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Research Article

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Encainide and Its Metabolites

Comparative Effects in Man on Ventricular Arrhythmia and Electrocardiographic Intervals

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Abstract. To assess the relative contributions of encainide and its putatively active metabolites, *O*-demethyl encainide (ODE) and 3 methoxy-*O*-demethyl encainide (3MODE), to the drug's pharmacologic effects, we compared intravenous infusions and sustained oral therapy in two phenotypically distinct groups of patients, extensive and poor metabolizers of encainide. Unlike poor metabolizers, extensive metabolizers had appreciable quantities of both metabolites detectable in plasma and had fourfold shorter elimination half-lives for encainide. By quantitating electrocardiogram intervals, arrhythmia frequency, and plasma concentrations, we found that, in poor metabolizers, arrhythmia suppression and ventricular complex (QRS) prolongation were correlated positively with encainide concentrations ($r \geq 0.570$, $P < 0.014$). In these two subjects, antiarrhythmic concentrations of encainide (>265 ng/ml) were at least fivefold higher than those sustained in the six extensive metabolizers during steady state oral therapy. In extensive metabolizers, encainide concentrations were uncorrelated with effects. Arrhythmia suppression and QRS prolongation in extensive metabolizers correlated best with ODE ($r \geq 0.816$, $P < 0.001$); QTc change correlated positively with both 3MODE and ODE. Arrhythmia suppression paralleled QRS prolongation; the relationship between them appeared similar in both phenotypic groups. In most patients, extensive metabolizers, encainide effects during oral therapy are mediated by metabolites, probably ODE.

Introduction

Encainide is a benzanilide derivative chemically identified as 4-methoxy-2'-(2-1-methyl-2-piperidyl ethyl) benzanilide, which has been investigated extensively in recent years as a new antiarrhythmic agent. Studies in man have shown it is highly effective in suppressing both high frequency ventricular ectopic depolarizations (VED)[1] (1) and more life-threatening arrhythmias, such as ventricular tachycardia (VT) (2, 3). In most series, 80–90% of such patients have responded satisfactorily to encainide therapy without limiting side effects (1–6). In association with its antiarrhythmic action, encainide administration also is marked by the production of characteristic changes in the electrocardiogram (ECG), including prolongation of the QRS and PR durations and, to a lesser extent, of the QT interval.

In an earlier series (1) of eleven patients treated in a placebo-controlled double-blind crossover protocol at our own institution, the single patient whose arrhythmia failed to respond had 20–100-fold higher steady state plasma concentrations of encainide than the mean for the other 10 responding patients. This patient also showed minimal ECG changes, a threefold longer elimination half-life for encainide and no detectable plasma metabolite concentrations. These observations, coupled with disparities noted in electrophysiologic effects dependent on the mode and timing of drug administration (6, 7), have

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1. *Abbreviations used in this paper:* ANOVA, analysis of variance; ECG, electrocardiogram; K_{el}, elimination constant; 3MODE, 3-methoxy-*O*-demethyl encainide; NDE, *N*-demethyl encainide; ODE, *O*-demethyl encainide; VED, ventricular ectopic depolarizations; VT, ventricular tachycardia.

strongly suggested the role of one or more active metabolites in the expression of encainide effects.

The main features of encainide metabolism have been outlined from animal studies and preliminary work in man (8, 9), as shown schematically in Fig. 1 *A* and *B*. Encainide taken orally is virtually completely absorbed from the gastrointestinal tract in all patients, but then undergoes a polymorphic pattern of "first-pass" metabolism in the liver. In about 90% of patients (10), there is extensive hepatic demethylation of the parent molecule (Fig. 1 *A*, site "A") to form *O*-demethyl encainide (ODE). These patients usually also have an accompanying metabolite detectable in their plasma, 3-methoxy-*O*-demethyl encainide (3MODE), which appears to be formed by addition of a methoxy group to ODE (Fig. 1 *A*, site "B"), perhaps via a catechol intermediate. Members of this phenotypic group of "extensive metabolizers" have systemic bioavailability of 25–45%; their elimination half-lives for encainide range from 1 to 4 h (8, 9).

About 10% of patients have a qualitatively different pattern of drug disposition, with little first-pass metabolism, much greater bioavailability, and much longer elimination half-lives (8–36 h). ODE is either undetected or found in greatly reduced quantities, and we have not seen detectable quantities of 3MODE in their plasma. These "poor" metabolizers sometimes accumulate measurable quantities of another metabolite, *N*-demethyl encainide (NDE), formed by removal of a methyl group (Fig. 1 *A*, site "C").

In animal studies, all three metabolites are active. ODE has electrophysiologic and antiarrhythmic activity of greater potency than encainide (11, 12, 13), and 3MODE has similar actions with about the same potency as the parent drug (11, 12). The milligram potency for antiarrhythmic activity by the NDE metabolite, however, is somewhat less than that of encainide (Gomoll, A. W., unpublished observation).

The purpose of the present study, then, was to gather data in man which might differentiate the relative contributions made by encainide itself and by each of its metabolites to the drug's overall antiarrhythmic and electrocardiographic effects. We proposed to do this by producing a spectrum of conditions over which the relative proportions of encainide and metabolites present in plasma would vary, and associated changes in arrhythmia frequency and ECG effects could be quantitated. Specifically, we sought to compare drug responses in poor and in extensive metabolizers during both acute and sustained oral therapy.

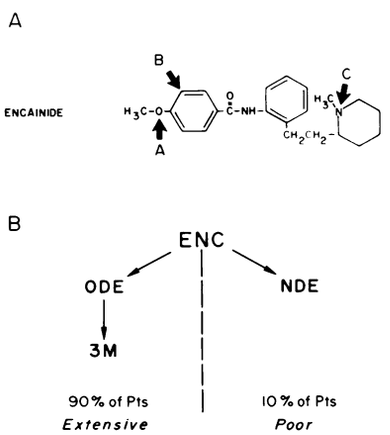

Figure 1. (*A*) Structure of the encainide molecule with hypothesized sites of oxidative metabolism. (*B*) Postulated pathways of encainide metabolism in extensive and poor metabolizers. ENC, encainide; Pts, patients.

Methods

Patients

Eight patients were chosen for study; all had stable, high frequency VED resistant to conventional antiarrhythmic agents. Informed consent was obtained from all patients in accordance with procedures of the Vanderbilt Committee for the Protection of Human Subjects. The patients' clinical and pharmacokinetic characteristics are listed in Table I. Six subjects were male, including both poor metabolizers; two were female. Age range was from 51 to 73 yr. All but two patients also had spontaneously occurring brief unsustained runs of VT. Changes in VT frequency and in intermediate grades of VED complexity paralleled changes in VED frequency (Table I), but in this paper only VED frequencies were used for correlation purposes.

Patients 1–6 proved to be extensive metabolizers (encainide $t_{1/2}$ = 1.67±0.27 h, $\bar{x}$±SEM). The seventh was found to be a poor metabolizer and the eighth was selected for this protocol after he was found, in a separate single-dose study of encainide metabolic patterns, to be a poor metabolizer.

Observation periods

All studies were performed in the Vanderbilt University Clinical Research Center at least 48 h or 4 half-lives, whichever was longer, after the cessation of other antiarrhythmic therapy. On the days of study, a 21-gauge stainless steel needle was inserted into a cutaneous arm vein and kept patent for sample collection with a dilute solution of heparin.

All patients were studied under two conditions: acute and sustained oral therapy. Acute dosing in patients 1–7 consisted of an intravenous infusion of 0.8 mg/kg administered over 20 min. If ≥80% VED suppression or ≥20% prolongation of the QRS complex were not seen within 30 min following this infusion, then a supplementary infusion was given to one of these two end points. Acute dosing in patient 8 was a single 50 mg dose by mouth.

On the day of encainide infusions, patients remained supine for at least 1 h before continuous ECG recording of a 1-h base-line arrhythmia frequency began to insure that ambient arrhythmia did not disappear or decline markedly as a result of change in posture. Blood samples were drawn immediately before the 20 min infusion began, every 5 min during the infusion, and 0.25, 0.5, 1, 1.5, 2.5, 4, 6, 9, and 20 h afterwards. All infusions were begun between 9 a.m. and 2 p.m. The patients remained supine until either VED frequency had returned to 10% of base line or until 2 h after completion of the infusion (whichever was longer). Thereafter, they were allowed to ambulate freely.

Sustained oral therapy in all cases was for at least 4 d on a maintenance dosage sufficient to produce ≥90% suppression of VED compared with base line. After satisfactory arrhythmia suppression was documented, a blood sample was obtained immediately before a final oral dose of encainide, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 20 h after the

Table I. Patient Characteristics

Patient No.	Etiology	VED/min	$t_{1/2}$ Encainide	Encainide dose	Peak VED suppression: acute/sustained	Peak suppression of VT: acute/sustained	Peak QRS % increase: acute/sustained
			h	*mg/timing*			
1	IHD	9.6	2.11	50 at 6 h	92/100	72.4/100	25/49
2	IDIO	37.5	0.79	50 at 6 h	100/100	100/100	65/41
3	IHD	7.4	2.88	50 at 8 h	100/100	100/100	23/51
4	IHD	7.1	1.26	100 at 8 h	100/100	—/—	24/62
5	IHD	9.0	1.59	50 at 6 h	80/100	100/100	14/31
6	HBP/MVP	8.8	1.38	50 at 6 h	100/100	100/100	29/48
Mean extensive metabolizers			1.67±0.27 SEM				
7	IHD	5.1	35.9	50 at 8 h	74/91	100/100	13/22
8	IDIO	6.8	8.43	50 at 6 h	94/100	—/—	13/29
Mean all patients		11.4±3.52 SEM					

Abbreviations used in this table: IDIO, idiopathic; IHD, ischemic heart disease; HBP, hypertension; MVP, mitral valve prolapse.

last dose. Observation periods continued following the last encainide dose for at least 24 h, and longer if resumption of arrhythmia did not occur during that period.

Base-line arrhythmia frequencies were determined as follows: for comparison with the infusions, supine frequency was measured during the 60-min period of observation immediately before drug was administered. Base line for sustained oral therapy was measured during a 4-h ambulatory period of observation at the end of the oral withdrawal study (at least 24 h after the last encainide dose in every instance and greater than 72 h for the two slow metabolizers). Defined in this way, the means for both base-line values varied by <10% from 12-h ambulatory arrhythmia counts performed on the same patients when they were free of antiarrhythmic therapy. Data analysis using the 12-h counts as base line for both the acute and sustained oral studies produced qualitatively similar results to those reported in this paper.

Plasma concentrations and pharmacokinetics

Plasma concentrations of encainide, ODE, 3MODE, and NDE were assayed by using a high-pressure liquid chromatography technique modified to utilize an internal standard (13, 14). For both oral and intravenous therapy, the negative slope (elimination constant, $[K_{el}]$) of the least-squares fit of the terminal portion of the log-concentration vs. time plot was derived. Elimination half-life was calculated as $0.693/K_{el}$.

Electrocardiographic monitoring and interval measurement

Cardiac rhythm was monitored continuously with a Hewlett-Packard telemetry system (Model 78100A, Hewlett-Packard Co., Palo Alto, CA). Before infusion periods were begun, ECG were recorded from the telemetry signal with a Honeywell Model 96 FM recorder (Honeywell, Inc., Test Instruments Div., Denver, CO). ECG at time periods corresponding to blood samples were printed at 100 mm/s on a Hewlett-Packard four-channel physiologic recorder (Model 7754A, Hewlett-Packard Co.). PR, QRS, RR, and QT intervals were measured visually for each recording so obtained; QTc was calculated by the method of Bazett (15) from the formula $QTc = QT/\sqrt{RR}$. Interval measurements were made by one investigator who was blinded to concomitant plasma level values.

Arrhythmia frequency

The taped ECG were analyzed by a computer operator who was unaware of the timing of encainide therapy and used a PDP 11/60 laboratory mini computer (Digital Equipment Corp., Maynard, MA) and a previously described and verified arrhythmia analysis program (16). For closely timed observation periods during the infusions, computer reports were verified by hand count. The time period chosen for reporting arrhythmia count was a 30-min interval which evenly bracketed the time of blood sampling; when sampling intervals were close enough that this definition would result in overlap, observation periods were reduced to the minimum time necessary to avoid overlap.

Data analysis

Regression. Simple linear regression lines were obtained by the least-squares fit technique. Strength of association in multiple linear regression (17, 18) was assessed by inspecting the normalized regression coefficient, the additive contribution to the R-value of the regression equation, and the partial correlation coefficients derived according to standard methodology (19) by using a stepwise program (CLINFO) (20).

Hysteresis. Time-ordered, concentration-effect (hysteresis) plots (21–23) of data collected during infusions were tested for significance by comparison of the area under the curves of their ascending and descending limbs by using *t* test for unpaired data. A difference between the two areas would indicate a different relationship between concentration and effect that was a function of time: possible explanations for counterclockwise hysteresis would include formation of active metabolites, delayed onset and/or termination of effect of drug at its active site, or the importance of drug concentration in a compartment other than plasma (23, 24). To allow for the possibility that the hysteresis noted for encainide-effect relationships was due to delayed tissue penetration, data sometimes were selected from only the descending limb of the hysteresis plot and then combined with the oral data for further regression analysis. These data were termed "postdistribution" data.

Statistics. A probability of <0.05 was sufficient to reject the null

hypothesis; when appropriate, the Bonferroni inequality (25) was utilized to adjust the P value for multiple comparisons. Differences of variables from base line were tested for overall significance by analysis of variance (ANOVA). If ANOVA rejected the null hypothesis of no difference, values from each time point were tested against the base-line values by using a modified t test for paired data with the ANOVA mean square error used as the standard error (25). Because of nonnormal distribution, the statistical test used for VED suppression was Wilcoxon signed ranks. For regressions, linear transformation of the VED data to the logistic function was done by using the formula: logit = ln (y/100 − y). Values for normalized suppression of VED >99.5% and <0.5% were assigned values of 99.5 and 0.5 in order to permit inclusion of such extreme values in the logistic function.

Results

Plasma concentrations and pharmacokinetics

All six extensive metabolizers of encainide had, in addition to encainide itself, both ODE and 3MODE detectable in their plasma on oral therapy. Following intravenous infusions, all had measurable encainide and ODE, but only four of the six had detectable 3MODE. The mean log-concentration vs. time plots for this group of patients after infusion and during withdrawal from sustained oral therapy are shown in Fig. 2 *A* and *B*. Encainide log-concentration vs. time plots for oral therapy in subjects 7 and 8, the two poor metabolizers, are shown for comparison in Fig. 3.

Encainide elimination half-lives for the eight subjects are summarized in Table I. There were no marked differences in the encainide elimination half-lives for any subjects between acute and chronic therapy. Because of his extremely long calculated $T_{1/2}$, subject 7 probably was not at steady state when studied on sustained oral therapy.

Antiarrhythmic and electrocardiographic effects

Oral dosages that resulted in ≥90% VED suppression are listed in Table I. Poor p wave definition precluded measurement of

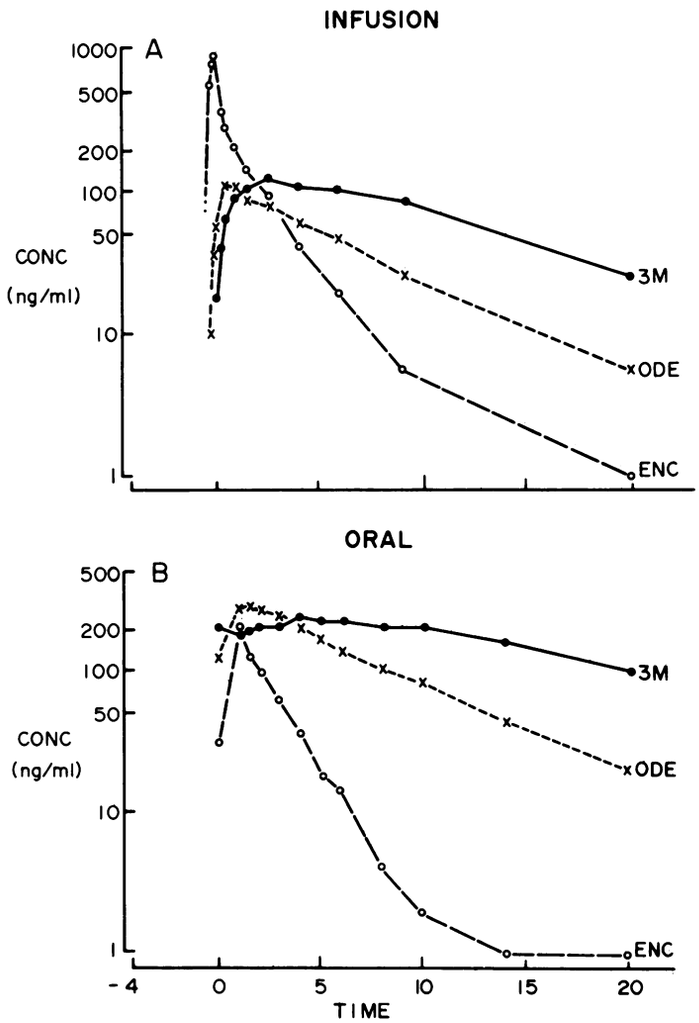

Figure 2. Time course (*h*) of mean plasma concentrations (log scale) of encainide and its ODE and 3MODE metabolites (*A*) after acute intravenous infusion and (*B*) during withdrawal from sustained oral therapy in subjects 1–6. 3M, 3MODE; CONC, concentration; ENC, encainide.

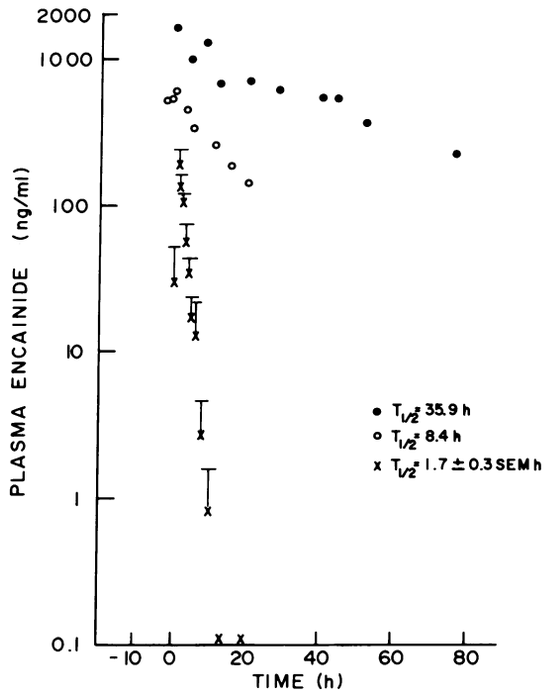

Figure 3. Time course of plasma encainide decline during withdrawal from oral therapy for subjects 1–6 (×), for subject 7 (•), and for subject 8 (○).

PR in subjects 6, 7, and 8; subject 5 developed atrial fibrillation during oral encainide therapy and thus neither PR nor QTc could be measured.

Maximum levels of effects on VT frequency, VED frequency, and QRS duration are listed for each subject in Table I. The mean maximum effects on PR and QTc durations for the available subjects were 34.4 and 17.7%, respectively.

Concentration-response curve when metabolites were undetectable

Subject 7 after intravenous therapy and subject 8 after an acute oral dose had no metabolites detectable in their plasma. During sustained oral therapy, subject 7 accumulated small quantities of ODE and NDE, and subject 8 accumulated very small quantities of ODE. We selected for study only those postdistribution time points at which either no metabolites were detectable or (for subject 7) at which the level of ODE was below the limits of sensitivity of the assay (<15 ng/ml). Concentration-response curves showed significant ($P < 0.001$, $r = 0.891$, 0.774) linear relationships between QRS width and plasma encainide (Fig. 4 *A* and *B*), and less close but still significant ($P < 0.014$, $r = 0.760$, 0.570) relationships between antiarrhythmic effect (expressed as logit VED) and plasma encainide (data not shown). The plasma concentrations of encainide in these two patients associated with >90% arrhythmia suppression (>265 ng/ml) when metabolites were undetectable were at least fivefold higher than the concentrations of encainide associated with comparable effects in the other patients when metabolites were present (range for encainide in subjects 1–6 was 0–47 ng/ml).

Relative contributions of parent and metabolite compounds to antiarrhythmic and electrocardiographic effects

For the extensive metabolizers, antiarrhythmic effects seen after intravenous and oral therapy were combined and plotted against plasma concentrations of encainide, ODE, and 3MODE. Linear regressions of mean data derived from each time point were calculated and *r* values obtained. Similar correlations were established for QRS prolongation. Also, mean data derived only from postdistribution time points were regressed in this fashion (Table II). Data for each subject also were subjected to regression analysis with similar results (data available upon request).

Overall, the strongest correlation between any one substance and either VED suppression or QRS effect was demonstrated for ODE. However, positive correlations with VED and QRS effects also were noted for encainide and for 3MODE. To characterize further the effects of each pharmacologic substance,

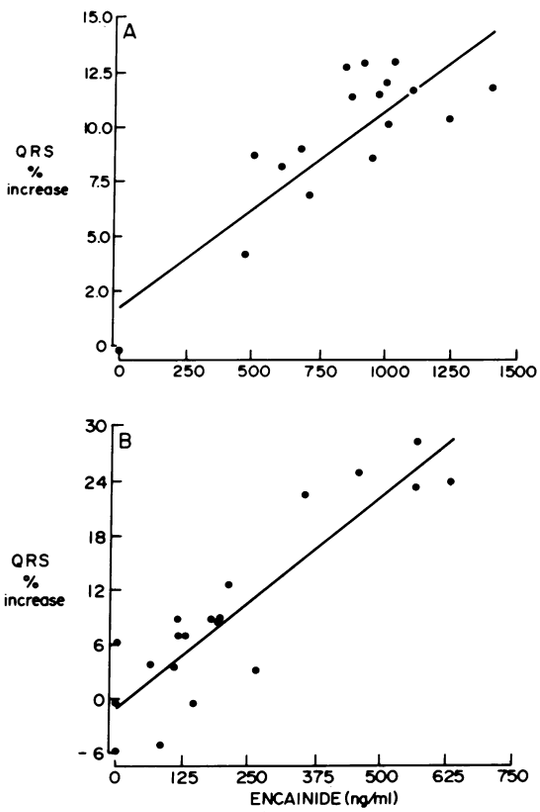

Figure 4. Linear regressions of percentage increase in QRS width on plasma encainide concentration: (*A*) subject 7, $P < 0.001$, $y = 1.91 + 0.009x$, $r = 0.774$, and (*B*) subject 8, $P < 0.001$. $y = -4.06 + 0.047x$, $r = 0.891$.

Table II. Correlation Coefficients for Multiple Linear Regression: Extensive Metabolizers, Mean Data

	Encainide	ODE	3MODE
Simple correlation, all data			
VED suppression	0.186	0.816*	0.621‡
QRS prolongation	0.137	0.929*	0.573‡
QTc prolongation	0.468§	0.814*	0.888*
Simple correlation, postdistribution data			
VED suppression	0.332	0.778*	0.637‡
QRS prolongation	0.565§	0.945*	0.557§
QTc prolongation	0.158	0.776*	0.869*
Partial correlation, all data			
VED suppression	NS	0.678*	0.075
QRS prolongation	NS	0.910*	−0.391
QTc prolongation	0.400	0.660§	0.818*
Partial correlation, postdistribution data			
VED suppression	NS	0.628§	0.298
QRS prolongation	0.356	0.722‡	0.193
QTc prolongation	NS	0.722‡	0.841*

Mean data refers to mean values at timed plasma collection intervals. NS, simple linear regression correlation was not statistically significant; the variable therefore was not included in the multiple regression equation.
* $P < 0.001$.
‡ $P < 0.01$.
§ $P < 0.05$.

additional quantitative approaches to data analysis were undertaken.

Hysteresis analysis. Fig. 5 *A–C* illustrates the percent reduction in VED plotted against the concentration of encainide, ODE, and 3MODE obtained during the infusion studies. For encainide, there was significant counterclockwise hysteresis (that is, less antiarrhythmic effect associated with a given plasma concentration early in the infusion than later on). For 3MODE, the reverse was true: there was clockwise hysteresis (that is, a greater effect associated with a given plasma concentration early in the infusion than later on). For the ODE metabolite, no significant hysteresis was detected. Similar relationships between QRS width and the encainide, ODE, and 3MODE plasma concentrations were observed.

Multiple linear regression. When either all data or only postdistribution data derived from infusion and oral therapy were subjected to multiple linear regression, the strong association of VED suppression and QRS effects with ODE concentrations persisted, while partial correlation coefficients for 3MODE and encainide fell below statistically significant levels (Table II). Similar relationships were seen for PR effect.

QTc effects

Regression analysis of QTc data for extensive metabolizers showed significant positive correlations for both 3MODE and ODE which persisted when partial correlation coefficients were calculated (Table II). Hysteresis analysis showed a marked counterclockwise loop for encainide; there was a trend for counterclockwise hysteresis for ODE and also for clockwise hysteresis for 3MODE.

Relationship between antiarrhythmic and electrocardiographic effects

Changes over time in VED frequency and QRS width occurred virtually simultaneously among the extensive metabolizers; there was no apparent hysteresis. A close linear relationship was found between VED suppression, expressed as the logit function, and QRS prolongation ($r = 0.907$, $P < 0.001$ for mean data). The slopes of the linear regression lines for logit VED suppression vs. QRS in the poor metabolizers did not differ significantly from that calculated for the extensive metabolizers, although there was a trend for the poor metabolizers to have proportionately more VED suppression for a given level of QRS effect (Fig. 6).

Discussion

Other antiarrhythmic agents have been shown to have actions mediated by active metabolites, including lidocaine (26), procainamide (27), and quinidine (22). In the case of encainide, this was a possibility first suspected in early studies based on a disparity between the pharmacokinetic characteristics of the parent drug and the pharmacodynamic responses observed in the study group of patients (1). The present study amplifies those disparities and provides strong support for the hypothesis that, among extensive metabolizers, a metabolite of encainide, probably ODE, is primarily responsible for the drug effects observed. In addition, evidence is presented for the first time that the parent drug, encainide, has antiarrhythmic and electrocardiographic activity of its own in man at high plasma concentrations (>265 ng/ml). Also, the data suggest that arrhythmia suppression parallels QRS prolongation and that the relationship between these two clinically observable effects is at least qualitatively similar in patients belonging to both the extensive and poor metabolizer groups.

That ODE is the principal mediator of encainide effects in extensive metabolizers is suggested by (*a*) the absence of significant time-ordered hysteresis loops of drug effects for this metabolite in the infusion studies, and by (*b*) the consistency of its correlation with drug effects in the multiple regression analyses. These consistent relationships between drug effects and ODE plasma concentrations in the extensive metabolizers were not found for either encainide or 3MODE plasma concentrations. Furthermore, the opposite directions of time-ordered

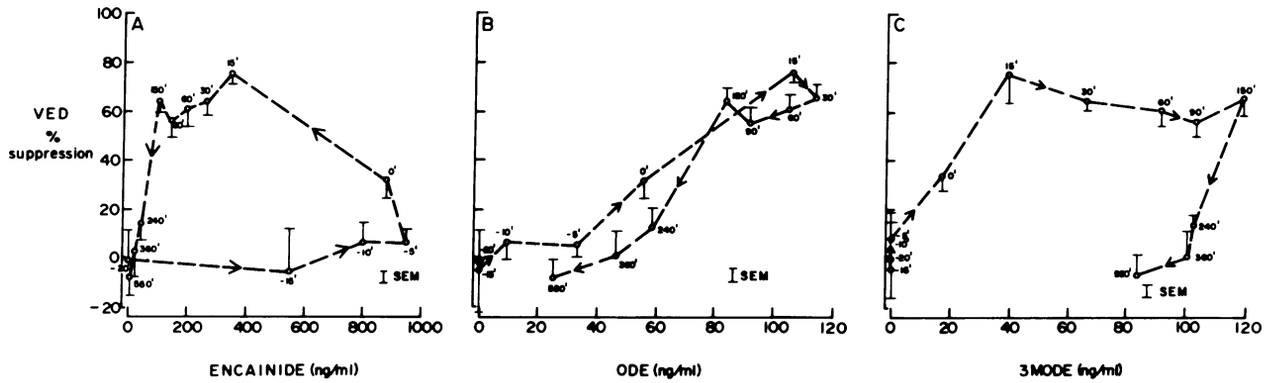

Figure 5. Hysteresis plots of percent suppression of VED against plasma concentrations of (*A*) encainide, $P < 0.05$, (*B*) ODE, $P > 0.3$, and (*C*) 3MODE, $P < 0.1$, for the infusion studies in extensive metabolizer subjects 1–6. The points are connected in the time order in which they were obtained. The area enclosed by the loop is an indication of temporal disparity in drug (or metabolite) effect. *P* values are for unpaired *t* tests of the areas under the ascending and descending curves from peak concentration to zero. Horizontal SEM omitted.

hysteresis loops for encainide and 3MODE point to a temporally intermediate factor as responsible for these drug effects (the factor being either ODE or another unmeasured variable which closely parallels the time course of plasma ODE). Additional evidence for the mediation of effects by metabolite(s) is provided by the fivefold disparity in encainide plasma concentrations associated with comparable levels of effect in the two phenotypic groups.

Some previous human studies (1, 7) have reported data demonstrating positive linear correlations between plasma encainide and ECG effects both among patients at peak effect and for individual patients at steady state on different encainide dosages, suggesting that effects were being mediated by the parent drug. Indeed, such correlations for individual extensive metabolizers were seen in this study if only intravenous or only oral data were utilized (data not shown). A correlation, of course, does not establish a relationship of cause and effect; it may be due to a coexisting correlation of both variables with a third, unspecified variable (19). The design and data analysis approach of this study were intended to avoid such potential pitfalls. The inclusion of two poor metabolizers for study, and the infusion protocol and withdrawal periods from sustained oral therapy in the extensive metabolizers provided maximum contrasts between high and low ratios of encainide-to-metabolites. In these ways, we minimized the positive correlations between parent drug and metabolites, thus providing an opportunity to assess the individual contribution of the parent compound and each of the two metabolites.

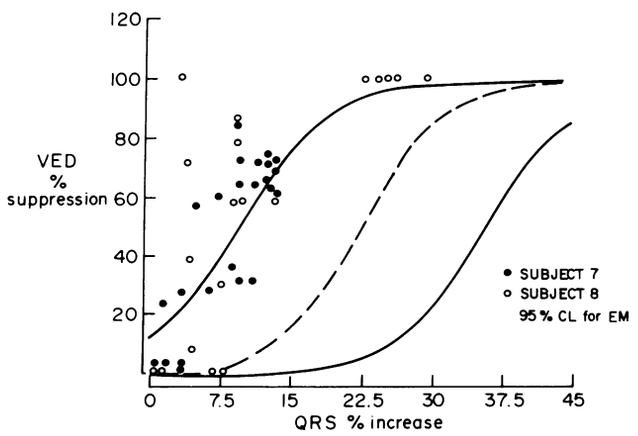

Figure 6. Comparison of the relationship between antiarrhythmic effect and QRS change in extensive and poor metabolizers. Dashed line is the transformed regression equation for logit VED suppression on QRS prolongation based on mean data in extensive metabolizers (*EM*); solid lines are 95% confidence limits (*CL*) for prediction. Filled and hollow circles are data from poor metabolizer subjects 7 and 8. Although data points lie to the left, they are not significantly different from the relationship in rapid metabolizers (see text). logit $y = -4.98 + 0.2236x$; $r = 0.907$.

Some restraint, however, should be observed in interpretation of these data. Results of multiple linear regression suggested that plasma ODE had the strongest and most consistent relationship to VED suppression and QRS prolongation. However, positive correlations existed between these effects and both encainide and 3MODE as well. A major limitation to the usefulness of multiple regression techniques is precisely that situation in which multiple independent variables are positively correlated with one another (28). Encainide and ODE levels were particularly correlated with each other during the "postdistribution" fall off phase; accordingly, these findings from multiple regression should be viewed as requiring additional confirmation.

The hysteresis data demonstrated that only the ODE metabolite had an essentially constant relationship between plasma level and drug effect throughout the entire infusion period of observation. But the finding of counterclockwise hysteresis for effect with encainide plasma concentration could have an al-

ternative explanation, a necessary time delay involved in the transport of encainide from plasma to a tissue site that is critical for effect. However, this objection is at least partially answered by the results obtained in multiple regression analysis of the "postdistribution" data, which ought to reflect events only after tissue levels have equilibrated with plasma. These data contained a strong correlation of effect for ODE, and none for encainide and 3MODE. However, in order to test this time delay hypothesis directly, it would be necessary to assay tissue encainide by employing myocardial biopsy.

In summary, our data point toward another explanation of the observed correlation in previous studies between plasma encainide and pharmacologic effect—that both these variables were related to each other through an intervening variable, namely plasma ODE.

In this, as in previous studies (1–4, 29), the antiarrhythmic effect of encainide paralleled the characteristic ECG effects, and no marked differences were found between the two patient groups. Two practical conclusions about encainide use can be drawn from these data: (*a*) Antiarrhythmic effects are a saturable function of encainide (or ODE) plasma concentration; ECG effects are linear functions which continue to increase past the plasma levels at which the antiarrhythmic effect has been maximized. (*b*) Expectation of antiarrhythmic effect can be related to the extent of QRS change, regardless of a patient's metabolic phenotype.

The QTc data should be regarded cautiously; after this study was completed, it was reported that marked temporal changes in QTc interval occurred following oral and intravenous administration of placebo (22). We did not use placebos; it is possible that some of the variation in QTc observed in this study was a temporal phenomenon. Yet, the data obtained by multiple regression and by examining hysteresis plots suggest that each metabolite contributes independently to QTc change.

Genetic variation in drug disposition has become recognized as an important variable in determining the pattern of response to an increasing number of pharmacologic agents (30–32), with implications both for therapeutic response and for the development of unwanted adverse effects. Investigations by us have linked encainide disposition to the phenotypic pattern of oxidation of the antihypertensive drug, debrisoquine (10). Debrisoquine disposition, in turn, has been linked to polymorphic oxidative patterns for other substances, such as sparteine (33), phenytoin (34), phenacetin (35), phenformin (36), nortryptyline (37), and several beta blockers (38, 39).

What implications should an understanding of the distinct oxidative phenotypes for encainide have for drug administration in man? Our data suggest that the antiarrhythmic activity of unmetabolized encainide appears only at concentrations (>265 ng/ml) well above those sustained on oral therapy in most patients (1, 9), i.e., the >90% who fall in the extensive metabolizer group. Such concentrations might be achieved transiently in extensive metabolizers either by rapid intravenous infusion or at the peak achieved immediately following oral ingestion, but then would fall off rapidly as the parent drug distributes to tissues and is oxidized to ODE. Thus, unchanged encainide would be expected to contribute substantially to the effects of orally administered drug only in poor metabolizers.

In both phenotypic groups, there is an active compound in plasma with a relatively long elimination $t_{1/2}$: ODE in the extensive metabolizers (>6 h) (9) and encainide in the poor metabolizers (>8 h). In all patients, the time course of pharmacologic effect will be considerably longer than the short 1–4-h half-life described originally for encainide in extensive metabolizers. Schedules for drug administration ought to reflect these pharmacodynamic considerations.

The evidence in this study suggesting a central role for the metabolite ODE in the mediation of encainide effects in most patients is, of course, inferential. Although there is strong evidence in animal models that ODE is electrophysiologically active (11, 12, 40, 41) and antiarrhythmic (13), direct demonstration in man would entail the administration of ODE, which is not yet available for use in humans. Such studies would be analogous to the development of *N*-acetylprocainamide, a procainamide metabolite, as a human antiarrhythmic agent in its own right (27). In broader terms, these demonstrations in clinical investigations of polymorphic patterns of metabolism and of the importance of metabolites in the mediation of drug effects have important implications for methodological approaches in future drug development. Such approaches might include the earlier identification of subjects with less typical metabolic phenotypes for pharmacokinetic and dynamic studies and also the earlier characterization of pharmacologic effects of metabolites.

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