# Antiarrhythmic activity, electrocardiographic effects and pharmacokinetics of the encainide metabolites *O*-desmethyl encainide and 3-methoxy-*O*-desmethyl encainide in man*

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ABSTRACT Although encainide is an effective antiarrhythmic agent, plasma concentrations and pharmacologic effects are not well correlated. One explanation is the generation of active metabolites: while in most patients (extensive metabolizers; EMs) concentrations of the metabolites *O*-desmethyl encainide (ODE) and 3-methoxy-*O*-desmethyl encainide (3MODE) are higher than those of encainide, a small subset (poor metabolizers; PMs) lack the ability to extensively biotransform encainide. Considerable data from studies in vitro and animal studies, as well as indirect evidence in patients, indicate that ODE and 3MODE produce the effects seen during long-term encainide therapy in EMs. We now report the initial direct evaluation of the pharmacologic actions of these metabolites of encainide in man. Nine patients with ventricular arrhythmias, seven of the EM phenotype and two of the PM phenotype, were studied. Chronic high-frequency ventricular arrhythmias were suppressed by encainide therapy in seven of nine; monitoring arrhythmia frequency during withdrawal of encainide allowed definition of plasma concentrations of encainide and metabolites associated with arrhythmia suppression. Intravenous infusions of both ODE and 3MODE suppressed chronic ventricular arrhythmias, while infusions of placebo had no effect. ODE clearance was a function of metabolizer phenotype, with higher clearance (mean 914 ml/min; range 554 to 1314) in EMs than in PMs (434, 298 ml/min); moreover, 3MODE was detected during ODE infusions in all seven EMs but in neither PM. 3MODE clearance was more uniform (mean 289 ml/min in EMs [range 180–410] vs 300 and 78 ml/min in the two PMs) and ODE was not detected in any subject during 3MODE infusion. Encainide itself was not detected after any infusion of ODE or 3MODE. During withdrawal of encainide therapy, ODE plasma concentration at the time of arrhythmia recurrence was 55 ± 40 ng/ml (mean ± SD), while ODE by infusion was effective at a concentration of 37 ± 15 ng/ml. Similarly, plasma concentration of 3MODE at the time of arrhythmia recurrence after withdrawal of chronic encainide was 116 ± 35 ng/ml and that during 3MODE infusion was 105 ± 50 ng/ml. While both compounds prolonged QRS duration, ODE was the more potent, increasing QRS by 9.2 ± 1.6% per 100 ng/ml vs 1.2 ± 0.5% per 100 ng/ml for 3MODE. On the other hand, 3MODE prolonged the corrected JT interval by 1.9 ± 0.6% per 100 ng/ml, while ODE shortened it by 2.7 ± 1.9% per 100 ng/ml. These data indicate that ODE and 3MODE are potent sodium channel-blockers that suppress arrhythmias at the low concentrations noted during long-term encainide therapy in EMs. The disposition of ODE was itself a function of metabolizer phenotype, while that of 3MODE was not strongly associated with metabolizer phenotype. These findings suggest that therapy with ODE would result in variable plasma concentrations, with particularly high values in PMs. 3MODE, however, appears to be a promising agent with different electrocardiographic characteristics than ODE and more uniform disposition, and it therefore merits further evaluation in man.

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WHILE ENCAINIDE is a highly effective antiarrhythmic agent,[1–8] considerable indirect evidence is available to suggest that active metabolites mediate most of the effects seen during long-term treatment. In our initial evaluation of the clinical pharmacology of encainide,[1] chronic stable nonsustained ventricular arrhythmias were abolished in 10 of 11 patients. This action was accompanied by marked PR and QRS prolongation, highly variable minimal effective plasma encainide concentrations, and rapid encainide clearance (mean elimination half-life 2.7 ± 0.2 hr). The eleventh, nonresponding patient had an aberrantly long elimination half-life (7.8 hr), mean plasma encainide concentrations greater than 20-fold higher than those in the other 10 patients, and minimal electrocardiographic (ECG) changes. These data alone raised the possibility that active metabolites (not generated in the eleventh patient) played a role in the effects seen. Subsequent plasma concentration analyses identified *O*-desmethyl encainide (ODE) and 3-methoxy-*O*-desmethyl encainide (3MODE) as the major metabolites in the plasma of the 10 responding patients. Only low concentrations of ODE and *N*-desmethyl encainide (NDE) were detected in the eleventh patient, while no 3MODE was present.

In 1977, Mahgoub et al[9] reported that while 93% of normal volunteers metabolized the antihypertensive agent debrisoquin to the inactive metabolite 4-OH debrisoquin ("extensive metabolizers"), the remainder ("poor metabolizers") were able to form only very little 4-OH debrisoquin and experienced marked hypotension after a usually ineffective dose of the drug.[10] This inability to metabolize debrisoquin is now known to be genetically determined[11, 12] and to be associated with aberrant metabolism of a number of other agents, including the β-blockers metoprolol and bufuralol[13, 14] and the antiarrhythmic propafenone.[15] We found that the patient with aberrant encainide metabolism was also a poor metabolizer of debrisoquin and that both her parents and her only sibling also demonstrated the poor metabolizer trait for encainide and debrisoquin disposition.[16] In subsequent studies, we have shown that the poor metabolizer trait for debrisoquin and aberrant metabolism of encainide are manifestations of the same defect.[17, 18] Specifically, subjects with the extensive metabolizer trait for debrisoquin cleared encainide rapidly (systemic clearance 1.89 ± 0.20 liters/min) to ODE and 3MODE, which were present at higher plasma concentrations than encainide during long-term treatment. In contrast, subjects with the poor metabolizer trait for debrisoquin cleared encainide much more slowly (0.177 ± 0.002 liter/min); in this group only low concentrations of ODE and NDE were occasionally detected, while 3MODE was not detected at all.[17, 18] Most recently, mass spectrometric urinary studies in normal volunteers who received isotopically labeled encainide have characterized greater than 90% of the metabolic products of the drug.[19] In these studies, ODE and 3MODE have been shown to be the major unconjugated metabolites of encainide in man, while other forms such as NDE, N, *O*-didesmethyl encainide, or *N*-desmethyl 3MODE were detected only in low concentrations.

Further indirect evidence supporting a role for ODE and 3MODE in man was obtained when we compared short-term intravenous infusions and maintained oral therapy with encainide in two groups of patients with cardiac arrhythmias for whom metabolizer phenotypes were known.[20] Only in poor metabolizers was a correlation found between plasma encainide concentrations and arrhythmia suppression and changes in ECG intervals. In extensive metabolizers, arrhythmia suppression and QRS prolongation correlated best with plasma ODE, while QT interval prolongation was correlated with the presence of both metabolites. Other investigators have similarly noted a striking failure of encainide plasma concentrations to correlate with pharmacologic effects[4–7, 21, 22]; frequently, arrhythmias have remained suppressed long after encainide itself is undetectable in plasma. Moreover, although long-term oral[23] and short-term intravenous[24] encainide both prolonged HV and QRS, only the long-term oral drug increased refractory periods in atrium and ventricle, again suggesting a role for active metabolites.

Animal studies and studies in vitro have confirmed the activity and potency of ODE and 3MODE. Elharrar and Zipes[25] showed that ODE was more potent than 3MODE and encainide in depressing maximum phase 0 upstroke slope ($\dot{V}_{max}$) in canine Purkinje fibers and ventricular muscle. Similarly, we and others have found ODE to be more potent than encainide in suppressing arrhythmias and slowing conduction in a range of animal preparations, while 3MODE potency has been intermediate.[26–32] Some differences have been reported: ODE and encainide did not alter ventricular refractoriness, while 3MODE and NDE prolonged it.[32] Moreover, 3MODE exerted no effect on ventricular defibrillation threshold,[33] while high concentrations of both ODE and encainide have rendered defibrillation more difficult,[33, 34] an action that may be linked to similar difficulty converting arrhythmias in man.

Thus, studies in vitro, animal experiments, and indirect evidence in patients all suggest that ODE and 3MODE mediate the effects of encainide therapy in

most patients. We now report our evaluation of the pharmacology of these metabolites in man. We examined the actions of intravenous ODE and 3MODE in patients with chronic nonsustained ventricular arrhythmias for whom the phenotype for debrisoquin 4-hydroxylation and previous responsiveness to encainide were known, asking the questions: (1) Are these metabolites active in man, i.e., do they suppress arrhythmias? (2) If so, at what plasma concentrations, particularly with respect to those during encainide therapy? (3) Do they alter electrocardiographic intervals? (4) What are their disposition kinetics? These data not only will be useful in monitoring treatment with encainide but also will suggest further structure-activity directions in drug development.

## Methods

**Overall protocol design.** Adults with chronic stable ventricular arrhythmias for whom debrisoquin phenotype and previous response to encainide therapy had been established were candidates for this trial. Patients with a history of sustained ventricular tachyarrhythmias during no drug treatment were not considered candidates since the protocol required observation periods off drug. In patients on long-term encainide therapy at the time of entry to the study, serial ambulatory electrocardiograms were obtained during drug withdrawal to establish the time of arrhythmia recurrence while serial plasma samples were collected for subsequent analysis of encainide, ODE, 3MODE, and NDE plasma concentrations. After arrhythmia frequency stabilized, the response to an infusion of placebo was assessed. Only patients in whom arrhythmia frequency was not modified by placebo were eligible to receive metabolites. All infusions of metabolite were administered by vein over 30 min, with dosages separated by at least 48 hr. The initial starting dosage of each metabolite was 5 mg; if this dosage produced no antiarrhythmic effect and marked ECG changes were absent (PR,QRS <50% increased), subsequent dosages were doubled. If lower dosages produced no effect in the first two patients, the starting dosage in subsequent patients was permitted to be increased. No patient was permitted to receive more than three infusions of each metabolite. The protocol was approved by the Vanderbilt Institutional Review Board and informed consent was obtained from all subjects on admission to the Research Center. ODE and 3MODE were supplied by Bristol Myers Research Laboratories (Evansville, IN).

**Infusion procedure.** For each infusion, the patient was brought to a treatment room and intravenous lines were inserted in both arms (one for blood sampling, the other for drug administration). Orthogonal vectorcardiographic leads were attached, and the patient remained supine for at least 60 min. Infusions (placebo or drug) were then begun and lasted 30 min. Patients remained supine in the treatment area for at least an additional 120 min or until arrhythmia recurred, whichever was longer. They were subsequently permitted to ambulate and periodic vectorcardiographic recordings and blood samples were obtained.

**Arrhythmia analysis.** Ambulatory electrocardiograms were recorded during withdrawal of long-term antiarrhythmic therapy as well as during each infusion and were analyzed with a Cardiotechnologies CT240 scanner. Arrhythmia frequency during the short periods before, during, and after infusions was also quantified by hand counts of continuous strip chart records run at slow paper speed. To evaluate minimal effective drug concentrations during long-term treatment, baseline arrhythmia frequency was that recorded for 24 hr starting 96 hr or more after withdrawal of long-term antiarrhythmic therapy. To assess metabolite efficacy, arrhythmia frequency during 120 min before drug infusion was compared to that during the 30 min after infusion. In either case, arrhythmias were considered suppressed if greater than 95% of ventricular ectopic depolarizations (VEDs) were abolished. Conversely, an arrhythmia was considered to have recurred if greater than 5% of the baseline number of VEDs had reappeared. This criterion was adopted to minimize a possible confounding influence of variable arrhythmia frequency. To analyze withdrawal from long-term oral therapy, arrhythmia frequency was assessed in hourly time intervals, while for intravenous infusions 5 min intervals were used.

Orthogonal three-lead electrocardiographic recordings were printed at 100 mm/sec on a three-channel physiologic recorder at the time each blood sample was obtained, and analyzed with use of a digitizing pad (Bit Pad One, Summagraphics, Fairfield, CT) and a microcomputer. QRS, QT, and RR were calculated as the mean of at least five complexes. Because encainide and its metabolites markedly prolong QRS duration, which directly influences measurement of the QT interval, the corrected JT (JTc), interval was used as an index of cardiac repolarization. JTc was calculated by dividing the difference between the QT and QRS intervals by the square root of the RR interval.

**Pharmacokinetic analysis.** Plasma samples for analysis of encainide, ODE, 3MODE, and NDE concentrations were obtained at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 14, 24, 36, 48, 60, and 72 hr after the final dose of oral encainide. At each metabolite infusion, samples were obtained at 0, 15, and 30 min; if no change in ECG intervals or arrhythmia frequency was noted, samples were obtained 2 and 6 hr after infusion. If a pharmacologic effect was observed, samples were obtained at 15, 30, and 60 min and 2, 3, 4, 6, 8, 12, 14, 24, and 36 hr after infusion. Plasma concentrations of encainide, ODE, 3MODE, and NDE were measured by a previously described high-pressure liquid chromatography assay[17, 18]; the lower limit of sensitivity was 10 ng/ml (10 ml sample) for each compound with a coefficient of variation of less than 6.5%.

Mean plasma concentrations during long-term oral encainide therapy were calculated as $AUC_o^\tau/\tau$, where $AUC_o^\tau$ is the area under the time-concentration curve calculated by the trapezoidal rule and $\tau$ the dosing interval. Elimination half-life of encainide and apparent elimination half-lives of the metabolites were calculated as 0.693/k, where k is the (negative) slope of the terminal portion of the time–natural log concentration plot. Concentration data during and after infusions were fitted to a biexponential disposition function, with weighting by 1/(predicted concentration). This fit was better than that obtained with a simpler monoexponential function (with one exception, which is presented in the tables), and triexponential fitting provided no improvement; fits were compared by a generalized F test.[35] Elimination half-lives were calculated as $0.693/\beta$, where $\beta$ was the smaller of the two exponential rate constants. Clearance was calculated as dose/$AUC_o^\infty$, where $AUC_o^\infty$ is the area under the time-concentration curve with the terminal phase extrapolated to infinity. Plasma concentrations at the time of arrhythmia suppression or recurrence were determined by interpolation of the log-linear terminal phase of elimination curves (withdrawal from chronic encainide) or by direct calculation with the use of the fitted biexponential disposition function with intravenous infusions.

**Data analysis.** All results are expressed as the mean ± SD. Regression relationships (concentration vs ECG changes) were obtained by standard least squares fit. Differences of variables (ECG changes) from baseline were tested for significance by

analysis of variance, with subsequent pairwise testing by use of Duncan's multiple-range test. A probability $p < .05$ was considered sufficient to reject the null hypothesis.

## Results

The study group consisted of six men and three women (table 1). Of the nine patients, seven were known to be extensive metabolizers of debrisoquin and encainide, while two were poor metabolizers. At the time of admission all extensive metabolizers were receiving long-term encainide: six of the seven had greater than 95% arrhythmia suppression, while the seventh was found to have only 75% suppression with long-term encainide therapy. In one of the poor metabolizers (patient 8) arrhythmia suppression had previously been demonstrated during long-term encainide therapy, but after its withdrawal, arrhythmias were only sporadic and were absent while the patient was recumbent, so assessment of the antiarrhythmic effect of the metabolite was not possible. The other poor metabolizer (patient 9) had failed to respond to high doses of encainide during our initial trial[1] and was receiving alternate therapy at the time of hospitalization.

The results obtained in one patient (patient 4) are presented in figure 1 to illustrate application of the protocol. After an initial observation period, long-term encainide therapy was withdrawn while serial plasma samples were collected and arrhythmia frequency was monitored. ODE and 3MODE were present at higher concentrations than encainide at all times during long-term encainide therapy, as would be expected in an extensive metabolizer. Ventricular ectopic depolarizations returned to within 5% of their ultimate off-drug frequency 9 hr after the last oral dose of encainide, when extrapolated plasma encainide was extremely low (<5 ng/ml). Placebo infusion did not alter arrhythmia frequency and the patient then received an infusion of 10 mg of ODE, which transiently suppressed arrhythmias and prolonged QRS duration. Note that 3MODE was detected early after infusion of ODE, but that no encainide was detected. Subsequent administration of 10 mg 3MODE resulted in higher 3MODE plasma concentrations (with no detectable ODE or encainide) but no substantial QRS widening or arrhythmia suppression.

**Antiarrhythmic responses.** In none of the eight patients with evaluable arrhythmias did placebo infusion alter arrhythmia frequency: the median number of VEDs per minute was 2.34 (range 0.67 to 11.33) before placebo, 2.04 (range 0.73 to 11.2) during the infusions, and 2.53 (range 0.75 to 15.17) in the hour that followed. ODE infusion was ineffective at a dose of 5 mg in two patients, but suppressed arrhythmias in four of eight patients who received 10 mg and two of four who received 20 mg. Forty milligrams of ODE was effective in the only patient who received this dose. This antiarrhythmic effect of ODE was noted at 26 ± 6 min into the 30 min infusion (range 15 to 30), and resolved at 80 ± 41 min after the end of the infusion (range 40 to 130).

3MODE was not effective at doses of 5 mg (two patients) or 10 mg (four patients), but suppressed arrhythmias in four of the seven patients who received 20 mg. The onset of this effect was at 18 ± 5 min into the 30 min infusion (range 15 to 25) and it resolved at 86 ± 32 min after the end of the infusion (range 60 to 125). The extensive metabolizer whose arrhythmia was not completely suppressed during long-term encainide therapy (patient 7) had total arrhythmia suppression with 20 mg of 3MODE but no change in arrhythmia frequency with the same dose of ODE, despite a 37%

**TABLE 1**
**Patient characteristics**

| Patient No. | Age (yr) | Sex | Metabolizer phenotype | Type of heart disease | Long-term ecainide dosage | VEDs/day (encainide) | VEDs/day (no drug) |
|---|---|---|---|---|---|---|---|
| 1 | 67 | M | EM | HHD | 35 mg q8hr | 350 | 5,005 |
| 2 | 65 | M | EM | HHD | 75 mg q12hr | 1 | 11,950 |
| 3 | 68 | M | EM | CAD | 75 mg q8hr | 57 | 17,322 |
| 4 | 66 | F | EM | HHD | 35 mg q8hr | 539 | 4,858 |
| 5 | 53 | F | EM | MVP | 50 mg q6hr | 738 | 9,289 |
| 6 | 56 | M | EM | CAD | 50 mg q8hr | 102 | 11,148 |
| 7 | 69 | M | EM | CAD | 50 mg q6hr | 1,109 | 5,158 |
| 8 | 57 | M | PM | NSD | 50 mg q12hr | — | — |
| 9 | 42 | F | PM | NSD | — | — | 36,726 |

EM = extensive metabolizer; PM = poor metabolizer; HHD = hypertensive heart disease; CAD = coronary artery disease; MVP = mitral valve prolapse; NSD = no structural disease.

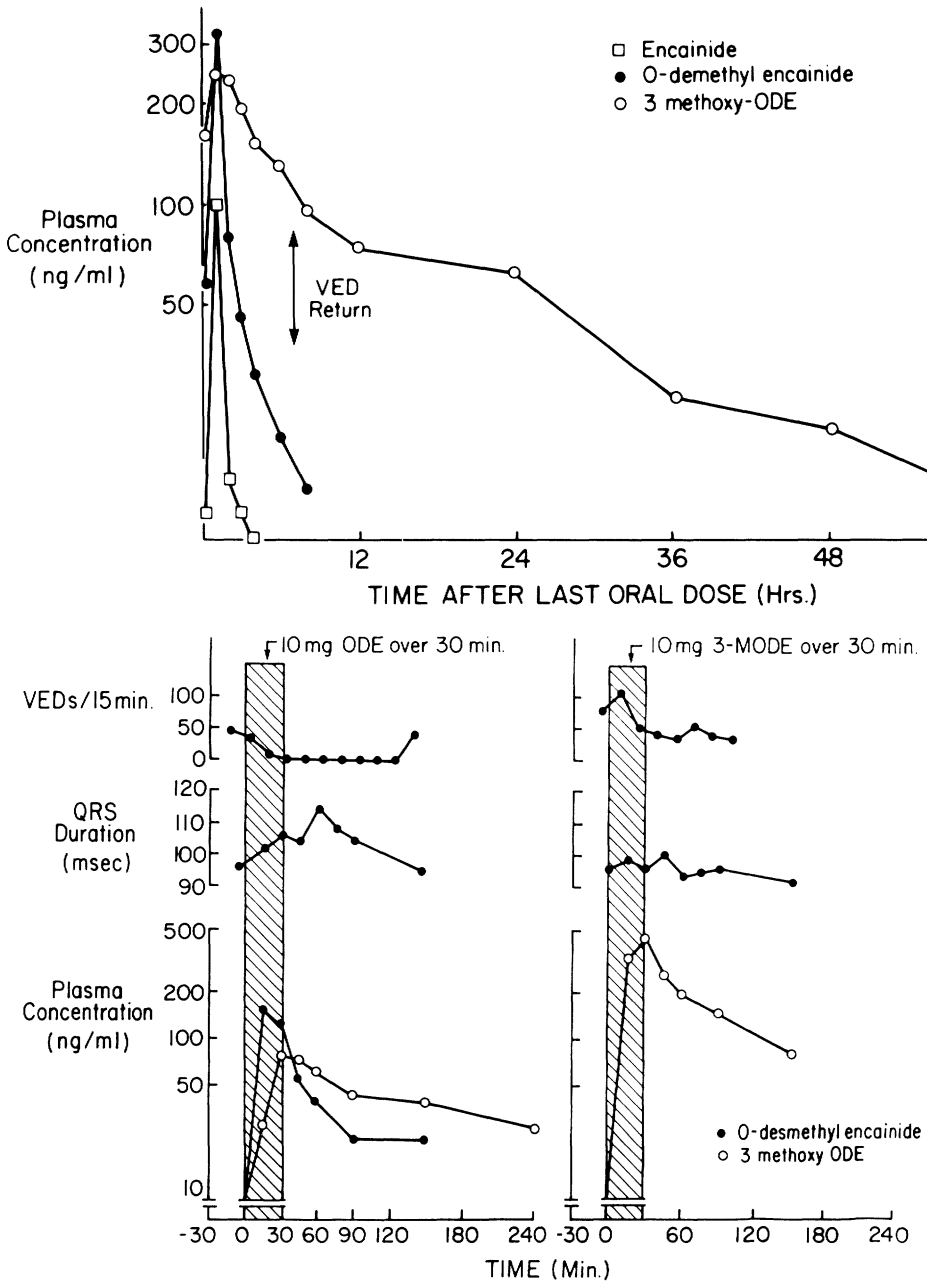


**FIGURE 1.** Study protocol and results in one patient (No. 4). *Top*, The patient was receiving oral encainide, 35 mg q8hr, and a last dose was given at time 0. Serial plasma sampling allowed an estimate of plasma concentrations present when VEDs returned (arrow). Only low concentrations of encainide (<5 ng/ml) were estimated, while the concentrations of metabolites were higher (ODE 18 ng/ml, 3MODE 97 ng/ml). *Bottom left*, Infusion of 10 mg of ODE resulted in prompt arrhythmia suppression and QRS widening; low concentrations of 3MODE were detected during and after the infusion. *Bottom right*, Infusion of 10 mg 3MODE resulted in high concentrations of 3MODE, but no antiarrhythmic effect or QRS widening.

increase in QRS duration. The poor metabolizer who had previously shown no response to encainide (patient 9) had transient abolition of arrhythmias with 40 mg of ODE and partial arrhythmia suppression with 20 mg of 3MODE. This 40 mg dose of ODE (used only once in the study) was associated with circumoral numbness; otherwise, all infusions were tolerated without side effects and no changes in blood pressure were observed.

**Pharmacokinetics (tables 2 and 3).** During withdrawal from long-term encainide therapy in extensive metabolizers, the apparent elimination half-life of ODE was 5.5 ± 1.6 hr and that of 3MODE was 17.1 ± 6.7 hr. In the poor metabolizer who was receiving encainide at the time of admission, low plasma concentrations of NDE, but not of ODE or 3MODE, were detected; compared with extensive metabolizers, this patient's mean plasma encainide concentration was higher (419

**TABLE 2**
**Pharmacokinetic data**

| Patient No. | Elimination $T_{1/2}$ (long-term encainide; hr) | | | ODE infusions | | | | 3MODE infusions | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Enc | ODE | 3MODE | Dose | $T_{1/2}\alpha$ (min) | $T_{1/2}\beta$ (hr) | Clearance (ml/min) | Dose | $T_{1/2}\alpha$ (min) | $T_{1/2}\beta$ (hr) | Clearance (ml/min) |
| Extensive metaboliers | | | | | | | | | | | |
| 1 | 4.5 | 5.7 | 31.6 | 5[A] | | | | 5[A] | | | |
| | | | | 10 | 8.1 | 1.9 | 1314 | 10 | 4.4 | 2.2 | 398 |
| | | | | | | | | 20 | 30.5 | 4.6 | 308 |
| 2 | 5.6 | 6.3 | 13.7 | 5[A] | | | | 20 | 31.9 | 10.7 | 180 |
| | | | | 10 | 8.7 | 3.0 | 1105 | | | | |
| 3 | 2.2 | 5.6 | 13.8 | 10[A] | | | | 5[A] | | | |
| | | | | 20 | 15.1 | 3.9 | 690 | 10 | 8.7 | 2.0 | 296 |
| | | | | | | | | 20 | 11.9 | 2.2 | 280 |
| 4 | 3.4 | 4.2 | 18.2 | 10 | 2.0 | 5.0 | 976 | 10 | 7.7 | 1.8 | 330 |
| 5 | 1.7 | 3.8 | 15.1 | 10 | 5.0 | 2.3 | 1214 | 10[A] | | | |
| | | | | 20 | 2.9 | 2.3 | 920 | 20 | 15.5 | 2.6 | 410 |
| 6 | 2.2 | 4.3 | 12.1 | 10 | 7.1 | 4.2 | 554 | 20 | 21.4 | 9.6 | 290 |
| 7 | 2.4 | 8.3 | 20.9 | 10[A] | | | | 20 | 20.6 | 14.3 | 180 |
| | | | | 20 | 5.3 | 4.5 | 694 | | | | |
| Mean | 3.1 | 5.5 | 17.1 | | 7.2 | 3.5 | 914 | | 17.8 | 6.4 | 289 |
| ±SD | 1.4 | 1.6 | 6.7 | | 4.2 | 1.2 | 274 | | 8.0 | 5.1 | 85 |
| Poor metabolizers | | | | | | | | | | | |
| 8 | 19.7 | — | — | 10 | 2.2 | 5.0 | 434 | 10 | 24.2 | 23.6 | 78 |
| 9 | 13.6[B] | — | — | 10 | 9.2 | 9.5 | 298 | 20 | 30.3 | 4.1 | 300 |
| | | | | 20[C] | — | 7.5 | 269 | | | | |
| | | | | 40 | 12.5 | 8.4 | 340 | | | | |

Enc = encainide; $T_{1/2}$ = half-life; $T_{1/2}\alpha$ = rapid ("distribution") half-life; $T_{1/2}\beta$ = slower ("elimination") half-life.

[A]No pharmacologic effect seen with these infusions and only limited plasma sampling performed (see text). For multiple infusions with pharmacokinetic data in the same patient, intrapatient mean used in the calculation of presented mean ± SD.

[B]Data previously obtained after withdrawal from oral encainide, 125 mg q6hr.[1]

[C]This data set best fit by monoexponential disposition function; for all others, biexponential function used as described in the text.

vs 81 ± 57 ng/ml) and the elimination half-life was longer (19.7 vs 3.1 ± 1.4 hr). Encainide elimination previously measured[1] in patient 9 had been 7.8 hr after a single oral 25 mg dose and 13.6 hr after withdrawal from subacute ineffective therapy.

After intravenous ODE, no encainide was detected in any plasma sample, while 3MODE was present in all extensive metabolizers and at the lower limits of the assay in one plasma sample in one of the two poor metabolizers. ODE elimination half-life in extensive metabolizers was shorter than in the two poor metabolizers (3.5 ± 1.2 vs 5.0 and 8.1 hr), while ODE clearance was higher (914 ± 274 vs 434 and 298 ml/min).

After administration of 3MODE, no ODE or encainide was detected in any patient. In the poor metabolizer (patient 9) who received 20 mg, 3MODE elimination half-life (4.1 hr) and clearance (300 ml/min) were within the range of the values observed in extensive metabolizers (6.4 ± 5.1 hr and 289 ± 85 ml/min). However, the other poor metabolizer received 10 mg of 3MODE, which was cleared more slowly (78 ml/min) and eliminated with a longer half-life (23.6 hr) than in any other patient.

**Plasma concentrations associated with arrhythmia suppression (table 3).** In the extensive metabolizers, plasma concentrations at the time of arrhythmia recurrence after withdrawal of long-term encainide were 11 ± 16 ng/ml (encainide), 55 ± 40 ng/ml (ODE), and 116 ± 35 ng/ml (3MODE). In the four patients with arrhythmia suppression during 3MODE infusions, the minimal effective 3MODE plasma concentration was 105 ± 50 ng/ml. In the six extensive metabolizer patients whose VEDs were suppressed during ODE infusions, the observed minimal effective ODE plasma concentration was 37 ± 15 ng/ml, while only low concentrations of 3MODE (22 ± 25 ng/ml) were noted at arrhythmia recurrence after ODE infusion. The seventh extensive metabolizer had no change in arrhythmia frequency at a peak ODE concentration of 137 ng/ml,

while plasma ODE associated with arrhythmia suppression in poor metabolizer patient 9 was 167 ng/ml.

**Changes in QRS and JTc intervals (figures 2 to 4):** The most frequently administered doses of metabolites were 10 mg ODE (n = 9) and 20 mg 3MODE (n = 7). As shown in figure 2, both significantly increased QRS, while only 3MODE infusions prolonged JTc. With the use of data generated from all infusions, the relationship between plasma metabolite concentration and changes in ECG intervals was then examined. Figure 3 shows that both agents prolonged QRS significantly; however, the slope of the relationship between plasma concentration and the increase in QRS was greater for ODE (9.2 ± 1.6% per 100 ng/ml) than for 3MODE (1.2 ± 0.5% per 100 ng/ml). In contrast, 3MODE prolonged JTc interval by 1.9 ± 0.6% per 100 ng/ml, while ODE shorted it by 2.7 ± 1.9% per 100 ng/ml (figure 4).

## Discussion

These data directly establish the activity of ODE and 3MODE in man and provide several important new pieces of electrocardiographic and pharmacokinetic information. First, ODE and 3MODE suppressed ventricular arrhythmias at plasma concentrations comparable to those observed during long-term encainide therapy in extensive metabolizers. These concentrations are one to two orders of magnitude lower than those required for standard agents such as quinidine or lidocaine, making ODE and 3MODE among the most potent antiarrhythmic agents heretofore used in man. Second, ODE clearance was, like that of encainide, a function of debrisoquin phenotype, and it was the more potent depressor of intraventricular conduction, producing a steeper slope in the relationship between plasma concentration and QRS. Third, 3MODE was shown to be a metabolite of ODE and, unlike ODE and encainide, its disposition was not strongly associated with the debrisoquin phenotype, and fourth, 3MODE prolonged cardiac repolarization while ODE shortened it.

The disposition of 3MODE was different in our two poor metabolizer patients. While clearance of ODE was lower in both subjects than in extensive metabolizers, in only one was 3MODE clearance apparently reduced. Whether this patient had a more severe oxidative enzyme defect or whether other metabolic characteristics dictate 3MODE elimination remains to be determined. The appearance of 3MODE only in extensive metabolizer patients after infusions of ODE strongly suggests that both encainide *O*-demethylation and ODE 3-methoxylation are dependent on the same isozyme. Hence the metabolic fate of encainide is likely represented by the scheme shown in figure 5.

Although infusions of the metabolite resulted in plasma concentrations comparable to those observed in extensive metabolizers during long-term encainide therapy, the elimination half-lives of ODE and 3MODE were shorter after acute intravenous administration than after withdrawal of long-term oral therapy. The

**TABLE 3**
**Plasma concentrations**

| Patient No. | Mean concentrations during long-term encainide | | | Plasma concentrations at arrhythmia recurrence | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Withdrawal of encainide | | | ODE infusion | | 3MODE infusion |
| | Enc | ODE | 3MODE | Enc | ODE | 3MODE | ODE | 3MODE | 3MODE |
| Extensive metabolizers | | | | | | | | | |
| 1 | 79 | 182 | 94 | 46 | 137 | 91 | 39 | 66 | 160 |
| 2 | 108 | 244 | 111 | 8 | 44 | 92 | 28 | 11 | |
| 3 | 192 | 381 | 291 | 2 | 63 | 181 | 20 | 11 | |
| 4 | 14 | 63 | 16 | 5 | 18 | 97 | 42 | 0 | |
| 5 | 54 | 161 | 209 | 9 | 48 | 146 | 63 | 34 | 132 |
| 6 | 65 | 160 | 83 | 5 | 55 | 91 | 28 | 8 | 53 |
| 7 | 53 | 133 | 193 | 0 | 20 | 115 | | | 74 |
| Mean | 81 | 189 | 142 | 11 | 55 | 116 | 37 | 22 | 105 |
| ±SD | 57 | 100 | 93 | 16 | 40 | 35 | 15 | 25 | 50 |
| Poor metabolizers | | | | | | | | | |
| 8 | 419 | 7.7 | 0 | | | | | | |
| 9 | | | | | | | 167 | 8 | |

All data are ng/ml. No encainide was detected during or after ODE infusions. No encainide or ODE was detected during or after 3MODE infusions.

Enc = encainide.

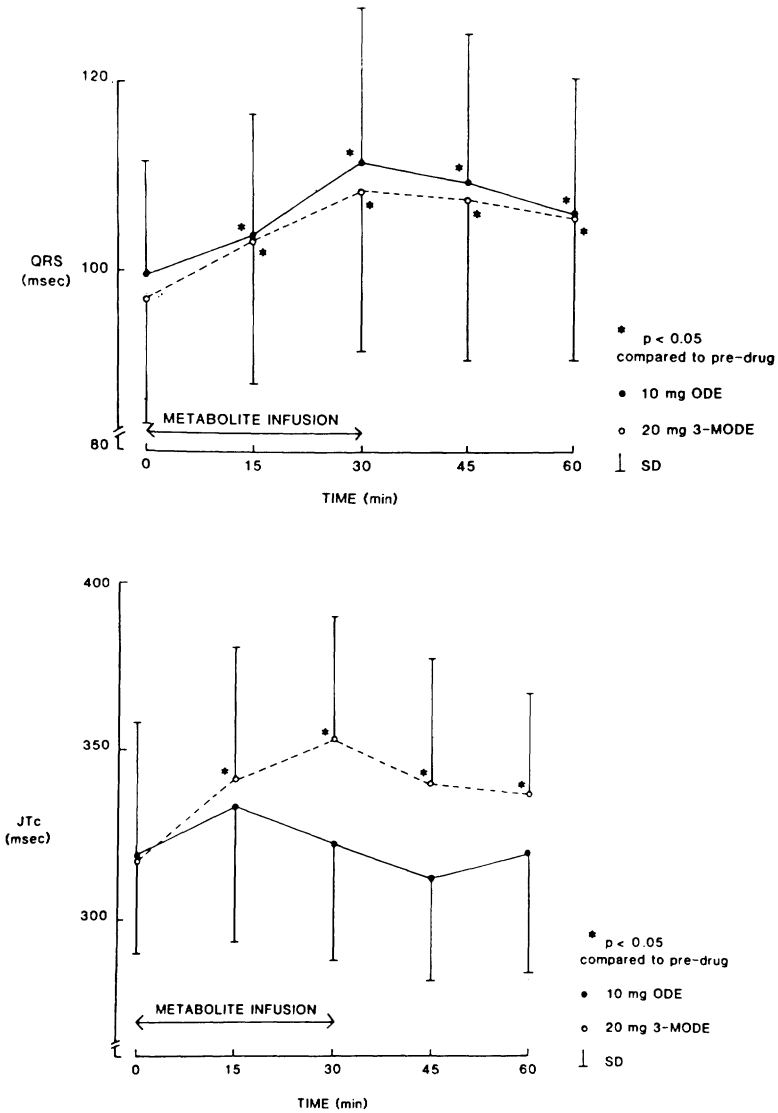


**FIGURE 2.** Changes in QRS (*top*) and JTc (*bottom*) as a function of time during and after infusion of ODE (10 mg; n = 9) and 3MODE (20 mg; n = 7). Both drugs prolonged QRS interval, but only 3MODE prolonged JTc. *p < .05 compared with baseline (analysis of variance).

likely explanation for this difference lies in the disposition characteristics of the two modes of administration used. Distribution is not evident after cessation of long-term therapy and so time-concentration curves reflect primarily elimination. Slow generation of metabolite from parent drug might also prolong apparent elimination half-life. However, this explanation is unlikely since ODE elimination was so much slower than that of encainide and 3MODE elimination was similarly slower than that of ODE.[36] In contrast to withdrawal after long-term oral therapy, the initial rapid decrease in plasma drug concentration after an intravenous dose presumably reflects distribution into peripheral sites. The second exponential time constant after intravenous drug may then be underestimated because concentrations required to determine its actual value are below the limit of detection of the assay.[36]

Our findings confirm the indirect evidence suggesting that ODE and 3MODE mediate the effects of encainide therapy in extensive metabolizers. They also clarify previous reports that QT interval changes observed during encainide therapy are variable:[6, 37] 3MODE when present alone prolongs JTc interval. It does therefore appear plausible that the QT interval may be prolonged during long-term encainide therapy beyond what is due to QRS widening and that these changes may be more noticeable depending on the relative concentrations of ODE and 3MODE present. Although low concentrations of 3MODE after ODE administration may have contributed to the steep slope of the ODE-QRS relationship, the data obtained with 3MODE itself suggest that the contribution of low 3MODE concentrations was small. While the QRS changes presumably reflect sodium-channel blockade with attendant conduction slowing, the ionic mechanisms underlying changes in repolarization are not known. Our finding that 3MODE prolonged repolarization while ODE did not is consistent with the data of

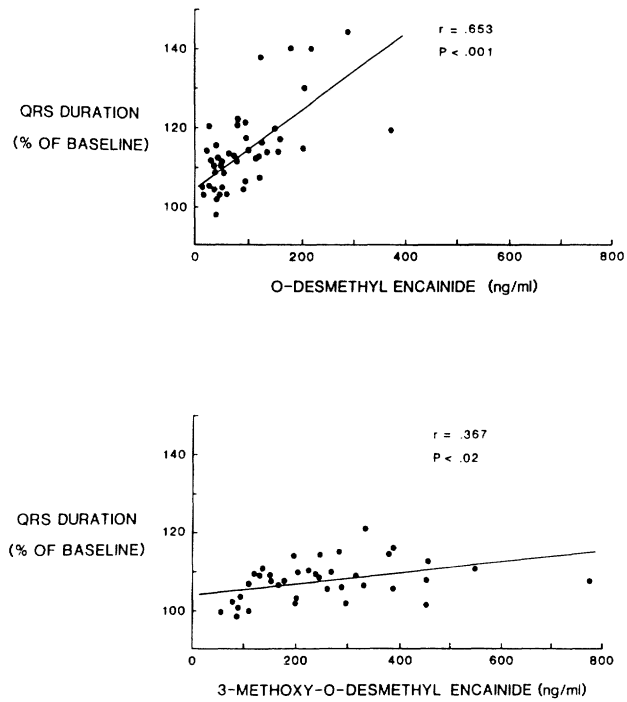


**FIGURE 3.** Relationship between plasma concentration of ODE (*top*) and 3MODE (*bottom*) and QRS. Both agents prolonged QRS in a concentration-dependent fashion, with the slope of the relationship being steeper for ODE than for 3MODE.

Davy et al.,[32] who reported that 3MODE prolonged refractoriness in dog ventricles while ODE and encainide did not. Thus, clinical therapy with encainide effectively results in treatment with a combination of agents whose electrophysiologic properties and potencies are dissimilar. Moreover, metabolites and parent drugs may antagonize each other's electrophysiologic properties. Bennett et al.[38] have reported that under appropriate conditions in vitro, sodium-channel blockade by lidocaine can be partially reversed by addition of glycine xylidide, a major lidocaine metabolite. No data are available to indicate whether similar interactions might occur among encainide and its metabolites. However, given their varying electrocardiographic and electrophysiologic actions, merely adding plasma concentrations of parent drug to those of active metabolite(s) is not an appropriate method for interpretion of plasma concentration data obtained during treatment with encainide, or any other antiarrhythmic drug with major active metabolites.

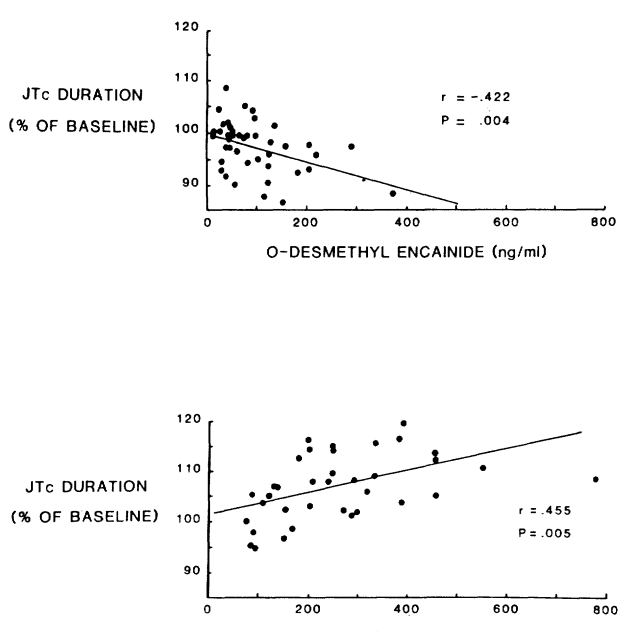


**FIGURE 4.** Relationship between plasma concentration of ODE (*top*) and 3MODE (*bottom*) and JTc. In contrast to the QRS changes shown in figure 3, ODE shortened JTc while 3MODE prolonged it.

Interpretation of plasma concentration data obtained during encainide therapy should rely on estimates of both minimally effective and maximally tolerated plasma concentrations of each compound studied. Our present findings, along with those of several earlier studies, allow a relatively convincing definition of minimum effective plasma concentrations.[4, 5, 21, 22] We had previously shown[20] that in the absence of metabolites (shortly after intravenous encainide or during long-term encainide therapy in poor metabolizers), encainide suppressed arrhythmias at concentrations greater than 265 ng/ml, but that in extensive metabolizers there was no correlation between lower plasma encainide concentrations and arrhythmia suppression. Similarly, Winkle et al.[22] reported a wide range of plasma encainide concentrations when arrhythmias recurred after withdrawal of long-term treatment; estimated minimal effective ODE concentrations were 72 ± 49 ng/ml and those of 3MODE were 172 ± 74 ng/ml. These data are in general agreement with those we found both after withdrawal of encainide (55 ± 40 ng/ml for ODE and 116 ± 35 for 3MODE) and after effective infusions (37 ± 15 for ODE; 105 ± 50 for 3MODE). Thus, minimally effective plasma concentrations appear to be approximately 50 ng/ml (ODE), 100 ng/ml (3MODE), and 250 ng/ml (encainide).

Much less information is available to define an acceptable upper limit for plasma concentrations of encainide or its metabolites. Although metabolite accumulation due to excessively short periods between increases in encainide dose has been postulated to explain some of the early incidence of arrhythmia aggravation by encainide,[39, 40] very little plasma concentration information from this period is available. More recently, Chesnie et al.[41] reported that a higher plasma ODE concentration (>307 ng/ml) was present in their patients experiencing serious drug toxicity.

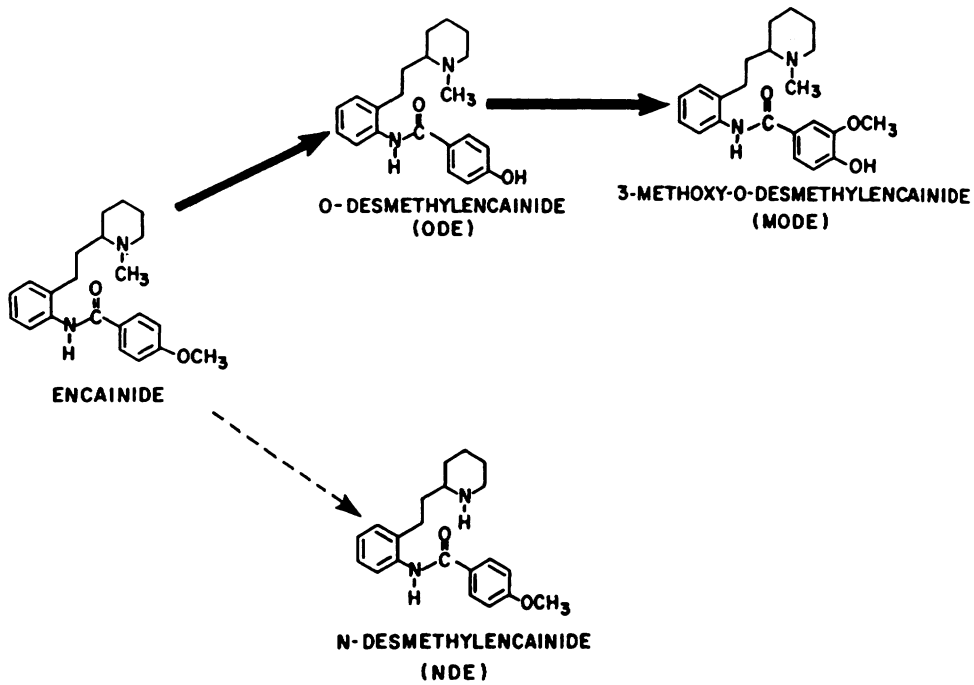


**FIGURE 5.** Pathways for encainide disposition. The heavy arrows indicate biotransformations that are dependent on debrisoquin phenotype.

Studies in animal preparations[33, 34] have implicated high plasma ODE (300 to 600 ng/ml) in decreased ventricular fibrillation thresholds or increased defibrillation thresholds, but the validity of extrapolating these concentration ranges to patients receiving encainide is uncertain. Such results must also be tempered by our lack of knowledge of possible electrophysiologic interactions among these agents, such as those described above.[38] In addition, appropriate concentration ranges may vary among patient populations. For flecainide, an agent with some similar electrophysiologic properties, an upper limit of plasma concentrations (1000 ng/ml) has been proposed[42]; this recommendation is based on the observation that in a small number of patients with serious aggravation of ventricular arrhythmia, such high concentrations are common. However, a second major contribution to this arrhythmia aggravation appears to be severe left ventricular dysfunction. Hence, setting an upper limit for plasma concentrations of drugs such as flecainide, encainide, ODE, and 3MODE may require stratification by type of heart disease. Among the patients in this study, none of whom experienced arrhythmia aggravation and all of whom had relatively preserved left ventricular function, the highest concentrations achieved were 535 ng/ml for ODE and 360 mg/ml for 3MODE during oral therapy and 374 ng/ml for ODE and 777 ng/ml for 3MODE with the intravenous infusions. It should be recognized that the efficacy of ODE and 3MODE reported here may be overestimated (and toxicity underestimated) since eight of nine patients in this study were known to be encainide responders.

In summary, interpretation of plasma concentration data obtained during encainide therapy will be facilitated somewhat by knowledge of the individual minimal effective plasma concentrations reported here. However, interindividual variability in metabolism and in the underlying heart disease and type of arrhythmia, as well as the differing electrophysiologic actions of the compounds involved, may make monitoring of plasma concentration of very limited value during encainide therapy. Exceptions may be in establishing the presence of minimally effective concentration of at least one compound during low-dose encainide, in monitoring compliance, and perhaps eventually in helping diagnose and/or avoid drug-induced arrhythmias in certain patient subsets. It should also be further emphasized that in poor metabolizers encainide may accumulate to sufficiently high concentrations to suppress arrhythmias in the absence of metabolites.[20]

Our findings suggest further directions for drug development. While ODE proved to be an extremely potent agent, it displayed polymorphic disposition similar to that of encainide and debrisoquin. This feature makes its further development as a therapeutic agent undesirable since poor metabolizers might develop extremely high concentrations after modest doses of the drug, with all the potential problems described above.

On the other hand, 3MODE appears to be a more promising agent: it suppressed arrhythmias at low concentrations, its elimination half-life is long, and its electrophysiologic properties appear somewhat different from those of ODE, including prolongation of cardiac repolarization and a lack of influence on cardiac defibrillation. Finally, its disposition was not strongly associated with the debrisoquin phenotype and it is not known to have any major unconjugated metabolites.[19] We therefore believe that 3MODE is a promising agent that requires further evaluation.

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