Moricizine (Ethmozine HCl) — A New Antiarrhythmic Drug: Is It Unique?

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The latest antiarrhythmic agent to be approved is moricizine (ethmozine hydrochloride), which is in some ways a unique agent. It was first synthesized in the U.S.S.R. and was used there for many years before its introduction to the U.S. where it has been investigated since 1977. It is a phenothiazine derivative, but is devoid of many of the adverse effects ascribed to this class of drugs. Whereas most of the available data involve its use for ventricular arrhythmia, the drug has electrophysiologic properties suggesting a role in supraventricular arrhythmias, although data are as yet limited.

Electrophysiologic effects: Moricizine is a class 1 antiarrhythmic agent, its major effect being a concentration-related blockade of the sodium channel and inhibition of sodium ion currents[1] (Table I). The reduction in the maximal upstroke velocity (Vmax) of phase 0 of the action potential results in a reduction in the velocity of impulse conduction throughout tissue that generates a fast sodium-initiated action potential, i.e., atrial and ventricular myocardium and the His-Purkinje system. Similar to other antiarrhythmic drugs, moricizine demonstrates the property of use dependency (i.e., its electrophysiologic actions are more pronounced at higher frequencies of stimulation).[2] These electrophysiologic effects resemble those produced by class 1C antiarrhythmic agents. However, similar to the class 1B agents, the drug increases the rate of membrane repolarization, shortening the action potential duration as a result of a shortening of phases 2 and 3.[1]

Moricizine alters the membrane threshold potential, making it less negative, thereby increasing the amplitude of current necessary to depolarize the cell and reducing membrane excitability.[3] As a result of the shortening of phases 2 and 3, moricizine depresses early delayed afterpotentials, a form of trigger automaticity.[1] Although moricizine does not alter the slope or rate of phase 4 depolarization, it does reduce the spontaneous automaticity of Purkinje fibers, especially during ischemia or in the presence of hypokalemia, as a result of the shift in threshold potential to a less negative level, increasing the duration of time before threshold is reached and an action potential generated.[4] Late or delayed afterpotentials, another form of triggered activity which results from catecholamines, ischemia or an acute myocardial infarction or with digitalis toxicity, are depressed by moricizine.[5]

These electrophysiologic data suggest that moricizine may be effective against arrhythmias regardless of their mechanism, i.e., reentry, enhanced automaticity, or triggered automaticity due to early or late delayed afterpotentials. Studies in the intact animal have confirmed that moricizine is effective against ventricular arrhythmias resulting from a myocardial infarction, epinephrine and aconitine, but it is not effective against strophanthidin.[1] Whereas the electrophysiologic effects of moricizine have been evaluated primarily in ventricular tissue, the drug also has antiarrhythmic actions on atrial tissue that resemble those in the ventricular myocardium.[1] However, this has not been sufficiently studied.

In the clinical electrophysiology laboratory, oral moricizine significantly shortens the sinus cycle length, but has no significant effect on sinus node recovery time or sinoatrial conduction time.[6] The drug does not effect the refractory periods of the atrial and ventricular myocardium, His-Purkinje system or atrioventricular node, and there is no change in the atrial cycle length at which nodal Wenckebach develops; however, it does slow the velocity of impulse conduction through these structures. As a result, the AH and HV intervals are significantly prolonged.[6]

On the surface electrocardiogram, the PR and QRS intervals are prolonged, reflecting the drug's membrane electrophysiologic effects. The JT interval, or repolarization time, is not altered or may be insignificantly shortened.

Pharmacology: Moricizine is available for oral use and the recommended doses are 200 to 400 mg administered orally 3 times daily based on dose-ranging studies[7] (Table II). The peak plasma level of the drug is achieved 1½ hours after oral administration. Although rapidly and completely absorbed, the systemic bioavailability of moricizine is only 38%, a result of its substantial and rapid first-past clearance by the liver.[8] The clearance of the drug follows 2 compartment pharmacokinetics. There is a rapid distribution phase, with a

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TABLE I Electrophysiologic Effects of Moricizine

Cellular
Sodium channel blockade—rate of depolarization and impulse conduction velocity decreased (class 1C activity)
Rate of repolarization, increased action potential duration shortened (class 1B activity)
Membrane threshold potential less negative—reduced membrane excitability and automaticity
Early and late afterpotentials depressed
Clinical
Shortens sinus cycle length
Prolongs AH interval—PR prolongation
Prolongs HV interval—QRS widening
No change in refractory periods of atrium, ventricle, AV node or His Purkinje system
Slows anterograde and retrograde conduction of accessory pathway

AV = atrioventricular.

TABLE II Pharmacology of Moricizine

Dose	200–400 mg 3 times daily (oral)
Absorption	Rapid and complete
Peak levels	1½ hours
Bioavailability	38%
Elimination half-life	2–60 hours (normal subjects) 6–13 hours (heart disease)
Protein binding	95%
Metabolism	Hepatic (first-pass effect) Multiple metabolites (? activity)
Drug interactions	Cimetidine Theophylline

? = unknown.

drug half-life of 4 to 20 minutes, whereas the half-life resulting from the terminal elimination phase is longer, usually 2 to 6 hours but as long as 13 hours in patients with significant heart disease. About 95% of the drug is bound to plasma proteins, involving both albumin and α-1-acid glycoprotein. The volume of distribution of moricizine is 300 liters, suggesting that there is extensive peripheral tissue binding.

Hepatic metabolism of moricizine is almost complete and many metabolites have been identified. Most appear to be devoid of antiarrhythmic activity, although 2, moricizine sulfoxide and phenothiazine-2-carbon acid ethyl ester sulfoxide, have some antiarrhythmic activity, but this is well established. The presence of congestive heart failure does not appear to alter the pharmacokinetic properties of moricizine, but associated hepatic dysfunction may affect drug metabolism and its half-life.

Drug interaction: Only a few interactions have been reported. There are no changes in the kinetics of warfarin or the prothrombin time when moricizine is administered.[9] Cimetidine, which inhibits hepatic oxidative enzymes, reduces the clearance of moricizine by up to 48%,[10] but this is not clinically significant. There are no significant interactions with digoxin or propranolol.

An interesting interaction with theophylline has been observed. As a result of a moricizine-induced increase in hepatic metabolism, the rate of theophylline clearance is increased and its half-life shortened. This may have clinically important effects in patients with asthma.

Hemodynamic effects: In the *in vivo* dog heart, moricizine has no effect on heart rate or blood pressure; vasomotor responses to norepinephrine, acetylcholine, histamine and angiotensin are not altered by the drug. Myocardial contractility of the dog heart and left ventricular hemodynamic parameters are not altered.

The clinical experience with moricizine in humans confirms its lack of significant effects on left ventricular contractility. There is no change in global right or left ejection fractions during therapy when evaluated with 2-dimensional echocardiography or radionuclide ventriculography, even in the subset of patients with a reduced left ventricular ejection fraction.[11] When exercise testing is used as a measure of left ventricular function, moricizine produces no change in exercise duration, resting or peak heart rate or resting and peak blood pressure.[11] With use of invasive hemodynamic measurements in patients at rest as well as during supine bicycle exercise, the drug does not alter mean pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac index, stroke volume index, left ventricular stroke work index or systemic vascular resistance.

Clinical trials: Moricizine has been well studied in patients with a wide range of ventricular arrhythmia. Initial clinical trials involved patients with little or no heart disease who had frequent ventricular premature complexes (VPCs) and moricizine was reported to be very effective, significantly reducing VPC frequency, including repetitive forms, i.e., couplets and runs of nonsustained ventricular tachycardia (VT).[12,13]

In a trial of 88 patients, moricizine therapy was administered for >1 year.[14] There was a >70% reduction of VPCs in 60% of patients during the entire follow-up period. In the Cardiac Arrhythmia Pilot Study (CAPS) involving 98 patients with a recent myocardial infarction, 66% of patients responded to doses of 600 to 750 mg/day.[15] After a 1-year follow-up, 65 patients continued to take moricizine with continued arrhythmia suppression. Moricizine is currently the only agent being used in the Cardiac Arrhythmia Suppression Trial (CAST)-II as the other agents, encainide and flecainide, were withdrawn because their use resulted in increased sudden death.[16] Unfortunately, long-term data regarding efficacy and outcome with moricizine are not yet available.[17]

In a number of trials involving patients with frequent VPCs, moricizine has been compared with other

antiarrhythmic drugs. In a double-blind, placebo-controlled comparative trial involving moricizine and propranolol, 20 patients were initially randomized to 1 week of therapy with moricizine (600 to 900 mg/day), moricizine plus propranolol, or propranolol alone (120 mg/day). Efficacy, defined as a >75% reduction in arrhythmia, was achieved in 70% of patients in whom VPCs were reduced 86% during ethmozine therapy. Only 10% of patients responded to propranolol and the reduction in VPCs was 41% ($p < 0.05$). Of the 14 patients who had runs of nonsustained VT, 79% had abolition of these forms during moricizine therapy while taking propranolol (response rate was 50%) (p = not significant). In a comparative trial, 29 patients, in random fashion, received 10 days of therapy with moricizine and disopyramide. With moricizine therapy, 52% of patients responded and there was a 90% reduction in VPCs compared with a 31% response rate and 65% reduction in VPCs ($p < 0.05$) with disopyramide. There was no significant difference in the reduction of couplets or runs of nonsustained VT.

In a third study involving 21 patients, moricizine (600 to 1,200 mg/day), quinidine (1,200 to 1,600 mg/day) or placebo were administered for 2 weeks. The response rate to the 2 agents (67% moricizine and 71% quinidine) was similar as was the mean reduction in VPCs (95%) and nonsustained VT (90%). The CAPS provided data permitting a comparison of moricizine (600 to 900 mg/day) with encainide (105 to 180 mg/day) and flecainide (200 to 400 mg/day).[15] The response rate to these 3 agents was 66, 79 and 83%, respectively.

Moricizine has also been evaluated in patients with a history of a serious sustained ventricular tachyarrhythmia. In a group of 82 patients with a history of ventricular fibrillation, sustained VT or symptomatic nonsustained VT, who had a high density or spontaneous ventricular arrhythmia, the antiarrhythmic effect of moricizine was evaluated with ambulatory monitoring and exercise testing.[18] Criteria for efficacy were total elimination of runs of nonsustained VT, >90% reduction in couplets and >50% decrease in VPC frequency using both methods of evaluation. Overall, 40% of patients responded to the drug. Response rate was related to the nature of the presenting arrhythmia and was 62% in those with nonsustained VT, 33% in patients with ventricular fibrillation and 19% in patients with sustained VT. Additionally, the drug was more effective and the response rate higher among patients with better left ventricular function. When left ventricular ejection fraction was >40%, 35% of patients responded compared with an 18% response rate among patients with an ejection fraction <40%. From the U.S. data base involving 263 patients with a serious ventricular arrhythmia refractory to previous antiarrhythmic drugs, 48% were judged to have responded to the drug; as previously noted, the response rate was greater in patients with nonsustained VT (61%) than in those with a sustained tachyarrhythmia (42%).[19]

Similar to other drugs, moricizine is less effective when evaluated by electrophysiologic techniques. An early study involving 47 patients reported that suppression of VT induction was achieved during moricizine therapy in 18% of patients, whereas those with nonsustained VT induced at baseline had a noninducibility rate of 27%.[6] In a review of the U.S. data base, there were 117 patients with paired electrophysiologic studies.[19] Among those with sustained VT induced in the baseline study, the drug prevented reinduction in 25%, whereas noninducibility was achieved in 36% who had nonsustained VT at baseline. Overall, noninducibility was achieved in 29%. However, an additional 45 patients with baseline electrophysiologic tests did not undergo a repeat study during moricizine therapy because of drug discontinuation for side effects or drug inefficacy based on noninvasive evaluation. When these patients are included in the analysis, the overall efficacy rate is 21%. In other studies, noninducibility with moricizine with electrophysiologic techniques is as low as 5%.[18]

Unfortunately, data on the outcome of long-term therapy with moricizine in patients with serious ventricular arrhythmia are sparse. When noninvasive methods were used to judge efficacy, the sudden death rate was 12%, whereas a nonfatal recurrence occurred in 12% after a 13-month follow-up.[18] Of 28 patients responding to moricizine (based on electrophysiologic testing) and continuing to take it for a mean of 6.8 months, there were 3 sudden deaths (10.7%) and a nonfatal recurrence in 6 (21.4%).[19]

Although moricizine has effects on atrial myocardium and the atrioventricular node, data on the role of this agent for therapy of supraventricular arrhythmias are sparse and no controlled studies are available. In 1 small series of 4 young patients with an ectopic atrial tachycardia, moricizine was effective in each patient.[20] An intravenous preparation of moricizine was evaluated in the U.S.S.R. in patients with supraventricular tachycardia. Among 16 patients with an accessory pathway, the drug (1.5 to 2 mg/kg) terminated the induced tachycardia in 9 patients, and prevented its reinitiation in 8.[21] In the remaining patients, the cycle length of the induced supraventricular tachycardia was lengthened. In many patients the drug did slow or abolish anterograde and retrograde conduction over the accessory pathway and prolonged its refractory period. In a second study, intravenous moricizine (1.5 to 2 mg/kg) was administered to 11 patients with atrioventricular nodal

TABLE III Most Frequent Adverse Effects from Moricizine–U.S. Data Base (n = 1,256)

	Adverse Reaction (%)	Drug Discontinued (%)
Overall	71.5	9
Cardiac	16.8	2.6
Arrhythmia aggravation	8.0	?
Congestive heart failure	7.1	0.9
Chest pain	2.8	?
Nervous system	37.7	0.6
Dizziness	15.1	
Headache	8.0	
Nervousness	2.5	
Paresthesias	2.4	
Sleep disorder	2.1	
Gastrointestinal	29.6	2.9
Nausea	9.6	
Abdominal pain	3.2	
Dyspepsia	3.1	
Vomiting	3.1	
Diarrhea	2.1	
Dry mouth	2.1	
Generalized	28.7	0.4
Fatigue	5.9	
Hypoesthesias	3.5	
Sweating	2.9	
Asthenia	2.7	
Chest pain	2.6	
Fever	0.2	
Respiratory	17.9	0.2
Musculoskeletal	10.8	?
Dermatologic	8.8	?
Urogenital	7.1	0.3
Laboratory abnormalities	0.9	0.4

? = unknown.

reentrant tachycardia.[22] The drug terminated the arrhythmia in 6 and prevented reinduction in each patient. A reduction in retrograde conduction through the fast atrioventricular nodal pathway was seen.

Adverse effects: Initial studies with moricizine using doses of <600 mg/day reported very few adverse effects, and these were primarily gastrointestinal.[12,13] In the dose-ranging, placebo-controlled trials in which >600 mg/day were administered, adverse effects were more common.[14] The most frequent were nausea (11%), dizziness (9%), abdominal discomfort (11%), weakness (4%), headache (3%), constipation (2%), dry mouth (2%) and blurred vision (2%). More serious side effects, usually resulting in drug discontinuation, were arrhythmia aggravation (4.2%), conduction abnormalities (2.5%), anxiety or depression (1.7%) and dizziness and syncope (1.7%). The U.S. data base, which includes 1,256 patients, reported that 71.5% of subjects had at least 1 adverse effect during the follow-up period which was up to 2 years[23] (Table III). However, the drug was discontinued in only 9% of patients, most often because of neurologic or gastrointestinal toxicity. The most frequent adverse effects were neurologic (dizziness, headache, fatigue, hypesthesia, asthenia, nervousness, paraesthesias and sleep disorder); gastrointestinal (nausea, abdominal pain, dyspepsia, vomiting, diarrhea and dry mouth); generalized complaints; respiratory complaints; musculoskeletal problems; and dermatologic and urologic problems. Drug fever, reduced platelet counts and liver function test abnormalities were rarely observed.

In the U.S. data base, the reported incidence of arrhythmia aggravation was 3.2%. In half of these cases, this represented a new sustained ventricular tachyarrhythmia, whereas in the remaining half, there was a statistically significant but nonserious increase in VPCs or runs of nonsustained VT. However, in a group of patients with significant heart disease presenting with serious ventricular tachyarrhythmias, the incidence of arrhythmia aggravation was 11%.[24] In the U.S. data base, congestive heart failure during therapy was observed in 7.1% of patients, but was probably or possibly due to the drug in only 2%.[25] The majority of patients with this adverse reaction had a previous history of congestive heart failure. A similar incidence of heart failure has been observed among patients with a history of a sustained ventricular tachyarrhythmia.[26]

Conclusion: Moricizine is a new antiarrhythmic agent with electrophysiologic properties similar to those produced by other class 1 antiarrhythmic agents. At doses of 600 to 1,200 mg/day it is effective for the suppression of spontaneously occurring VPCs, couplets and runs of nonsustained VT. It is less effective in patients presenting with a sustained ventricular tachyarrhythmia, especially when significant left ventricular dysfunction is present. Although there are few direct comparisons with other antiarrhythmic agents, efficacy rates with moricizine appear to be lower than those reported with drugs that are more potent. An important advantage is less frequent nuisance side effects when compared with other agents. More serious adverse effects (primarily cardiac) do occur, but are less common than with other agents. Moricizine appears to be safe in postinfarction patients and is not associated with the increased mortality seen with encainide and flecainide. Its safety and low incidence of adverse effects are important advantages; however, it is as yet unknown if this drug will reduce the risk of sudden death in postinfarction patients or in any other group, especially those surviving out of hospital sudden death. Therefore, the answer to the question "Is it unique?" awaits the results of CAST-II.

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Medical, Ethical and Legal Issues Regarding Thrombolytic Therapy in the Jehovah's Witness

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We recently cared for a patient who received thrombolytic therapy for an acute myocardial infarction. The patient was a Jehovah's Witness and subsequently had a hemorrhagic death, refusing blood transfusion. The case raised several questions about the medical, ethical and legal considerations involved with the use of thrombolytic therapy in Jehovah's Witnesses and other patients who refuse blood transfusions a priori.

The patient was a 57-year-old woman who presented to a local emergency room complaining of chest discomfort. An electrocardiogram was consistent with an acute inferior myocardial infarction and the patient consented to participate in the Thrombolysis and Angioplasty in Myocardial Infarction 5 investigation. She was randomized to receive thrombolysis with both tissue plasminogen activator and urokinase followed by acute cardiac catheterization. Her initial hemoglobin was normal and thrombolytic therapy was administered within 6 hours from the onset of the symptoms. The patient was a practicing Jehovah's Witness and clearly stated an objection to the use of any blood products in her care. Several days later, she became progressively hypotensive. The patient's stool was melenic and her hematocrit was 20%. After being advised that her clinical condition was life-threatening, the patient again refused the administration of blood or blood products.

Gastrointestinal bleeding continued despite treatment with both sucralfate and an H_2 blocker; her he-

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