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Electrophysiologic Effects of a New Antiarrhythmic Agent, Recainam, on Isolated Canine and Rabbit Myocardial Fibers

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Recainam (Wy 42,362) is a new antiarrhythmic agent undergoing clinical evaluation, but its electrophysiologic effects in cardiac muscle are poorly defined. With microelectrode techniques, its profile in isolated preparations of dog and rabbit hearts was determined using drug concentrations of 10 to 300 μM. Recainam induced a concentration- and frequency-dependent decrease in the maximal rate of rise of the phase 0 of the action potential ($\dot{V}_{max}$), action potential amplitude and overshoot potential, with little or no change in the effective refractory period except in Purkinje fibers, in which it was markedly reduced. At a 300 μM concentration, $\dot{V}_{max}$ was reduced 51% ($p < 0.001$) in ventricular muscle and 44% ($p < 0.001$) in atrial muscle, with no change in action potential duration or effective refractory period. At the same drug concentration in Purkinje fibers, $\dot{V}_{max}$ was decreased by 41% ($p < 0.01$), action potential duration at 90% repolarization by 36% ($p < 0.01$) and effective refractory period by 34% ($p < 0.01$). Recainam had no significant effect on the sinoatrial node, but it depressed phase 4 depolarization in isoproterenol-induced automaticity in Purkinje fibers. The drug had no effect on slow channel potentials induced by high concentrations of potassium and isoproterenol.

The data indicate that the electrophysiologic profile of recainam in isolated cardiac muscle is consistent with the overall effects of class IC agents without having an effect on the slow calcium channel. Its major action is to depress $\dot{V}_{max}$, with little effect on refractoriness. As in the case of other class IC compounds, the differential effects of recainam on the action potential duration in ventricular muscle and Purkinje fibers may predispose to the drug's proarrhythmic actions by accentuating heterogeneity in refractoriness in the heart.

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In recent years, the development of new antiarrhythmic agents for the control of ventricular arrhythmia has focused on compounds such as amiodarone (1,2) and sotalol (3,4), which act predominantly by prolonging repolarization, and on those whose major action is to inhibit depolarization (5–7). In the latter category are compounds such as encainide, flecainide, lorcainide, propafenone and indecainide. These agents have been subclassified as class IC compounds from their associated effects on repolarization and their kinetics of recovery of the fast channel after inactivation (5,6).

Recainam hydrochloride (Wy 42,362) (Fig. 1) is a new class IC antiarrhythmic agent that has been shown to elevate the ventricular fibrillation threshold and to abort ventricular tachyarrhythmias induced by ouabain or coronary artery ligation in experimental animals (8). In preliminary studies (9), it was found that the drug shortened the action potential duration in canine Purkinje fibers, in which it reduced the upstroke velocity of the action potential. The effects of the drug in other cardiac tissues are poorly defined.

The purpose of the present study was to determine the electrophysiologic profile of recainam by assessing the effects of varying concentrations of recainam in isolated tissue preparations of rabbit heart and canine Purkinje fibers and ventricle.

Methods

Experimental preparations. New Zealand white male rabbits (weighing 2.0 to 3.0 kg) were utilized for the studies

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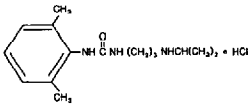


Figure 1. Chemical structure of recainam (Wy 42,362).

of the sinoatrial node and atrial myocardium. The rabbits were anesthetized with sodium pentobarbital (30 mg/kg intravenously), and the heart was rapidly removed and dissected in oxygenated Tyrode solution. Atria including the sinoatrial node were mounted with the endocardial surface facing up in a tissue bath (10 ml in volume).

Adult mongrel dogs of either sex (15 to 25 kg) were used for studies on Purkinje fibers and ventricular myocardium. After anesthesia with intravenous sodium pentobarbital (30 mg/kg), the heart was rapidly removed through a left lateral thoracotomy. Further dissection resulted in preparations that included a right ventricular papillary muscle and a portion of the endocardial right ventricular free wall with the intervening false tendons attached. Only the proximal and distal segments of the muscle were pinned to the tissue bath, leaving the Purkinje fibers undisturbed and entirely surrounded by the superfusing media. All preparations were superfused with Tyrode solution (7.5 to 15 ml/min) at 36.0 ± 0.5°C. The composition of Tyrode solution was as follows (*mM*): sodium chloride (NaCl) 130, potassium chloride (KCl) 4.0, calcium chloride ($CaCl_2$) 1:8, magnesium sulfate ($MgSO_4$) 0.5, sodium hydrogen phosphate (Na_2HPO_4) 1.8, sodium bicarbonate ($NaHCO_3$) 18.0 and glucose 5.5. Tyrode solution was bubbled with gas containing 95% oxygen (O_2) and 5% carbon dioxide (CO_2), and its pH was maintained at 7.40 ± 0.02.

Electrophysiologic recordings. Sinoatrial node preparations (rabbit) were allowed to beat spontaneously, and atrial and ventricular muscle preparations (dog) were electrically stimulated through bipolar silver wire electrodes at 2.5 and 1 Hz, respectively. Rectangular pulses at twice threshold voltage (2 ms in duration) were delivered by a Grass S88 stimulator with isolated output. Action potentials were recorded through glass microelectrodes filled with 3*M* of potassium chloride (K) (tip resistance 15 to 30 MΩ). Signals were amplified with a microelectrode amplifier (Mentor N-950) with capacity compensation and were displayed on an oscilloscope (Tektronics R564B) and photographed on Polaroid film. The maximal upstroke velocity of phase 0 of the action potential (V_{max}) was obtained by electronic differentiation. After an equilibration period of 60 to 90 min, action potentials were recorded in the standard manner. Sinoatrial node action potentials were recorded during spontaneous rhythm from the same cells throughout the entire experiment. Rabbit atrial action potentials were recorded from the crista terminalis while the adjacent myocardium was paced at 2.5 Hz.

Canine ventricular preparations were paced continuously at 1 Hz. Purkinje fiber action potentials were recorded from free-running bundles near their insertion into the right ventricular papillary muscle (the area of maximal action potential amplitude and duration). Ventricular action potentials were obtained from the papillary muscles at a site near the stimulation electrode. Effective refractory periods were determined by introducing extrastimuli having progressively shorter coupling intervals after every 8 to 10 basic paced beats. The effective refractory period was defined as the longest premature interval at which a propagated response could not be elicited.

Production of slow channel-dependent potentials. Slow response potentials (10) were produced in isolated ventricular muscle preparations stimulated at 1 Hz when superfused with Tyrode solution containing 20 m*M* of potassium chloride and 2×10^{-6} *M* of isoproterenol. The possibility of these potentials being attenuated fast response potentials was excluded by the addition of tetrodotoxin (0.2 μg/ml), which had no effect. To determine the cycle length dependency of the action potential characteristics, Purkinje fibers were stimulated at various drive cycle lengths. The effect of isoproterenol (2×10^{-6} *M*) on spontaneous discharge in Purkinje fibers was also tested before and after 3.0, 10.0 and 300 μ*M* of recainam. By this method, a detectable increase in rate and magnitude of diastolic depolarization usually developed after isoproterenol. After the effects of isoproterenol were determined and recorded in control superfusate, recainam was administered for ≥10 min before a second application of isoproterenol was made in the presence of the drug. Ascorbic acid was added to the superfusate to retard the degradation of isoproterenol.

Method of drug superfusion. For all experiments, a stock solution of recainam was prepared fresh each day by dissolving crystalline recainam hydrochloride (Wyeth Laboratories) in distilled water to make the final concentration from 1 to 300 μ*M* in Tyrode solution. Multiple concentrations of recainam were administered by the method of cumulative addition. Usually, the effects of the drug were examined after 30 min of superfusion at each concentration.

Measurements and data analysis. Variables measured from sinoatrial node action potentials were: spontaneous sinus cycle length, maximal diastolic potential, action potential amplitude, threshold potential of phase zero depolarization, slope of phase 4 depolarization, action potential duration at 100% repolarization and maximal rate of rise of phase 0 (V_{max}) (11,12). Action potentials, membrane resting potential, V_{max}, action potential duration at 50% (APD_{50}) and 90% (APD_{90}) repolarization time and effective refractory period were also measured from atria, Purkinje fiber and ventricular muscle preparations.

Because of the electrophysiologically heterogeneous na-

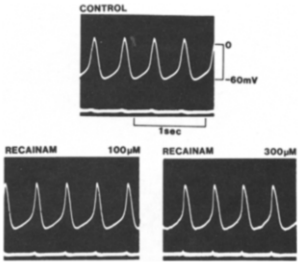


Figure 2. Effects of recainam on the action potential recorded from the sinus node in the rabbit. Note that the drug exerted a trivial or no effect on action potential characteristics, including phase 4 depolarization and threshold potential (see text).

ture of the sinoatrial node cells, only data from those experiments in which a single sinoatrial node cell remained impaled by the microelectrode throughout the study are included for analysis.

Statistical analysis. The data were analyzed statistically by analysis of variance and Student's *t* test and are expressed as mean values ± SD. The values were based on the individual averages of the data from each preparation (that is, multiple impalements).

Results

Effects of Recainam on Sinus Node and Atrial Myocardium in the Rabbit

Rabbit sinoatrial node. The effects of varying concentrations of recainam on the sinus node of rabbit were examined in three preparations (Fig. 2). Recainam did not induce any changes in action potential variables of the sinus node after 1 h of superfusion with a high drug concentration (300 μM). However, a modest shortening of the action potential duration occurred in all preparations.

Rabbit atria. The effects of recainam on rabbit atria were determined in five atrial preparations (Table 1). Recainam had no significant effect on action potential amplitude, resting membrane potential or the action potential duration at 50 or 90% repolarization time, nor was there a significant effect on the effective refractory period. However, the upstroke velocity of phase 0 (V_{max}) was decreased by recainam. There was a 22% ($p < 0.05$) reduction in V_{max} after superfusion with 30 μM and a 78% ($p < 0.05$) reduction after superfusion with 100 μM of recainam.

Effects of Recainam on Canine Purkinje Fibers and Ventricular Muscle

Effects on transmembrane resting and action potentials. The mean data demonstrating the effects of varying concentrations of recainam on canine ventricular muscle (n = 5) and Purkinje fibers (n = 5) are summarized in Tables 2 and 3. As in the case of atrial muscle, the most striking and consistent effect of recainam was on the upstroke velocity of phase 0 (V_{max}) in ventricular muscle and Purkinje fibers. In the range of concentrations used, the resting membrane potential was not altered significantly in either tissue; the effects of the drug in Purkinje fibers and ventricular muscle differed qualitatively. In Purkinje fibers, a concentration-related shortening of the action potential duration occurred at both 50% (APD_{50}) and 90% (APD_{90}) repolarization time (Fig. 3), whereas in ventricular muscle fibers there was no effect on APD_{50} and APD_{90} (Fig. 4).

A concentration of 1 μM of recainam had no significant effect on either action potential duration or V_{max}. However, 30 μM of the drug reduced V_{max} by 16.2% ($p < 0.05$) and shortened APD_{50} by 27.5% ($p < 0.05$); 100 μM of the drug decreased V_{max} by 30.3% and shortened APD_{50} by 47% ($p < 0.01$) and APD_{90} by 20.2% ($p < 0.01$) in Purkinje fibers. After superfusion of Purkinje fibers with 300 μM of recainam, the

Table 1. Effects of Recainam on the Electrophysiologic Properties of Rabbit Atrial Muscle (five preparations)

Condition	APA (mV)	MRP (mV)	V_{max} (V/s)	APD_{50} (ms)	APD_{90} (ms)	ERP (ms)
Control	103 ± 6	84 ± 3	198 ± 43	45 ± 5	79 ± 6	85 ± 2
Recainam 10 μM	102 ± 8	81 ± 3	200 ± 66	43 ± 5	79 ± 10	86 ± 2
Recainam 30 μM	95 ± 5	83 ± 2	145 ± 21*	42 ± 3	80 ± 5	88 ± 7
Recainam 100 μM	88 ± 3	81 ± 2	111 ± 42†	40 ± 4	79 ± 13	93 ± 7

Statistical significance of difference from control: *$p < 0.05$, †$p < 0.025$. APA = action potential amplitude; APD_{50} and APD_{90} = action potential duration at 50 and 90% repolarization time, respectively; ERP = effective refractory period; MRP = membrane resting potential; V_{max} = maximal upstroke velocity of phase 0 of the action potential.

Table 2. Effects of Recainam on the Action Potential Variables of Canine Ventricular Muscle

Condition	APA (mV)	MRP (mV)	V_{max} (V/s)	APD_{50} (ms)	APD_{90} (ms)	ERP (ms)
Control (n = 12)	99 ± 8	80 ± 5	188 ± 15	169 ± 22	198 ± 24	211 ± 18
Recainam 10 μM (n = 9)	105 ± 7	78 ± 5	172 ± 27	170 ± 11	212 ± 10	223 ± 15
Recainam 30 μM (n = 12)	105 ± 6	80 ± 4	144 ± 35*	168 ± 23	213 ± 32	215 ± 24
Recainam 100 μM (n = 9)	99 ± 7	79 ± 4	113 ± 33*	164 ± 11	212 ± 17	210 ± 11
Recainam 300 μM (n = 7)	95 ± 9	78 ± 4	92 ± 42† (−51%)	160 ± 24	196 ± 31	200 ± 40

Significance of difference from control: *p < 0.01; (n) indicates the number of animals from which data were obtained. Five to 10 impalements were made for the study condition in each preparation for all the studies. Abbreviations as in Table 1.

$\dot{V}_{max}$ diminished by 46% ($p < 0.01$) and APD_{50} was shortened by 49.8% ($p < 0.01$) and APD_{90} by 29.2% ($p < 0.05$). In ventricular muscle, there was a 28.4% ($p < 0.01$) reduction in $\dot{V}_{max}$ after superfusion with a 30 μM concentration, a 39% reduction ($p < 0.01$) after a 100 μM concentration and a 46% reduction ($p < 0.01$) after a 300 μM drug concentration.

In Purkinje fibers, the reduction in $\dot{V}_{max}$ was accompanied by a decrease in the action potential amplitude and the effective refractory period shortened in parallel with the acceleration of repolarization. In ventricular muscle, there was no significant change in the effective refractory period.

Changes in membrane responsiveness. The effect of recainam on the relation between $\dot{V}_{max}$ and membrane potential (membrane responsiveness) in Purkinje fibers was determined by the use of premature excitation at different coupling intervals during phase 3 of the action potentials elicited at a constant driven frequency of 1 Hz. This was tested under control conditions and after superfusion successively with 10, 30 and 60 μM concentrations of recainam: the membrane responsiveness curve was consistently shifted in the hyperpolarizing direction as a function of drug concentration.

At 30 and 60 μM, recainam abolished the premature responses from reduced membrane potentials that were associated with a low $\dot{V}_{max}$. For example, under control conditions, the earliest response could be evoked from a membrane potential of −60 mV, with a $\dot{V}_{max}$ of 40 V/s. After superfusion with 10 μM of recainam, there was a minimal effect. At higher concentrations of the drug, a response was elicited only at a higher membrane potential. At 30 μM concentrations of recainam, premature responses could not be elicited until −70mV was reached; the $\dot{V}_{max}$ of such an action potential was 145 V/s.

Table 3. Effects of Recainam on the Electrophysiologic Properties of Canine Purkinje Fibers

Condition	APA (mV)	MRP (mV)	V_{max} (V/s)	APD_{50} (ms)	APD_{90} (ms)	ERP (ms)
Control (n = 11)	116 ± 8	86 ± 7	480 ± 56	258 ± 38	331 ± 49	317 ± 41
Recainam 10 μM (n = 7)	116 ± 9	84 ± 5	454 ± 57	256 ± 23	342 ± 28	323 ± 28
Recainam 30 μM (n = 11)	116 ± 7	82 ± 6	398 ± 100*	169 ± 26†	259 ± 34†	238 ± 37†
Recainam 100 μM (n = 7)	102 ± 8† (−12%)	83 ± 3	337 ± 62† (−30%)	126 ± 16† (−51%)	232 ± 15† (−30%)	215 ± 17† (−32%)
Recainam 300 μM (n = 5)	103 ± 10* (−11%)	80 ± 5	277 ± 67† (−40%)	121 ± 14† (−53%)	213 ± 19† (−36%)	210 ± 34† (−34%)

Significance of difference from control: *p < 0.025, †p < 0.01. Abbreviations as in Table 1.

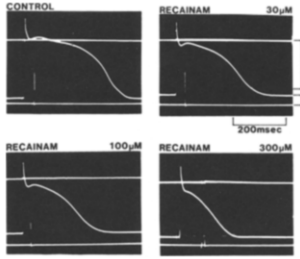


Figure 3. Changes in canine Purkinje fiber potentials induced by recainam as a function of drug concentration. In each panel, the **upper trace** shows zero potential, the **middle trace** shows the time course of the transmembrane action potential and the **lower trace** shows the maximal rate of rise of the phase 0 of the action potential duration ($\dot{V}_{max}$). Note the stepwise decrease in $\dot{V}_{max}$ as a function of drug concentration and the progressive acceleration in phases 2 and 3 of the action potential duration. This was accompanied by a corresponding decrease in the effective refractory period (see text).

Frequency-dependent effects on the $\dot{V}_{max}$ of the action potential. The pertinent data from studies obtained at each stimulus frequency (from 1 to 5 Hz) from five Purkinje fibers were analyzed. The $\dot{V}_{max}$ was determined 5 min after the change in frequency after the duration of stimulation. A steady state change in $\dot{V}_{max}$ had been established in all preparations before recainam was administered. The $\dot{V}_{max}$ was only slightly affected over the entire range of frequencies used under control conditions before recainam was given. At each increment in frequency, recainam had a significantly greater depressant effect on $\dot{V}_{max}$. The difference was evident not only when the data were analyzed by comparing individual values with the control values, but also when the effect was tested on the basis of the slopes of the changes induced by different stimulus frequencies at a given drug concentration. At 300 μM, it was not possible to elicit a response at stimulus frequencies >3 Hz. The frequency-dependent reduction in $\dot{V}_{max}$ induced by recainam was also found in canine ventricular muscle fibers and rabbit atrial muscle fibers.

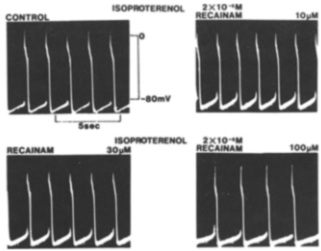
Effects of recainam on automaticity in canine Purkinje fibers. The effects of recainam on enhanced automaticity induced by isoproterenol were determined in three Purkinje fiber preparations (Fig. 5). Superfusion with isoproterenol (2×10^{-6} M) induced regular spontaneous firing at a mean rate of 48 beats/min. Lower concentrations of recainam (10 and 30 μM) did not reduce the mean rate of firing, but there was a decrease in the mean rate of firing to 36 beats/min at the high concentration (100 μM).

Effects on slow response action potentials in canine Purkinje and ventricular muscle fibers. Figure 6 shows a representative set of records illustrating the effects of recainam on slow channel-dependent potentials in ventricular muscle fibers induced by high extracellular potassium concentration (K^+_o) and isoproterenol (2×10^{-6} M). Similar recordings could be obtained in Purkinje fibers. The characteristics of the slow channel potentials produced in this manner were not influenced by the addition of tetrodotoxin (10.2 μg/ml). The highest concentration of recainam had no significant effects on the slow response (Fig. 6). However, slow response action potentials were abolished when verapamil (1×10^{-5} M) was added to the superfusate.

Discussion

Electrophysiologic effects of recainam. Antiarrhythmic agents have been shown to exert their salutary effects in preventing arrhythmias by blocking the fast sodium channels, inhibiting the electrophysiologic effects of sympathetic transmitters to the heart, by selectively lengthening the cardiac action potential or by inhibiting the slow response potentials in cardiac tissues (13–15). Our data with the new antiarrhythmic agent recainam hydrochloride indicate that the compound exerts its dominant electrophysiologic action by an effect on the fast sodium channel. This is inferred from changes in $\dot{V}_{max}$ in atrial and ventricular tissues, as well as in Purkinje fibers in which the drug shifted the membrane-responsiveness curve in the hyperpolarizing direction. Furthermore, recainam exerted a potent depressant effect on $\dot{V}_{max}$ as a function of stimulus frequency. The drug was devoid of effects on slow response potentials induced in

Figure 4. Effects of recainam on the action potentials recorded from canine ventricular myocardium. Note the striking effect on $\dot{V}_{max}$, which is markedly reduced by the drug, especially at higher concentrations. Unlike the effect in Purkinje fibers, the time course of repolarization is not altered.



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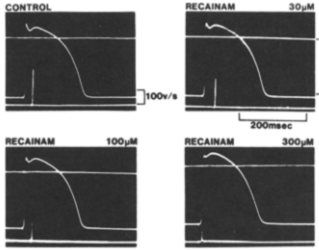


Figure 5. Effects of varying concentrations of recainam on automaticity induced by isoproterenol in canine Purkinje fibers. Note that at the highest concentration of recainam (100 μM), phase 4 is significantly depressed, leading to a slowing of automaticity.

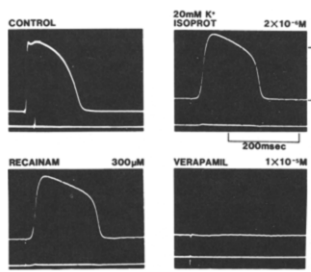
Purkinje fibers and ventricular muscle by depolarizing concentrations of potassium in the presence of isoproterenol.

Comparison with the actions of other antiarrhythmic agents. Our data indicate that the overall effects of the drug are consistent with a class I electrophysiologic action. However, the effects of recainam differed from the known actions of quinidine, procainamide, or disopyramide, which retard the terminal phase of repolarization and markedly increase myocardial refractoriness. In ventricular and atrial muscle, recainam had no significant effect on the action potential duration, there being no effect on the effective refractory period. In contrast, in canine Purkinje fibers, it produced a marked *shortening* of the action potential duration, with a corresponding reduction in the effective refractory period. The effects on repolarization in ventricular and Purkinje fibers induced by recainam are thus similar to those reported by our laboratory (6) for flecainide. As in the case of other class I agents, recainam shifted the membrane-responsiveness curve in the hyperpolarizing direction, consistent with a change in dependence on voltage of the inactivation of the sodium channels. Our data also emphasize the use-dependent nature of the inhibitory effects of recainam on sodium channels over a wide range of stimulus frequencies, a characteristic property of local anesthetic types of antiarrhythmic compounds (6,7,16). In the present series of experiments, the onset and offset kinetics of $\dot{V}_{max}$ depression were not determined. However, in an independent study in our laboratory (Kamiya et al., unpublished observations), the recovery time constant of the slow phase of sodium channel reactivation varied between 13.3 to 17.2 s. These values are comparable with those previously reported for flecainide (5), lorcainide (17) and propafenone (18,19), all of which, on the basis of offset kinetics of $\dot{V}_{max}$, are included in the category of class IC antiarrhythmic agents (5). They are likely to exert a comparable spectrum of antiarrhythmic actions.

Effects of recainam on myocardial refractoriness. In common with other class IC agents, recainam exerted a marked depressant effect on $\dot{V}_{max}$, the major determinant of conduction. However, there was little or no effect on the effective refractory period in the atrium and ventricle, but a marked shortening commensurate with the abbreviation of the action potential duration at 90% repolarization time was found in Purkinje fibers. Again, such an effect is characteristic of class IC agents such as flecainide (6,17) lorcainide (17), propafenone (20) and encainide (21). As with these agents, the effective refractory period in the Purkinje fiber under the action of recainam was significantly shortened despite a marked reduction in $\dot{V}_{max}$. This did not occur either in ventricular muscle or in the atria, in which repolarization was not affected and, despite significant decreases in $\dot{V}_{max}$, the effective refractory period also did not change. In the case of recainam, the differential effect on repolarization in Purkinje fibers and ventricular muscle, shortening it in the former and lengthening it in the latter, is a property that the compound shares with other class IC agents. As suggested elsewhere (6), such a proclivity is likely to exaggerate heterogeneity in the recovery of excitability in cardiac muscle, thereby producing a tendency toward focal reexcitation, a potential basis for the arrhythmogenic effects of class IC agents (22).

Clinical and experimental correlations and therapeutic implications. Although experimental data cannot be extrapolated directly to the clinical setting, the preliminary elec-

Figure 6. Effects of recainam and verapamil on the slow response action potentials in ventricular muscle fiber. Note the development of a slow response potential in a medium of potassium (K^+) (20 mM) and isoproterenol (ISOPROT) (2×10^{-6} M). Note also that after superfusion with 300 μM of recainam, there is no effect; in verapamil (1×10^{-5} M), the slow response potential is abolished. Recainam is, therefore, devoid of calcium channel blocking actions.



trophysiologic findings in human patients are in accord with our in vitro data. Intravenous administration of recainam in humans (Luceri et al., unpublished observations) produced a prolongation of the QRS duration and the HV interval (a measure of infranodal conduction), with a slight increase in the effective refractory period in ventricular myocardium; there was no effect on the corrected QT interval. These overall findings are consistent with a predominant inhibitory effect on the fast sodium channels. Because recainam reduced the tendency for spontaneous activity in Purkinje fibers and exerted a markedly depressant action on $\dot{V}_{max}$ (and thus conduction) in our studies, the drug is likely to be effective in suppressing arrhythmias due to both automaticity and reentry.

The potent inhibitory effect of recainam on conduction should be emphasized. It is likely to be the basis for its markedly suppressant effect on premature ventricular and supraventricular beats because these are not likely to propagate in the presence of the drug. On the other hand, the drug's marked depressant effect on conduction is likely to aggravate existing conduction system disease and elevate the threshold of excitability, which may interfere with the function of artificial pacemakers. Furthermore, recainam's potential to produce a differential effect on repolarization in Purkinje fibers and ventricular muscle, coupled with severe depression in conduction, may be the basis for the development of proarrhythmic actions, as is the case with all class IC agents. However, the induction of torsade de pointes is unlikely because repolarization is not lengthened by the drug.

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