Treatment of Frequent Ventricular Arrhythmia with Encainide: Assessment Using Serial Ambulatory Electrocardiograms, Intracardiac Electrophysiologic Studies, Treadmill Exercise Tests, and Radionuclide Cineangiographic Studies

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SUMMARY The effects of encainide on ventricular arrhythmia and left ventricular function were studied in 21 patients with chronic, high-grade ventricular arrhythmia using a prospective, 3-month, placebo-controlled, single-blind trial design. Encainide caused a 96% decrease in the average hourly frequency of ventricular premature complexes (VPCs) and comparable reductions in salvo of nonsustained ventricular tachycardia (VT) and episodes of sustained VT. Intracardiac electrophysiologic testing showed prolonged intratrial and intraventricular conduction times and increased atrial, atrioventricular nodal, and ventricular refractory periods with both i.v. and oral encainide without His-Purkinje block, despite marked prolongation of HV and QRS intervals. Induced repetitive ventricular beating after ventricular extrastimuli in 15 patients showed persistent repetitive ventricular beating with chronic oral encainide in seven patients, four of whom had sustained VT within 2 months of treatment on encainide. Encainide did not reduce exercise capacity or left ventricular ejection fraction at rest or during supine exercise. Minor adverse effects of encainide in 11 of 21 patients included dose-related visual disturbances, dizziness and sinus pauses (<3 seconds). Major adverse effects included the new appearance of sustained VT in three of 20 patients (15%). Oral encainide effectively reduces the frequency and grade of VPCs, prolongs intraventricular conduction times, and does not impair left ventricular performance. However, it is associated with frequent minor side effects and uncommon but potentially severe major side effects (sustained VT), both of which apparently have a direct relationship to the size of the dose.

ENCAINIDE, a benzanillide derivative, is a new antiarrhythmic agent recently shown to have great efficacy in suppressing ventricular ectopy.1,7 Initial electrophysiologic studies in animals have shown that encainide decreases automaticity, reduces the upstroke velocity and duration of the cardiac action potential and consequent prolongs the effective refractory period of the action potential.1 Subsequent studies have shown that encainide is effective in suppressing atrial and ventricular arrhythmias in a variety of species with varying experimental interventions.2,9 This study was designed to prospectively investigate the effectiveness of encainide given orally every 6 hours in reducing the frequency of ventricular premature complexes (VPCs) as confirmed on frequent ambulatory electrocardiographic recordings, serial exercise tests and invasive electrophysiologic tests.

To minimize the effects of spontaneous variability on VPC frequency,8,10 patients with chronic, high-frequency ventricular arrhythmia were studied. In addition, the study design included quantification of ventricular arrhythmia during multiple 24-hour ambulatory ECG recordings obtained during alternating placebo and encainide treatment phases. The effects of encainide on exercise-related ventricular arrhythmia were also evaluated during treadmill testing. Exercise duration and myocardial performance were studied off and on encainide using treadmill exercise testing and radionuclide cineangiography at rest and during exercise. The electrophysiologic effects of acute i.v. and chronic oral encainide, including the response to provocative extrastimulus techniques, were determined at cardiac catheterization.11,12

Methods

Patient Characteristics (table 1)

All patients were older than 21 years of age and had a history of frequent ventricular arrhythmias (minimum mean VPC frequency ≥60 beats/hour for at least 48 hours) for more than 3 months, without known reversible cause. No other antiarrhythmic agents were allowed during the trial; however, diuretics, diuretics and potassium supplements for patients with congestive heart failure and β-blockers for patients with angina pectoris were continued without modification (table 1). Each patient gave informed consent before the study. The protocol was approved by the human research committees of the participating institutions. Additional informed
**Table 1. Clinical Characteristics of Patient Sample**

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<th>Pt</th>
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<th>Sex</th>
<th>Diagnosis</th>
<th>Duration (years)</th>
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<th>VPCs</th>
<th>Medications (mg/day)</th>
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<td>Prop 480</td>
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</table>

*Indicates patients in whom the efficacy of prior antiarrhythmic regimens is not well documented.

Abbreviations: CABG = coronary artery bypass grafting; CAD = coronary artery disease; CHF = congestive heart failure; D = disopyramide; DPH = diphenylhydantoin; HBP = high blood pressure; HCTZ = hydrochlorothiazide; Hydral = hydralazine; ISDN = isosorbide dinitrate; KCl = potassium chloride; MI = myocardial infarction; NaCl = sodium chloride; NTG = nitroglycerin; PCA = procainamide; PRZ = prazosin; prop = propranolol; Q = quinidine.

Consent was obtained before electrophysiologic and radionuclide cineangiographic testing.

Criteria for exclusion were obstructive airways disease requiring sympathomimetic treatment; recent (less than 1 year) myocardial infarction or cardiovascular surgery; unstable angina pectoris; or any other severe concomitant illness, evidence for noncompliance or an inability to understand the nature of the investigation. Unlike a previous study, patients with heart failure or angina were not excluded.

**Study Design**

The study was a prospective, 3-month, single-blind, placebo-controlled evaluation of encaaine given orally every 6 hours using the antiarrhythmic response or appearance of side effects as the end point of dosage adjustments. The study had five sequential phases (fig. 1). During the entire study, patients were given study drug capsules orally every 6 hours, which consisted of either encaaine, 10-, 25- and 50-mg capsules, or an identical number of placebo capsules (supplied by Mead Johnson Pharmaceutical Division). Phase 1 was initiated upon admission to the progressive coronary care unit of the Veterans Administration Medical Center or the George Washington University Medical Center, Washington, D.C. Telemetric monitoring in these units provided patients with self-care activities and ambulation during concurrent monitoring by...
ENCAINIDE STUDY DESIGN

![Graphical representation of the study design]

By encainide and by computer (Hewlett-Packard, 
#78225 arrhythmia computer) of the patient's ECG tracing. To assess baseline ventricular ectopic activity, patients underwent at least 48 hours of simultaneous ambulatory ECG recordings during this phase that was obtained after withdrawal of all other antiarrhythmic therapy for at least 48 hours. Before beginning treatment with encainide, patients were required to demonstrate an average of at least 60 VPCs per hour for the entire ambulatory ECG recording period, while on treatment with oral placebo every 6 hours.

Phase 2, the dose-titration phase of the study, followed immediately unless delayed for 12-24 hours in order to perform electrophysiologic testing while on placebo treatment. During phase 2, patients began encainide therapy with 25 mg every 6 hours for at least 4 doses. Individual doses were increased at increments of 25 mg, provided patients remained at a given dose for at least 24 hours, the frequency of VPCs was not suppressed by more than 80% and side effects did not appear. When the VPC frequency decreased by approximately 80% as determined by multiple 8-hour segments of monitoring and the drug dosage was constant for 24 hours, a repeat 24-hour ambulatory ECG was done to confirm the effect of encainide on the frequency of VPCs. If the frequency of VPCs was not decreased by at least 80% before the onset of side effects, the patient was dropped from further participation. Before phase 3, the outpatient titration phase, electrophysiologic testing was again performed at the nadir of the chronic oral dose (i.e., 1-hour predose).

Phase 3 consisted of approximately four outpatient visits, 1 week apart. Dosage modifications were made as necessary to limit drug-related side effects and maintain effective outpatient control of the VPC frequency. Ambulatory ECG recordings were done to assure at least an 80% suppression of the VPC frequency after any dosage modifications. At the end of phase 3, a 24-hour ambulatory ECG recording was performed to confirm the effect of the established dose of encainide on the frequency of VPCs.

Phase 4 involved inpatient continuous telemetric monitoring and began with the sudden withdrawal of encainide by replacement with the same number of identical placebo capsules every 6 hours. Patients were monitored using an on-line ECG analysis system for the appearance of an increased number of VPCs while on placebo. During the first 7 days, if semiquantitative review of 8-hour ECG monitoring records revealed a probable increase in VPC activity of greater than 50%, an ambulatory ECG recording was begun. If no increase in VPC frequency was observed, an ambulatory ECG recording was begun on the seventh day to confirm this observation and the patient was discontinued from further study. Forty-eight hours of ambulatory ECG recordings were obtained while the patient was on placebo. If symptomatic ventricular tachycardia (VT) occurred, placebo treatment was terminated.

At the conclusion of this second placebo phase (phase 4), maintenance treatment with encainide was reinstituted at the previously established dose to begin phase 5 (fig. 1). This final phase included two outpatient visits 3 weeks apart and was terminated by a final 24-hour ambulatory recording.

A laboratory profile, including a complete blood count, platelet count, urinalysis, blood sugar, BUN, creatinine, SGOT, bilirubin, alkaline phosphatase, LDH, uric acid, serum electrolytes, calcium and fluorescent antinuclear antibody titer, was obtained before entry into the study and at the end of each phase. Fifteen-lead ECGs (12 standard leads and X, Y and Z orthogonal leads) were done each day during inpatient phases and at each outpatient visit. An ophthalmologic examination (including slit-lamp) was performed before beginning encainide during phase 2 and at the completion of the study.

Electrocardiographic Measurements

Standard 12-lead and X, Y and Z orthogonal ECGs were recorded at 25 mm/sec and 10 mm/mV (Marquette Data acquisition cart). In addition, a high-resolution, signal-averaging computer was used to obtain summated and amplified electrocardiographic data displayed at a simulated speed of 100 mm/sec and amplitudes of 10, 200 and 4000 mm/mV (MAC-1, Hi Res module, Marquette Electronics).

All ECG measurements were made independently.
by at least two of the investigators and without knowledge of the patient's study phase.

**Ambulatory ECG Recordings**

Ambulatory ECG recordings were made on 24-hour, two-channel, reel-to-reel recorders (Del Mar Avionics) and analyzed by a central laboratory (Cardio-Dynamics) whose methods and validation techniques have been described. Analysis of recorded ECG data included quantitative VPC frequency and hourly VPC grades, as assigned according to the following definitions (modified Lown grades): 0 = absence of VPCs; 1 = isolated, uniform VPCs with a frequency 3 or fewer per minute; 2 = isolated uniform VPCs with a frequency of more than 3 per minute; 3 = multiformal VPCs, 3 or fewer per minute; 3A = multiformal VPCs, more than 3 per minute; 4A = couplets (i.e., consecutive VPCs); and 4B = runs of 3 or more VPCs (termed salvos). To determine a mean hourly grade, grades 3A and 4A and 4B were considered equivalent to number grades 4, 5 and 6 before averaging.

**Treadmill Exercise Testing**

Two treadmill exercise tests were performed: one during treatment with placebo (phase 1 or 4) and one during encaïnide treatment (phase 2, 3 or 5). The sequence of tests was alternated so as to avoid routinely performing exercise on either placebo or encaïnide initially. Each exercise test consisted of identical sequential 3-minute stages of increasing work load, speed (mph) and percent elevation, on a calibrated motor-driven treadmill, according to a modification of the Bruce protocol. The elevation of VPC frequency during each exercise test was accomplished by manual counts of VPCs taken from resting, peak exercise and thenteenth-minute postexercise rhythm strips (> 60 seconds each). Both the frequency and grade of ventricular arrhythmia were recorded for each period.

**Radionuclide Cineangiography**

Radionuclide cineangiography was performed with the subjects in a supine position at rest during maximum symptom-limited supine bicycle exercise as previously described. The left ventricular ejection fraction was determined by computer-assisted analysis of left ventricle time-activity curves using a commercially available nuclear medicine computer system (Med. IV, Nova III computer, General Electric). Excellent correspondence ($r = 0.90, p < 0.001, n = 32$) of radionuclide ejection fractions with those obtained by contrast angiography has been established for this laboratory. After images were obtained at rest, supine bicycle exercise was begun with 100-kpm increments in exercise load at 2-minute intervals. Exercise was continued until limitation by severe fatigue, chest pain or severe dyspnea. Imaging was begun when the patient indicated moderate fatigue, and continued until the symptom-limited end point. Data acquired over the last 2–3 minutes of exercise were used to determine ejection fraction using the methods described above. Heart rate and blood pressure (measured using arm cuff sphygmomanometry) were recorded at 1–2-minute intervals during exercise.

**Intracardiac Electrophysiologic Testing**

Sixteen of the 21 patients in this study underwent sequential intracardiac electrophysiologic testing. Each of these patients underwent a baseline test during placebo therapy (phase 1); 12 patients (nos. 6, 9, 11–16, 18 and 19) had an acute retest beginning 5 minutes after the bolus administration (over 5–7 minutes) of i.v. encaïnide (0.9 mg/kg body weight). These studies were completed in 20–40 minutes. Patients 1, 2, 4 and 5 had an acute retest 1–2 hours after 50 mg of oral encaïnide. Fifteen patients (1, 2, 4–9, 11–16, 18) underwent repeat testing after at least 48 hours of maintenance oral encaïnide therapy, referred to as the chronic test (during phase 2).

All patients were in the postabsorptive state, with only light diazepam sedation, if needed, when studied. Baseline tests were performed at the end of phase 1 and were followed by acute retesting after encaïnide. Catheters were introduced percutaneously into the right atrium across the tricuspid valve for His bundle recordings, and to the right ventricular apex for ventricular stimulation. Stimulation was performed with a specially designed programmable stimulator and the recordings were made on an Electronics for Medicine VR 16 recorder or Siemens Mingograf recorder 1650 with simultaneous recording on analog tape (Honeywell model 96). Stimulation was done with 2-msec square-wave impulses at twice diastolic threshold. At least three surface ECG leads were recorded (usually leads I, II and V1), as well as at least two intracardiac positions (His bundle, high right atrial or right ventricular apex). Baseline intervals were recorded at a paper speed of 150 mm/sec; stimulation studies were recorded at 75–100 mm/sec.

**Measurements**

Baseline measurements of the heart rate, P-wave duration, QRS duration, QT interval, PR interval, onset of P wave to the low right atrium (PA interval), AH interval, HV interval, sinus node recovery time, sinoatrial conduction time, atrial refractory period, atrioventricular (AV) nodal refractory and ventricular refractory periods were made according to standard methods. Coupled atrial pacing was performed by introducing increasingly premature atrial stimuli after each spontaneous sinus beat.

Assessment of repetitive ventricular beating was evaluated with a series of provocative extrastimulus techniques. Incremental ventricular pacing (in bursts of six to 10 beats at 10-beat/min increments), to a rate of 200 beats/min was accomplished unless VT was induced at a lower rate. Then, ventricular extrastimulus techniques were used with both atrial and ventricular drive at a cycle length of 700 msec and ventricular drive at 600 msec. Premature extrastimuli were introduced after eight driven beats with a progressively shortening interval of prematurity until ventricular
refractoriness was reached. A second premature stimulus was then introduced after the first extrastimulus; the time between the first and second extrastimuli was progressively shortened until ventricular refractoriness was reached. A third extrastimulus was introduced in similar fashion. Sustained VT was defined as 10 or more repetitive beats. Responses to ventricular stimulation using the above techniques were categorized as nonrepetitive or repetitive ventricular responses. A nonrepetitive response was defined as having none or only one repetitive beat after the last paced beat. Patients with repetitive ventricular beats were divided into those who had two to 10 repetitive intraventricular reentrant beats, termed nonsustained repetitive ventricular responses, and those who had 10 or more intraventricular reentrant beats and usually required intervention by pacing or electrocardioversion, termed sustained repetitive ventricular responses (fig. 2). Intraventricular reentrant beats were defined as beats with a horizontal or frontal QRS vector distinctly different from that of the stimulated beats and those that were not preceded by a His deflection.

In 12 of the 16 patients studied on placebo, the baseline study was followed by a 15-minute infusion of encaïnide (0.9 mg/kg body weight). The study was repeated 5 minutes after the infusion was finished. Four patients received 50 mg of oral encainide before repeat study. If the response was deemed inadequate in suppressing repetitive ventricular beating, that is, there was the persistence of a nonsustained or sustained repetitive response, additional infusions of 0.45 mg/kg were administered, each over 15–30 minutes, until either the drug response was deemed adequate, the drug was thought to have exacerbated the arrhythmias, or three additional infusions were made. Drug exacerbation of arrhythmias was defined as the new appearance of a sustained ventricular response. Standard intervals and atrial and ventricular pacing studies were performed completely for the first and final i.v. dose. The chronic test on oral encainide was performed with the reintroduction of a temporary pacing catheter in a manner similar to that for the baseline test. The test was begun during the expected nadir of the encainide effect (i.e., during the fifth hour of an every 6-hour dosing schedule).

Data Analysis
Data are expressed as the mean ± sd. Statistical analysis was performed using a two-tailed test for paired and unpaired data, as appropriate. Comparison of the number of patients who demonstrated sustained VT on and off encainide treatment was done using the chi-square analysis. A p value less than 0.05 was considered significant.

Blood Levels
Encainide blood levels were determined by methods previously described using a radioimmunoassay technique. Specimens were assayed by Biomedical Reference Laboratories, Inc. Only free encainide levels in plasma were assayed.

Results
Twenty-one patients (19 males and two females), mean age 55 ± 12 years (range 31–69 years), were studied. Their clinical characteristics are summarized in table 1. Clinical criteria for congestive heart failure (CHF) included exertional dyspnea, fatigue, cardiomegaly and systemic and pulmonary venous congestion. Quantitative comparisons of the antiarrhythmic efficacy of prior drug regimens with each other were generally not available; however, in 16 of the 21 patients, therapy with other antiarrhythmic agents was determined to be unsuccessful, based on clinical evaluation of the effectiveness of VPC suppression or the appearance of intolerable side effects.

Clinical Antiarrhythmic Effects (table 2)
Encainide treatment produced at least an 80% reduction in the VPC frequency in each of the 20 patients who satisfactorily completed the initial placebo and initial encainide treatment phases (table 2). One patient died before VPC control during the initial encainide-dose titration phase (vide infra). The frequency of VPCs averaged 870 ± 780 (mean ± sd) VPCs per hour during the 48 hours of ambulatory ECG recordings obtained during the initial placebo phases. This VPC frequency was reduced significantly by encainide treatment (mean dose 75 ± 20 mg every 6 hours) after gradual encainide dose titration

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Repetitive ventricular responses in 15 patients on placebo and on chronic oral encainide and their clinical follow-up. Each of eight patients with a nonrepetitive response on chronic oral encainide remained free of clinical sustained ventricular tachycardia in 2 months of follow-up; only two of six patients with a nonsustained repetitive response on encainide have remained free of clinical sustained VT (p < 0.05). One of the four episodes of new clinical sustained VT probably resulted from faulty patient compliance. Asterisk represents the only case in which an exacerbation of the repetitive ventricular response followed encainide treatment. Double asterisk represents two patients who had sustained VT when encainide was replaced by placebo.
Table 2. Ambulatory Electrocardiographic Results During Each Phase of Study

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<td>Encainide</td>
<td>Encainide</td>
<td>Placebo</td>
<td>Encainide</td>
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<td>VPCs/hour</td>
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<td>VPCs/1000 beats</td>
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<td>0.1 ± 0.3†</td>
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<tr>
<td>Salvos VPCs/24 hours</td>
<td>207 ± 752</td>
<td>0.1†</td>
<td>0.5 ± 1.6</td>
<td>831 ± 3210†</td>
<td>0.1†</td>
</tr>
<tr>
<td>Highest average VPC grade*</td>
<td>5.1 ± 0.9</td>
<td>1.9 ± 1.5§</td>
<td>2.1 ± 1.6</td>
<td>4.9 ± 0.7†</td>
<td>1.6 ± 1.3†</td>
</tr>
</tbody>
</table>

Values are mean ± sd.
*Grades of 3A, 4A and 4B have been referred to as 4, 5 and 6.
The p value reflects comparison with value during the previous phase of the study:
†p < 0.05.
‡p < 0.01.
§p < 0.001.
Abbreviation: VPC = ventricular premature complex.

over 4.1 ± 1.1 days (phase 2). Similarly, the average hourly VPC grade increased significantly on enca

iene treatment. Fourteen patients demonstrated a reduction in their highest VPC grade during enca

iene treatment (phase 2) compared with the initial placebo period, including six patients with sustained VT on placebo, eight patients with runs of non-sustained VT on placebo and none with couplets on placebo; none of these grades were observed in, or exceeded by, these patients on enca

iene treatment (phase 2).

The frequency of couplets and salvos decreased significantly during enca

iene treatment compared with placebo during the initial two phases of study. Couplets were reduced 99.8% on enca

iene. Runs of nonsustained VT (salvos) were reduced more than 99% on enca

iene. These runs of nonsustained VT were observed on ambulatory ECG recordings in 13 patients during placebo treatment and at a much lower frequency in only five of these patients during enca

iene treatment (p < 0.05).

Sustained VT was documented by telemetric monitoring, treadmill exercise testing or ambulatory ECG recordings in 11 of the 21 patients (52%). Six patients demonstrated sustained VT during placebo treatment only, five during enca

iene treatment only, and 10 were free of sustained VT. During placebo treatment, six patients had sustained VT at rates of 125–190 beats/min (mean 151 ± 31 beats/min). Reversion to sinus rhythm occurred spontaneously in two of the six and was accomplished in two additional patients, by electrocardioversion in one and i.v. lidocaine in one. In the other two patients, frequent and intermittent sustained VT was asymptomatic and without hemodynamic compromise. Because of many unsuccessful attempts at reversion of VT in both of these patients before entry into the study, these episodes of VT were observed without intervention during placebo treatment. Each of these six patients with sustained VT on placebo was free of sustained VT on the dosage of enca

iene that reduced the mean frequency of VPC by at least 80%. The reinstatement of placebo therapy was associated with the reappearance of sustained VT in four of these six patients.

Five patients demonstrated sustained VT during enca

iene treatment, with rates of 156–190 beats/min (one patient during phase 2, two patients during phase 3 and two during phase 5). The patient who developed sustained VT during phase 2 (no. 15) had had sustained VT before entry into the study. However, four other patients who had sustained VT during enca

iene treatment had not had it on placebo or treatment with other antiarrhythmic drugs.

Patient 15, who developed sustained VT on both placebo and enca

iene, was the only patient who did not show a substantial reduction in the VPC frequency during dose titration up to 400 mg day. This patient died during resuscitative efforts to revert an episode of sustained VT while he was undergoing a further incremental dosage titration from 100 mg to 125 mg every 6 hours.

Suppression of ventricular ectopic activity during outpatient treatment was statistically similar to the initial inpatient antiarrhythmic response. The average frequency of VPCs per hour, couplets per 24 hours and salvos per 24 hours observed at the end of phase 2 compared with phase 3 were not significantly different despite directional trends in the mean values (table
2). During phase 3, however, patients 1 and 9 had episodes of nonfatal sustained VT, which is a higher grade of ventricular arrhythmia than that observed during phase 1 or 2. Each required hospitalization. Patient 1 was excluded from further encainide treatment during this phase of study.

The sudden substitution of placebo for encainide at the onset of phase 4 was associated with an increase in the frequency of ventricular arrhythmia, confirmed by 48 hours of ambulatory ECG recordings. No difference with respect to VPC frequency, average hourly VPC grade and the number of salvos per 24 hours was observed in the second placebo phase compared with the first placebo phase for each of these events (table 2). The recorded frequency of couplets per 24 hours, however, was significantly less during the second phase than during the initial placebo phase ($p < 0.05$) (table 2). In none of 19 patients did the decrease in VPC frequency produced by encainide persist during treatment with placebo for longer than 4 days (mean time to onset ambulatory recording from first dose of placebo was $1.7 \pm 1.3$ days).

The placebo phase was terminated in patient 7 by the development of sustained VT that was refractory to cardioversion by overdrive pacing but reverted to sinus rhythm immediately after 50 mg of i.v. encainide. In all other 18 patients, the placebo phase was terminated after 48 hours of ambulatory recording.

After phase 4 placebo treatment, patients 3, 6 and 10 were excluded from further participation in the protocol: one monoptic patient believed his already impaired vision was further impaired by encainide despite failure to document this by objective testing, one patient was unconvinced of further need for medication and one was excluded because of an unrelated medical problem (discovery of metastatic carcinoma).

Fifteen patients entered the fifth phase of study, which represented a reintroduction of encainide treatment at previously established maintenance dosages after a phase of placebo treatment. In this group, comparison of the 24-hour ambulatory ECG recordings done at the termination of phase 5 on encainide, and the final 24-hour ambulatory ECG recordings obtained on placebo similarly demonstrated that encainide produced a significant reduction of $97.7\%$ in the mean VPC frequency. No significant difference was found between the VPC frequency in phases 2, 3 and 5.

Encainide treatment during the final outpatient phase also produced a reduction of greater than $99\%$ in the frequency of couplets and salvos per 24 hours (table 2).

During treadmill exercise, the comparison of the pre-, peak and postexercise periods showed a significant reduction in the frequency and grade of ventricular arrhythmias during encainide treatment compared with placebo, similar to that observed on the ambulatory ECG recordings (table 4). The differences in the frequency or grade of ventricular

<table>
<thead>
<tr>
<th>TABLE 3. Treadmill Exercise Test Results on Chronic Oral Encainide Compared with Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mm Hg)</strong></td>
</tr>
<tr>
<td><strong>Diastolic blood pressure (mm Hg)</strong></td>
</tr>
<tr>
<td><strong>Mean blood pressure (mm Hg)</strong></td>
</tr>
<tr>
<td><strong>Rate-pressure product (beats × mm Hg/ min × 100)</strong></td>
</tr>
<tr>
<td><strong>Maximum ST-segment displacement (mV)</strong></td>
</tr>
<tr>
<td><strong>VPCs per 1000 beats</strong></td>
</tr>
<tr>
<td><strong>Highest VPC grade (modified Lown)</strong></td>
</tr>
<tr>
<td><strong>ST-segment change (mV)</strong></td>
</tr>
<tr>
<td><strong>Exercise duration (minutes)</strong></td>
</tr>
<tr>
<td><strong>Exercise end point</strong></td>
</tr>
<tr>
<td><strong>Angina</strong></td>
</tr>
</tbody>
</table>

Values are mean ± sd.  
* $p < 0.02$  
† $p < 0.01$  
‡ $p < 0.001$  
§ Two patients with new, sustained ventricular tachycardia immediately after exercise on encainide only.  
Abbreviation: VPC = ventricular premature complex.
TABLE 4.  Radionuclide Cineangiography Test Results on Chronic Oral Encainide Compared with Placebo

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Encainide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest (n = 16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>75 ± 13</td>
<td>76 ± 13</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>131 ± 19</td>
<td>139 ± 28</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>80 ± 11</td>
<td>85 ± 9</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>92 ± 13</td>
<td>103 ± 11</td>
</tr>
<tr>
<td>Rate-pressure product (beats · mm Hg/100)</td>
<td>100 ± 20</td>
<td>106 ± 27</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>46 ± 13</td>
<td>47 ± 14</td>
</tr>
<tr>
<td>Peak exercise (n = 12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>123 ± 19</td>
<td>121 ± 27</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>188 ± 28</td>
<td>191 ± 34</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>99 ± 13</td>
<td>101 ± 12</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>126 ± 16</td>
<td>129 ± 18</td>
</tr>
<tr>
<td>Rate-pressure product (beats · mm Hg/100)</td>
<td>233 ± 56</td>
<td>234 ± 77</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>53 ± 15</td>
<td>52 ± 14</td>
</tr>
<tr>
<td>ΔEjection fraction (exercise — rest; %)</td>
<td>4.3 ± 6.9</td>
<td>1.9 ± 4.9</td>
</tr>
<tr>
<td>Exercise time (seconds)</td>
<td>608 ± 232</td>
<td>614 ± 210</td>
</tr>
</tbody>
</table>

Values are mean ± sd.  
*p < 0.05.

arrhythmia were not statistically significant between the resting (or preexercise) and peak exercise periods on placebo or encainide (table 3). The postexercise period similarly reflected the general reduction in VPC frequency and grade on encainide compared with placebo. Patients 12 and 18 developed sustained VT on encainide during phase 5. Each developed the arrhythmia immediately after exercise while transiently at dosages approximately 25% higher than the dose finally found necessary for 80% control of VPCs.

Repetitive Ventricular Responses During Sequential Intracardiac Electrophysiologic Testing

The technique of Greene et al.30 using atrial drive at a 700-msec cycle length with a single premature ventricular extrastimulus was compared with ventricular drive at the same rate and single, double or triple premature ventricular extrastimuli. During the initial placebo phase for our group, only three of 15 patients had one or more VPCs after the test stimulus during the atrial drive technique; whereas 12 of 15 patients had one or more repetitive beats during the ventricular drive technique.

With either or both techniques, two of 15 patients on placebo had a nonrepetitive response and 13 had repetitive responses, three of which were sustained (fig. 2). The two patients with a nonrepetitive response on placebo remained the same after chronic oral encainide; six of the 10 patients with a nonsustained repetitive response became nonrepetitive on chronic oral encainide (fig. 2). The three patients with a sustained repetitive response and three of the 10 patients with a nonsustained repetitive response improved to a nonrepetitive response during oral encainide treatment.

On follow-up (mean 12 months, range 10–14 months), all eight patients who had a nonrepetitive response to ventricular extrastimuli while on chronic oral encainide remained free of clinically recognized sustained VT. Seven of these eight had failed prior trials of antiarrhythmic therapy.

Seven of the 10 patients with a nonsustained repetitive response to extrastimuli on placebo did not improve during chronic oral encainide; six remained nonsustained and one became sustained (fig. 2). Compared with each of the eight patients with nonrepetitive responses on chronic encainide, only two of the seven patients with repetitive responses on chronic oral encainide remained free of clinically recognized sustained VT. Sustained VT was defined as VT longer than 1 minute in duration, requiring emergency medical intervention or accompanied by syncope. The other five patients (nos. 1, 9, 12, 15, 18) with repetitive responses on encainide demonstrated episodes of symptomatic sustained VT on follow-up despite confirmed suppression of greater than 80% of VPCs by encainide in all but one patient (no. 15). In this patient, sustained VT was a recurrence; it had also occurred before VPC suppression of 80% or more; however, in the other four patients, the sustained VT was a new clinical arrhythmia despite a 1–12-year history of VPCs. Patient 1 was dropped from further encainide treatment and has had no further episodes of sustained VT on a combination of tocainide and propranolol. In patients 12 and 18, sustained VT, recorded on treadmill exercise testing performed within 3 hours of oral encainide administration, did not occur at 6 hours. Arrhythmia could not be provoked by exercise after the encainide dosage was decreased by 25%. In patient 9, who demonstrated new sustained VT on encainide, poor drug compliance was suggested by decreases in QRS duration and the blood level of encainide compared with the values during the inpatient treatment phase. When encainide was given in the hospital at the previously effective dose, he did not have sustained VT. This patient was discharged and had no recurrence in 10 months of follow-up.

Patients 1, 9, 12, 15 and 18, who developed sustained VT during encainide therapy, failed to show important differences in ECG intervals (including QT intervals) or refractory period measurements compared with the rest of the group.

Treadmill Exercise Testing (table 3)

Fifteen of the 21 patients studied underwent sequential symptom-limited treadmill exercise tests, once on placebo and once on the dose of encainide that suppressed 80% of VPCs. Six patients did not undergo these studies, four because of severe cardiac limitations, one patient because of a physical handicap and one who died before adequate arrhythmia suppression. In each case, exercise was terminated because of fatigue, arrhythmia or chest pain. These limitations to continued exercise were not statistically different for encainide compared to placebo; however, both epi-
sodes of new sustained VT observed on the treadmill occurred immediately after exercise during encainide treatment.

Hemodynamics at rest and peak exercise and the average exercise duration were not significantly different on encainide compared with placebo (table 3). At rest, the mean maximum ST-segment depression for the group in any lead of the standard ECG on encainide tended to be greater than that on placebo, but this difference was not significant. At peak exercise, however, the maximum ST-segment depression in any lead of the standard ECG was significantly increased on encainide compared with placebo ($p < 0.02$; table 3).

Radionuclide Cineangiography (fig. 4, table 4)

Sixteen of the 21 patients studied underwent sequential radionuclide cineangiographic studies, once on placebo and once on the dose of encainide that suppressed 80% of VPCs. Three patients did not undergo these studies, two who had very frequent VPCs that interfered with gated data acquisition and one who died before reaching an effective dose of encainide. Completed studies in two patients were technically inadequate. The average interval between the two nuclear studies was 2.3 weeks (range 0.5–9 weeks). No patient had a cardiac event between studies. Radionuclide cineangiograms were performed at rest in each of the 16 patients and during exercise in 12 of these 16. Four patients could not exercise, three who had severe cardiac limitations and one patient who was physically handicapped.

The average ejection fraction, heart rate, systolic blood pressure and rate-pressure product at rest or with exercise in the 16 patients on maintenance encainide treatment were not significantly different from the average values on placebo treatment (table 4). No patient had a change in ejection fraction at rest or with exercise exceeding 5 percent (fig. 3). Five percent represents the upper limits of variability established by sequential testing in 14 other patients who did not undergo drug intervention.

A separate analysis of ejection fractions determined at rest and at peak exercise stress on encainide were performed with patients stratified according to the preexisting level of resting left ventricular function during placebo treatment. Six patients with preexisting left ventricular functional impairment (defined as an average ejection fraction of 45% or less) were compared with 10 patients in whom left ventricular function at rest was not significantly impaired (ejection fraction greater than 45%). Encainide was not associated with a change in ejection fraction, peak heart rate, systolic blood pressure or rate-pressure product in either group (table 4, fig. 3).

Electrocardiograms (table 5)

All patients were in sinus rhythm. One patient who was treated with propranolol showed a prolonged PR interval (>0.20 second) and only one patient had a prolonged QRS of greater than 0.12 second on placebo treatment. All other patients had normal PR intervals and QRS durations. During encainide treatment, 14 patients (67%) developed first-degree AV block; the maximum PR interval observed in two patients was 0.28 second. One patient who inadvertently received 100 mg every 6 hours of encainide for 48 hours instead of 50 mg every 6 hours demonstrated a transient type 2 second-degree AV block, right bundle branch block and asymptomatic sinus pauses (<3 seconds). No patient had greater than first-degree AV block on the dosage found effective in suppressing 80% of VPCs.

Compared with placebo, oral encainide produced a significant prolongation in P-wave duration, PR interval, QRS duration, QT interval and corrected QT interval. Intraatrial conduction time, reflected by the P terminal force in lead V₁, increased 54%, though inter-

![Figure 3. The individual patient responses for left ventricular ejection fraction determined by radionuclide cineangiography at rest and at maximal exercise during placebo and encainide treatments.](image-url)
Table 5. Electrocardiographic Effects on Chronic Oral Encainide Compared with Placebo on the Standard and Intracardiac ECG

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Encainide</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard ECG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR interval (second)</td>
<td>0.77 ± 0.15</td>
<td>0.72 ± 0.14</td>
<td>-6</td>
</tr>
<tr>
<td>P-wave duration (second)</td>
<td>0.11 ± 0.02</td>
<td>0.13 ± 0.02*</td>
<td>18</td>
</tr>
<tr>
<td>PTF-V1 (mm/sec)</td>
<td>0.028 ± 0.034</td>
<td>0.034 ± 0.041</td>
<td>54</td>
</tr>
<tr>
<td>PR interval (second)</td>
<td>0.17 ± 0.03</td>
<td>0.22 ± 0.04</td>
<td>29</td>
</tr>
<tr>
<td>Holter (second)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS duration</td>
<td>0.09 ± 0.02</td>
<td>0.13 ± 0.03</td>
<td>44</td>
</tr>
<tr>
<td>QT interval</td>
<td>0.39 ± 0.04</td>
<td>0.41 ± 0.05*</td>
<td>5</td>
</tr>
<tr>
<td>QTc interval</td>
<td>0.45 ± 0.11</td>
<td>0.48 ± 0.13*</td>
<td>6</td>
</tr>
<tr>
<td>Intracardiac ECG (msec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA interval</td>
<td>47 ± 13</td>
<td>66 ± 17*</td>
<td>40</td>
</tr>
<tr>
<td>AH interval</td>
<td>83 ± 23</td>
<td>109 ± 25*</td>
<td>31</td>
</tr>
<tr>
<td>HV interval</td>
<td>52 ± 12</td>
<td>78 ± 14*</td>
<td>50</td>
</tr>
</tbody>
</table>

Values are mean ± sd. PTF-V1 refers to the P wave terminal force in lead V1; RR interval is the cycle length.

*p = 0.001.

Individual variability limited statistical significance. Sinus cycle lengths during placebo and encainide treatments were comparable.

Sequential Intracardiac Electrophysiologic Testing (tables 6 and 7)

Normal sinoatrial recovery times (corrected) and normal sinoatrial conduction times in 12 patients remained normal on encainide; however, abnormal control sinoatrial recovery times in two patients became even more prolonged after treatment with encainide. Each of these patients and another patient, who had sinus dysfunction for the first time after encainide, developed dose-related sinus pauses on encainide that were infrequent and of minor degree (all shorter than 3 seconds).

Intracardiac conduction intervals were uniformly prolonged after oral encainide treatment in all 15 of 21 patients studied (fig. 4). The HV interval increased by the largest percentage change; however, the observed prolongation in the PR interval produced by encainide resulted from similar absolute delays in the subintervals of proximal and distal conduction (table 5).

Encainide produced a significant increase in the Wenckebach cycle length, atrial, AV nodal and ventricular refractory periods (table 6). During encainide treatment, no infranodal block was induced during electrophysiologic testing with atrial extrastimulus or incremental atrial pacing despite the occurrence of markedly prolonged HV intervals during encainide treatment.

Atrial extrastimulus testing induced sustained intra-atrial tachycardia, with cycle lengths of 280–330 msec and rapid ventricular responses of 181–214 beats/min in two of 15 patients studied during encainide treatment. Patient 1 progressed from intraatrial tachycardia with a rapid ventricular response to VT during electrophysiologic study with encainide.

Blood Levels

Plasma levels of free encainide declined rapidly from a peak level usually observed 1/2 to 1 1/2 hours after ingestion to trough levels achieved before the next scheduled dose (every 6 hours); interindividual variations were marked (up to 20-fold variations of plasma levels). During acute i.v. administration, the mean plasma level of free encainide was 386 ± 198 ng/ml, a value more than twice the free encainide plasma level at the nadir of chronic oral therapy (163 ± 101 ng/ml). This is in sharp contrast to the electrophysiologic alterations produced by drug therapy (table 7), which are greater at the nadir of chronic oral encainide treatment compared with the acute i.v. administration.

Adverse Effects

Eleven of 21 patients demonstrated minor dose-related symptoms on encainide (blurred vision in seven patients and dizziness in four). One patient complained of blurred vision on placebo. Dose-related sinus pauses on encainide observed in three of the above 11 patients were infrequent and of minor degree (all less than 3 seconds). Each of these symptoms was related temporally to drug administration (onset oc-

Table 6. Intracardiac Measurements for Patients Studied at Baseline (Placebo) and 1 Hour Before Dosing on Chronic Oral Encainide

<table>
<thead>
<tr>
<th>RR Baseline</th>
<th>Atrial ERP (msec) Baseline</th>
<th>Wenckebach cycle length Baseline</th>
<th>AV nodal ERP (msec) Baseline</th>
<th>AV nodal FRP (msec) Baseline</th>
<th>HV (msec) Baseline</th>
<th>Ventricular ERP (msec) Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>709 ± 155</td>
<td>238 ± 41</td>
<td>360 ± 75</td>
<td>301 ± 66</td>
<td>425 ± 73</td>
<td>52 ± 12</td>
<td>252 ± 21</td>
</tr>
<tr>
<td>776 ± 145</td>
<td>285 ± 34</td>
<td>427 ± 53</td>
<td>367 ± 124</td>
<td>462 ± 74</td>
<td>78 ± 14</td>
<td>276 ± 30</td>
</tr>
</tbody>
</table>

Mean % change: 9.4% 19.7% 18.6% 21.9% 8.7% 50% 9.5%

p = 0.05 < 0.001 < 0.001 < 0.05 < 0.05 < 0.001 < 0.05

Mean values for paired data.

Abbreviations: AV = atrioventricular; ERP = effective refractory period; FRP = functional refractory period; HV = His-Purkinje conduction time; RR = cycle length.
TABLE 7. **Mean Values for Intracardiac Measurements**

<table>
<thead>
<tr>
<th>RR interval (msec)</th>
<th>Initial i.v. % change from baseline</th>
<th>Final i.v. % change from baseline</th>
<th>Chronic oral Q6H nadir</th>
<th>Chronic % change from final i.v.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Initial dose§</td>
<td>Final dose¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>± SD</td>
<td>Mean</td>
<td>± SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Mean</td>
<td>741 ± 157</td>
<td>719 ± 132</td>
<td>−3 NS</td>
<td>694 ± 104</td>
</tr>
<tr>
<td>PA interval (msec)</td>
<td>Mean</td>
<td>± SD</td>
<td>Mean</td>
<td>49 ± 14</td>
</tr>
<tr>
<td>AH interval (msec)</td>
<td>Mean</td>
<td>± SD</td>
<td>Mean</td>
<td>81 ± 22</td>
</tr>
<tr>
<td>HV interval (msec)</td>
<td>Mean</td>
<td>± SD</td>
<td>Mean</td>
<td>50 ± 13</td>
</tr>
<tr>
<td>WCL (msec)</td>
<td>Mean</td>
<td>± SD</td>
<td>Mean</td>
<td>354 ± 75</td>
</tr>
<tr>
<td>Atrial ERP (msec)</td>
<td>Mean</td>
<td>± SD</td>
<td>Mean</td>
<td>236 ± 40</td>
</tr>
<tr>
<td>AV nodal ERP (msec)</td>
<td>Mean</td>
<td>± SD</td>
<td>Mean</td>
<td>304 ± 69</td>
</tr>
<tr>
<td>AV nodal FRP (msec)</td>
<td>Mean</td>
<td>± SD</td>
<td>Mean</td>
<td>420 ± 67</td>
</tr>
<tr>
<td>Ventricular ERP (msec)</td>
<td>Mean</td>
<td>± SD</td>
<td>Mean</td>
<td>256 ± 21</td>
</tr>
<tr>
<td>Mean dosage (mg)</td>
<td>Mean</td>
<td>± SD</td>
<td>Mean</td>
<td>0 ± 21</td>
</tr>
<tr>
<td>Mean blood level</td>
<td>Mean</td>
<td></td>
<td>Mean</td>
<td>198 ± 10</td>
</tr>
</tbody>
</table>

*p < 0.05.
†p < 0.01.
‡p < 0.001.
§Initial i.v. dose = 0.9 mg/kg body weight.
¶Final i.v. dose = dose deemed adequate to suppress repetitive responses, exacerbate arrhythmias or until 3 boluses of 0.45 mg/kg body weight were administered.

**Abbreviations:** ERP = effective refractory period; FRP = functional refractory period; WCL = Wenckebach cycle length; Q6H = every 6 hours.

During encainide administration) and in only one patient, with preexisting visual impairment, did minor side effects preclude continued treatment with encainide. During this trial, three patients had a worsening of CHF, one patient during both placebo and encainide treatments, one during placebo treatment and one during encainide treatment.

Two patients died, one of refractory CHF and one of refractory VT (associated with a probable inferior wall myocardial infarction). Both patients were in New York Heart Association functional class IV, one with angina and one with heart failure, and each had been successfully resuscitated from spontaneous ventricular fibrillation in the month before entry into the study. Three patients had new episodes of sustained VT on encainide; in one other patient, apparently new sustained VT probably resulted from poor drug compliance. In the first three patients, new sustained VT probably represented encainide toxicity.

No drug-associated laboratory abnormalities were identified by laboratory profile. No drug-related ophthalmologic abnormalities were identified by routine and slit-lamp examination after encainide treatment. Adverse effects from i.v. encainide were limited to transient bradycardia in one patient and transient hypotension in one patient.

**Discussion**

This study shows that oral encainide markedly reduced the frequency and complexity of VPCs that...
substantially exceeded the expected spontaneous variation in ventricular arrhythmia.8–10

This effect of encainide was demonstrated in patients with predominantly abnormal cardiac function secondary to coronary and cardiomyopathic diseases, 48% of whom had CHF or angina pectoris. Nonetheless, encainide, in doses effective in suppressing ventricular ectopic activity, was not associated with clinical deterioration of cardiac function, a decrease in exercise capacity, or depression of left ventricular ejection fraction at rest or during exercise.

Although encainide might be suspected of having negative inotropic effects similar to those of other membrane-depressant antiarrhythmic agents,7 the lack of a decrease in left ventricular ejection fraction even in patients with poor left ventricular function during effective encainide treatment confirms the safety of oral encainide administration in this regard. This is in agreement with previous studies that have reported the hemodynamic effects of i.v. encainide.1, 2, 11, 12 The safety of encainide with respect to cardiac performance is further supported by its insignificant effects on rest and exercise hemodynamics and exercise capacity, determined by treadmill exercise, compared with placebo; however, conclusions relative to drug safety in severe CHF are not warranted in view of the relatively small sample size with evidence of severely reduced systolic function. We are aware of two instances of worsening CHF during encainide titration (Scheinman MM: personal communication).

Oral encainide produced significant prolongations of the PR, QRS, QT and corrected QT intervals on standard ECG in this group. The prolongation of ECG intervals by encainide was studied by Roden and others.8–10 Intracardiac electrophysiologic measurements confirmed that the PA, AH and HV intervals and the atrial, AV nodal and ventricular effective refractory periods were significantly prolonged after encainide. Sami et al.11 studied acute i.v. administration, with results similar to those of our study. The present study is the first to show that the acute changes in ECG intervals and refractory period changes produced by single-dose i.v. encainide are similar to those produced by chronic oral encainide. In each instance, the HV interval and QRS duration during the nadir of chronic therapy (at dosages sufficient to suppress VPCs by > 80%) exceeded the changes observed after acute i.v. administration of encainide. In addition, blood levels of free encainide showed strikingly lower values on chronic therapy compared with acute i.v. therapy. These observations suggest that the more prolonged and greater effect of chronic oral therapy on intraventricular conduction compared with i.v. therapy is due to either a build-up of an active and unmeasured metabolite with a longer biologic half-life or to the presence of a deep compartment for encainide at its site of action.5–7 Since the metabolism of encainide may proceed rapidly after it is administered, the accumulation of metabolite in concert with the activity of free encainide probably accounted for the acute changes in this study. The presence of an O-demethyl metabolite of encainide was confirmed to act synergistically with free encainide in an in vitro preparation.7

While the intracardiac evaluation of ventricular vulnerability is not a standard clinical method, this technique appears to offer important prognostic information.23, 24, 25 The ability to induce VT that is morphologically similar to the clinical event without treatment and observe its disappearance with drug administration has been correlated with long-term success in arrhythmia control.26–28 Three responses in our patient group, during intracardiac provocative testing after initial i.v. or chronic nadir encainide treatment, were associated with long-term success in ventricular arrhythmia control: the disappearance of induced VT in three patients, disappearance of repetitive firing of greater than one beat in three patients and the persistence of a nonrepetitive response in two patients. These eight patients have done well on chronic encainide. In contrast, five of the other seven patients, who showed persistent or increased repetitive responses to ventricular extrastimulation, have had a significantly higher incidence of recurrent ventricular arrhythmia (exclusively sustained VT). The substrate for repetitive firing, coupled with the prolongation of conduction times produced by encainide, may have increased the ability to sustain reentry circuits in patients with a higher incidence of recurrent arrhythmia. The patients at risk for new, sustained VT were indistinguishable from others by virtue of similar prolongation of ECG intervals and refractory periods and similar VPC suppression. Hence, no apparent

**Figure 4.** Intracardiac recordings from patient 9 show the acute intravenous 1.35 mg/kg body weight and chronic oral encainide effects on the surface ECG lead II and the His bundle electrogram (HBE). All paper speeds are 150 mm/sec.
ECG change or level of VPC activity appears to be correlated with the emergence of new VT; however, provocative ventricular extrastimulus techniques were associated with this new event in this limited follow-up period and patient group.

Encainide therapy was associated with a relatively high incidence of minor side effects that were clearly dose-related and in only one patient precluded continued treatment with encainide. More important, encainide treatment was associated with the new appearance of sustained VT in three of the 20 patients (nos. 1, 12 and 18), which indicates drug aggravation of arrhythmia as described for other antiarrhythmic agents. These episodes were invariably symptomatic and occurred despite marked VPC suppression that was indistinguishable in magnitude and complexity from that for the overall group observed on ambulatory ECG recordings. The probable relationship of episodes of sustained VT to increased dosages of encainide allowed continued successful management in patients 12 and 18 after dosage reduction. Encainide was discontinued in patient 1 because it produced a new refractory arrhythmia.

Quantitation of exercise-related ventricular arrhythmias during treadmill exercise or after exercise on different antiarrhythmic regimens is an unstandardized tool for the evaluation of drug efficacy. It is also less sensitive than ambulatory ECG recordings for the detection of ventricular arrhythmias. However, because this readily available method for studying arrhythmias may reveal unique information with regard to electrophysiologic mechanisms, we reviewed the effect of encainide compared with placebo on exercise-related arrhythmia. The antiarrhythmic effects of encainide during treadmill exercise were identical to those demonstrated by ambulatory ECG recording for the group with one important exception. During treadmill exercise, two patients demonstrated new sustained VT immediately after placebo. These two patients did not show this arrhythmia when tested at encainide dosages reduced by approximately 25%. Thus, in these two patients, treadmill exercise provided information unavailable by ambulatory ECG recording and that was consistent with the results of electrophysiologic testing. Therefore, while VPC reduction during exercise testing is similar to that observed during ambulatory monitoring, it may occasionally permit the noninvasive detection of potentially dangerous arrhythmias associated with higher dosages of encainide. Exercise testing should be performed at the time of expected peak and trough plasma levels.

Acknowledgment

The authors gratefully acknowledge the invaluable help of Dr. Robert Saunders and the physician and nursing staffs of the progressive coronary care and intensive care units of the Veterans Administration Medical Center and George Washington University Medical Center for their cooperation and excellent patient care; the VA Medical Center Heart Station and Catheterization Laboratory staffs for electrophysiologic studies of high quality; Rodney Noss and Ann Rusk for the performance of cardiac nuclear studies; and Joan DiBianco and Wanda Johnson for their secretarial assistance.

We especially thank Raymond L. Woosley, M.D., Ph.D., Vanderbilt University, for his thoughtful manuscript review and Howard Miller, M.D., Director, Clinical Research, Pharmaceutical Medical Research, Mead Johnson Pharmaceutical Division, Evanston, Illinois, for supplying study drugs.

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_Circulation_. 1982;65:1134-1147
doi: 10.1161/01.CIR.65.6.1134

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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