


Clinical Pharmacology and Antiarrhythmic Efficacy of Encainide in Patients with Chronic Ventricular Arrhythmias

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SUMMARY We determined the pharmacokinetics, efficacy and therapeutic plasma concentration of encainide, a new antiarrhythmic drug that affects His-Purkinje conduction but not ventricular refractoriness. Nine patients with frequent and complex premature ventricular complexes were studied in a 3-day double-blind protocol. Each day, each patient received 75 mg of i.v. or oral encainide or placebo. Frequent blood samples for encainide plasma concentration determination and continuous ambulatory ECGs were obtained. There was a marked intersubject variation in bioavailability (mean 42 ± 24%, range 7.4-82%), clearance (13.2 ± 5.6 ml/min/kg), and half-life (3.4 ± 1.7 hours i.v., 2.5 ± 0.8 hours oral). Eight of nine patients had more than 90% suppression of premature ventricular complexes for 3-36 hours. Minimal antiarrhythmic plasma concentration was higher (39 ± 54 ng/ml, range 3.5-170 ng/ml) after i.v. dosing than after oral dosing (14 ± 16 ng/ml, range 1.5-48 ng/ml), suggesting an active metabolite after oral dosing in many patients. Minimal side effects were seen despite high peak plasma concentrations (range 794-1556 ng/ml i.v., 36-495 ng/ml oral). The minimal ratio of toxic to therapeutic plasma concentration ranged from 4.3-326 (median 23) after oral dosing. Antiarrhythmic action was associated with an 11-44% widening of the QRS complex that was not associated with other adverse effects. We conclude that encainide effectively suppresses ventricular arrhythmias. Despite a variable bioavailability, high clearance and short half-life, its wide ratio of toxic to therapeutic concentration and probable active metabolite permit a long duration of action, which should allow a reasonable dose schedule in most patients during chronic oral dosing.

ENCAINIDE (4-methoxy-2'[(2-1-methyl-2-piperidyl) ethyl] benzanilide hydrochloride) is a new compound with antiarrhythmic activity. In a canine Purkinje fiber preparation, the drug depresses the rate of rise of phase 0 of the action potential, shortens the action potential duration without significantly changing the effective refractory period and decreases the rate of spontaneous phase 4 depolarization. Encainide abolishes aconitine-induced atrial fibrillation and ventricular arrhythmias induced by digitalis and coronary artery ligation in a variety of animal species. The drug also elevates the ventricular fibrillation threshold in the dog. In a closed-chest anesthetized dog model, encainide caused a plasma-concentration-dependent prolongation of the HV interval and QRS complex. The drug had no effect on other electrophysiologic measurements, including ventricular refractoriness. In man, i.v. encainide in doses of 0.6 and 0.9 mg/kg over 15 minutes resulted in a 31% prolongation of the HV interval and a 17% increase of QRS duration associated with peak plasma concentrations of 110-1150 ng/ml.

Encainide is of value for treating some patients with refractory life-threatening recurrent ventricular tachycardia and fibrillation and effectively suppressed ventricular ectopic beats in a fixed-dose comparison with quinidine. Kesteloot and Stroobandt found that single i.v. doses of encainide abolished ventricular ectopic beats in 31 of 33 patients, and Roden et al. reported complete suppression of ventricular arrhythmias in 10 of 11 patients after oral dosing. The present study was performed to provide further data about the efficacy and clinical pharmacology of encainide.

Methods

Nine patients (six males and three females) with frequent and complex ventricular ectopy were studied. The average age of the patients was 60.5 ± 7.6 years (range 49–77 years). The clinical characteristics of the patients are listed in table 1.
All antiarrhythmic drugs were discontinued at least five half-lives before the study. Patients with renal or hepatic disease, seizure disorders, uncompensated heart failure or advanced degrees of atrioventricular block were excluded. Each patient gave written informed consent and the protocol was approved by the Stanford Human Subjects Committee.

Protocol Design

Before entering the study, each patient underwent 24-hour ambulatory ECG monitoring. Patients who met the entry criterion of at least one premature ventricular complex (PVC) per minute averaged over the 24-hour recording period were hospitalized in the Cardiology Unit at Stanford Medical Center for continuous telemetry ECG monitoring to determine that their ventricular ectopic beats persisted in the hospital. Patients were then entered into a 3-day protocol. During the protocol patients ate their regular diet, including a moderate breakfast each morning several hours before drug administration. On each day of the study, heparin locks were placed in a peripheral vein in each forearm between 8:00 and 10:00 a.m. Each patient was then connected to a 24-hour ambulatory ECG recorder to make a permanent record of the ECG. Continuous on-line telemetry monitoring was also performed for patient safety. The time of ambulatory ECG placement varied slightly from patient to patient, but was constant for all days for each patient. Patients were then instructed to remain ambulatory for 1 hour. At the end of this hour patients returned to bed and each morning were given three tablets and a 32-ml, 20-minute i.v. infusion by means of a Harvard infusion pump. On one morning, the three tablets and the i.v. solution were placebo. On one day, the tablets were placebo and the i.v. infusion contained 75 mg of encainide. On the final day, 75 mg of encainide were given as three 25-mg tablets that were identical to the placebo in appearance and taste, and the i.v. solution was placebo. The three study days were consecutive days in all patients except patient 5, in whom 1 additional day was necessary between each drug day because the duration of total arrhythmia suppression exceeded 24 hours. The sequence of days was randomized from patient to patient and only the person who prepared the tablets and i.v. solutions was aware of their content. Others responsible for judging efficacy and side effects were unaware of the therapy being given on any day. The code was broken only after the entire study was completed. Approximately 20 minutes after the end of the 20-minute infusion, patients were again instructed to become ambulatory and were encouraged to remain active during the remainder of the day. They were carefully instructed to maintain similar activity levels on each of the three protocol days.

Pharmacokinetic Analysis

On each of the 3 days, 5-ml blood samples were obtained from the heparin lock in the arm not used for drug infusion. Blood samples were obtained immediately before the i.v. infusion and oral tablets and 3, 5, 10, 15, 20, 25, 30, 40, 50, 60, 90, 120, 180, 240, 360, 600, 960 and 1440 minutes after drug administration. Samples were collected in heparinized tubes and centrifuged, and the plasma was frozen for later analysis. Samples were analyzed* for encainide concentration using a radioimmunoassay technique of Mayol and Gammons.14 Half-life after oral and i.v. dosing was calculated using a log-linear least-squares fit of the terminal log-linear portion of the plasma concentration time data. Clearance was calculated from the area under the plasma concentration time curve after i.v. dosing. Bioavailability was calculated

*Analysis performed by Dr. Jeffrey Travis, Orange County Institute, Newport Beach, California.
by dividing the area under the plasma concentration time curve after oral administration by that obtained after i.v. administration.

Antiarrhythmic Efficacy

The frequency of PVCs on the entry ambulatory ECG and on ECGs obtained during the study period was determined using the Stanford computer ambulatory ECG analysis system, which classifies each QRS complex according to morphology and prematurity and permits operator selection of PVC families. The accuracy of arrhythmia analysis was determined for each tape in each patient using a beat-by-beat evaluation of both randomly selected and PVC-rich minutes of ECG at frequent intervals throughout the tape. All showed less than 10% error rates. All episodes of pairs, runs, bigeminy and trigeminy are also tabulated. To define the responses of individual patients to encainide, the number of PVCs per hour was tabulated for each hour after drug administration and compared with the number in the 1 hour of recording before drug administration each morning. A previous study from our laboratory in a similar in-hospital setting indicated that in patients with known frequent PVCs, 90% reduction of arrhythmias for longer than 1 hour rarely occurs spontaneously. For the current study, data are presented for both 80% and 90% reduction of arrhythmias. The number of continuous hours of each level of reduction are given after oral, i.v. and placebo dosing. In most instances the return of ventricular arrhythmias was reasonably abrupt after suppression by encainide and it was possible to define precisely the time at which arrhythmias returned. By examining corresponding times on graphs of encainide plasma concentration vs time, the encainide plasma concentration corresponding to the time of return of ventricular arrhythmias was determined. The minimal toxic-to-therapeutic ratio after oral dosing was defined as the ratio of the highest plasma concentration achieved without side effects to the plasma concentration at the time of return of ventricular ectopic beats.

Results

Pharmacokinetics

The pharmacokinetic data for these nine patients are summarized in tables 2 and 3. The peak plasma concentration after i.v. dosing was 996.7 ± 315 ng/ml (range 640-1556 ng/ml). The peak plasma concentration after oral dosing was 241 ± 190 ng/ml (range 36-587 ng/ml). The time of peak oral plasma concentration ranged from 1.5-3.0 hours, with an average of 1.67 ± 0.66 hours. While there was only a two-and-one-half-fold range of peak plasma concentrations after i.v. dosing, the 16-fold range after oral dosing reflected the wide range of bioavailability in these patients (average 41.9 ± 24.3%, range 7.4-82.2%). There was also a wide range of clearances, ranging from 210-1790 ml/min (average 1157± 522 ml/min). There was a wide range of body weights in this study, but correction for body weight did not markedly improve the wide range of clearances, which still varied from 3.75-22.1 ml/min/kg (average 13.2 ± 5.6 ml/min/kg). Encainide exhibited a short half-life consistent with its high clearance. The average half-life after i.v. dosing was 3.38 ± 1.68 hours (range 2.05-6.91 hours). After oral dosing the half-life tended to be shorter in most patients, averaging 2.47 ± 0.78 hours (range 1.57-3.72 hours).

Antiarrhythmic Effect

The average hourly frequency of PVCs during the placebo day in these nine patients ranged from 303-1785 PVCs/hr (median 418 PVCs/hr).

Eight of the nine patients were considered as antiarrhythmic responders to encainide. Table 4 gives the antiarrhythmic response to encainide, and the responses of three patients are shown in figures 1, 2 and 3.

Table 2. Encainide Pharmacokinetics

<table>
<thead>
<tr>
<th>Pt</th>
<th>T₁/₂ (hrs)</th>
<th>Bioavailability (%)</th>
<th>Clearance (ml/min/kg)</th>
<th>Peak Cp</th>
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<tr>
<td></td>
<td>i.v.</td>
<td>Oral</td>
<td></td>
<td>i.v.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td>Time</td>
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<td>3.26</td>
<td>2.52</td>
<td>82.2</td>
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<td>2</td>
<td>5.44</td>
<td>3.44</td>
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<td>9.57</td>
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<td>4</td>
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<td>6.91</td>
<td>3.72</td>
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<td>2.51</td>
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<td>40.4</td>
<td>13.9</td>
</tr>
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<td>13.2</td>
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<td>0.68</td>
<td>0.78</td>
<td>24.3</td>
<td>5.61</td>
</tr>
<tr>
<td>SEM</td>
<td>0.56</td>
<td>0.26</td>
<td>8.1</td>
<td>1.87</td>
</tr>
</tbody>
</table>

Abbreviations: T₁/₂ = half-life; Cp = plasma concentration.
The inclusion of a placebo day provides a control against attributing spontaneous variation of PVC frequencies to an antiarrhythmic effect of encainide. By examining the percentage change in PVC frequency after placebo, we determined that only patient 6 had a 90% decline in frequency of PVCs compared with the control level; this level of reduction was only maintained for 1 hour. In fact, the overall conclusions of the study are little affected by relaxing the response criterion to 80% because the same hour that showed 90% reduction in patient 6 was the only hour to achieve 80% reduction during the placebo day.

The duration of continuous 90% suppression after i.v. encainide ranged from 1-36 hours (median 8 hours). Only two patients failed to achieve 90% suppression of PVCs; one of them (patient 3) was considered to be an encainide nonresponder, and the other was considered to have had some antiarrhythmic response to i.v. encainide because he achieved 3 successive hours of 80% suppression of PVCs. For almost all patients the number of hours of 80% suppression was virtually identical to that of 90% suppression. This fact reflected the abrupt and nearly total or total suppression of PVCs after encainide administration and the fairly abrupt return of PVCs in most patients when its effects were no longer present. Using an hourly average PVC count tended to underestimate slightly the actual duration of antiarrhythmic response in most patients because for many the initial hour of onset of antiarrhythmic effect and the hour of offset of effect did not achieve 80% or 90% suppression of PVCs even though considerable portions of these hours were almost totally free of arrhythmias. Because the PVCs often tended to disappear after only a few minutes of i.v. encainide, we
could not determine the plasma concentrations associated with the onset of suppression of PVCs. However, plasma concentration at the time arrhythmias returned after i.v. dosing ranged from 3.5-170 ng/ml, with an average of 39 ± 54.6 ng/ml (median 21.5 ng/ml) (table 3).

After the 75-mg oral dose of encainide, eight of the nine patients achieved greater than 90% arrhythmic suppression that lasted 3-25 hours. The average plasma concentration at the time of return of PVCs after oral dosing was 14.26 ± 16.20 ng/ml (range 1.5-48 ng/ml, median 8 ng/ml) (table 3). Six of the eight subjects who responded to encainide had considerably lower plasma concentrations at the time of arrhythmia return after oral dosing than after i.v. dosing, which suggests the possibility of active metabolites after oral dosing. For the eight patients who responded to encainide, the ratio of plasma concentration at the time of arrhythmia return after i.v. dosing to that after oral dosing ranged from 0.72-10.9 (mean 4.06 ± 3.45).

Subjects were able to tolerate high plasma concentrations of encainide without toxicity and had antiarrhythmic action that persisted in most patients even at low plasma concentrations. The minimal toxic to therapeutic ratio after oral dosing in this study ranged from 4.3-326 (median 23). The actual toxic to therapeutic ratio cannot be determined because no patient had side effects after oral dosing.

QRS duration was measured from the ambulatory ECG strips recorded at a paper speed of 25 mm/sec. Encainide resulted in an increase in QRS duration from a baseline of 96 ± 15 msec to a maximum of 127 ± 19 msec (oral) and 121 ± 18 msec (i.v.). The maximal percentage increase in QRS duration was 32 ± 11% after the oral dose (range 18-44%) and 27 ± 10% after i.v. dosing (range 11-44%).

For these patients the reduction in complex ventricular ectopics (pairs, runs, bigeminy, number of morphologies) paralleled the reduction in total ectopics and was complete or nearly complete.

Five of the subjects were placed on chronic oral maintenance therapy and are currently involved in a study of the long-term efficacy of encainide. Repeated ambulatory ECG recordings in these subjects have shown continuous and total or nearly total suppression of their ventricular arrhythmias.

Side Effects

Only patient 5 experienced side effects definitely caused by encainide. This patient experienced dizziness upon standing after the encainide infusion. At the time of her dizziness she was noted to have a normal pulse rate. She immediately returned to bed and became very anxious. She then had a decrease in blood pressure and a severe bradycardia associated with a junctional escape rhythm at a rate of approximately 25 beats/min and required atropine. It was considered that encainide had produced significant postural hypotension (decrease in systolic pressure from 110 to 80 mm Hg) or dizziness that was followed by anxiety and a vasovagal reaction, or that encainide had caused some direct depression of sinus node function. Two additional patients were started in this protocol but did not complete the study. One patient was withdrawn 12 hours after his i.v. dose of encainide because of a recurrence of sustained ventricular tachycardia that had been occurring approximately once per week. We did not consider this episode to be related to encainide therapy, because subsequent unblinded treatment with encainide resulted in total suppression of PVCs, and complete elimination of the recurrent sustained ventricular tachycardia. The other patient experienced ventricular fibrillation 2 hours after receiving oral encainide. This patient was awaiting cardiac transplantation because of numerous previous cardiac arrests and in retrospect was found to have a potassium of 3.0 the morning of his ventricular fibrillation. It is possible that encainide was a precipitating factor in the episode of ventricular fibrillation. The patient was successfully defibrillated to sinus rhythm and was not rechallenged with encainide.

Discussion

The present evaluation of encainide was designed when little was known about the clinical pharmacology or the antiarrhythmic efficacy of encainide in man. The present double-blind study was designed to provide data in both these areas in the same subjects and permit a correlation between plasma drug concentration and antiarrhythmic effect. Although efficacy was also determined before unblinding of the investigators, there was less need for blinding in this regard because the efficacy criteria were objective. Several precautions were taken to guard against misinterpretation of antiarrhythmic response because of spontaneous variability of ventricular arrhythmias. First, each patient was required to have frequent complex ventricular ectopic beats on a 24-hour screening Holter before entering into the study. Each subject was also required to have a persistence of frequent ectopic beats after hospitalization on a cardiac unit. The study was designed so we could apply the criterion

![Figure 3. Antiarrhythmic response in patient 5, who had the longest duration of antiarrhythmic effect. Duration of total suppression of premature ventricular complexes (PVCs) exceeded 24 hours after both the oral and i.v. doses.](image-url)
of 90% arrhythmia reduction persisting for 1 hour or more after acute administration of encainide, which had been defined as a reasonable criterion of drug response in a previous study in similar patient population.10 Finally, the introduction of a randomized placebo day permitted us to evaluate the degree to which spontaneous variation might result in this degree of arrhythmia suppression in our patient population.

In this study, encainide was extremely effective in suppressing chronic ventricular arrhythmias. Eight of the nine patients were antiarrhythmic responders to encainide. In all cases there could be little doubt that arrhythmia reductions were due to encainide. During i.v. dosing, the suppression of arrhythmias was immediate and after oral dosing it usually occurred within 30–60 minutes. In all instances, arrhythmia reduction was marked and sustained and arrhythmias returned after the period of arrhythmia reduction. Several of the patients had arrhythmias that were not suppressed by clinically tolerated doses of several other standard and experimental antiarrhythmic agents. In our experience with a large number of currently available and experimental antiarrhythmic drugs, the response of these patients to encainide exceeded that which we have observed with any other agent.

Our study indicates that encainide has considerable intersubject variability in pharmacokinetics and has a wide range of bioavailabilities and clearance. Its generally high clearance and short half-life seem to make it poorly suited for chronic oral antiarrhythmic therapy because of the potential need for frequent dosing. However, the drug’s very high-toxic-to-therapeutic ratio and probable active metabolite will permit a reasonable chronic oral dosing interval in most patients despite the short half-life and high clearance. This situation makes encainide unique among membrane-active antiarrhythmic compounds, because with other membrane-active drugs, which have narrow toxic-to-therapeutic ratios, infrequent dosing intervals depend on long half-lives and low drug clearances. The findings of our study agree with those of Roden et al.,10 who found that despite encainide’s 1.9–3.8-hour half-life in most patients, a wide margin between efficacy and side effects permitted a 6–12-hour dose interval.

Our measurements of bioavailability were made from areas under the plasma concentration time curves after oral and i.v. drug administration on separate days. Because the data were obtained on two separate days we cannot exclude the possibility of a slight change in clearance from day to day, which would diminish the reliability of our bioavailability calculations. However, on each day, the drug was administered under identical circumstances and there was no obvious difference in the patient’s clinical status from day to day.

In addition to the wide range of encainide’s pharmacokinetics, there appears to be wide range of minimal plasma concentrations above which ventricular arrhythmias are suppressed (i.e., the so-called minimal therapeutic plasma concentration). The fact that several patients showed a large discrepancy in plasma concentrations at which arrhythmias returned after oral and i.v. dosing suggests that some patients may form considerable amounts of an active metabolite after oral dosing. This would be compatible with the low bioavailability documented in many of these patients. Near the completion of this study a new high-pressure liquid chromatographic assay was developed, which separately measures encainide and several of its metabolites.11 Samples from one of our patients (fig. 4) were analyzed using this assay and confirmed levels of encainide metabolites that were much higher than those of the parent drug.

For many drugs, especially those with a wide intersubject variation in drug disposition as is seen with encainide after oral dosing, measuring drug plasma concentration contributes to the optimal use of the drug. However, several factors suggest that measuring the plasma concentration of encainide may not ultimately be of major value for the optimal clinical use of this compound in many situations. The wide variations in plasma concentration from very low before a dose to hundreds of times higher after a dose result in extremely wide and rapidly changing plasma concentrations over one dosing interval. Thus, extraordinarily precise timing of samples and doses would be necessary with this drug to interpret plasma concentration data correctly. Further, the wide range of minimal plasma concentrations at which effect was seen and the discrepancy of the relationship between antiarrhythmic effect and plasma concentration after oral compared with i.v. dosing (presumably due to active metabolites) would also tend to minimize the clinical value of encainide plasma concentrations. Several factors make it desirable to monitor the therapeutic effect of this drug rather than its plasma concentration. These include the marked (almost total in most patients) arrhythmia suppression, with fairly abrupt onset and offset that make it easy to monitor.

**Figure 4.** Plasma concentrations of encainide and two of its metabolites — 0-demethyl (ODM) and 3-methoxy-0-demethyl encainide — in patient 8 after oral dosing. The patient’s arrhythmias returned after 10 hours of total suppression. At that time the encainide plasma concentration was 2 ng/ml and the plasma concentration of each metabolite was more than ten times higher. (Plasma samples analyzed by Drs. Mayol and Gammans.) (Reprinted with permission from Am Heart J 100: 1051, 1980.)
antiarrhythmic effects in patients who have frequent arrhythmias. This requires only the ability to record the ECG continuously and in some manner create trend plots of arrhythmia frequency. Second, encainide has a readily available bioassay for monitoring pharmacologic effect. Because it routinely prolongs His-Purkinje and intraventricular conduction, it results in a widening of the QRS complex. In the clinical use of this drug for multiple dosing, one usually gives the drug until QRS widening is achieved and maintained throughout the duration of the dosing interval, but is not excessive after a dose. However, the exact relationship between encainide’s effect on the QRS and its antiarrhythmic actions are not fully understood. It is difficult to provide a value for the safe upper limit of QRS widening for encainide, but our experience indicates that 30–50% widening is well tolerated over long periods.

Previous studies indicate that encainide may have a unique electrophysiologic action that makes it different from other type I agents. Prototype type I antiarrhythmic agents are considered to cause a slowing of conduction in the His-Purkinje system and a prolongation of ventricular refractoriness. Encainide appears to be either a subgroup of the type I agents or a new class of antiarrhythmic compounds that possess only the former effect and not the latter. Our recent studies of procainamide and N-acetylprocainamide indicate that drug metabolites can have considerably different electrophysiologic properties from the parent compound. This may also be true for encainide, as a recent preliminary report suggests that after multiple oral doses, encainide prolongs atrial and ventricular refractory periods. One explanation for this finding would be an electrophysiologic action of encainide metabolites that is different from the parent compound.

Acknowledgment

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