Electrophysiologic actions of O-demethyl encainide: an active metabolite

HENRY J. DUFF, M.D., ALBERT K. DAWSON, PH.D., DAN M. RODEN, M.D., JOHN A. OATES, M.D., RAPHAEL F. SMITH, M.D., AND RAYMOND L. WOOSLEY, M.D., PH.D.

ABSTRACT Differences between the electrophysiologic actions of the antiarrhythmic agent encainide have been reported after short-term intravenous and oral administration. Only prolongation of the HV interval and QRS duration have been described immediately after short-term intravenous administration of encainide in dogs and man. However, during oral therapy or more prolonged infusions, prolongation of the AH interval and atrial and ventricular effective refractory periods have also occurred. In most patients receiving encainide therapy, metabolites (O-demethyl encainide and 3-methoxy-O-demethyl encainide) accumulate during prolonged therapy to concentrations greater than those of the parent drug. We compared the electrophysiologic action of O-demethyl encainide with that of saline in anesthetized dogs to determine if this metabolite has pharmacologic activity and whether its electrophysiologic effects could account for the disparities noted between effects of intravenous and oral encainide therapy. An initial pharmacokinetic evaluation allowed design of a series of loading and maintenance infusions that produced plasma concentrations similar to those seen during encainide therapy in man (concentration after first maintenance dose, 149 ± 27 ng/ml [± SE] and after second maintenance dose, 230 ± 45 ng/ml). Significant increases in atrial effective refractory period and ventricular refractoriness, and prolongation of AH interval and HV conduction time were observed. These effects are similar to those reported after prolonged oral encainide therapy but are substantially different from those seen after short-term infusions of encainide. These findings indicate that the difference between the electrophysiologic actions of intravenous and oral encainide may be due to pharmacologic effects of at least one encainide metabolite, O-demethyl encainide.


ENCAINIDE is an investigational antiarrhythmic agent that has been found to be effective in the treatment of ventricular arrhythmias. Differences have been noted between the electrophysiologic actions of encainide observed immediately after an intravenous infusion and those during long-term oral therapy. Shortly after infusions of encainide in dogs and man, Sami et al. noted only an increase in the HV interval and QRS duration. However, after oral encainide and during more prolonged intravenous therapy with the drug, Jackman et al. and Samuelsson and Harrison have reported prolongation in AH conduction and increases in atrial and ventricular refractoriness. Results of a number of studies have suggested that metabolites of encainide accumulate during oral therapy and contribute to the electrophysiologic and antiarrhythmic actions. The presence of active metabolites was suggested by our preliminary observation, showing that the antiarrhythmic efficacy of encainide was linked to the presence of the metabolite O-demethyl encainide. Subsequently, we have also shown that O-demethyl encainide was 50 times more potent than encainide in the aconitine rat model of ventricular arrhythmias. Also, we and others have found that, in the majority of patients, O-demethyl encainide accumulates during prolonged therapy to concentrations greater than those of the parent compound and that O-demethyl encainide concentrations correlate with pharmacologic effects (antiarrhythmic activity and QRS prolongation) better than do encainide concentrations. These findings provide further support for the hypothesis that O-demethyl encainide has independent

From the Division of Clinical Pharmacology, Departments of Pharmacology and Medicine, Vanderbilt University School of Medicine, and Nashville Veterans Administration Medical Center, Nashville.
Supported by grants from the National Institutes of Health, The U. S. Public Health Service (GM 15431, GM 31304, and GM 07569), the Canadian Heart Foundation (BRSG RR-5424), and the Veterans Administration.
Address for correspondence: Raymond L. Woosley, M.D., Ph.D., Department of Pharmacology, Vanderbilt School of Medicine, Nashville, TN 37232.
Received May 17, 1982; revision accepted April 7, 1983.
Dr. Duff is a Scholar of the Alberta Heritage Medical Research Foundation.
Dr. Roden is a recipient of the Clinician-Scientist Award of the American Heart Association.
electrophysiologic actions that contribute to the differences in the electrophysiologic actions seen during oral and long-term intravenous encainide therapy. To assess this possibility, the pharmacokinetics and electrophysiologic effects of O-demethyl encainide were evaluated in dogs in a randomized, placebo-controlled study.

Methods

Study design. Before the electrophysiologic studies were performed, the pharmacokinetic characteristics of O-demethyl encainide were determined in four dogs. With the use of these pharmacokinetic data, a series of loading and maintenance infusions were designed to achieve O-demethyl encainide plasma concentrations similar to those observed during long-term oral therapy in man\(^1\), \(^2\) (concentration after first maintenance dose, 100 to 150 ng/ml and after second maintenance dose, 200 to 250 ng/ml).

Electrophysiologic measurements were made in each of eight dogs used in the study before and after infusions of O-demethyl encainide, and also before and after infusions of saline, in a randomized crossover manner. Saline and O-demethyl encainide infusions were continued for similar durations, and the electrophysiologic measurements were made at similar times. At least 3 days were allowed to elapse between saline and O-demethyl encainide infusions. Electrophysiologic measurements were recorded at baseline and 15 min after the beginning of the maintenance infusions of O-demethyl encainide or saline. Plasma O-demethyl encainide concentrations were determined before and just after the electrophysiologic data were recorded.

Electrophysiologic studies. Eight mongrel dogs weighing between 17 and 22.5 kg were anesthetized with 1 mg/kg im morphone and 100 mg/kg iv chloralose and were ventilated with room air with the use of a Harvard animal respirator. Bipolar ventricular and atrial pacing electrode catheters, a tripolar electrode catheter for recording His bundle activity, and a suction bipolar electrode catheter for recording monophasic action potential durations were inserted in each dog by a sterile technique, via the right and left external jugular veins and right and left femoral veins, respectively. The ventricular monophasic action potential recordings were obtained with a bipolar endocardial suction electrode (ABO trading, Tullv., 1138, S-430 41 Kullavik, Sweden) and by techniques described by Olsson et al.\(^3\), \(^4\) and Brorson and Olsson.\(^5\) This technique has been previously validated by comparison with intracellular recordings of action potential duration by Hoffman et al.\(^6\) After placement in the right atrium, the monophasic action potential catheter was advanced across the tricuspid valve and brought into contact with the wall of the right ventricular septum. When a monophasic electrical potential was observed, suction was applied (100 mm Hg) for not more than 3 min. A unipolar intracavitary electrocardiogram from the peripheral electrode of the suction catheter was recorded with the left leg as reference. The monophasic action potential recording was discarded if the unipolar intracavitary electrocardiogram revealed ST segment elevation. The monophasic action potential durations were determined during ventricular pacing at a constant rate (RR = 300 msec). After each recording the suction electrode catheter was withdrawn to the right atrium and it was repositioned by fluoroscopy to a site similar to the original one when further recordings were required. The monophasic action potential signal and the unipolar electrogram were amplified with a DC-coupled Electronics for Medicine differential amplifier (Model PHD) with a frequency response from 0 to 1000 Hz. The signal was recorded at 100 mm/sec on an Electronics for Medicine (Model DR-8) recorder. The duration of at least three monophasic action potentials were measured at 90% repolarization\(^7\) and averaged. Measurements were made after 30 ventricularly paced beats and when the configuration and duration of monophasic action potential duration had become stable.

Right ventricular refractoriness was established from strength interval curves. A Bloom stimulator (Model DTU-110) was used to pace the ventricle at a cycle length (S1-S2) of 300 msec and to introduce a premature stimulus (S3) after every twelfth paced beat. After 2 min of pacing, a premature stimulus was introduced late in diastole (S2 = 250 msec), and the current intensity was increased until the extrastimulus produced a ventricular response. The minimal current producing a ventricular response was recorded, the coupling interval of the extrastimulus was progressively shortened at 5 msec intervals, and the process was repeated until the extrastimulus reached a preset upper limit of 10 mA. To generate a strength interval curve, the minimal current intensity required to produce a ventricular response was plotted against the coupling interval of the extrastimulus. For the purpose of data analysis, ventricular effective refractory period at twice diastolic threshold and at 10 mA were recorded. Atrial effective refractory period (AERP) was determined with the use of the extrastimulus technique at twice diastolic threshold.

The surface electrocardiographic leads II and V\(_1\) and His bundle electrograms were recorded on the Electronics for Medicine recorder. The PR and QRS intervals were measured for each recording so obtained.

Drug assay. The high-performance liquid chromatography system described by Mayol and Comer\(^8\) was used to separate and quantify encaïnide, O-demethyl encainide, and other metabolites (N-demethyl encainide; O, N-dimethyl encainide; and 3-methoxy-O-demethyl encainide). This assay was modified to use S-15531 (supplied by Riker Laboratories, Minneapolis) as an internal standard.

Pharmacokinetic assessment. After morphine-chloralose anesthesia, 15 mg of O-demethyl encainide was administered as a rapid infusion over 15 sec to four dogs. Plasma samples for analysis of O-demethyl encainide concentrations were obtained 5, 15, 30, 45, 60, 90, 120, 150, 180, and 210 min after this dose. The negative slope (elimination constant) was calculated from least squares fit of the terminal portion of the time–log concentration plot. The area under the curve (AUC) was calculated by the trapezoidal rule with extrapolation to infinity.\(^9\) The concentration at time zero (C\(_0\)) was determined by back extrapolation of the elimination phase of the log concentration–time plot to time zero. The volume of distribution (V\(_{dl}\)) was calculated with the formula V\(_{dl}\) = Dose/C\(_0\), systemic clearance was calculated with the formula Clearance = Dose/AUC, and the loading dose to achieve a desired concentration was calculated with the formula Dose = V\(_{dl}\) × Desired concentration. The maintenance infusion rate to produce a desired concentration was calculated as Infusion rate = Clearance × Desired plasma concentration. The infusion protocol was designed so that an initial O-demethyl encainide concentration of 150 ng/ml could be maintained and so that, after a second loading infusion, a concentration of 250 ng/ml could be maintained. O-Demethyl encainide was administered with a Harvard Model 600 syringe-driven pump.

Statistical analysis. Analysis of covariance\(^1\) was used to characterize changes due to drug and to time (in the saline control dogs). If this analysis demonstrated a significant treatment (drug) effect, the Newman-Keuls test was used to detect differences between pairs of groups. Linear regression was used to assess the relationship between extent of change in a parameter and O-demethyl encainide concentrations. Regression lines were obtained by least square fit technique. A p < .05 was
sufficient to reject the null hypothesis. All data are expressed as mean ± SE.

Results

Pharmacokinetics. The plasma concentration–time curve after rapid infusion of 15 mg of O-demethyl encaainide is shown in figure 1. Table 1 presents the results of pharmacokinetic analysis of these data. Based on this analysis, O-demethyl encaainide was given as a series of loading and maintenance infusions to the eight dogs undergoing electrophysiologic studies. The first loading infusion of O-demethyl encaainide was at a rate of 57 μg/kg/min for 15 min followed by maintenance infusion rate of 7 μg/kg/min. The first maintenance infusion resulted in a mean concentration of 149 ± 27 ng/ml before and 146 ± 27 ng/ml after the electrophysiologic measurements were made. To increase the plasma concentration, a second loading infusion of 31 μg/kg/min for 15 min was given followed by a second maintenance infusion at a rate of 13 μg/kg/min. The second maintenance infusion resulted in a mean plasma concentration of 226 ± 39 ng/ml before electrophysiologic measurements were made and 232 ± 45 ng/ml after these measurements. A period of 15 min was allowed to elapse after the beginning of the maintenance infusions before the measurements were made.

Electrophysiologic data (tables 2A and 2B). Marked drug treatment–related prolongation was noted in con-

![Figure 1](http://circ.ahajournals.org/)

**FIGURE 1.** Mean plasma concentrations of O-demethyl encaainide after the rapid infusion of 15 mg (n = 4).

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Weight (kg)</th>
<th>VdER (l)</th>
<th>ClER (l/hr)</th>
<th>KER (hr⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24.5</td>
<td>100</td>
<td>53</td>
<td>0.48</td>
</tr>
<tr>
<td>2</td>
<td>22.7</td>
<td>106</td>
<td>55</td>
<td>0.42</td>
</tr>
<tr>
<td>3</td>
<td>23.6</td>
<td>143</td>
<td>56.6</td>
<td>0.39</td>
</tr>
<tr>
<td>4</td>
<td>19.2</td>
<td>88</td>
<td>50.8</td>
<td>0.56</td>
</tr>
</tbody>
</table>

K_E = elimination constant; all other abbreviations are as in Pharmacokinetic assessment section of text.

**TABLE 2A**

Electrophysiologic data (mean ± SE) in dogs receiving saline (control)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Saline time control 1</th>
<th>Saline time control 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR interval</td>
<td>146±13</td>
<td>138±18</td>
<td>146±22</td>
</tr>
<tr>
<td>AH interval</td>
<td>112±14</td>
<td>107±16</td>
<td>115±23</td>
</tr>
<tr>
<td>HV interval</td>
<td>29±2</td>
<td>30±3</td>
<td>30±2</td>
</tr>
<tr>
<td>QRS duration</td>
<td>53±3</td>
<td>57±6</td>
<td>56±5</td>
</tr>
<tr>
<td>mAPD</td>
<td>197±7</td>
<td>197±12</td>
<td>197±8</td>
</tr>
<tr>
<td>AERP</td>
<td>131±13</td>
<td>129±10</td>
<td>127±11</td>
</tr>
<tr>
<td>Ventricular refractory period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 × diastolic</td>
<td>159±6</td>
<td>160±6</td>
<td>165±5</td>
</tr>
<tr>
<td>10 mA</td>
<td>137±5</td>
<td>137±5</td>
<td>139±5</td>
</tr>
<tr>
<td>Atrial excitability threshold</td>
<td>0.3±0.1</td>
<td>0.2±0.1</td>
<td>0.3±0.1</td>
</tr>
<tr>
<td>Ventricular excitability threshold</td>
<td>0.3±0.1</td>
<td>0.3±0.2</td>
<td>0.3±0.2</td>
</tr>
</tbody>
</table>

mAPD = monophasic action potential duration.

**TABLE 2B**

Electrophysiologic data in dogs receiving O-demethyl encaainide

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Maintenance 1</th>
<th>Maintenance 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR interval</td>
<td>141±9</td>
<td>182±9^</td>
<td>205±13^</td>
</tr>
<tr>
<td>AH interval</td>
<td>115±9.1</td>
<td>141±8^</td>
<td>154±11</td>
</tr>
<tr>
<td>HV interval</td>
<td>29±2</td>
<td>47±3^</td>
<td>52±2^</td>
</tr>
<tr>
<td>QRS duration</td>
<td>53±2</td>
<td>75±5^</td>
<td>80±6^</td>
</tr>
<tr>
<td>mAPD</td>
<td>183±5</td>
<td>196±7</td>
<td>199±10</td>
</tr>
<tr>
<td>AERP</td>
<td>95±10</td>
<td>154±9^</td>
<td>177±15^</td>
</tr>
<tr>
<td>Ventricular refractory period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 × diastolic</td>
<td>156±6</td>
<td>177±5^</td>
<td>181±5</td>
</tr>
<tr>
<td>10 mA</td>
<td>133±5</td>
<td>143±6</td>
<td>147±6</td>
</tr>
<tr>
<td>Atrial excitability threshold</td>
<td>0.4±0.2</td>
<td>0.7±0.2</td>
<td>5.0±2.0</td>
</tr>
<tr>
<td>Ventricular excitability threshold</td>
<td>0.3±0.1</td>
<td>0.2±0.1</td>
<td>0.3±0.2</td>
</tr>
</tbody>
</table>

mAPD = monophasic action potential duration. ^p < .01 for maintenance 1 vs baseline; ^p < .05; ^p < .01 for maintenance 2 vs maintenance 1 (group comparisons performed only if analysis of covariance rejected the hypothesis of equal means).
duction parameters AH, PR, and HV intervals and QRS duration. The extent of prolongation of these parameters was linearly related to plasma concentration (AH, r = .88, p < .001; PR, r = .79, p < .001; QRS, r = .67, p < .001; HV, r = .44, p < .03; figure 2). Also, there was a marked increase in AERP (p < .001; figure 2). The slopes of these relations were (in % change/ng/ml): AH, 0.2; PR, 0.2; QRS, 0.15; HV, 0.2; AERP, 0.5. In contrast to the marked changes in AERP, ventricular refractoriness was affected less (figures 3 and 4). When assessed at twice diastolic threshold, the difference between drug treatment and baseline (14%) was found to be statistically significant after the analysis of covariance was performed to “factor out” time-related changes. The similar trend seen when data at 10 mA were examined did not meet this criterion for statistical significance, nor did the changes in monophasic action-potential duration. A significant (fivefold) increase in the atrial excitability threshold was noted at high concentrations of O-demethyl encainide (p < .01). No change was seen in the ventricular excitability threshold.

Another metabolite, 3-methoxy-O-demethyl encainide, was measurable in the plasma of four of the eight animals during the O-demethyl encainide infusions. The concentrations were at the lower limits of detectability (less than 30 ng/ml) in three of these dogs. In the single dog with substantial levels of 3-methoxy-O-demethyl encainide (300 ng/ml) the qualitative and quantitative changes in electrophysiologic parameters observed were similar to those seen in animals that did not have measurable amounts of 3-methoxy-O-demethyl encainide in their plasma. Exclusion of the data from this animal does not alter the significance of the results summarized above. No measurable amount of encainide, N-demethyl encainide, or O, N-dimethyl encainide were seen in plasma during any of these infusions.

**Discussion**

When a lack of correlation between plasma concentrations of a drug and pharmacologic response is observed, the possibility of the presence of one or more active metabolites is a reasonable consideration.21 This

**Figure 2.** Relationship between O-demethyl encainide concentration (abscissa) and changes in AH interval (left panel), AERP (center), and HV interval (right).

**Figure 3.** Changes in ventricular refractory period (mean ± SE) at twice diastolic threshold (circles) and 10 mA (squares). The closed symbols represent data obtained during O-demethyl encainide treatment, and the open symbols represent data from saline treatment. BL = baseline; M1 = first maintenance period; M2 = second maintenance period. **p < .01 compared with baseline.
principle is illustrated in patients with renal failure when the relationship between toxic manifestations and plasma levels of procainamide are examined. Under these circumstances, the active metabolite N-acetylpencainamide accumulates and the toxic manifestations do not correlate with the concentration of the parent compound. We have demonstrated a similar lack of a consistent relationship between plasma encaínide concentrations and pharmacologic response (antiarrhythmic effects) in man, suggesting the presence of active metabolites.

Another characteristic that suggests the presence of active metabolites is the difference observed between the pharmacologic effects immediately after intravenous and after oral drug administration. This principle is illustrated in the studies by Holford et al., who noted differences in the slopes of the QT prolongation vs plasma quinidine curves when intravenous and oral quinidine were compared. The slope after oral administration was higher, suggesting that active metabolites, which independently prolonged the QT interval, were present. Similarly, Sami et al. found no significant increases in AH interval or in atrial and ventricular refractoriness after short-term infusion of encainide in dogs while other investigators have reported substantial dose-related changes in these same parameters after more prolonged administration. We have also shown that immediately after short-term encainide injections in man, the parent compound is predominantly present in plasma, and low metabolite concentrations are observed. However, after more prolonged infusions, or during oral encainide therapy, the concentration of O-demethyl encainide is substantially greater than that of the parent. Hence, the evaluation of the pharmacology of drugs that are extensively metabolized should include assessment of the effects of the individual metabolites early in the development.

Evidence from a number of sources suggests that O-demethyl encainide contributes substantially to the pharmacologic effects seen during oral encainide therapy in man. First, during long-term oral encainide therapy this metabolite accumulated to concentrations greater than those of the parent compound in 90% of patients and the pharmacologic effects observed (antiarrhythmic efficacy and QRS prolongation) correlated with the concentration of O-demethyl encainide better than with that of the parent compound. Second, the significant increases in AH interval and atrial and ventricular refractoriness we observed have not been seen with short-term encainide

FIGURE 4. Representative examples of strength interval curves obtained during O-demethyl encainide infusion (left) and control saline infusion (right). ODME M1 = maintenance period 1; ODME M2 = maintenance period 2.
infusions in man or dog, but are characteristic of the changes reported during oral encainide therapy in man and during more prolonged infusions of encainide in dogs. Third, results of studies by us and others, conducted after discontinuation of encainide treatment, have shown persistent antiarrhythmic and electrocardiographic effects at times when O-demethyl encainide was still present in plasma but there were little or no detectable concentrations of the parent drug.

The presence of the multiple metabolites of encainide complicates the understanding of its pharmacology. In 95% of patients receiving encainide the drug is metabolized to O-demethyl encainide, which can be further metabolized to 3-methoxy-O-demethyl encainide; pharmacologic effects (QRS widening and arrhythmia suppression) correlate best with plasma O-demethyl encainide in this group. This is consistent with animal and in vitro data showing O-demethyl encainide to be more active than encainide or 3-methoxy-O-demethyl encainide. In 10% of patients, O-demethylation appears to be genetically impaired; in these individuals, encainide accumulates to much higher concentrations and, in some patients, exerts an antiarrhythmic effect.

The pharmacologic actions of metabolites may also be involved in adverse reactions during encainide therapy. Since the elimination half-life of encainide is less than 3 hr in most patients, investigators have often increased the dosage of encainide quickly, assuming that near steady-state conditions would be obtained within 12 to 15 hr. However, the metabolites appear to have substantially slower elimination in man, and the rapid increase in dosage before steady-state conditions are achieved for the metabolites could lead to very high (and possibly toxic) concentrations of metabolites. This could explain some cases of worsening of ventricular arrhythmias during encainide treatment. In support of this possibility, we have shown that high concentrations of O-demethyl encainide (greater than 300 ng/ml) can significantly lower the ventricular fibrillation threshold in an ischemic canine model.

In summary, this study indicates that the differences between the electrophysiologic actions of intravenous and oral encainide may be due to the presence of O-demethyl encainide during oral therapy. Besides prolonging HV intervals and QRS duration, O-demethyl encainide, like short-term intravenous doses of the parent, prolonged PR and AH durations and refractoriness in the atrium and, to a lesser degree, in the ventricles. Further characterization of the role that O-demethyl encainide plays in man will require its administration to patients.

We are indebted to Deborah Fisher and Janice Neely for assistance in the preparation of this manuscript.

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Electrophysiologic actions of O-demethyl encainide: an active metabolite.

Circulation. 1983;68:385-391
doi: 10.1161/01.CIR.68.2.385
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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