Antiarrhythmic Efficacy, Clinical Electrophysiology, and Pharmacokinetics of 3-Methoxy-O-Desmethyl Encainide (MODE) in Patients With Inducible Ventricular Tachycardia or Fibrillation

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In most patients, the clinical effects of therapy with encainide are mediated by the generation of the active metabolites O-desmethyl encainide and 3-methoxy-O-desmethyl encainide (MODE). Data from in vitro and animal studies have indicated that MODE has electrophysiologic and pharmacokinetic features that make its further evaluation desirable; in earlier studies, we found that MODE suppressed chronic high-frequency nonsustained ventricular arrhythmias at plasma concentrations of 50–160 ng/ml. We now report the clinical electrophysiology, antiarrhythmic activity, and pharmacokinetics of MODE in 17 patients with inducible ventricular tachyarrhythmias (VTs) in whom programmed electrical stimulation was performed before drug administration and after one or two sequences of loading and maintenance infusions of MODE. Because the relation between plasma concentration and effect had been incompletely defined, a dose-titration approach was adopted: available pharmacokinetic data were used to construct loading and maintenance infusion regimens that were predicted to attain low plasma concentrations in initial patients while higher infusion rates were evaluated in subsequent patients. MODE prevented VT induction in three of 17 patients and VT cycle length was increased by 100 msec in a further seven of 17; most responses to MODE occurred at plasma concentrations >556 ng/ml (>1 SD above mean plasma MODE during encainide therapy). Response to MODE did not predict subsequent response to oral therapy with encainide. MODE increased intracardiac conduction times, QT intervals during atrial and ventricular pacing, and right ventricular effective refractory periods (RVERP); changes in RVERP were most prominent at rapid pacing rates, while changes in intracardiac conduction were rate-independent at cycle lengths between 400 and 600 msec. Plasma MODE concentrations measured during electrophysiologic study correlated well with those predicted by the pharmacokinetic simulations ($r=0.91$, $p<0.001$). Serial plasma sampling after programmed electrical stimulation indicated a minimum MODE elimination half-life of 8.2±5.4 hours. Side effects were confined to three instances of asymptomatic conduction system depression in subjects with latent conduction system disturbances. We conclude that MODE slows intracardiac conduction, delays repolarization, and can suppress or substantially modify inducible VT. Moreover, it was only with the adoption of the dose-titration strategy that we were able to safely demonstrate that plasma MODE concentrations higher than those routinely observed during encainide therapy were required to substantially alter cardiac electrophysiology. (Circulation 1989;80:1247–1258)

In most patients, the antiarrhythmic agent encainide is rapidly cleared to the active metabolites O-desmethyl encainide (ODE) and 3-methoxy-O-desmethyl encainide (MODE) (Figure 1), which accumulate to plasma concentrations greater than those of encainide.$^{1–5}$ Both metabolites have pharmacologic activity equal to or more than the parent drug in a variety of in vitro and in vivo settings$^{6–13}$; thus, in the majority of patients (in whom this extensive biotransformation of encainide does
FIGURE 1. Structures of encaïnide, O-desmethylencaïnide (ODE), and 3-methoxy-O-desmethylencaïnide (MODE).

occur), the active metabolites ODE and MODE are largely responsible for the effects observed during long-term encaïnide therapy. In a minority of patients (approximately 7% of caucasians and blacks), the specific hepatic cytochrome P450 responsible for encaïnide O-demethylation is functionally absent on a genetic basis. In such “poor metabolizers,” encainide clearance is markedly reduced, ODE plasma concentrations are low, MODE is not detected in plasma, and encainide itself accumulates to antiarrhythmic concentrations. Many drugs, including the antihypertensive debrisoquin, have been used as probes for the presence of this cytochrome, termed P450\textsubscript{dbl}. We have previously shown that the metabolism of ODE to MODE is dependent on the same genetic polymorphism as that controlling encaïnide O-demethylation. Thus, long-term administration of ODE to patients with the poor metabolizer phenotype might lead to undesirable accumulation of this very potent sodium channel blocker. In our initial studies of the pharmacology of the two metabolites in patients with chronic nonsustained ventricular arrhythmias, however, the disposition kinetics of MODE appeared more uniform: MODE clearance varied from 180 to 410 ml/min in seven extensive metabolizers and was 78 and 300 ml/min in two poor metabolizers. Moreover, the intravenous administration of MODE was associated with suppression of chronic ventricular ectopic depolarizations (VEDs) in four of seven extensive metabolizers at plasma concentrations of 53–160 ng/ml; this plasma concentration range was comparable to the plasma MODE concentrations observed during long-term encaïnide therapy (16–291 ng/ml). Thus, these limited data suggested that MODE was active in this plasma concentration range.

Further evaluation of MODE appears desirable because of its apparently fairly uniform disposition kinetics as well as its long apparent elimination half-life. In addition, both our studies in humans, as well as other studies in dogs, suggest that MODE exerts somewhat different electrophysiologic effects from those of encaïnide or ODE. Specifically, all three are sodium channel blockers in vitro and prolong QRS in vivo, although ODE appears most potent. On the other hand, in canine studies, MODE prolonged ventricular refractoriness, whereas ODE did not; in our studies in humans, MODE prolonged repolarization while ODE did not. In addition, while encaïnide and ODE both increased ventricular defibrillation energy requirements in dogs, MODE did not.

Therefore, the aims of our study were to define the clinical electrophysiologic effects and the range of effective doses and plasma concentrations of MODE (data were obtained in patients with recurrent ventricular tachyarrhythmias whose management was guided by programmed electrical stimulation) and to characterize the disposition kinetics of MODE in this patient population to further examine the dependence of MODE clearance on the P450\textsubscript{dbl} polymorphism.

Because the range of effective doses and plasma concentrations of this agent had not been completely defined in humans, we adopted a dose-titration strategy in our study. That is, the dosages chosen for study in the first patients were low and were increased in subsequent patients only if ventricular arrhythmia remained inducible and side effects did not develop. Although this strategy is widely applied to evaluate dose-response relations for antiarrhythmic (and other) drugs in stable populations, it has not, until now, been adopted to systematically explore concentration-response relations in these more unstable patients.

Methods

Overview

Patients referred to or followed by the Vanderbilt Arrhythmia Service for the management of known or suspected ventricular tachycardia or ventricular fibrillation were eligible for participation in this study. Patients were hospitalized in the coronary care unit or in a stepdown monitored area, and all antiarrhythmic drugs withdrawn before study. Those in whom very frequent episodes of ventricular tachycardia developed in the absence of drug did not undergo electrophysiologic evaluation and were, therefore, not eligible for this study. Other exclusion criteria included baseline QRS of more than 140 msec or PR of more than 250 msec, myocardial
infarction within 1 month, or amiodarone therapy within 3 months. The study was approved by the Vanderbilt University Committee for the Protection of Human Subjects (Health Sciences), and informed consent for MODE administration was obtained from each patient before the study. MODE was supplied by Bristol Myers Pharmaceutical Research and Development Division (Wallingford, Connecticut).

Before drug administration, standard methods described below were used to measure intracardiac conduction times, determine refractory periods, and assess inducibility of ventricular tachyarrhythmias. If ventricular tachycardia or ventricular fibrillation was reproducibly induced in the absence of drug, MODE was administered (Figure 2) by a 15-minute loading infusion followed by a maintenance infusion during which intracardiac intervals, refractory periods, and inducibility of tachyarrhythmias were redetermined. If ventricular tachycardia or ventricular fibrillation remained inducible, a second loading-maintenance sequence was administered, and intracardiac intervals, refractory periods, and inducibility of ventricular tachyarrhythmias were again determined. If the first load-maintenance sequence suppressed inducibility of ventricular tachyarrhythmias, the second sequence was not administered. A maximum of two loading-maintenance sequences were administered in each patient. Loading-maintenance doses predicted to result in low plasma MODE concentrations were used in the initial two patients (target 1, 75 ng/ml; target 2, 150 ng/ml). Doses were increased after every second patient tested until a regimen resulting in side effects or arrhythmia suppression was identified (Table 1). For the purposes of this study, an increase in QRS interval to more than 200 msec or a 33% increase in QT (during atrial pacing at a cycle length of 600 msec) were also predefined end points for dose ranging.

After completion of programmed electrical stimulation during the last loading-maintenance sequence, MODE infusion was discontinued. Frequent plasma samples were obtained during MODE administration and for 24 hours after discontinuation of MODE for subsequent pharmacokinetic analysis. Patients were then reevaluated during oral encainide therapy. Those in whom ventricular tachycardia recurred during oral encainide did not undergo subsequent electrophysiologic testing. In the remainder of the patients, a repeat electrophysiology study was performed to assess inducibility of ventricular tachycardia after 3 or more days on a stable dose of oral encainide.

The clinical features of the 17 patients participating in this study are shown in Table 2. Twelve were men, and five were women (age range, 32–67 years; mean age 51.3±11.1 years). All but one patient (12) had the extensive metabolizer phenotype for P450_{hab}. The most common underlying heart disease was coronary artery disease with previous myocardial infarction in 11. Eight patients presented with a cardiac arrest, six with sustained monomorphic ventricular tachycardia, and three with syncope. Sustained monomorphic ventricular tachycardia was induced in the electrophysiology laboratory in 13 pre-MODE, while the baseline rhythm was ventricular fibrillation in two, sustained polymorphic ven-

<table>
<thead>
<tr>
<th>Table 1. Target Plasma Concentrations and Infusion Rates</th>
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<td>Regimen</td>
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<td></td>
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tricular tachycardia in one, and long episodes of nonsustained polymorphic ventricular tachycardia in one. Also shown in Table 2 are current antiarrhythmic regimens for each patient. Six have undergone placement of automatic implantable cardioverters-defibrillators (AICD-B or Ventak-AICD, CPI, St. Paul, Minnesota); five of these patients also take antiarrhythmic drugs. Drug therapies include amiodarone in four patients, propafenone in three, encainide in two, quinidine and sotalol in one each, and combinations of antiarrhythmics in five.

**Electrophysiology Methods**

Patients were brought to the clinical electrophysiology laboratory in the postabsorptive state, and electrode catheters were placed in the high right atrium and the right ventricular apex and across the tricuspid valve in the usual manner. One percent carbocaine was used for local anesthesia. In addition to five surface electrocardiographic leads (I, II, III, aV_{L_2}, and V_{J}), intracardiac electrograms filtered at 30–250 Hz were recorded from the high right atrium, right ventricle, and His-bundle region. A femoral artery was cannulated to monitor blood pressure. Sedation was limited to small intravenous doses of diazepam. Before any pacing intervention, baseline intervals, including PR, QRS, QT, RR, AH, and HV, were determined from data recorded on paper at a speed of 100 mm/sec. Data from five consecutive cycles were measured with a digitizing tablet linked to a microcomputer and the mean calculated. QRS, QT, AH, and HV were also measured during high right atrial pacing at a cycle length (CL) of 600 msec. QTc during sinus rhythm was calculated as QT/√RR.

The high right atrium was then driven for 30 seconds at CLs of 600, 500, 430, and 400 msec, with 30–60 seconds between pacing sequences. The times between the last driven atrial depolarization and the first spontaneous depolarization recorded in the high right atrial electrogram ("primary pause") and between the first and second spontaneous atrial depolarizations ("secondary pause") were determined for each CL. The longest pause, primary or secondary, was designated the sinus node recovery time (SNRT); the corrected sinus node recovery time (CSNRT) was then the SNRT minus baseline RR. The high right atrial site was then driven at a CL of 400 msec (or longer if CL of 400 msec was not associated with 1:1 atrioventricular [AV] conduction), and the CL decreased by 10 msec every 5 seconds until intermittent AV block occurred, defining the Wenckebach CL. Except in one instance described below, block developed in and not below the AV node.

Single atrial extrastimuli (S2) were then inserted every eight to 10 beats during sinus rhythm, starting at a coupling interval of 580 msec and decrementing by 10–20 msec every S₂. The longest extrastimulus that failed to result in atrial depolarization was the atrial effective refractory period (AERP), and the

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**Table 2. Patient Characteristics**

<table>
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<th>Patient</th>
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<th>Gender</th>
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CAD, coronary artery disease; CA, cardiac arrest; VTₜₐ, sustained monomorphic ventricular tachycardia; AICD, automatic implantable cardioverter-defibrillator; CM, nonischemic cardiomyopathy; VF, ventricular fibrillation; RHD, rheumatic heart disease; VTₚ, nonsustained (<15 seconds) ventricular tachycardia.

*Ratio of urinary debrisoquin to 4-OH debrisoquin after a test dose of oral debrisoquin. A metabolic ratio >12.6 indicates the presence of the poor metabolizer phenotype (patient 12).²

²Debrisoquin testing not performed. Plasma samples during long-term encainide indicate the extensive metabolizer phenotype (see Table 4).
longest atrial extrastimulus that failed to result in AV nodal transmission was the AV effective refractory period (AVERP). The atrial extrastimulus scan was then repeated using eight-beat trains of atrial pacing at a CL of 600 msec separated by 2-second pauses.

Similarly, single extrastimuli were used to determine the effective refractory period of the right ventricular site (RVERP) during sinus rhythm and during ventricular pacing (S1) at CLs of 600, 500, 430, and 400 msec. QRS and QT at the end of eight-beat trains of ventricular pacing at these CLs were measured from recordings made at a paper speed of 100 mm/sec. If single extrastimuli did not result in sustained ventricular tachycardia or ventricular fibrillation, double extrastimuli first in sinus rhythm and then at the decreasing ventricular drive CL listed above and then triple extrastimuli were used. In one patient, ventricular tachycardia was not inducible at the right ventricular apex but was at a right ventricular outflow tract site. In none of the patients in our study was isoproterenol used to facilitate induction of ventricular tachyarrhythmias. Coupling intervals were limited to 200 or more msec, except in the single extrastimulus scan to determine refractory periods. All stimuli were delivered at twofold to fourfold late-diastolic threshold.

Before the administration of MODE, ventricular tachyarrhythmias were induced at least twice in each patient. Ventricular tachycardia was defined as sustained if it lasted more than 15 seconds or if hemodynamic symptoms required cardioversion before 15 seconds. The CL of the induced arrhythmia was calculated by averaging 10 consecutive RR intervals recorded from the right ventricular electrogram. In patients who developed ventricular fibrillation or in whom sustained ventricular tachycardia was rapid enough to be associated with a prompt loss of consciousness, cardioversion with an initial energy of 200 W-sec was used to restore normal rhythm. In patients with sustained ventricular tachycardia in whom loss of consciousness did not immediately develop, termination with ventricular pacing was initially attempted.

MODE was considered completely effective in suppressing ventricular tachycardia only if triple extrastimuli with ventricular pacing did not induce more than 5 seconds of ventricular tachycardia, regardless of the stimulation sequence resulting in ventricular tachycardia before MODE administration.

Pharmacokinetics

Our previous studies with MODE in patients with chronic nonsustained VEDs characterized MODE pharmacokinetics after 30-minute intravenous infusions of drug. These were analyzed by a standard two-compartmental model approach, and the coefficients and exponents A, α, B, and β defining the disposition characteristics of a unit bolus dose were derived. A computer program based on the superposition principle was then used to determine infusion rates that would achieve desired target concentrations after infusions of various durations. A simulated infusion regimen, its associated concentrations, and the timing of electrophysiology study and blood sampling are shown in Figure 2. The target concentrations for the end of each loading and maintenance infusion and the infusion rates used are shown in Table 1. For the purposes of this calculation, the maintenance infusions were assumed to last 60 minutes, although their length was variable and depended on the length of the electrophysiology data acquisition procedure, which began 15 minutes after the start of each maintenance infusion. Simulations such as those shown in Figure 2 predicted that pseudo–steady-state conditions (i.e., stable plasma concentrations) would be present during the electrophysiology data acquisition periods: concentrations during the last 45 minutes of the first maintenance level were predicted to be 97.3–103.2% of the target at the end of the infusion, whereas the corresponding calculated range for the second maintenance level was 99.3–107%.

Blood samples (10 ml) were obtained from the arterial sheath before MODE administration, at the end of each loading period, 15 minutes after the start of each maintenance period, and at the end of each maintenance period (Figure 2). In addition, plasma samples were obtained by venipuncture (or from an indwelling intravenous line maintained patent with dextrose in water) at 15, 30, 60, 90, 120, 150, 180, 240, 300, 360, 540, 840, and 1,440 minutes after the end of MODE administration. Oral antiarrhythmic therapy was begun after the last blood sample was collected.

Plasma MODE was measured by Dr. Robert Kates at Analytical Solutions (Sunnyvale, California) with a modification of the high-performance liquid chromatography method of Mayol et al. The coefficient of variation of the assay was 1.6–3.2%, and the detection limit was 20 ng/ml for a 5-ml sample of plasma. The same method was used to measure plasma encainide, ODE, and MODE from samples obtained during long-term encainide therapy.

Phenotyping for P450dbl

Metabolizer phenotype was determined with either encainide (n=5) or debrisoquin (n=12) as a probe drug. In patients who underwent debrisoquin phenotyping, 10 mg debrisoquin was administered while the patient was receiving no other antiarrhythmic agents (generally the night before planned electrophysiology study), and urine was collected for the subsequent 8 hours. The metabolic ratio, the percent recovery of debrisoquin to that of 4-hydroxy debrisoquin in the 8-hour urine collection, was determined: a metabolic ratio of more than 12.6 defines those in whom the poor metabolizer trait is present. In patients in whom debrisoquin phenotyping was not performed, phenotype was determined by examination of the plasma concentration of MODE and of the ratio of ODE to encainide.
during long-term encainide therapy after MODE was administered.14,15

Data Analysis

The apparent MODE elimination half-life was determined by a best fit to the terminal portion of the log concentration-time plot. The total area under the plasma concentration-time curve was calculated with the trapezoidal rule after the curve was extrapolated to infinity by the terminal-phase half-life determined above. Clearance was then calculated as total administered dose divided by this area under the curve. In patients receiving lower doses of MODE, postinfusion plasma MODE concentrations rapidly fell to the limits of assay detection; therefore, elimination half-life and clearance data are reported only for those patients in whom the final MODE plasma concentration during the maintenance infusion was more than 500 ng/ml.

To assess the significance of changes in cardiac electrophysiology seen during MODE administration, differences among predrug, maintenance level 1, and maintenance level 2 data were analyzed by two-way analysis of variance. Duncan's post hoc test was used if the hypothesis of equal means could be rejected at the 0.05 level. For this analysis, only data obtained in patients under all three study conditions were included. The relations between plasma MODE concentrations and pharmacologic effects were determined by first calculating the mean plasma concentration during the first maintenance phase for each patient and then using linear regression to analyze concentration versus effect (percent change from baseline) relations. For this analysis, only effects observed during the first maintenance period were analyzed because not all patients received both loading-maintenance sequences. All values are given as mean±1 SD.

Results

Six infusion regimens were assessed in these 17 patients. The first (lowest dose) regimen was evaluated in the first two patients. The next highest dose regimen appeared to block induction of ventricular tachycardia in patient 4, so this regimen was evaluated in three patients (3-5). Because no substantial pharmacologic effect was observed in patients 3 or 5, higher doses were tested in subsequent patients. The third, fourth, and fifth regimens were tested in two patients each, and the sixth regimen was evaluated in the remaining six patients. The pharmacokinetically based derivation of infusion regimens accurately predicted (r=0.91, p<0.001) plasma concentrations actually attained during the electrophysiology study (Figure 3).

Programmed Electrical Stimulation

Ventricular tachycardia was no longer inducible during MODE infusion in three patients (4, 13, and 15). In the remaining 14 patients, MODE generally slowed ventricular tachycardia, and cardioversion was required much less frequently. Before MODE, 14 of the 17 patients required cardioversion for termination of pre-MODE arrhythmia, while in two, ventricular pacing was successful, and in one, multiple episodes of polymorphic ventricular tachycardia terminated spontaneously. In contrast, among the 14 patients whose arrhythmias remained inducible after the first loading-maintenance sequence of MODE, cardioversion was required only in four, ventricular pacing was effective in six, and arrhythmias were self-terminating after 7-9 seconds in an additional four. Of the 13 patients who were evaluated after a second loading-maintenance sequence, cardioversion was required in two, ventricular pacing was effective in eight, and induced rhythms self-terminated after 8-10 seconds in the remaining three. Overall, the CL of induced ventricular arrhythmias prolonged by 100 or more msec in seven patients. The morphology of ventricular tachycardia induced before MODE was the same as that induced during drug in seven patients (first loading-maintenance level in three, the second level in three, and both levels in one). In these seven patients, ventricular tachycardia CL increased 75±24 msec (range, 60-125 msec; p<0.001).

Maintenance plasma MODE concentrations varied over a wide range (29-1,055 ng/ml). As shown in Figure 4, most suppression or modification of induced ventricular tachycardia occurred at plasma concentrations of more than 600 ng/ml. Among 10 evaluations at ventricular tachycardia induction with maintenance plasma MODE of less than 200 ng/ml, ventricular tachycardia was not induced in one of 10, and the CL of induced ventricular tachycardia was increased by more than 100 msec in an additional three of 10. On the other hand, among 11 evaluations with maintenance plasma MODE of more than 600 ng/ml, ventricular tachycardia was not induced in two of 11, and the CL of induced ventricular tachycardia was increased by more than 100 msec in an additional six of 11. The effects of
MODE in patients who received the three highest infusion regimens (plasma MODE, 323–1,055 ng/ml) were analyzed as a function of dose administered (Table 3), whereas concentration–response data for all patients are discussed below. MODE significantly prolonged PR, QRS, AH, and HV during sinus rhythm. Spontaneous sinus CL decreased and no change was seen in QT, but calculated QTc prolonged significantly. QRS, QT, AH, and HV also increased during atrial pacing at a CL of 600 msec. Significant changes were found in RVERP during ventricular drive at the faster CL (500, 430, and 400 msec) but not at a CL of 600 or during sinus rhythm. MODE did not alter AERP, CSNRT, or WCL. Changes were greater during the second maintenance period than during the first (Table 3); these differences were statistically significant for QRS during sinus rhythm, QT during atrial pacing, and RVERP at a CL of 400 msec.

As shown in Table 3 and in the bottom panel of Figure 5, the changes in RVERP produced by MODE were frequency dependent. MODE also slowed intraventricular conduction (prolonged QRS); however, as shown in the top panel of Figure 5, this change was not dependent on frequency using a CL in the 400–600-msec range. As shown in the middle panel of Figure 5, the fraction of the cardiac cycle occupied by repolarization (paced QT/RR) was greater at rapid rates than at slower rates and was increased by MODE at all CLs. As discussed further below, these data suggest that both MODE-related changes in sodium channel function and in repolarization contributed to changes in RVERP. Significant correlations were found between maintenance plasma MODE and percent change in PR ($r=0.79$, $p<0.001$), QRS ($r=0.74$, $p<0.01$), QTc ($r=0.54$, $p<0.05$), AH during atrial pacing ($r=0.59$, $p<0.05$), and RVERP during pacing at CL of 500 ($r=0.54$, $p<0.05$) and of 400 msec ($r=0.60$, $p<0.05$). For other effect parameters, correlation coefficients were positive but not statistically significant.

Sixteen of the 17 patients subsequently received encainide (Table 4). Responses to MODE and encainide (e.g., changes in inducibility, change in ventricular tachycardia CL) did not appear concordant. Ventricular tachycardia occurred very frequently in four patients taking encainide, including one patient in whom MODE suppressed arrhythmia (13). In three, encainide suppressed inducible tachyarrhythmias; in only one of these
patients (15) did MODE also suppress inducible ventricular tachycardia. Mean plasma MODE during encainide therapy was 327±229 ng/ml (excluding patient 12 who had the poor metabolizer phenotype for debrisoquin metabolism).

**Pharmacokinetics**

Plasma MODE concentrations over the 24 hours after infusion in the six patients who received the highest loading and maintenance sequences are shown in Figure 6. Once the concentrations dropped to less than 50–100 ng/ml, they appeared stable over the short period of observation. The apparent terminal-phase elimination half-life measured over this 24-hour period in patients 9–17 (in whom end infusion MODE concentrations were more than 500 ng/ml) was 8.2±5.4 hours (range, 3.4–18.9 hours), and clearance was 269±79 ml/min (range, 131–362 ml/min). Of these nine patients, one (12) was a poor metabolizer of debrisoquin. MODE clearance in this subject was 159 ml/min, which was toward the lower end of the range observed in the remaining eight patients but was not the lowest value. No correlation was found between either ejection fraction and clear-

**Adverse and Other Effects**

No patient complained of symptoms during MODE infusion. Two patients (6 and 17) developed right bundle branch block during MODE (plasma concentrations, 268 and 583 ng/ml); both also developed transient right bundle branch block during subsequent long-term antiarrhythmic therapy—quinidine plus mexiletine in one patient and sotalol plus mexiletine in the other. Patient 15 had a modestly increased CSNRT (910 msec) as well as split His potentials and infra-Hisian block during the baseline atrial extrastimulus scan. He had previously displayed pauses of as long as 6 seconds during procainamide treatment of atrial fibrillation. During MODE (766 ng/ml), CSNRT prolonged to 3,003 msec. He has subsequently been treated with encainide and a permanent pacemaker.

Patient 9 had manifest preexcitation as well as sustained ventricular tachycardia. Before MODE, the antegrade refractory period of the bypass tract was 340 msec. Within 5 minutes of starting MODE (estimated plasma concentration, ~300 ng/ml), the Δ wave disappeared; no reciprocating tachycardia was elicited before or during MODE.

Patient 11 had a severe ischemic congestive cardiomyopathy and underwent right heart catheterization before MODE and immediately after MODE infusion was discontinued (no cardioversion had been necessary at baseline or during MODE). Plasma MODE was 1,055 ng/ml. Cardiac output rose from 3.6 to 4.1 l/min, blood pressure did not change, and calculated systemic vascular resistances were 2,312 before and 2,009 dyne·sec/cm² after MODE. No changes were observed in right atrial, right ventricular, pulmonary artery, or pulmonary capillary wedge pressure; the latter rose from a mean of 9 to a mean of 11.

**Discussion**

Our previous study examining the clinical pharmacology of MODE in patients with chronic VEDs suggested an antiarrhythmic effect could be elicited at plasma concentrations of 50–160 ng/ml that is comparable to that seen in most patients receiving long-term encainide therapy. The data contained in this report indicate that this concentration range is, in fact, the lower end of the range of effective MODE concentrations for prevention of ventricular tachycardia induction by programmed electrical stimulation. In this group of patients, plasma MODE during long-term encainide therapy was 327±229 ng/ml (i.e., plasma MODE of 556 ng/ml was 1 SD above the mean). Plasma concentrations of MODE considerably higher than those observed during encainide therapy were achieved and were required to modify cardiac electrophysiology (Figure 4). Therefore, in extensive metabolizer patients receiving long-term encainide, both ODE and MODE (as well as any residual encainide) may contribute to
TABLE 4. Responses to MODE and Encainide

| Patient | MODE level 1 | | MODE level 2 | | Encainide therapy |
|---------|--------------|--------------|--------------|--------------|
| | Δ VTCL | MODE* | Δ VTCL | MODE* | Dose | Δ VTCL | E | ODE | MODE |
| 1 | 114 | 76 | -13 | 120 | — | — | — | — | — |
| 2 | -8 | 29 | 4 | 61 | 35 | No VTs | 24 | 222 | 219 |
| 3 | 43 | 140 | 21 | 151 | 50 | No VTs | 29 | 584 | 152 |
| 4 | No VT | 78 | — | — | 35 | 60 | 0 | 180 | 211 |
| 5 | 105 | 77 | 90 | 167 | 35 | 105 | 0 | 101 | 903 |
| 6 | 77 | 169 | 93 | 268† | 50 | 111 | 35 | 181 | 417 |
| 7 | 80 | 145 | 180 | 238 | 35 | 70 | 9 | 400 | 527 |
| 8 | 10 | 323 | 10 | 408 | 25‡ | — | — | — | — |
| 9 | 45 | 686 | 50 | 977 | 35 | 120 | 25 | 179 | 125 |
| 10 | 65 | 549 | 55 | 563 | 50 | 125 | 32 | 227 | 164 |
| 11 | 125 | 550 | 215 | 864 | — | — | — | — | — |
| 12 | 100 | 885 | 110 | 1,055 | 75 | 100 | 528 | 10 | 0 |
| 13 | No VT | 645 | — | — | — | — | — | — | — |
| 14 | 90 | 822 | 110 | 1,052 | 35 | 110 | 11 | 299 | 203 |
| 15 | No VT | 766‡ | — | — | 50 | No VTs | 8 | 210 | 280 |
| 16 | 150 | 807 | 150 | 803 | 70 | Spontaneous VTs# | 26 | 450 | 523 |
| 17 | 0 | 583‡ | — | — | 35 | Spontaneous VTs# | 11 | 88 | 200 |

Δ VTCL, increase in ventricular tachycardia cycle length (vs. drug-free; msec); dose, dose during chronic encainide (mg/8 hr); E, plasma encainide (ng/ml); ODE, plasma O-desmethyl encainide (ng/ml); MODE, plasma 3-methoxy-O-desmethyl encainide (ng/ml); VT, sustained ventricular tachycardia.

*Mean of maintenance period plasma concentrations prior to and following programmed stimulation.
†Right bundle branch block (see text).
‡Marked increase in corrected sinus node recovery time (see text).
§Recurrent VT during treadmill exercise.
#VT, recurred spontaneously >10 times over 24 hr.

the clinical effects observed. Because the two metabolites produce different pharmacologic effects and in particular because combinations of antiarhythmic entities may produce additive or antagonistic electrophysiologic actions, no inference can yet be drawn on which is most important during long-term therapy with the parent drug. Our study design precludes any rigorous comparison between intravenous MODE and subacute oral encainide. Nevertheless, the concentration-effect data shown in Table 4 suggest that response to MODE was not concordant with response to encainide.

**Clinical Electrophysiology of MODE**

MODE both slowed conduction and prolonged atrial and ventricular refractoriness in a concentration-related manner. These changes were qualitatively similar to those seen during long-term oral treatment with encainide and other agents with class "Ic" properties. Jackman et al. found that long-term oral encainide increased mean QRS by 27.7% and RVERP by 13%, while Oetgen et al. reported increases by flecainide of 50% and 15%, respectively. In the patients receiving the three highest MODE regimens, these changes were 26±7% and 13±8%. Interestingly, Sami et al. found that acute intravenous encainide prolonged QRS 18±9% without altering RVERP; the discrepancy between acute intravenous and long-term oral therapy has been attributed to accumulation of ODE and MODE.
Longer infusion of encainide did prolong monophasic action potential duration, AERP, and RVERP.\textsuperscript{32} MODE did prolong QRS, reflecting its sodium channel–blocking properties; however, unlike other agents such as lidocaine or procainamide,\textsuperscript{33–35} this effect was not frequency dependent in the 400–600 msec range of CL (Figure 5). This finding is consistent with the slow time constant for recovery from sodium channel block reported for drugs such as encainide\textsuperscript{36} or flecainide.\textsuperscript{37} Such sodium channel block may itself cause a delay in recovery of excitability (i.e., prolong RVERP).\textsuperscript{38} In addition, MODE prolonged repolarization times including QT\textsubscript{s}, QT during atrial pacing, and QT during ventricular pacing; these changes would also be expected to prolong RVERP.\textsuperscript{38} For example, sotalol, an agent devoid of sodium channel–blocking properties at clinically useful doses, prolongs indexes of repolarization and RVERP.\textsuperscript{39–41} Thus, we believe that prolongation of RVERP by MODE is attributable to effects on both sodium channels and repolarization. Moreover, the frequency dependence of the RVERP changes likely reflects the drug's effects on repolarization because the QRS changes were not frequency dependent at these rates.

MODE prolonged JT interval (i.e., QT–QRS) during sinus and atrial paced rhythms. However, we believe this parameter must be interpreted with caution. It is recognized that drugs such as encainide or flecainide that markedly prolong QRS often also increase QT interval. The JT interval has been proposed to “correct” for any contribution to QT increase by this QRS prolongation. However, QT interval prolongation (in the absence of T wave vector changes) may equally represent increased action potential duration in the first ventricular cells to depolarize (and the last to repolarize).\textsuperscript{42} In support of this argument is the finding by Ikeda et al\textsuperscript{43} that flecainide increased action potential duration in ventricular muscle (but not in Purkinje tissue).

Recently, encainide and flecainide have been found to increase mortality significantly compared with placebo in patients with nonsustained ventricular arrhythmias after myocardial infarction.\textsuperscript{44} MODE, like encainide, is a potent depressor of cardiac conduction; however, its effects on repolarization and refractoriness, both in previous work\textsuperscript{12,13} as well as in this study, appear more prominent than those of the parent drug. In addition, MODE, unlike encainide or ODE,\textsuperscript{45} did not increase energy requirements for defibrillation,\textsuperscript{20} an action that recent studies have linked to prolongation of repolarization.\textsuperscript{46} Because difficulty defibrillating patients is one facet of the potential electrophysiologic toxicity of encainide,\textsuperscript{47} this latter finding raises the possibility that such toxicity might not be as manifest during long-term MODE as during encainide therapy. In the present study, responses to encainide and MODE appeared discordant, although the numbers were small. Overall, encainide and MODE do exert somewhat different electrophysiologic effects; it is not known whether these differences would prevent an adverse effect of MODE in the postmyocardial infarction patient with nonsustained ventricular arrhythmias.

**Pharmacokinetics of MODE**

The pharmacokinetic data generated in the course of this study confirm that MODE disposition is not strongly correlated with the debrisoquin polymorphism. For drugs whose disposition does depend on this particular hepatic cytochrome, the difference between patients of the extensive and poor metabolizer phenotype is striking: the very high plasma concentration of encainide (528 ng/ml) and the absence of measurable plasma MODE in the poor metabolizer patient (12) in this study provide a good example. On the other hand, in both this study and our previous study, MODE clearances in poor metabolizer patients fell within or slightly below the range of clearances calculated in those with the extensive metabolizer phenotype. Recent studies at our center have fully elucidated the metabolic fate of radiolabeled encainide. In these studies, ODE, MODE, and their conjugates account for more than 90% of the fate of encainide, with the remainder being the parent drug and minor metabolites such as 3-hydroxy encainide, N-desmethyl encainide, or N-desmethyl MODE.\textsuperscript{48} Thus, MODE itself does not appear to undergo extensive oxidative metabolism, further strengthening the argument that its disposition is not linked to the debrisoquin oxidative phenotype. Our data also confirm that the drug has a long elimination half-life; because plasma sampling was only carried out for 24 hours after discontinuation of the drug (and the plasma concentration-time curves shown in Figure 6 display at least two exponential components), the true elimination half-life will necessarily be underestimated.\textsuperscript{21} Thus, it is apparent that the elimination half-life of MODE is a minimum of 8 hours. MODE elimination during long-term encainide therapy appears even slower\textsuperscript{2,13}: possible explanations are the artifact imposed by a limited postinfusion sampling period or competition with encainide or ODE for renal excretion sites (as we have recently described for procainamide and its major metabolite, N-acetylprocainamide\textsuperscript{49}).

**Concentration-Response Information**

One of the most important findings of this study is the demonstration that a dose-ranging approach can be safely and effectively adopted in the evaluation of new pharmacologic entities in patients with recurrent sustained ventricular tachyarrhythmias. The alternate approach, conducting studies of clinical electrophysiology or efficacy after a fixed-bolus dose, clearly neither offers similar flexibility nor, more important, allows a full exploration of the concentration-response curve in this group of patients. Such data are routinely obtained in patients with temporally stable ventricular arrhythmias, but it is widely recognized that extrapolation from this
population, in whom treatment may not even be indicated, to other populations such as the one we studied may be unwarranted.

Global indexes of cardiac electrophysiology, such as overall QRS duration or QT interval, generally tracked plasma concentration reasonably well, whereas indicators of drug effect on the microelectrophysiological environment responsible for induction of sustained ventricular tachyarrhythmias (e.g., change in ventricular tachycardia CL) did not. The failure of such a correlation likely reflects both the potential that drug in plasma was not in equilibrium with drug in heart as well as marked variability in the sensitivity of an individual microreentrant loop to drug. Weight was not a predictor of plasma MODE or effect, presumably reflecting the fact that other pharmacokinetic and electrophysiological factors were much more important in determining response. This observation cannot, of course, be extrapolated outside the limited range of weights in this study; nevertheless, dosing schemes for adult patients should not be normalized for weight unless data are available demonstrating this is an important factor for a particular drug. One major determinant of response to MODE appeared to be type of heart disease: MODE prevented ventricular tachyarrhythmia reinduction in three of six patients with nons ischemic heart disease and in none of 11 with ischemic heart disease (p=0.05, Fisher’s exact test). Further studies will be required to examine whether this observation is serendipitous and what its mechanistic implications might be. Very limited data generated in the course of this study also suggest no major adverse hemodynamic effect as well as a potential role in bypass tract-mediated arrhythmias.

MODE is an interesting new drug entity. In animal studies, as well as in this and other studies in humans, it has more prominent effects on indexes of repolarization (e.g., QT, RVERP) than the parent drug, as well as blocking sodium current and slowing conduction. Similarly, its effect on ventricular defibrillation energy requirement, an electrophysiological parameter of increasing importance, is dissimilar to that of encainide or ODE. It is not known whether such differences would result in a clinical spectrum of action different from the parent drug. It was only with the adoption of a dose-ranging approach such as the one used here that the full range of effective doses and concentrations of this promising new agent were identified. Future evaluations of new antiarrhythmic entities in this patient population should use this or a similar strategy.

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