinki Declaration. The study was approved by the institutional review committee.

References

1. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. Multicenter

Automatic Defibrillator Implantation Trial – II (MADIT II). N Engl J Med 2002; 346:877–883.
2. Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997; 337:1576–1583.
3. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Circulation 2018;138:e272–e391.
4. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Pediatric and Congenital Cardiology (AEPC). Eur Heart J 2015;36:2793–2867.
5. Holstege CP, Rushton W. Procainamide. In: Encyclopedia of Toxicology, 3rd ed. Elsevier; 2014. p. 1070–1072.
6. Claro JC, Candia R, Rada G, Baraona F, Larrondo F, Letelier RM. Amiodarone versus other pharmacological interventions for prevention of sudden cardiac death. Cochrane Database Syst Rev 2015;12:CD008093.
7. Kuhlkamp V, Mewis C, Mermi J, Bosch RF, Seipel L. Suppression of sustained ventricular tachyarrhythmias: a comparison of d-I-sotalol with no antiarrhythmic drug treatment. J Am Coll Cardiol 1999;33:46–52.
8. Waldo AL, Camm AJ, de Ruyter H, et al. Survival with oral d-sotalol in patients with left ventricular dysfunction after myocardial infarction: rationale, design, and methods (the SWORD trial). Am J Cardiol 1995;75:1023–1027.
9. Julian DG, Camm AJ, Frangin G, et al. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. European Myocardial Infarct Amiodarone Trial Investigators. Lancet 1997;349:667–674.
10. Connolly SJ, Dorian P, Roberts RS, et al. Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) Investigators. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter-defibrillators: the OPTIC study: a randomized trial. JAMA 2006;295:165–171.
11. Cardiac arrest in Seattle: conventional versus amiodarone drug evaluation (the CASCADE study). Am J Cardiol 1991;67:578–584.
12. Ferreira-Gonzalez I, Dos-Subirà L, Guyatt GH. Adjunctive antiarrhythmic drug therapy in patients with implantable cardioverter defibrillators: a systematic review. Eur Heart J 2007;28:469–477.
13. Kelson K, de Souza I. Procainamide versus amiodarone for stable ventricular tachycardia. Acad Emerg Med 2019;26:1099–1101.
14. Ortiz M, Martin A, Arribas F, et al. on behalf of the PROCAMIO Study Investigators. Randomized comparison of intravenous procainamide vs. intravenous amiodarone for the acute treatment of tolerated wide QRS tachycardia: The PROCAMIO study. Eur Heart J 2017;38:1329–1335.
15. Kayden HJ, Steele JM, Clark LC, Brodie BB. The use of procainamide in cardiac arrhythmias. Circulation 1951;4:13–22.
16. Kayden HJ, Brodie BB, Skele JM. Procainamide: a review. Circulation 1957; 15:118–126.
17. Giardina E-GV. Procainamide: clinical pharmacology and efficacy against ventricular arrhythmias. Ann NY Acad Sci 1984;432:177–188.
18. Giardina E-GV, Fenster PE, Bigger JT Jr, Mayersohn M, Perrier D, Marcus FI. Efficacy, plasma concentrations and adverse effects of a new sustained release procainamide preparation. Am J Cardiol 1980;46:855–861.
19. Koch-Weser J, Klein SM. Procainamide dosage schedules, plasma concentrations and clinical effects. JAMA 1971;215:1454–1460.
20. Gottlieb SS, Kukin ML, Medina N, Yushak M, Packer M. Comparative hemodynamic effects of procainamide, tocainide, and encainide in severe chronic heart failure. Circulation 1990;81:860–864.
21. Briongos-Figuero S, Estèvez A, Pèrez ML, et al. Prognostic role of NYHA class in heart failure patients undergoing primary prevention ICD therapy. ESC Heart Fail 2020 Feb;7:279–283.
22. Sweeney MO, Sherfesee L, DeGroot PJ, Wathen MS, Wilkoff BL. Differences in effects of electrical therapy type for ventricular arrhythmias on mortality in implantable cardioverter-defibrillator patients. Heart Rhythm 2010;7:353–360.
23. Oseran DS, Gang ES, Rosenthal ME, Mandel WJ, Peter T. Electropharmacologic testing in sustained ventricular tachycardia associated with coronary heart disease: value of the response to intravenous procainamide in predicting the response to oral procainamide and oral quinidine treatment. Am J Cardiol 1985;56:883–886.
24. Parkash R, Nault I, Rivard L, et al. Effect of baseline antiarrhythmic drug on outcomes with ablation in ischemic ventricular tachycardia: a VANISH substudy (Ventricular Tachycardia Ablation Versus Escalated Antiarrhythmic Drug Therapy in Ischemic Heart Disease). Circ Arrhythm Electrophysiol 2018;11:e005663.
25. de Chillou C, Lacroix D, Klug D, et al. Isthmus characteristics of reentrant ventricular tachycardia after myocardial infarction. Circulation 2002; 105:726–731.
26. Marchilinski FE, Callans DJ, Gottleb CD, Zado E. Linear ablation lesions for control of unmappable ventricular tachycardia in patients with ischemic and nonischemic cardiomyopathy. Circulation 2000;101:1288–1296.
27. Komatsu Y, Hocini M, Nogami A, et al. Catheter ablation of refractory ventricular fibrillation storm after myocardial infarction. Circulation 2019;14(139):2315–2325.
28. Li DL, Cox ZL, Richardson TD, et al. Quinidine in the management of recurrent ventricular arrhythmias. JACC Clin Electrophysiol 2021;7:1254–1263.
29. Talbot RG, Nimmo J, Julian DG, et al. Treatment of ventricular arrhythmias with mexiletine (Kö 1973). Lancet 1973;2:399–404.
30. Chamberlain DA, Jewitt DE, Julian DG, et al. Oral mexiletine in high-risk patients after myocardial infarction. Lancet 1980;2:1324–1327.
31. Sapp JL, Wells GA, Parkash R, et al. Ventricular tachycardia ablation versus escalation of antiarrhythmic drugs. N Engl J Med 2016;375:111–121.