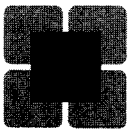

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Moricizine: pharmacodynamic, pharmacokinetic, and therapeutic profile of a new antiarrhythmic

GABRIEL VANERIO, MD AND JAMES D. MALONEY, MD

■ Moricizine (Ethmozine) is a phenothiazine derivative recently approved in the United States for the treatment of malignant ventricular arrhythmias. Moricizine closely resembles group IA antiarrhythmic agents in the intensity of its effect on the sodium channel, but it differs from the IA subclass in that it shortens the action potential duration in ventricular tissue. Moricizine suppresses frequent ventricular premature depolarizations and nonsustained ventricular tachycardia in 60% to 70% of patients, and it suppresses induced ventricular tachycardia in 15% to 25% of patients. It is well tolerated, with a low incidence of adverse effects. The suggested dosage is 600 to 900 mg per day in three divided doses. Treatment of arrhythmias with prognostic significance should be initiated in the hospital, and monitored with electrophysiologic studies. Additional clinical experience is needed to better define moricizine's role in antiarrhythmic therapy.

□ INDEX TERMS: MORICIZINE; ARRHYTHMIA □ CLEVE CLIN J MED 1992; 59:79–86

PRELIMINARY RESULTS of the Cardiac Arrhythmia Suppression Trial (CAST)[1–3] have led many clinicians to question the rationale for treating ventricular premature complexes (VPCs) after myocardial infarction. These well-publicized findings implicated two of the three study drugs, flecainide and encainide, in relatively high mortality rates. The third drug, moricizine hydrochloride (Ethmozine), now the only drug under active investigation in CAST, was recently approved by the Food and Drug Administration for the treatment of life-threatening ventricular arrhythmias.[4]

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In clinical studies, moricizine has been used by 1,072 patients with a low incidence of both short-term and long-term side effects. Its clinical efficacy and safety profile suggest that moricizine may gain wide acceptance. This article reviews the characteristics of the drug and its applicability to the clinical setting.

DESCRIPTION

Moricizine is a phenothiazine derivative (*Figure 1*). It has no dopamine-antagonist activity, and a low pK (6.4) compared to other phenothiazines. This may explain the low incidence of significant central nervous system effects reported with its use, because it does not traverse the blood-brain barrier.

Moricizine is a class I antiarrhythmic agent. Class I drugs interfere with sodium conduction during phase 0

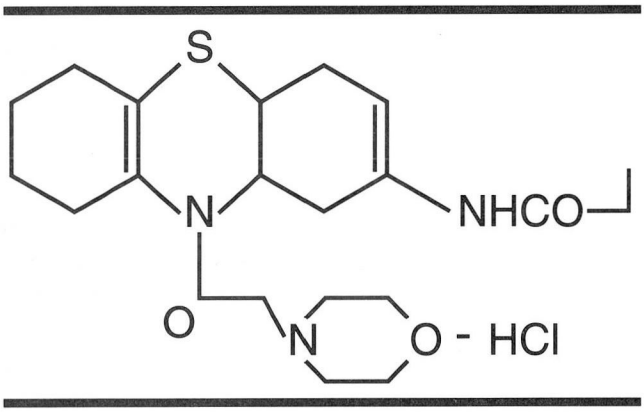

FIGURE 1. Structure of moricizine hydrochloride (HCl) (10-(3-morpho-linopropionyl) phenothiazine-2-carbamic acid ethyl ester hydrochloride). From Bigger[9] with permission.

of the cardiac action potential and, therefore, impair impulse propagation in sodium-dependent tissues.[5–6]

Class IA antiarrhythmics (quinidine, procainamide, and disopyramide) decrease the maximum rate of phase 0 depolarization (V_{max}) while prolonging the duration of the action potential and the effective refractory period. Class IB drugs (lidocaine, mexiletine, and tocainide) also decrease V_{max}, but with less potency than class IA drugs. They shorten both the action potential and the refractory period. Class IC agents (flecainide, encainide, and propafenone) produce the greatest decrease in V_{max} and have minimal effects on the refractory period.

The actions of moricizine make it difficult to classify, but it most closely resembles class IA drugs because of the intensity of its effect on the sodium channel.

EFFECTS ON ARRHYTHMOGENIC MECHANISMS

Causes of arrhythmias

The underlying mechanisms that cause arrhythmias have implications for the selection of therapy. The most common arrhythmogenic mechanisms are reentry, enhanced automaticity, and triggered activity.[7]

Reentry is characterized by a new wave of depolarization initiated by propagation from an area that was excited by the previous wave of depolarization. Reentry is responsible for most sustained monomorphic ventricular tachycardia associated with coronary artery disease.[8]

Automatic rhythms occur spontaneously as the result of phase 4 depolarization, requiring no previous trigger, and are not commonly responsible for ventricular tachycardia. Automaticity can be subdivided into normal and abnormal based on the diastolic membrane potential.

Triggered activity results from oscillations, or after-depolarizations, in the membrane potential. Early after-depolarizations occur before complete repolarization and are the proposed mechanism for torsade de pointes, a polymorphic ventricular tachycardia associated with QT prolongation. Delayed after-depolarizations occur after complete repolarization and are the proposed mechanism of arrhythmias observed in digitalis toxicity.

Mechanism of action

The sodium channel opens with activation of the cell. This allows moricizine to enter the channel, bind it, and block it. The greater the frequency of activation, as occurs with increased heart rate, the greater the blocking effect. Thus, the blocking is a rate-dependent or use-dependent phenomenon. In addition, there is a concentration-dependent decrease in V_{max} during phase 0, which explains the prolongation of the PR and QRS intervals observed with higher doses of moricizine.[9,10]

Moricizine increases the speed of repolarization of both phases 2 and 3, decreasing the action potential duration and the effective refractory period. Lidocaine has similar effects on repolarization.

Moricizine has no effect on the slope of phase 4 depolarization, but in animal models it suppresses normal and abnormal automaticity in Purkinje fibers by increasing transmembrane threshold voltage.

In humans, moricizine decreases conduction velocity within the atrioventricular (AV) node and ventricular myocardium with increase in the AH, HV, PR, and QRS intervals.[7] The QT interval usually remains unchanged because of concomitant shortening of the JT interval, calculated as QT minus QRS. The prolonged PR and QRS intervals and the shortened JT are dose-dependent.[9] Moricizine has little effect on atrial and ventricular refractoriness. Patients in whom moricizine is effective have significantly greater lengthening of the AH and QRS intervals. In patients with sinus node dysfunction, moricizine may induce sinus bradycardia, increase sinus recovery time, and produce sinoatrial block.[10] Our recent anecdotal clinical experience suggests that moricizine must be carefully used in patients with suspected sinus node dysfunction.

These electrophysiologic properties explain its antiarrhythmic effects on ventricular arrhythmias. The decrease in phase 0 of the action potential duration

may alter conduction on reentrant circuits; the increased speed of repolarization during phases 2 and 3 may terminate ventricular arrhythmias due to early after-depolarizations.[10]

PHARMACOKINETICS

Moricizine is completely absorbed after oral administration. However, due to a high hepatic clearance, its systemic bioavailability is 38%.[11,12] Peak blood levels are reached within 0.8 to 2.0 hours after oral administration. Significant antiarrhythmic activity generally occurs 16 to 20 hours after therapy is initiated.[11,13]

Moricizine undergoes an extensive first-pass metabolism in the liver, and has a large apparent volume of distribution, probably related to peripheral tissue binding.[11,12] Plasma protein binding is about 95%, and biotransformation of moricizine is almost complete, with less than 10% excreted unchanged in the urine. Enterohepatic cycling also occurs.

Twenty to 30 metabolites of moricizine have been identified in human urine. Some of these metabolites have shown antiarrhythmic activity in preclinical investigation, but more studies are needed. Moricizine elimination half-life is 2 to 6 hours, but the antiarrhythmic action is much longer—probably because of active metabolites. The combined half-life for the metabolites is about 84 hours.[11]

CLINICAL TRIALS

Noncomparative trials

In noncomparative studies, "life-threatening ventricular arrhythmias" were defined as sustained ventricular tachycardia (more than 15 complexes), ventricular flutter, and ventricular fibrillation. "Potentially life-threatening ventricular arrhythmias" were defined as symptomatic nonsustained ventricular tachycardia associated with significant structural heart disease. "Response" was defined as a reduction in the frequency of VPCs of at least 75% during 24-hour Holter monitoring.[13]

Among 1,072 patients with life-threatening ventricular arrhythmias, potentially life-threatening ventricular arrhythmias and benign ventricular arrhythmias, 67% responded to moricizine treatment. The optimal dosage ranged from 600 to 900 mg daily in two or three divided doses.[13]

A study of 46 patients with life-threatening ventricular arrhythmias assessed the safety and efficacy of moricizine by noninvasive monitoring techniques. Nonsustained ventricular tachycardia was suppressed in 60% of these patients. The mean total VPC frequency was reduced by 94%.[14]

A compassionate-use study of moricizine was carried out in the form of a multicenter, open-label, long-term, outpatient trial involving 263 patients.[14] Of these, 187 had life-threatening ventricular arrhythmias and 75 had potentially life-threatening arrhythmias. Moricizine was administered to 254 patients in an average dose of 11 mg/kg/day. This regimen was effective in 121 (48%) patients, particularly in the group with potentially life-threatening ventricular arrhythmias.

Hession and associates studied 75 patients by Holter criteria using the Lown grading system.[15] Thirty-one (44%) patients met the criteria for drug efficacy; ie, 90% reduction of the number of hours with 4A (repetitive VPCs) and 4B (runs of ventricular tachycardia) arrhythmia, and more than 50% reduction in VPCs. They found moricizine to be particularly effective in patients with symptomatic runs of non-sustained ventricular tachycardia, and normal or slightly impaired left ventricular function.

Ventricular arrhythmias and PES-guided therapy

Several studies,[14–19] including the compassionate-use trial, employed programmed electrical stimulation (PES) before and after moricizine administration. Fifty-three percent of the patients had a history of sustained ventricular tachycardia, and 29% had histories of ventricular fibrillation. Coronary artery disease (with or without myocardial infarction) was the most common form of heart disease. A mean of 4.7 drug trials were performed before moricizine therapy. Moricizine was administered for an average of 6 days before the second electrophysiologic study, with a mean dose of 936 mg/day. The drug suppressed sustained ventricular tachycardia in 15% to 25% of patients (*Figure 2*).

Hession and associates studied 20 patients,[15] most of whom had coronary artery disease and were unable to be evaluated by Holter because of the low frequency of their spontaneous arrhythmias. Of the 20, 12 patients had inducible sustained monomorphic ventricular tachycardia, and 8 had nonsustained ventricular tachycardia with an average of seven repetitive cycles. All underwent electrophysiologic testing. After moricizine treatment, only 1 patient was not inducible, and 2 had nonsustained ventricular tachycardia all from the sustained ventricular tachycardia group (15% of responders).

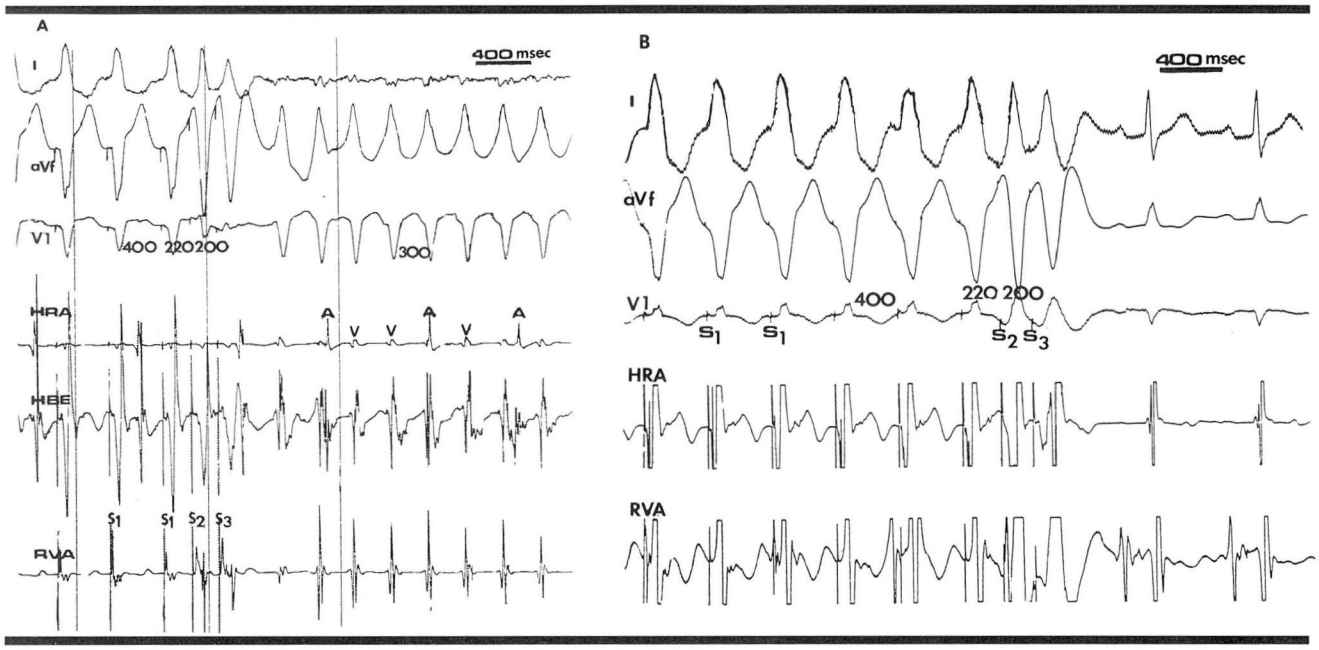

FIGURE 2. (A) Sustained monomorphic ventricular tachycardia induction during an electrophysiologic study. An 8 beat drive at 400 msec (S1–S1), with two extrastimuli (S2 at 220 msec and S3 at 200 msec) at the right ventricular apex, induced sustained monomorphic ventricular tachycardia with left bundle, right axis morphology, and 300 msec cycle length. Atrioventricular dissociation is evident. HRA, high right atrium; HBE, His bundle electrogram; A, atrial depolarization; V, ventricular depolarization. (B) Six days later, after treatment with moricizine 900 mg/d, the arrhythmia was not inducible despite using the same induction sequence or three extrastimuli. HRA, high right atrium; HBE, His bundle electrogram; A, atrial depolarization; V, ventricular depolarization.

Moricizine compared with other antiarrhythmics

Moricizine was compared with propranolol in a double-blinded, placebo, baseline-controlled crossover study.[20,21] The study found that moricizine achieved the Holter efficacy criterion of >75% VPCs per hour reduction; ie, 86% average decrease compared to 41% with propranolol. When propranolol and moricizine were administered in combination, VPC frequency decreased by 90%. When moricizine was given alone, fewer moricizine patients needed to discontinue therapy because of side effects compared to patients taking propranolol.

Moricizine was compared with quinidine and disopyramide in double-blind, placebo-controlled, crossover-studies in patients with non-life-threatening arrhythmias.[22–25] In reducing VPC frequency by 75% or more, moricizine was superior to disopyramide (90% vs 65% response rates, respectively), and comparable to quinidine (67% vs 71%, respectively). It was also comparable to quinidine in achieving 90% suppression of nonsustained ventricular tachycardia (57% for both groups).

The Cardiac Arrhythmia Pilot Study (CAPS)[26] included patients who, after a myocardial infarction had more than 10 VPCs per hour; moricizine, flecainide, imipramine, encainide and placebo were assessed. The suppression goal was a 70% reduction of VPCs and a 90% to 100% reduction in non-sustained ventricular tachycardia. Of 98 patients who received moricizine, the efficacy criteria was achieved in 66%, compared to 79% for encainide and 83% for flecainide. These results led to the CAST,[1] designed to compare the effects of moricizine, flecainide and encainide.

SAFETY AND ADVERSE EFFECTS

Left ventricular function

Several studies used non-invasive and invasive methods for evaluating left ventricular function during moricizine administration.[27–29] Among 81 patients evaluated by two-dimensional echocardiography, the left ventricular ejection fraction was 47% before and 46% during moricizine therapy.[28] In addition, no changes were observed in patients with low ejection fractions (31% before and after).[28] Invasive hemodynamic studies showed no differences between moricizine and

placebo for parameters as heart rate, blood pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac index, stroke volume index and systemic vascular resistance.[28] Of the 1072 patients from the moricizine database,[30] the reported incidence of congestive heart failure, defined as New York Heart Association class III or IV, was 7.1%. The frequency was higher among patients with prior history of congestive heart failure (15.4%) than in those without (0.8%). The development of CHF was unrelated to the drug dosage.

Proarrhythmia

Proarrhythmia, a major concern during antiarrhythmic therapy, can be categorized as either aggravation of existing arrhythmias (ie, increase in duration and frequency and/or alteration in rate), or the development of new arrhythmias.[30–33]

Among 908 patients, proarrhythmic events (defined by Holter criteria as a 10-fold increase or greater in VPC frequency), were observed in 29 patients (3.2%).[33] No proarrhythmic events were detected in patients with benign ventricular arrhythmias. Fifteen patients developed serious proarrhythmic events, 11 had new onset sustained ventricular tachycardia, 2 had a new onset of ventricular flutter-fibrillation, 1 developed torsade de pointes, and 1 had a syncopal episode. Four deaths were probably secondary to proarrhythmic effects; all four deaths occurred within 7 days of initiating moricizine therapy, and 90% of their proarrhythmic events occurred in the first 14 days. The incidence of proarrhythmia among patients with a prior history of CHF was not significantly different from other groups, despite the significance of CHF as a risk factor for proarrhythmia.[29]

Noncardiac adverse effects

The most frequently reported noncardiac adverse effects were gastrointestinal (eg, nausea), and neurologic (eg, dizziness). These effects occur in between 10% to 15% of the patients during short-term therapy, and in 20% to 25% during long-term therapy (longer than 1 year).[34–35] Organ toxicity is rare and is characterized by elevated liver enzyme levels.[35]

Drug interactions

Digoxin and moricizine administered together have additive effects on intranodal tissue with prolongation of the PR interval.[11,36,37] First degree AV block or bundle branch block has been reported during concomitant moricizine and digitalis therapy.[11,37] Moricizine does not affect digoxin plasma levels.[11]

Cimetidine, an inhibitor of hepatic microsomal oxidative enzymes, markedly reduces moricizine clearance.[11,38] Despite the changes in moricizine concentration and disposition, no marked differences in the electrocardiographic parameters have been observed.

Theophylline clearance increases with moricizine use. Theophylline serum levels should be monitored closely when both drugs are used.[11]

Warfarin elimination half-life decreases with moricizine, but no changes in prothrombin time were observed. Clinical experience indicates that there is not significant pharmacokinetic or pharmacodynamic interaction between moricizine and warfarin.[11]

THERAPEUTIC RECOMMENDATIONS

Moricizine is available in tablets of 200, 250, and 300 mg. The minimum effective oral dose seems to be 600 mg per day, with the optimal dosage ranging from 600 to 900 mg daily every 8 hours.[11,13]

In most cases, treatment should be initiated in the hospital and guided, if possible, by electrophysiologic studies, with the patient under close observation. Because of the drug's extensive and complex metabolism, assessing its action (but not efficacy) through measurement of PR, QRS, and QT intervals seems to be more useful than monitoring the moricizine serum level.

Exercise testing has been proposed to evaluate the rate-dependent augmentation effects of various antiarrhythmic agents.[40–43] During sinus tachycardia, use-dependent sodium channel blockade by class IA and IC antiarrhythmic drugs may enhance slow conduction; this effect, along with a weak effect on ventricular refractoriness, creates the appropriate conditions for reentry.[39,40,42]

Exercise testing may detect a patient's potential for proarrhythmic response to moricizine or other antiarrhythmic agents (*Figure* 3).

RATIONALE FOR TREATING VENTRICULAR ARRHYTHMIAS

It is generally agreed that treatment is indicated for ventricular arrhythmias that are symptomatic or have prognostic significance. Arrhythmias with prognostic significance are defined as symptomatic or asymptomatic "life-threatening" arrhythmias, and are evaluated by history, ventricular function, invasive and noninvasive techniques.

Before starting therapy, the patient's symptoms must

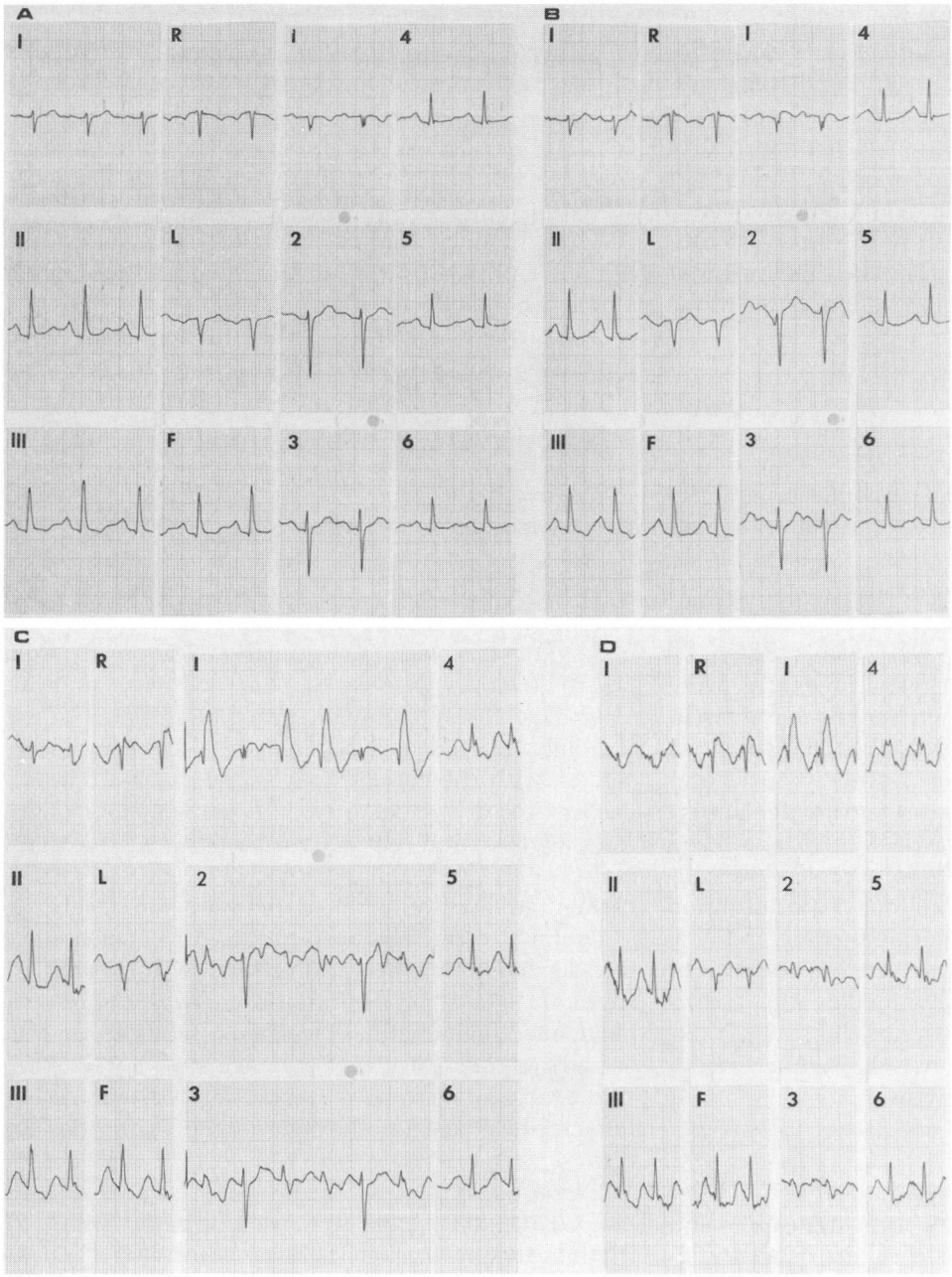

FIGURE 3. A 41-year-old woman with a history of cardiomyopathy and sustained ventricular tachycardia was treated with moricizine 900 mg/day, guided by electrophysiologic testing. During treatment, prolongation of the PR interval was observed, with no modifications in the QRS or QT. Before discharge, the patient underwent a treadmill exercise stress test to detect possible proarrhythmic effects. A baseline 12-lead standing ECG (*A*) shows a heart rate of 102 bpm, mild PR prolongation (210 msec), and a QRS duration of 100 msec. At 1.7 mph and a 10% grade (*B*) the heart rate increased to 121 bpm and the PR prolonged to 240 msec, with no changes in the QRS. At 2.5 mph and a 12% grade (C), intermittent right bundle branch block developed at a heart rate of 144 bpm (lead V1), with no further prolongation of the PR interval. The right bundle branch block (*D*) persisted until the termination of the test. The initial forces of the QRS do not markedly differ from *A* and *B*, suggesting a use-dependent effect at the level of the right bundle branch, with no proarrhythmic effect.

be carefully correlated with the nature of the arrhythmia. For example, the presence of palpitations due to PVCs is not an indication for pharmacological therapy per se. When palpitations are frequent and occur in combination with dizziness, neck-pounding sensation, weakness, and other symptoms that interfere with the patient's activity, then it is reasonable to start treatment.

The prognostic significance of arrhythmias are independent of the severity of symptoms, and are related to the presence or absence of structural heart disease and impaired left ventricular function, and to the ease of inducing sustained monomorphic ventricular tachycardia.[42]

The role of moricizine

Patients who have arrhythmias with prognostic significance—with or without symptoms—are appropriate candidates for moricizine therapy, particularly if other drugs have been ineffective or tolerated poorly.

Drug therapy, chosen by noninvasive or invasive protocols, can protect patients against the recurrence of life-threatening arrhythmias. Individualization of therapy requires appropriate evaluation of the clinical arrhythmia in the patient, trial and error, and the weighing of the relative advantages and disadvantages of the available options.[43]

The selection of an antiarrhythmic agent is based on its safety, efficacy, and incidence of side effects. Depending on modulating factors (particularly autonomic tone), beta blockers can be an excellent option for some patients, particularly those with coronary artery disease. Class IA agents—isolated or in combination with beta blockers—are the first line option. If these agents fail, moricizine may be a reasonable choice, because of its efficacy compared to other antiarrhythmic agents, and low incidence of side effects and proarrhythmia.[44]

Although moricizine has an efficacy profile comparable to other antiarrhythmic agents, and a good safety profile, further clinical evaluation is needed of the drug's effects, particularly in combination with other agents.

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