Recainam, A Potent New Antiarrhythmic Agent: Effects on Complex Ventricular Arrhythmias

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The antiarrhythmic efficacy and safety of intravenous recainam, a newly synthesized compound displaying potent class I antiarrhythmic activity, were tested in 10 hospitalized patients with frequent (>30/h) complex ventricular ectopic beats. There were seven men and three women of average age 57 years (range 21 to 74); five had ischemic heart disease, three had cardiomyopathy and two had valvular heart disease. Recainam was given as a 3.0 mg/kg per 40 min loading infusion followed by a 0.9 mg/kg per h maintenance infusion over a 24 hour observation period. Arrhythmia response was assessed both in the short term (comparing 2 hours before and 1 hour after drug loading) and in the long term (comparing 48 hours before drug loading and 23 hours of maintenance infusion).

The median frequency of total premature ventricular complexes decreased in the short term by 99.6% (from 392.5 to 1.5/h, $p < 0.005$) and in the long term by 99.7% (from 435 to 1.3/h, $p < 0.01$). Repetitive beats were suppressed by a median of 100% both in the short term ($p < 0.006$) and during 24 hour infusion (from 80.9 to 0/h, $p < 0.003$). More than 90% suppression of repetitive beats occurred in all 10 patients (100%) and more than 90% suppression of total arrhythmias occurred in 9 patients (90%) during the maintenance period. Electrocardiographic PR and QRS intervals increased by 19% ($p < 0.001$) and 24% ($p < 0.003$), respectively, during therapy, but the JTc interval decreased ($p < 0.001$). Plasma recainam concentrations averaged 5.2 ± 0.9 µg/ml after loading and 3.0 ± 0.5 µg/ml during maintenance therapy. No adverse symptoms occurred.

In summary, recainam is a promising, highly efficacious and well tolerated agent when administered intravenously for short-term and maintenance suppression of complex ventricular arrhythmias. The efficacy of oral and intravenous recainam for arrhythmia management deserves further evaluation.

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There is substantial need for the development of versatile new antiarrhythmic agents, particularly those effective by both intravenous and oral routes and those effective against complex ventricular arrhythmias (1–6). The approach to antiarrhythmic therapy is currently in a state of flux because of 1) the availability for testing of several new antiarrhythmic agents and other novel therapies, and 2) evolving concepts regarding the risks of arrhythmias and the need for therapy (7,8). Because current antiarrhythmic therapy is frequently incompletely effective and often associated with adverse effects, the need for new agents with increased efficacy and reduced side effects by both intravenous and oral routes is evident in many clinical situations.

It has now been established that complex ventricular arrhythmias may be associated with an increased risk of mortality in certain clinical situations, commonly manifested as sudden death due to ventricular fibrillation (9–14). Despite this increased risk, evidence that therapy with standard antiarrhythmic agents can substantially reduce risk has not yet been established (15,16). However, studies to date have been fraught with methodologic problems and have been limited by antiarrhythmic agents with limited efficacy and excessive adverse effects. More ideal agents (17) are thus required to adequately test the "premature ventricular complex (PVC) hypothesis" of sudden death. In addition, there is a need for improved therapy of complex ventricular arrhythmias which are associated with significant symptoms (palpitation, fatigue, dyspnea, light-headedness or syncope, alone or in combination).

Recainam (WY-42,362) is a newly synthesized propylurea antiarrhythmic compound (Fig. 1) that has shown favorable pharmacologic effects in animals, suggesting therapeutic potential in humans (18,19). Preliminary results of
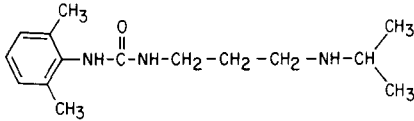
Figure 1. Molecular structure of recainam (Wy-42,362),N-(2,6-dimethylphenyl)-N'-[3-(1-methylethylamino)propyl] urea.

electrophysiologic testing in animal preparations place recainam in antiarrhythmic class I (20,21), but definitive electrophysiologic evaluation in patients has not been reported. In animal experiments, recainam increases the ventricular fibrillation threshold and leads to marked suppression of arrhythmias induced by ouabain, aconitine and coronary ligation (18). Animal pharmacokinetic data suggest a two-compartment disposition model, a half-life of about 2 hours and a substantial renal clearance (19). Initial studies (22–25) with single intravenous and oral doses of recainam in humans have suggested its potential for sustained antiarrhythmic activity. Recainam elimination half-life after a single intravenous injection was found to be 3.6 hours (23).

On the basis of this promising early testing experience, we undertook a phase II intravenous study to test the efficacy and safety of a 24 hour infusion of intravenous recainam in hospitalized patients with complex ventricular arrhythmias.

Methods

Patient selection criteria. Patients with complex arrhythmias for which therapy was recommended (that is, those causing symptoms or associated with perceived increase in mortality risk) were candidates for this study. A frequency of at least 30 premature ventricular complexes per hour was required, occurring as isolated beats, couplets or nonsustained ventricular tachycardia (ventricular tachycardia ≥ 3 successive beats but < 1 minute in duration and

not causing syncope or requiring earlier intervention). Admission to the coronary care unit and written, informed consent were required before entry into the study.

Exclusion criteria included age of 75 years or more, pregnancy, advanced heart failure (New York Heart Association functional class III or IV), uncontrolled arterial hypertension (blood pressure > 170/100 mm Hg), clinically advanced hepatic, renal, respiratory or endocrine disease, other potentially terminal illness and syncope due to tachyarrhythmia. Patients who had had a myocardial infarction within 3 months were also excluded.

Concurrent antiarrhythmic medications were not allowed, and previous antiarrhythmic drugs were discontinued for at least four half-lives before entry. Digitalis was permitted if required for treatment of congestive heart failure.

Patient entry characteristics. Ten patients were entered into the study (Table 1). There were seven men and three women with an average age of 57 ± 16 years (range 21 to 74). Underlying heart disease included coronary artery disease in five (all with previous myocardial infarction), cardiomyopathy in three and valvular heart disease in two. Left ventricular ejection fraction, determined by either radionuclide or contrast angiographic methods, averaged 0.51 ± 0.16 (range 0.35 to 0.76). Patients were further characterized by an average of 2.9 ± 1.7 unsuccessful antiarrhythmic trials (due to either intolerance or inefficacy) and qualifying arrhythmias on 24 hour ambulatory (Holter) electrocardiogram while receiving no therapy.

Study design. The study was designed as a 24 hour, open label, acute intervention protocol. The primary end point was the arrhythmia response over a 23 hour, 20 minute period (after the 40 minute loading infusion) as compared with results on the baseline 48 hour recording obtained after discontinuation of antiarrhythmic therapy and (secondarily) with those during a 24 hour postdrug washout period. Effective arrhythmia suppression was defined as an 80% or

Table 1. Patient Characteristics

Case	Age (yr)	Sex	Cardiac Diagnosis	Rhythm Diagnosis	Symptoms	Number of Previous Antiarrhythmic Trials
1	54	M	CAD	PVCs/Cps/runs	Dizziness	1
2	48	M	CAD	PVCs/Cps/runs	Palpitation	4
3	71	F	CM	PVCs/Cps/runs	Palpitation, dyspnea	5
4	61	F	CM	PVCs/Cps/runs	Palpitation	3
5	59	M	CAD	PVCs/Cps/runs	Palpitation	4
6	21	M	CM	PVCs/Cps/runs	Light-headedness	0
7	73	M	CAD	PVCs/Cps/runs	Tingling in left arm	1
8	64	F	MVP,MVR	PVCs/Cps/runs	Palpitation, fatigue	3
9	49	M	AI/AS	PVCs/Cps/runs	Palpitation	4
10	74	M	CAD	PVCs/Cps/runs	Palpitation	4
	57.4 ± 15.8	M = 7; F = 3	CAD = 5; CM = 3; VHD = 2			2.9 ± 1.7

AI/AS = aortic insufficiency/aortic stenosis; CAD = coronary artery disease; CM = cardiomyopathy; Cps = couplets; F = female; M = male; MVP = mitral valve prolapse; MVR = mitral valve regurgitation; PVCs = premature ventricular complexes; VHD = valvular heart disease.

greater reduction in total premature ventricular complex frequency during treatment and a 90% or greater reduction in repetitive forms, compared with the 48 hour baseline recording (26–28). Patients were hospitalized and, during the period of drug infusion and washout, were confined to bed (first 6 hours) or to bed-chair activities (after 6 hours), as necessitated by the continuous intravenous infusion.

The baseline recording was made after discontinuation of previous antiarrhythmic therapy for at least four half-lives. Holter monitor recordings were made on a computer-based, operator interactive system (Marquette) and analyzed by a technician unaware of patient characteristics or study treatment plan. The actual time of the control monitor recording averaged 48.4 ± 4.0 hours (range 44.4 to 59.1). Total arrhythmia frequency was subdivided into isolated beats, couplets and beats and events of nonsustained ventricular tachycardia. Ventricular arrhythmias were also documented directly by trendscription (Trendscriber, American Optical) during a 2 hour lead-in control period, during initial drug loading and for 2 hours after the loading infusion. Trendscription was used to assess short-term drug response and Holter monitoring was used to assess overall (maintenance) response. Comparisons of Holter monitor (computer-derived) and trendscription (direct count) frequency assessment of arrhythmias were made for concurrently monitored times. An excellent correlation was observed, with a correlation coefficient (r) value of 0.97 for logarithmically transformed values and greater than 0.999 for absolute values, comparing Holter- and trendscription-derived frequencies. Day to day baseline arrhythmia variability in our group was assessed by comparison of control day 1 with day 2 frequencies (28).

Recainam dosing regimen. Recainam, 15 mg/kg body weight, was diluted with 1,000 ml of 0.9% saline solution and a loading dose of 3.0 mg/kg was given over 40 minutes by constant infusion using an IVAC 560 pump (IVAC Corporation). After completion of the loading dose, a maintenance infusion was initiated at a rate of 0.9 mg/kg per h for the balance of the 23 hour, 20 minute treatment period.

Clinical observations. Continuous electrocardiographic observations were made, and interval hard copy electrocardiographic assessments were obtained as follows: 12 lead electrocardiogram before drug administration and at 1, 3, 6, 12 and 24 hours, and rhythm strips at a speed of 50 mm/s for PR, QRS and QT determinations before study and at 20 and 40 minutes and 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 18, 20, 22 and 24 hours. Simultaneously, a Holter electrocardiographic recording (for the entire 24 hour treatment period) and initially trendscription, to validate Holter assessment, for 4 hours and 40 minutes (as defined) were obtained.

Vital signs were measured frequently and recorded before drug administration (at −2, −1.5, −1 and −0.5 hours) and at 5, 10, 20 and 40 minutes and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36 and 48 hours after initiation of drug

administration. Complete blood count, 20 channel blood biochemistry survey and urinalysis were obtained before study and within 3 days of completion of drug treatment.

Blood sampling for drug levels. Blood samples for determination of recainam plasma concentrations were drawn before study, at 20 minutes into the loading period, at the completion of the loading period and at 1, 1.5, 2, 4, 8, 12, 18, 24, 26, 28, 30 and 36 hours. Samples were drawn from the arm opposite to the infusion site. Blood was collected in heparinized tubes and centrifuged immediately, and plasma was separated and frozen. Samples were analyzed by Wyeth Laboratories. Plasma concentrations of recainam were determined using the method of Kimmel (29), which is a specific, high pressure liquid chromatographic procedure. Additional blood samples were drawn at 2, 4, 8, 12 and 24 hours for on-site drug concentration assays for safety reasons and were analyzed immediately, using the same technique.

Statistical methods. Because arrhythmia frequencies and frequency responses were not normally distributed, nonparametric methods were used to establish statistical significance (30). The Newman-Keuls method was used in analyzing significance of variances in data sets (baseline, treatment, washout) and the Mann-Whitney method was used for assessing differences between any two of the three data sets where overall differences were observed. A probability (p) value of less than 0.005 was regarded as definitive of a treatment effect. The primary end points, the response during treatment versus baseline control, were analyzed using the Wilcoxon rank-sum method for paired samples. The Student paired t test was applied to assess electrocardiographic interval changes, heart rate and blood pressure changes during therapy. Arrhythmia frequency is reported as both median and mean response together with range, also because of abnormal distributions. A p value of less than 0.05 (two-tailed hypothesis) was considered significant.

Results

Baseline arrhythmia frequency. The frequency of total premature ventricular complexes on the baseline 48 hour Holter recording averaged 794/h (median 435, range 114 to 1,952). A similar frequency of 564/h (median 392.5, range 10.5 to 1,807.5), suggesting stability of arrhythmia occurrence, was also observed in these patients during the 2 hour lead-in control period. The method described by Pratt et al. (28) was used to measure spontaneous variability between baseline days 1 and 2 and to describe the reduction in premature ventricular complexes necessary to exclude spontaneous variability as a cause of suppression. The spontaneous variability was relatively small. The standard deviation was equal to 50 premature ventricular complexes/day; 99% of the total variability in premature ventricular complexes was due to differences among patients and 1% was due to spontaneous variability within patients. A reduction of only

43%, comparing the treatment day with the 2 control days, was calculated to be sufficient to exclude spontaneous variability, and hence demonstrate drug effect, within 95% confidence limits. Thus, the validity of our initial indications of therapeutic success (>80% premature ventricular complex suppression) was confirmed.

Initial Response to Recainam (0 to 1 hour after loading)

Short-term group response of ventricular arrhythmias (Table 2). Repetitive beats were essentially eliminated after drug loading (p < 0.006, Wilcoxon). The median repetitive beat frequency decreased by 100%, from 24.4 to 0/h. Mean repetitive beat suppression was 94%, from a mean of 39.5 to 2.4/h.

The suppression of total ventricular arrhythmias (total premature ventricular complexes) was also highly significant for the first hour after drug loading (p < 0.005, Wilcoxon). The median total premature ventricular complex frequency decreased by 99.6%, from 392.5 to 1.5/h. Mean total pre-

mature ventricular complex suppression was 95%, from a mean of 564 to 29/h.

Individual short-term percent suppression of premature ventricular complexes. Eight (80%) of the 10 patients had greater than 80% suppression of total premature ventricular complexes; 5 of these patients showed more than 99% suppression. The median response was 99.2% suppression. Seven (88%) of the eight patients with repetitive beats (couplets or runs) during the 2 hour lead-in control period demonstrated a successful (>90% suppression) response, with each of these patients showing complete (100%) suppression.

Arrhythmia Response During Maintenance Therapy (2 to 24 hours)

Group arrhythmia response to maintenance recainam infusion (Table 2, Fig. 2 and 3). Suppression of repetitive beats was highly significant during the maintenance infusion (p < 0.003, Wilcoxon). All patients had couplets and runs of tachycardia during the 48 hour baseline Holter recording.

Table 2. Short- and Long-Term Group Response of Ventricular Arrhythmias

Case	Baseline Arrhythmia Frequency/h*		Treatment Arrhythmia Frequency/h*	
	48 Hours	2 Hours	1 Hour After Loading	22 Hours, 20 Minutes Maintenance
1	211.9/198/6.2/0.5 —	82.5/82.5/0/0 —	1/1/0/0 (98.8/98.8/-/-)	19/19/0/0 (91/90.4/100/100
2	242.1/231/4.6/0.5 —	10.5/10.5/0/0 —	2/2/0/0 (81/81/-/-)	0.2/0.2/0/0 (99.9/99.9/100/100)
3	1,761.5/1,309/66.8/48.6 —	1,280.5/1,128/39.5/22 —	1/1/0/0 (99.9/99.9/100/100)	0.04/0.04/0/0 (97.7/97/100/100)
4	1,456/171/458.9/90.2 —	538/497/20.5/0 —	214/214/0/0 (60/56.9/100/-)	1,761.4/1,685/17.4/0.36 (-21/-885/96.2/99.6)
5	160.3/138/9.3/0.8 —	133/125/3.9/0 —	3/3/0/0 (97.7/97.6/100/-)	0.04/0.04/0/0 (100/100/100/100)
6	114.4/108/2.9/0.04 —	14.5/14.5/0/0 —	67/43/12/0 (-362/-196.5/↑/-)	2.38/2.3/0.04/0 (97.9/97.9/98.6/100)
7	1,952.4/1,348/232.6/42.1 —	1,807.5/1,726/30/6.5 —	0/0/0/0 (100/100/100/100)	0/0/0/0 (100/100/100/100)
8	1,171.5/338/62.6/62.8 —	696.5/637/29/0.5 —	2/2/0/0 (99.7/99.7/100/100)	3.7/3.7/0/0 (99.7/98.9/100/100)
9	521/422/34.9/6.8 —	828.5/827.5/0.5/0 —	0/0/0/0 (100/100/100/-)	1.1/1.1/0/0 (99.8/99.7/100/100)
10	349.8/278/33.6/0.8 —	247/193/27/0 —	0/0/0/0 (100/100/100/-)	1.5/1.5/0/0 (99.6/99.5/100/100)

*Data are presented (from left to right) as total number of premature ventricular complexes, total number of isolated premature ventricular complexes, total number of couplets and total number of runs per hour. The percent suppression of the respective arrhythmias is shown below each line in right-hand columns in parentheses.
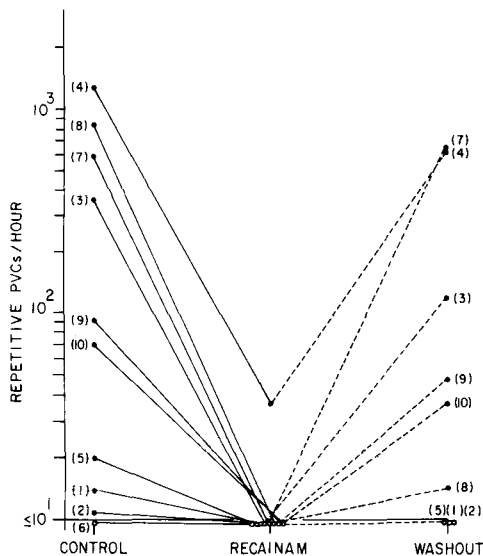
Figure 2. Individual patient responses to treatment of frequent repetitive ventricular complexes (PVCs). Treatment period is on the **abscissa**; 48 hour control, 22 hour, 20 minute drug maintenance and 24 hour postinfusion periods are presented. Individual patient entry numbers are indicated to **left** and **right** of **data points**. No washout data are available for Patient 6.

The median frequency of couplets decreased by 100%, from 34.2 to 0/h during maintenance infusion (mean couplet decrease was 98%, from 91.2 to 1.7/h, $p < 0.003$, Wilcoxon). The mean number of runs of tachycardia decreased by 99.8%, from 25.3 to 0.04/h ($p < 0.003$, Wilcoxon). The median frequency of all repetitive beats decreased by 100%, from 81 to 0/h. Mean repetitive beat suppression was 99%, from 329 to 3.6/h.

Suppression of total arrhythmias was also highly significant during the maintenance infusion ($p < 0.01$, Wilcoxon). The median total premature ventricular complex frequency decreased by 99.7%, from 435 to 1.3/h. Mean total premature ventricular complex suppression was 77.5%, from a mean of 794 to 179/h.

Individual percent suppression of premature ventricular complexes during maintenance infusion. All 10 patients (100%) showed a successful response (>90% suppression) with respect to suppression of repetitive beats. Moreover, all 10 had essentially 100% suppression of runs, and 8 had 100% suppression of couplets. The other two had greater than 96% suppression of couplets. Nine patients (90%) responded at a level of greater than 80% suppression of total premature ventricular complexes. All nine showed greater than 90% suppression, and six showed greater than 99% suppression. The median response was 99.6% suppression.

In one nonresponding patient (Case 4), percent suppression was −21%. She did, however, show partial (60%) suppression in the period immediately after drug loading at a higher recainam plasma concentration (4.95 μg/ml) than achieved during maintenance infusion (3.1 μg/ml). Her re-

petitive arrhythmias were responsive both in the short term and during maintenance infusion (97.2% suppression).

Arrhythmia Recurrence During Drug Washout

Twenty-four hour postdrug arrhythmia response (Fig. 2 and 3). The 24 hour postdiscontinuation period was not a pure "washout" period, as it began with recainam blood levels that were initially therapeutic. Recainam continued to be detectable (in low concentrations) for at least 12 hours. However, premature ventricular complexes generally recurred during this 24 hour period. For the entire postdrug day, premature ventricular complex frequency averaged 578/h (median 427, range 29 to 1,330), which was significantly greater than during therapy ($p < 0.025$, Wilcoxon). Repetitive beat frequency averaged 195/h (median 47, range 0.1 to 607), which was also a significant increase from treatment ($p < 0.004$, Wilcoxon). However, total premature ventricular complex frequency was significantly different (lower) in the first postdrug day than in the predrug baseline study, as might be expected ($p < 0.025$, Wilcoxon). Repetitive beat frequencies also differed significantly in the two periods ($p < 0.04$, Wilcoxon).

End-washout arrhythmia recurrence (22 to 24 hours). Arrhythmia frequencies during the 2 hour end-washout period were compared with those for the 2 hour predrug and 1 hour postloading responses. This comparison thus constituted a true drug washout comparison. Differences in frequency among these three periods were highly significant ($p < 0.003$, Newman-Keuls). Each control period differed from the treatment period ($p < 0.001$ to 0.003, Mann-Whitney) but not from each other. The average total pre-
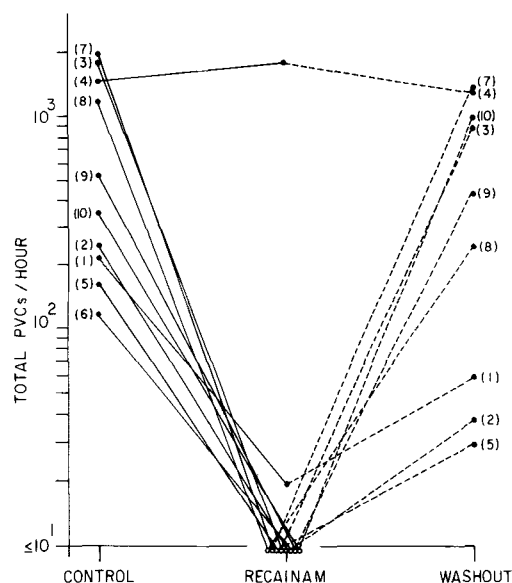

Figure 3. Individual response to treatment of total premature ventricular complex (PVC) frequency. Treatment period is on the **abscissa** (similar to Figure 2). Patient numbers as in Figure 2.

Table 3. Pharmacokinetic Variables in 10 Patients

	Measurement	
I. Plasma Drug Concentration	Cp:Mean $\pm$ SD (μg/ml)	Cp:Range (μg/ml)
A. End-loading (40 minutes)	5.2 $\pm$ 0.9	3.9 to 7.3
B. Maintenance (average 2 to 24 hours, n = 8/patient)	3.0 $\pm$ 0.5	2.0 to 4.4
	Cp:Mean $\pm$ SD (μg/ml)	Median Time (h)
C. At onset of "antiarrhythmic effect" ($\geq$80% PVC suppression)	4.5 $\pm$ 1.6	0.67
D. At escape of "antiarrhythmic effect" (<80% PVC suppression)	1.4 $\pm$ 1.1	28 (4 hours after drug discontinuation)
II. Elimination Half-Life (h)	Mean $\pm$ SD	Median	Range
	4.8 $\pm$ 0.5	4.9	3.3 to 5.1

Cp = plasma concentration; n = number of patients; PVC = premature ventricular complexes.

mature ventricular complex frequency was 476/h for the 2 hour end-washout period versus 564/h for the 2 hour baseline (p = NS, Wilcoxon). This was also the case for repetitive beat frequencies (76 versus 40/h, respectively, p = NS). Total and repetitive premature ventricular complex frequencies differed in a highly significant fashion, for the 2 hour end-washout versus the 1 hour treatment periods (p < 0.004, Wilcoxon).

Plasma Drug Kinetic Observations

Plasma drug concentrations (Table 3). Initial recainam therapy resulted in mean plasma concentrations of 5.2 $\pm$ 0.9 μg/ml (range 3.9 to 7.3) at the end of the 40 minute loading phase. Average levels during maintenance were lower but remained relatively constant from 2 to 24 hours, averaging 3.0 $\pm$ 0.5 μg/ml (range 2.0 to 4.4).

Plasma elimination half-life. The elimination half-life of recainam, after 24 hour infusion, averaged 4.8 $\pm$ 0.5 hours (range 3.3 to 5.1).

Plasma concentration-response profiles. The median suppression in arrhythmia frequency for the entire period of recainam infusion in all patients is presented together with the plasma drug concentration in Figure 4. Parallel trends in plasma drug concentrations and median responses are noted. A parallel escape in arrhythmia control was associated with decreasing drug levels in plasma after discontinuation of the recainam infusion.

The mean plasma concentration at the onset of antiarrhythmic effect (>80% premature ventricular complex suppression) during drug loading was 4.5 $\pm$ 1.6 μg/ml, and the median time of onset of suppression was 0.67 hour. Escape of antiarrhythmic effect (to <80% premature ventricular complex suppression) was observed at a median of 4 hours after discontinuation of treatment when recainam plasma concentration averaged 1.4 $\pm$ 1.1 μg/ml (range 0.6 to 3.5).

Response of Vital Signs and Electrocardiographic Intervals

The mean values of vital signs and electrocardiographic intervals are presented for the control and treatment periods (averaged) in Table 4. Electrocardiographic PR and QRS intervals, but not QT intervals, increased. Mean PR interval increased by 19%, from 188 $\pm$ 25 to 224 $\pm$ 41 ms (p < 0.001). The mean increase of QRS interval averaged 24% from a baseline of 95 $\pm$ 20 ms to a treatment interval of 118 $\pm$ 31 ms (p < 0.003). The heart rate-corrected QT (QTc) interval was unchanged (425 $\pm$ 46 ms at baseline and 419 $\pm$ 47 ms during treatment). The heart rate-corrected JT interval (JTc), which reflects independent effects on repolarization, actually decreased ($-$13%) (326 $\pm$ 39 ms at
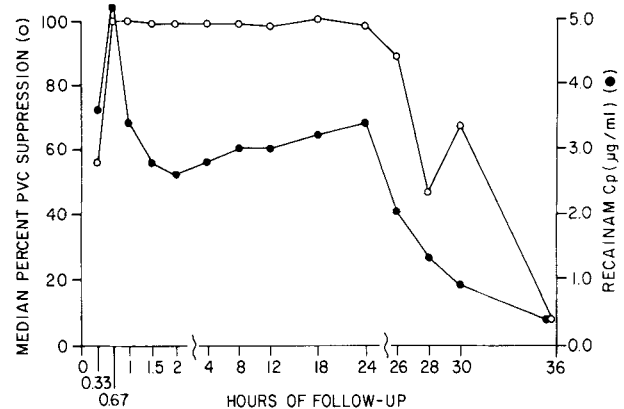

Figure 4. Comparisons of efficacy (PVC SUPPRESSION) and plasma drug concentrations (Cp) during the 36 hour observation period. Time is shown on the **abscissa**. At time zero, recainam infusion is begun and at 24 hours, recainam is discontinued. Median values for individual percent premature ventricular complex (PVC) suppression are given in the **upper curve** as **open circles** (scale is given on the **left ordinate**). Corresponding average plasma drug concentrations are shown in the **lower curve** as **closed circles** (scale is given on the **right ordinate**).

Table 4. Electrocardiographic and Hemodynamic Responses

	Control*	Recainam†	Δ (absolute)	Δ (%)	p Value
Heart rate (beats/min)	70 ± 12	75 ± 10	+ 5	↑ 7%	0.003
PR (ms)	188 ± 25	224 ± 41	+ 36	↑ 19%	0.001
QRS (ms)	95 ± 20	118 ± 31	+ 23	↑ 24%	0.003
QT (ms)	389 ± 29	368 ± 36	− 21	↓ 5%	0.003
QTc (ms)	425 ± 46	419 ± 47	− 6	↓ 1.4%	NS
JT (ms)	295 ± 27	250 ± 18	− 45	↓ 15%	0.001
JTc (ms)	326 ± 39	284 ± 25	− 42	↓ 13%	0.001
SBP (mm Hg)	130 ± 15	129 ± 12	− 1	↓ 0.8%	NS
DBP (mm Hg)	81 ± 11	86 ± 8	+ 5	↑ 6%	NS

*Baseline value, 5 minutes before infusion, except supine vital signs, which represent mean of all measurements averaged for each patient (n = 4) during 2 hour preinfusion period. †Values represent mean of all measurements averaged for each patient (n = 17) during infusion period, 5 minutes to 24 hours, except supine vital signs, averaged only until 2 hours (n = 8). DBP = diastolic blood pressure; NS = not significant; SBP = systolic blood pressure.

baseline to 284 ± 25 ms during treatment [p < 0.001]). There was a small associated increase in heart rate during therapy, from 70 ± 12 (baseline) to 75 ± 10 beats/min (drug) (p < 0.003).

A slight increase (+ 5 mm Hg) was observed in the mean diastolic blood pressure during the treatment phase, but this change did not reach significance. Moreover, diastolic blood pressure did not exceed the defined adverse effect threshold of 100 mm Hg in any patient.

Adverse reactions. No clinically significant adverse reactions attributed to recainam were noted during the infusion in any patient. No adverse individual electrocardiographic or hemodynamic changes occurred.

Discussion

Study summary. The results of the present study suggest that recainam is a highly effective new antiarrhythmic agent. Intravenous recainam rapidly attained and maintained control of complex ventricular arrhythmias in our group of 10 hospitalized patients. Symptomatic tolerance to recainam was excellent. Moderate electrocardiographic effects were noted which suggest a unique electrophysiologic profile.

Initial efficacy of intravenous recainam. The initial loading regimen of recainam was well tolerated and rapidly resulted in arrhythmia control. At the end of the 40 minute loading infusion, 7 (88%) of 8 patients showed complete suppression of repetitive beats (median response 100%) and 8 (80%) of 10 showed suppression of total premature ventricular complexes (median response, 99.2% suppression).

Sustained antiarrhythmic efficacy and safety during maintenance infusion. The initial excellent therapeutic response was maintained by the maintenance infusion dose. All 10 patients (100%) noted essentially complete suppression of repetitive arrhythmias (median response, 100% suppression). Nine patients showed greater than 90% suppression of total premature ventricular complexes, and six had greater than 99% suppression. This degree of

suppression has not been observed with other antiarrhythmic agents except, perhaps, for selected class IC agents (4,5,31,32). The response to recainam becomes more impressive in view of the nature of the patients selected for this study, with most having undergone multiple prior antiarrhythmic trials (average 2.9).

Safety and adverse response profile. The tolerance profile for recainam was equally impressive. No adverse subjective effects were noted. In particular, gastrointestinal and neurologic effects were not observed. Similarly, objective tolerance was excellent. Minor increases in diastolic blood pressure in individual patients did not pose a problem and may reflect volume expansion. No significant overall changes in blood pressure occurred.

Facilitation of ventricular arrhythmia (proarrhythmia) in a certain percent of patients is a characteristic of all antiarrhythmic drugs so far tested (33), including those with class IC effects (34,35). In our small study, a proarrhythmic response was not seen. Patient 4 showed increases in isolated premature ventricular complexes, but suppression of repetitive beats at the lower drug levels achieved during maintenance (versus loading) infusion. Greater relative suppression of repetitive than of isolated premature ventricular complexes is also characteristic of other antiarrhythmic drugs (36).

Pharmacokinetic observations. Our observations suggest that recainam plasma concentrations averaging about 3.0 μg/ml (range 2.0 to 4.4) are associated with high levels of antiarrhythmic efficacy (averaging >90% premature ventricular complex suppression), based on our maintenance drug infusion experience. The antiarrhythmic effect first appeared at higher plasma concentrations (4.5 ± 1.6 μg/ml) during drug loading than those associated with the disappearance of antiarrhythmic effect during drug washout (1.4 ± 1.1 μg/ml). This observation suggests delayed equilibration of the drug between the plasma compartment and the tissue compartment representing the site of drug action, presumably the myocardial cellular or subcellular level. Recainam's average elimination half-life of approximately 5

hours is similar to that of most available orally effective antiarrhythmic agents. It thus suggests that convenient oral dosing of recainam (three or four times a day) is feasible.

Electrocardiographic and hemodynamic effects. Recainam showed moderate effects on the electrocardiogram but little effect on vital signs during intravenous infusion. Both PR and QRS intervals increased moderately (19 to 24%) in the absence of prolongation of the QT interval. These changes are suggestive of a class IC effect (34,37). Uniquely, however, the JTc interval (heart rate-corrected JT interval, from the end of the QRS complex to the end of the T wave), a marker of independent drug effect on repolarization, actually decreased (by 13%, p < 0.001), an effect usually ascribed to class IB agents (37). Decreases in the JTc interval have not been seen with other class IC agents such as flecainide or encainide (31,32,34). Because IC agents such as flecainide occasionally have been associated with QT prolongation and proarrhythmia in susceptible patients (34,38), the apparently unique shortening effects of recainam on the JTc interval may be of particular value from a safety viewpoint. The occasional mild increases in diastolic blood pressure associated with recainam infusion have also been seen in carefully monitored studies of other intravenously active agents, including lidocaine (4), and may reflect volume loading or minor acute vasoconstrictor effects in individual patients. However, no overall change in blood pressure was observed, and no evidence for heart failure or clinical depression in myocardial function was noted.

Limitations of the present study. Limitations of our small study should be kept in mind. This was a short-term intervention study in a small and select group of patients. The study was not double-blinded, but Holter recordings are objective and were read by observers who were unaware of other patient data. Also, hospitalization of the patients may have had some effect on arrhythmia frequency. However, the extremely high degree of antiarrhythmic efficacy far exceeds the determined day to day variability in our patient group (only a 43% reduction in premature ventricular complexes was required to show drug effect within 95% confidence limits). The degree of placebo response observed in other similar studies has been low (generally 0 to 30%) (31,32,39). Adverse proarrhythmic potential, not observed here, will require assessment in a much larger group of patients. The lack of adverse hemodynamic effects must be corroborated by more objective assessments of cardiac function in larger patient groups, including those with more depressed ventricular function. Although recainam has been shown to be bioavailable when administered orally, antiarrhythmic efficacy by the oral route will require separate evaluation.

Conclusions. A clinical protocol for initial and longer term (24 hours) administration of intravenous recainam, a new antiarrhythmic drug, was completed. Excellent (un-

surpassed) antiarrhythmic efficacy and tolerance in response to recainam were observed in a group of hospitalized patients with complex ventricular ectopic activity. Recainam thus appears to be a highly promising new drug for intravenous treatment of complex ventricular arrhythmias and also appears to be suitable for evaluation of oral therapy.

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