Antiarrhythmic Efficacy of Ethacizine Assessed by Programmed Electrical Stimulation in Patients with Ventricular Tachycardia

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KAIK, J., ET AL.: Antiarrhythmic Efficacy of Ethacizine Assessed by Programmed Electrical Stimulation in Patients with Ventricular Tachycardia. *The efficacy of ethacizine, a Class Ic drug, was assessed by programmed electrical stimulation (PES), delivering single, double, and triple extrastimuli at paced drives of 100 and 140 beats/min from two right ventricular sites (apex and outflow tract) in 38 patients with recurrent sustained ventricular tachycardia (VT). Underlying disease was coronary artery disease (CAD) in 26 (group I) and other conditions in 12 patients (group II; hypertrophic cardiomyopathy in 7, mitral valve prolapse in 1, and no apparent heart disease in 4). In the baseline study VT was induced in all patients. After a single intravenous dose (0.6–0.7 mg/kg) of ethacizine, VT was still inducible in six patients in group I and seven patients in group II. Ethacizine was administered on a long-term basis to all patients in a dose of 200–400 mg per day. All but one CAD patient remained free of recurrences after a mean follow-up of 16.5 (range 3–22) months, while there were recurrences in six of 12 patients in group II. We conclude that: (1) ethacizine appears to be effective in the treatment of VT in CAD patients; (2) the study demonstrates the clinical utility of PES in the management of VT, although some patients in whom VT remains inducible on ethacizine may have good clinical outcome; and (3) the efficacy of ethacizine in other forms of heart disease remains to be studied. (PACE, Vol. 15, November, Part II 1992)*

ethacizine, ventricular tachycardia, programmed ventricular stimulation

Introduction

Ethacizine is a phenothiazine derivative with Class Ic electrophysiological properties. Previous studies[1–3] have revealed that ethacizine appears efficacious in patients with both atrial and ventricular arrhythmias. However, very little data have been reported regarding the effectiveness of ethacizine in electrically inducible sustained ventricular techycardia (VT). The purpose of this study was: (1) to determine the short-term preventive effect of ethacizine in patients with various heart diseases by means of programmed electrical stimulation (PES); (2) to evaluate the long-term efficacy of this drug; and (3) to study the utility of ethacizine testing using PES.

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Methods

Patients

Thirty-eight patients (33 men and 5 women) ranging in age from 24 to 70 years (mean 58 years) with recurrent sustained VT were studied. All patients had one or more electrocardiographically documented spontaneous episodes of symptomatic sustained VT, which was inducible during baseline electrophysiological study. In 26 patients (group I) the underlying disease was coronary artery disease (CAD). Twenty-five patients had a history of myocardial infarction and nine patients had been resuscitated from one or more cardiac arrests. A recent acute myocardial infarction was excluded by electrocardiographic and serum enzyme studies. A left ventricular aneurysm was present in 11 patients. The left ventricular ejection fraction ranged from 21% to 62% (mean 38% ± 12%).

Twelve patients (group II) had other condi-

tions. Seven patients had hypertrophic cardiomyopathy, one had mitral valve prolapse, and no apparent heart disease was noted in four patients.

Electrophysiological Study

The patients underwent baseline electrophysiological study in the postabsorptive, nonsedated state. Antiarrhythmic medications were discontinued for at least five half-lives of elimination before the procedure. Using standard electrophysiological techniques, two quadripolar electrode catheters were inserted percutaneously and positioned at the right ventricular apex and outflow tract. The distal pair of the electrodes was used for stimulation, and the proximal for recording local endocardial electrograms. Intracardiac recordings were filtered at 40 to 500 Hz, displayed simultaneously with surface leads 1, aVF, and V_1 on a multichannel oscilloscope. Recordings were made with a multichannel ink-jet recorder (Siemens-Elema Mingograph 4, Solna, Sweden) at a paper speed of 50 or 100 mm/sec. Cardiac stimulation was performed with rectangular pulses of 2-msec duration at twice diastolic threshold using a digital programmable stimulator.

PES was performed at two basic drive cycle lengths (430 and 600 msec) of eight beats. Single, double, and triple extrastimuli were introduced at both ventricular sites. Bursts of rapid ventricular pacing (cycle lengths between 300 and 200 msec) for 4–20 beats were used to induce VT if programmed extrastimulation failed. The end point of stimulation was the induction of sustained VT or, after drug administration, completion of the protocol.

Following the baseline study, drug efficacy was tested using the same stimulation protocol. Ethacizine was administered intravenously at a dose of 0.6–0.7 mg/kg. The drug was considered effective when sustained VT was no longer inducible or when VT terminated spontaneously in < 30 seconds.

Oral Treatment and Follow-Up

After intravenous drug trials, ethacizine was administered to all patients in a dose of 200–400 mg (mean 220) per day. Clinical follow-up was carried out in an outpatient arrhythmia clinic and consisted of direct personal contacts with one of the investigators. All patients were followed at regular intervals up to 16.5 months (range 3 to 22 months). Physical examination, 12-lead ECG, and Holter monitoring were obtained monthly, and stress testing every 6 months. Patients were specifically evaluated for recurrence of sustained VT.

Statistical Analysis

Values are expressed as mean ± standard deviation. The results were tested for significance by means of paired *t*-test.

Results

Characteristics of Baseline VT

By study design, all 38 patients had sustained VT induced during baseline electrophysiological study. In 33 cases it was monomorphic and in five it was polymorphic. The data on induced VT at baseline study are shown in Table I.

The cycle lengths of induced tachycardia ranged from 190 to 400 msec. The monomorphic tachycardia morphology was that of right bundle branch block in 20 cases and of left bundle branch block in 13 cases. In six patients two or more different morphologies were initiated. In nine patients VT evolved to ventricular fibrillation (VF). Twelve patients required cardioversion for termination of VT or VF, 17 patients required burst stimulation, and in 9 patients VT ended spontaneously. No significant differences in the inducibility, morphology, cycle length, or mode of termination of the electrically induced VT were observed in group I versus group II patients.

Ethacizine Effect on VT

After a single intravenous dose of ethacizine the induction of sustained VT was prevented in 25 of 38 (65.8%) patients. Sustained VT was still inducible in six patients in group I and in seven patients in group II. In all but two patients VT was terminated by burst pacing. In 11 patients the VT morphologies were similar to those observed during the baseline studies. The rate of VT was significantly slowed by ethacizine: the cycle length increased from 264 ± 62 msec at baseline to 386 ± 49 msec after treatment ($P < 0.05$). In two cases ethacizine caused undersirable effects on the in-

Table I.
VT Induced at Baseline

	Number of Cases	VT CL (msec)	Induction Mode			
			S2	S2S3	S2S3S4	Burst
Monomorphic	33	272 ± 30	3	18	11	1
Group I	23	278 ± 46	2	15	6	0
Group II	10	270 ± 28	1	3	5	1
Polymorphic	5	219 ± 35	0	1	2	2
Group I	3	220 ± 27	0	1	1	1
Group II	2	218 ± 48	0	0	1	1

CL = cycle length; VT = ventricular tachycardia.

duction of VT. In both cases evolution of monomorphic into polymorphic VT and a decrease in VT cycle length were observed.

Follow-Up

During the follow-up period ranging from 3 to 22 months, all but one (96.2%) patient with CAD remained free of VT recurrences (Fig. 1). One patient died suddenly 2 months after discharge. In group II (Fig 2) recurrences of sustained VT were observed in six patients (50%) (five with hypertrophic cardiomyopathy and one without apparent heart disease). Five recurrences were nonfatal, and one patient with cardiomyopathy died suddenly 7 months after discharge from the hospital.

All seven patients with recurrences had inducible VT after the intravenous administration of ethacizine.

Adverse Effects of Ethacizine

Ethacizine was well tolerated. Two cases of proarrhythmic effects were observed, consisting of the evolution of monomorphic to polymorphic VT. The most common side effects were dizziness and headache. They lead to a reduction of ethacizine doses in seven patients (18.4%), but in no case forced the interruption of treatment.

Discussion

Ethacizine is a well tolerated drug and is effective in supressing spontaneous ventricular arrhythmias.[1-3] Data about the ability of ethacizine to prevent electrically inducible VT are limited, while the inducibility of sustained VT or of VF has been shown to be useful in predicting the occurrence of spontaneous VT and sudden death.[4-7] In patients with CAD the efficacy rate of ethacizine during evaluation of its short-term effectivness was as high as 76.9% (20/26 patients; Fig. 1). Sustained VT was induced in only six patients and the arrhythmia was slower and better tolerated. The long-term clinical response was even more favorable since a VT recurrence was observed in one patient only. Thus, ethacizine seems to be very effective in the treatment of electrically induced VT in patients with CAD. In contrast, another

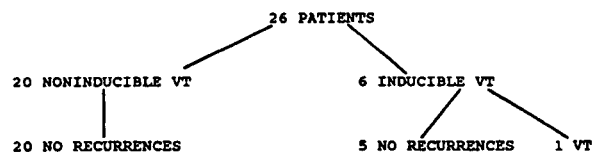

Figure 1. *Short-term efficacy of ethacizine and clinical outcome in group I patients.*

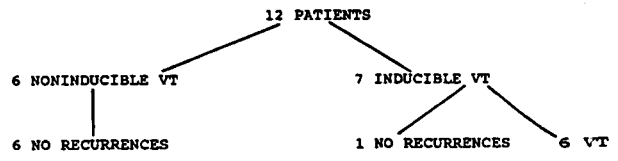

Figure 2. *Short-term efficacy of ethacizine and clinical outcome in group II patients.*

phenothiazine derivative, ethmozine, uniformly failed to prevent VT induction in the study by Mann et al.[8] In patients with other conditions the effectiveness of ethacizine appeared to be limited—the short-term efficacy rate was 41.7% (Fig. 2). Sustained VT was induced in seven out of 12 patients (58.3%) and arrhythmia recurrences during the follow-up period occurred in six out of 12 patients (50%).

The study demonstrates the clinical utility of PES in management of VT with ethacizine, although an unfavorable response to PES in five patients with CAD did not accurately predict good clinical outcomes. The predictive accuracy of PES was higher in group II patients, where the persistence of VT inducibility predicted recurrences in six out of seven patients (85.7%).

We conclude that: (1) ethacizine appears to be effective in the treatment of electrically inducible VT in patients with CAD; (2) the study demonstrates the clinical utility of PES in the management of VT with ethacizine, although some patients, in whom VT remains inducible on ethacizine may have, nevertheless, good clinical outcomes; and (3) the efficacy of ethacizine in other heart diseases remains to be studied.

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