特 集 (special edition)

Arrhythmias associated with myocardial ischemia and their modulation by antiarrhythmic drugs

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Introduction

Arrhythmias occurring on myocardial ischemia are common among cardiac patients and have been good targets for pharmacological and other antiarrhythmic treatments. Such arrhythmias often occur suddenly and become very serious transforming into ventricular fibrillation (VF). We have been studying the efficacy of various antiarrhythmic drugs on ventricular arrhythmias occurring in the chronic phase of canine myocardial infarction, i. e. two-stage coronary ligation arrhythmia[1,2]. Class I, II, III and IV antiarrhythmic drugs and also coronary vasodilators and positive inotropic agents were examined. In those studies, the antiarrhythmic plasma concentration data were obtained. Plasma concentrations which produced 50% reduction of the control arrhythmias, IC_{50}, were used for quantitative comparison of the potencies of antiarrhythmic drugs.

Also we have started experiments using ventricular arrhythmias occurring in the acute phase of myocardial ischemia, occurring during ischemia, and those occurring on reperfusion in dogs using several class III agents[3,4].

This review summarizes our results of drug effects on these two stage coronary ligation, acute ischemia induced and reperfusion arrhythmias in dogs.

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Two-stage coronary ligation induced ventricular tachycardia

All the experiments were performed in accordance with Guidelines for Animal Experiments, Yamanashi Medical College.

As reported earlier[1,2], beagle dogs were anesthetized initially with intravenous thiopental Na and intubated. The chest was opened and a two-stage coronary ligation of the left anterior descending artery (LAD) was performed under halothane anesthesia.

Experiments were done without anesthesia 24 and 48 hr after coronary ligation. Drugs were given by either intravenous bolus injection, intravenous infusion or oral administration. Venous or arterial blood samples were drawn for drugs plasma concentration determinations.

Summary of drug actions on the two-stage coronary ligation arrhythmias

After two stage coronary ligation, ventricular ectopic beats started to appear 6-8 hours after the ligation as the heart rate gradually increased, and about 1 day after the ligation, the arrhythmia turned to multifocal ventricular tachycardia (VT), with almost no conducted beats[1,2]. This arrhythmia might be classified as that equivalent to Lown's classification[5] of

4B, and it did not spontaneously turn to ventricular fibrillation (VF). After 24 hr of ligation, the total heart rate was about 200/min, and gradually decreased afterwards, but the VT equivalent to 3 or 4A Lown's classification continued at least until the 2nd day. Effective drugs given to the dog under an unanesthetized condition decreased the number of conducted beats and arrhythmic ratio (ratio of the number of ectopic beats divided by the total heart rate), as its plasma concentration rose, and usually the changes in the plasma concentration paralleled the changes in the arrhythmic ratio. This arrhythmia was stable and long-lasting, so useful for studying not only drug effects on arrhythmia but also on the central nervous and circulatory effects. It differs, however, from most of the clinical arrhythmias of acute

Table 1 Antiarrhythmic drugs on canine two-stage coronary ligation ventricular arrhythmias

Drugs	Canine antiarrhythmic plasma concentration (IC_{50}, μg/ml) for Coronary ligation Arrhythmia	In vitvo Na-channel block conc.(μg/ml)	kinetics	Action potential duration	Canine Ca-channel block
Class I					
AFD-19	4.2	0.9	Slow	(-)	
AHR 10718	9.0	2		Shorten	
AN-132	8.3	5	Slow		
Aprindine	5.2	0.5	Slow	Shorten	
Bidisomide	15.1	4	Slow	Shorten	
Cibenzoline	3.7	0.5-1	Slow	(-)	(+)
Disopyramide	5.9	5	Slow	Lengthen	(+)
E-0747	3.6	1	Slow	Shorten	
Etacizin	0.83	0.1	Slow	(-)	
Flecainide	4.6	3	Slow	(-)	
KW-3407	8.1	5	Slow	Lengthen	?
Lidocaine	14.7	10	Fast	Shorten	(-)
Mexiletine	3.3	2	Fast	Shorten	
Nicainoprol	21.7	4		Shorten	
NS-2	4.3	0.8	Slow	(-)	(-)
OPC 88117	23.0	29	Fast	Lengthen	(+)
Penticainide	7.9	6	Slow	Shorten	
Phenytoin	17.8	5-20		Shorten	(+)
Pilsicainide	5.8	3	Slow	Shorten	
Pirmenol	1.2	0.4-4		Lengthen	
Procainamide	98.9	30	Slow	Lengthen	(-)
Propafenone	4.5	0.25-2	Slow	Shorten	(+, β-Block)
SA 3212	52.8	2	Fast	Shorten	(+)
Tocainide	9.7	60	Fast	Shorten	
TYB-3823	16.2	0.7	Slow	Shorten	(+, β-Block)
YUTAC	0.48	0.3-1	Slow	(-)	(+)
Class II					
Betaxolol	(-)	30			(β-Block)
Bupranolol	(-)	(+)			(β-Block)
Pindolol	2.4	6			(β-Block)
Tilisolol (N-696)	7.6	60			(β-Block)
Class III					
Amiodarone	(+)	(+)	Fast	Lengthen	(+)
E-4031	(-)	(-)		Lengthen	(-)
MS-551	(-)	(-)		Lengthen	(-)
d-Sotalol	(-)	(-)		Lengthen	(β-Block?)
Class IV					
Gallopamil	(-)	(+)			(+)
KT-362	8.1	1.5-5	Slow	(-)	(+)
Verapamil	(-)	10			(+)
Miscellaneous					
Dilazep	(+)				
Milrinone	(-)	(-)		(-)	
OPC 18790	(-)	(-)			
Vesnarinone	(-/W)	(-)		Lengthen	

myocardial infarction in that it never turned to VF. The mechanism of generation of this arrhythmia may be mainly due to increased automaticity of the surviving Purkinje fibers[6], and it was observed that atrial or ventricular overdrive stopped the arrhythmia.

Table 1 summarizes effects of drugs we have studied on the canine 24 hr coronary ligation arrhythmias. New class III agents, E-4031, MS-551 and d-sotalol, which increase QT interval after i. v. injection, did not show antiarrhythmic effects[4]. Lidocaine is listed as ineffective, because at the concentration attained, conscious dogs responded to lidocaine with strong but not fatal central nervous system stimulatory effects, including convulsions. Nicorandil is a K channel opener and used as an effective antianginal agent, but did not show any antiarrhythmic effect on the arrhythmia[7].

Drugs other than class I drugs also suppressed this arrhythmia, but only at plasma concentrations suppressing Na channels. They are β blockers with membrane stabilizing action, pindolol and tilisolol, and a coronary dilator, dilazep[2]. Class IV Ca channel blockers were not effective on this arrhythmia, except for KT-362. Thus we think that Na channel block is the mechanism of antiarrhythmic action of drugs on this arrhythmia based on similarity between the *in vitro* Na channel blocking and antiarvlythmic plasma concentrations of class I drugs[2]. How does the Na channel block relate to the antiarrhythmic efficacy? Theoretically it can suppress intraventricular or intraatrial conduction to endanger stable reentry excitation, or decrease automaticity of Purkinje fiber. It is usually difficult, however, to identify which property is primarily responsible for the antiarrhythmic action of a drug. We used the isolated blood-perfused ventricular preparation to approach this problem[8]. This preparation was made from two dogs, the larger dog served as a donor and smaller was used as a recipient. The heart was excised and the papillary muscle preparations consisting of an anterior papillary muscle attached to the intraventricular septum were used. The anterior septal artery (ASA) was directly cannulated and the His bundle of the ventricular septum was electrically driven. The intraventricular conduction time was measured as the time between the stimulus artifact and distal electrogram at the tip of the

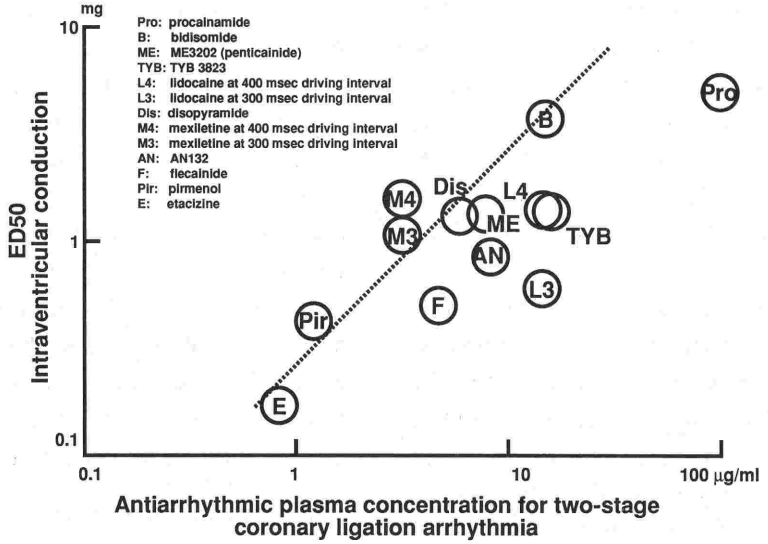

Fig. 1 Correlation between the Na channel blocking effect (to decrease intraventricular conduction) and the antiarrhythmic effect for two-stage coronary ligation arrhythmia.

papillary muscle. Class I drugs injected into the ASA prolonged the conduction time dose-dependently. The doses that produced a 50% increase in the intraventricular conduction time, ED_{50} (IVCT) was calculated for class I drugs. We examined the correlation between the intraarterial ED_{50} doses and the effective plasma concentrations obtained in the two-stage coronary ligation arrhythmia studies. As shown in Fig. 1, there is a good correlation and this may indicate that the antiarrhythmic mechanism of a class I drug is closely related to the decrease in the intraventricular conduction.

Arrhythmias occurring on acute myocardial ischemia and reperfusion

Beagle dogs were used and most of them were anesthetized initially with intravenous thiopental Na and intubated. Anesthesia was maintained by 1.0% halothane and the chest was opened and the LAD was isolated just proximal to the first diagonal branch. Drugs were infused intravenously. Since the incidence of occurrence of coronary occlusion arrhythmias and reperfusion arrhythmias is known to be quite variable, experiments were randomized using a pair of beagles (by coin-flip); one received drug infusion and the other received saline infusion. After 30 min of the start of the drug or saline infusion, LAD ligation was performed using a silk thread for 30 min then released to examined reperfusion responses. The drug solution was infused during the whole course of the experiment.

QT interval was assessed from the lead II ECG and the ventricular surface electrogram at a fast 100 mm/sec recording speed. The QTc interval was calculated using Bazett's formula, $QTc=QT/\sqrt{RR}$. Arterial blood samples were obtained through another lumen of the cannula just before 1) the start of drug infusion, 2) LAD occlusion and 3) LAD reperfusion.

In a part of d-sotalol experiments, beagles were anesthetized with pentobarbital Na. Other procedures were the same as the experiments described above and the effects of 10 mg/kg/h d-sotalol were examined.

MS-551

The speed of MS-551 infusion employed was 3.6 mg/kg/h. The heart rate and mean blood pressure in beagles anesthetized by halothane, were 108 ± 8 beats/min and 99 ± 10 mmHg ($n=12$). The QTc interval in the saline injected beagles was 0.27 ± 0.01 sec and did not change significantly just before LAD occlusion. As shown in Fig. 2, 30 min of infusion of MS-551 induced torsades de pointes type VT in one dog, but no arrhythmias occurred by saline infusion. During the 30 min of LAD complete occlusion, ventricular arrhythmias including ventricular premature contractions (VPCs) and VT defined as more than three consecutive VPCs occurred in both the MS-551 and saline treated beagles, and there were no statistically significant differences in the number of total VPCs in the 30 min of occlusion, 517 ± 641 and 222 ± 339 ($n=6$) beats/30 min, respectively. However on reperfusion only 1 beagle out of 6 died of reperfusion VF in the MS-551 treated group as compared to 5 beagles out of 6 in the saline treated group as shown in Fig. 3. These fatal VF occurred soon after reperfusion. The QTc interval in the MS-551 injected beagles was 0.29 ± 0.05 sec and increased significantly just before LAD occlusion to 0.43 ± 0.10 sec (48%) and just before LAD reperfusion to 0.42 ± 0.10 sec (45%). The heart rate during the sinus rhythm decreased only 8% in the saline treated beagles, but decreased in the MS-551 treated group 22% just before LAD occlusion and 25% before reperfusion. MS-551 linearly increased QTc as the plasma concentration increased.

d-Sotal in halothane anesthetized beagles

The d-sotalol infusion speed of 10 and 15 mg/kg/h was employed. As shown in Fig. 4,

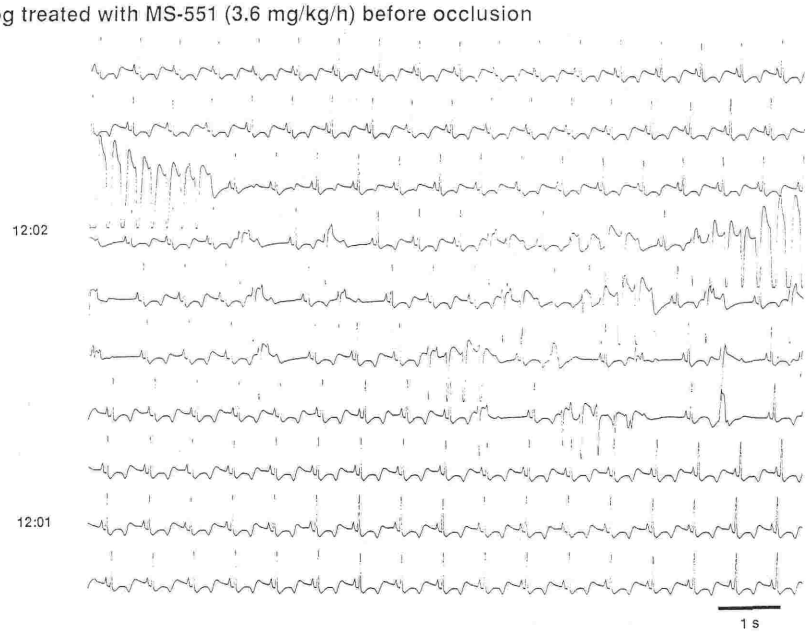

Fig. 2 Arrhythmogenic effect of MS-551 observed during the control period of coronary ligation and reperfusion arrhythmia experiment.

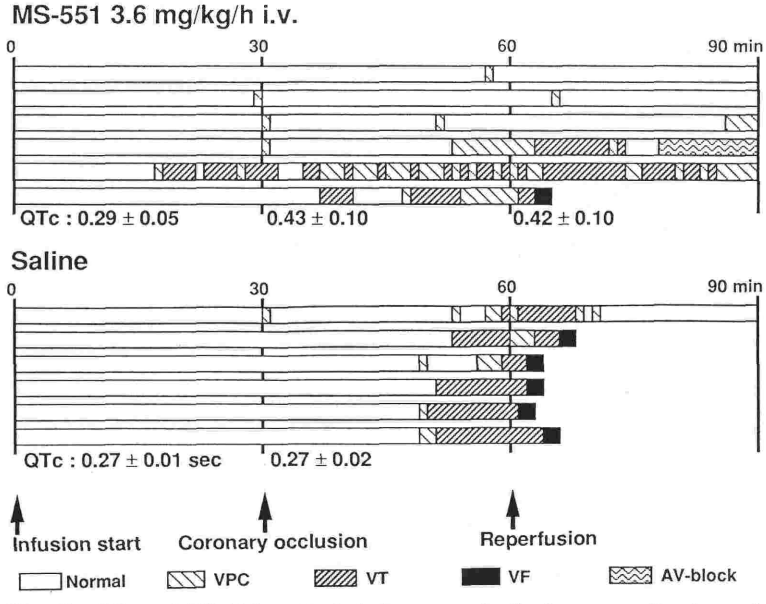

Fig. 3 Effect of MS-551 on the halothane anesthetized coronary ligation and reperfusion arrhythmia experiment.

30 min of infusion of d-sotalol and saline did not induce any ventricular arrhythmias. During the 30 min of LAD occlusion, ventricular arrhythmias including VPCs and VT occurred in both the d-sotalol, 10 mg/kg/h, and saline treated beagles, and there were no statistically significant differences in the number of total VPCs in the 30 min of occlusion. However on reperfusion 3 beagles out of 7 died of reperfusion VF in d-sotalol, 10 mg/kg/h, treated group and 3 beagles out of 7 of saline treated group died as shown in Fig. 5. The QTc interval in

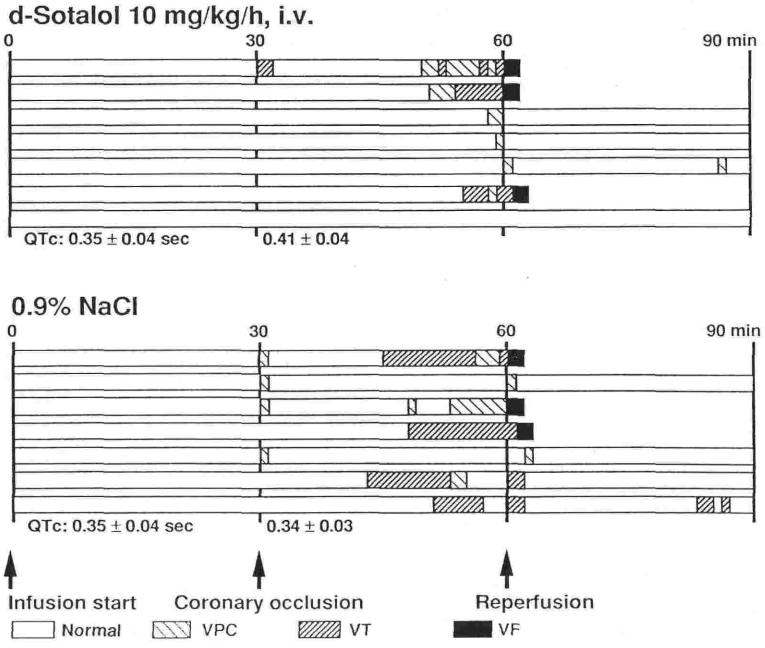

Fig. 4 Effect of 10 mg/kg/h d-sotalol on the halothane anesthetized coronary ligation and reperfusion arrhythmia experiment.

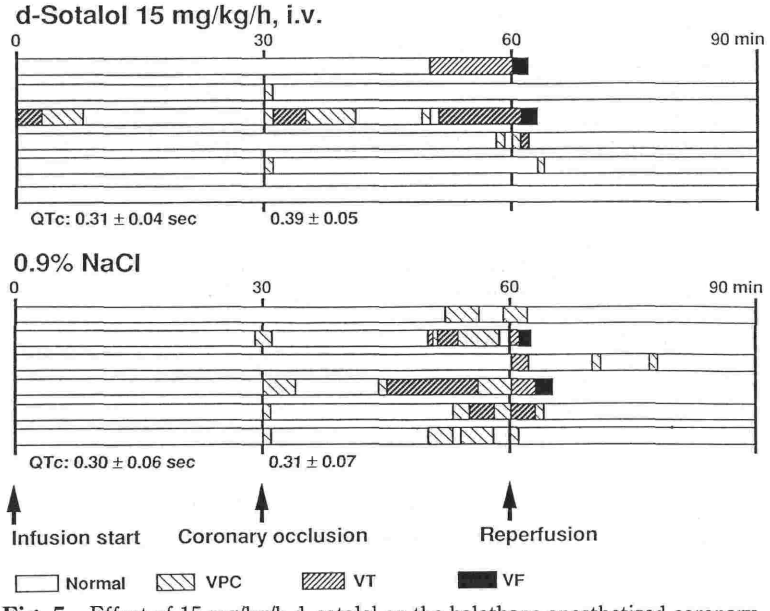

Fig. 5 Effect of 15 mg/kg/h d-sotalol on the halothane anesthetized coronary ligation and reperfusion arrhythmia experiment.

the d-sotalol, 10 mg/kg/h, infused beagles was 0.35±0.04 sec and increased 17% just before LAD occlusion. The heart rate decreased 23% in the d-sotalol, 10 mg/kg/h, treated group just before LAD occlusion.

Since there was no antifibrillatory effect in the d-sotalol, 10 mg/kg/h, treated group, another experiment using d-sotalol 15 mg/kg/h was performed. As shown in Fig. 5, 30 min of infusion of d-sotalol and saline did not induce

any ventricular arrhythmias. During the 30 min of LAD occlusion, VPCs and VT occurred in both the d-sotalol, 15 mg/kg/h, and saline treated beagles, and there were no statistically significant differences in the number of total VPCs in the 30 min of occlusion. However on reperfusion 2 beagles out of 6 died of VF in d-sotalol, 15 mg/kg/h, treated group and 2 beagles out of 6 of saline treated group died as shown in Fig. 5. The QTc interval in d-sotalol, 15 mg/kg/h, injected beagles was 0.31±0.04 sec and increased 26% just before LAD occlusion. The heart rate decreased in the d-sotalol, 15 mg/kg/h, treated group 30% just before LAD occlusion. d-Sotalol linearly increased QTc as the plasma concentration increased.

d-Sotalol in pentobarbital anesthetized beagles

Since there have been reports that d-sotalol is effective against reentry experimental arrhythmias models under pentobarbital anesthesia[9], we repeated the 10 mg/kg/h d-sotalol experiment in pentobarbital anesthetized beagles. The heart rate and mean blood pressure were 177±25 beats/min and 123±14 mmHg (n=14). The QTc interval in the saline injected beagles was 0.34±0.03 sec and did not change significantly just before LAD occlusion. As shown in Fig. 6, 30 min of infusion of d-sotalol induced VPCs and VT in one beagle. During the 30 min of LAD occlusion, VPCs and VT occurred in both the d-sotalol, 10 mg/kg/h, and saline treated beagles, and there were no statistically significant differences in the number of total VPCs in the 30 min of occlusion, and one beagle in d-sotalol group died of VF. However on reperfusion only 1 beagle out of 6 died of VF in d-sotalol, 10 mg/kg/h, treated group as compared to 4 beagles out of 7 in the saline treated group. The QTc interval in the d-sotalol, 10 mg/kg/h, injected beagles was 0.35±0.02 sec and increased 11% just before LAD occlusion. The heart rate decreased in the d-sotalol, 10 mg/kg/h treated group 33% just before LAD occlusion. d-Sotalol linearly increased QTc as the plasma

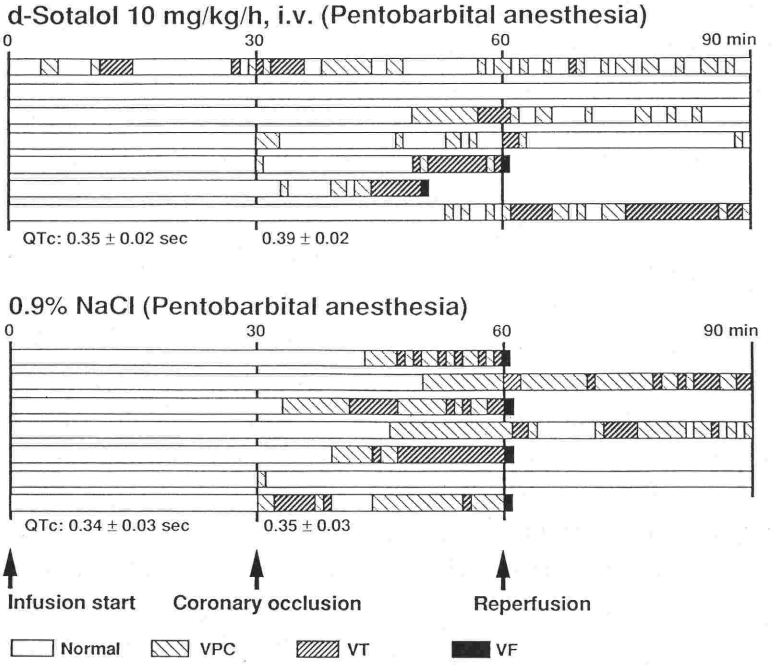

Fig. 6 Effect of 10 mg/kg/h d-sotalol on the pentobarbital anesthetized coronary ligation and reperfusion arrhythmia experiment.

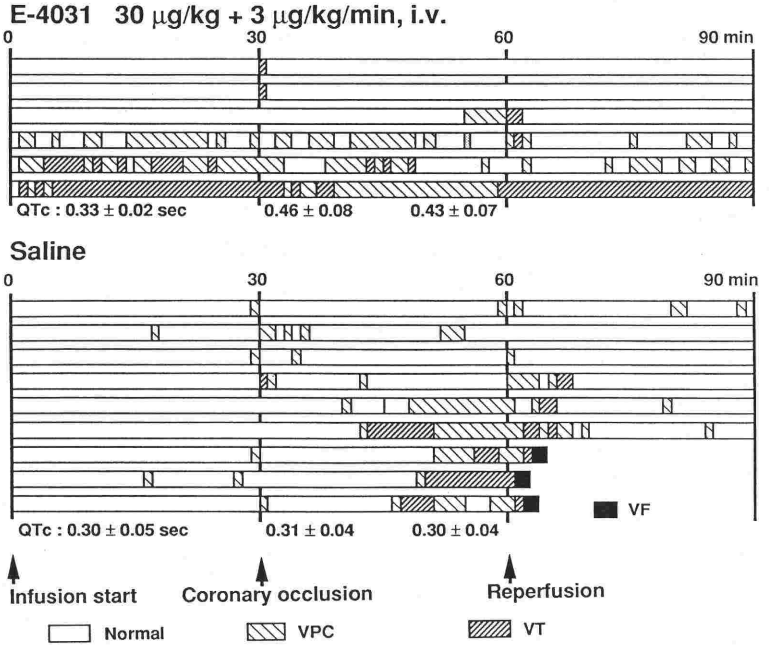

Fig. 7 Effect of E-4031 on the halothane anesthetized coronary ligation and reperfusion arrhythmia experiment.

concentration increased.

E-4031

As shown in Fig. 6, ventricular arrhythmias including VPCs and VT occurred in both the E-4031 and saline treated beagles, and there were no statistically significant differences in the number of total VPCs in the 30 min of occlusion. On reperfusion, 3 saline treated dogs developed fatal VF within 4 min. In the E-4031 treated beagles, a bolus injection of 30 μg/kg followed by 3 μg/kg/min increased the QTc interval 39% and decreased the heart rate 23%. As shown in Fig. 7, 3 dogs developed ventricular ectopic beats and bigeminal rhythm soon after administration of E-4031 and showed torsades de pointes in 2 dogs. On reperfusion, there was no occurrence of VF, but in 2 dogs, VT was induced 1 min after reperfusion. All 6 dogs survived the 30 min of reperfusion period.

Amiodarone (i. v.)

The speed of amiodarone infusion employed was 6.7 mg/kg/h. Thirty min of infusion of amiodarone induced VPC in one dog, but no arrhythmias occurred by saline infusion. During the 30 min of LAD complete occlusion, ventricular arrhythmias including VPCs and VT occurred in both the amiodarone and saline treated beagles, and there were no statistically significant differences in the number of total VPCs in the 30 min of occlusion. On reperfusion 5 beagles out of 6 died of reperfusion VF in the amiodarone treated group as compared to 4 beagles out of 6 of saline treated group. The QTc interval in the amiodarone injected beagles was 0.38±0.02 sec and did not change by amiodarone infusion. The heart rate decreased only 3% in the saline treated beagles, but decreased 28% in the amiodarone treated group just before LAD occlusion.

Discussion

As for the model of myocardial ischemia related arrhythmias occurring in the late phase, we compared the effects of various drugs on the two-stage coronary ligation induced canine spontaneously occurring ventricular ar-

rhythmias. Class I Na channel blocking drugs except lidocaine were all effective on the two-stage coronary ligation arrhythmia, and the antiarrhythmic plasma concentrations were almost similar to concentrations *in vitro* which suppressed the $\dot{V}_{max}$ of the action potentials of the normal canine or guinea-pig ventricular tissues. Though it is debatable whether the IC_{50}s can be defined as the best measure of drug antiarrhythmic concentrations, and whether comparing plasma concentrations, which are the sum of free and bound drug concentrations, with *in vitro* concentrations of drugs in artificial crystalline solutions is relevant, the result indicates that the class I antiarrhythmic drugs suppress two-stage coronary ligation arrhythmias by their primary effects on the cardiac membrane which suppress Na channels[10]. This was also shown by the good correlation between the antiarrhythmic IC_{50}s of class I drugs and the intraarterial dose of ED_{50}s of class I drugs decreasing the intraventricular conduction time in the blood-perfused canine ventricular tissue.

Recently Na channel blockers have been classified according to the rate of their binding or dissociation from the putative binding sites in Na channels, or preference of binding to those sites at different states of the channels, i. e. to open channels or closed channels, according to the modulated receptor hypothesis[11]. The tables also list information on these characteristics using slow or rapid kinetic drugs, and list effects on action potential duration which is the basis of the class I subclassification by Vaughan Williams. It seems that no definitive relationship exists between these electrophysiological characteristics and their effectiveness on the two-stage coronary ligation arrhythmias. This may indicate that the most important characteristics of drugs in their antiarrhythmic effects are properties suppressing Na channels.

As for the arrhythmias occurring in the acute phase of myocardial infarction, the results of the present investigation indicate that in halothane anesthetized beagles MS-551 and E-4031 were effective in suppressing the occurrence of coronary reperfusion VF, but d-sotalol and amiodarone were not effective[3,4]. However when pentobarbital was used as an anesthetic, d-sotalol was effective in suppressing the occurrence of coronary reperfusion VF. Though the rate of occurrence of reperfusion arrhythmia was not high and reported to be variable[12], the low occurrence of VF in beagles in the MS-551 and E-4031 group might be related to the beneficial effect of prolonging the refractory period as predicted from the prominent prolongation of QTc interval and the resulting suppression of re-entry type arrhythmia. The mechanism of the reperfusion arrhythmia is thought to be re-entry of excitation in and around the acutely infarcted myocardium[6,13]. However in the case of d-sotalol, 10 and 15 mg/kg/h infusion, QTc of the halothane anesthetized beagles increased only 17 and 26%, respectively. In the pentobarbital anesthetized beagles, lower speed of d-sotalol, 10 mg/kg/h increased QTc only by 11%, but unexpectedly suppressed reperfusion VF. Though there are significant differences between the blood pressure and heart rate values between halothane and pentobarbital anesthetized groups, it is not known whether this is related to the use of different anesthetics. As for the effect of d-sotalol, it was reported that reperfusion VF after 20 min coronary occlusion in dogs was not suppressed, while the occurrence of ventricular arrhythmias during coronary occlusion was suppressed[14]. The same group also reported that during the LAD occlusion, ventricular arrhythmia was suppressed by 5 mg/kg d-sotalol in pentobarbital anesthetized dogs[14,15] also reported that electrical stimulation given to dogs with 3-7 days old anterior myocardial infarction induced ventricular arrhythmias and fibrillation, and

cumulative doses up to 8 mg/kg of d-sotalol suppressed those arrhythmias in pentobarbital anesthetized dogs. Our finding that d-sotalol was not effective in suppressing arrhythmias during occlusion, but suppressed reperfusion VF is different from those reports even using the same anesthesia. The reason for the low rate of occurrence of VF during occlusion in control and drug treated groups in our study and the different results from other reports are not known.

Related to the plasma concentration related effects, MS-551 linearly increased QTc as the plasma concentration increased, and compared to the 30% increase by about 3 μg/m*l* MS-551 in healthy volunteers (personal communication), the slope in our halothane anesthetized beagles was about twice as steep. Similar linear relationships were also obtained for d-sotalol experiments. The slopes of the d-sotalol experiments using halothane and pentobarbital anesthesia differed considerably, but the reason for this was not shown in the present experiment.

As for the arrhythmogenic effect of MS-551 and E-4031 in the control period before applying the coronary ligation and reperfusion, other papers did not mention this effect[16]. This may be due to the use of halothane, because the arrhythmogenic effect could be seen only in our halothane anesthetized dogs. Halothane is known to decrease the sinoatrial rate and the use of halothane in our experiment kept the sinoatrial rate relatively slow. Halothane is also known to sensitize the cardiac cell to the arrhythmogenic effect of catecholamines, probably because halothane interferes with the cell to cell coupling and thus decreases the conduction velocity[17]. So with the concomitant use of halothane, MS-551 and E-4031 showed an arrhythmogenic effect and such side effects may occur in clinical situations when the QT interval is dramatically increased after the use of class III drugs. As for the arrhythmogenic effect of d-sotalol, it did not induce arrhythmias in halothane anesthetized beagles unaccompanied by protection of reperfusion VF and minor QTc prolongation. However in pentobarbital anesthetized beagles, d-sotalol also induced arrhythmia (1 out of 7 beagles) accompanied by protection of reperfusion VF and slight QTc prolongation. It may be concluded that the suppression of reperfusion VF rather than the extent of QTc prolongation is related to arrhythmogenic effect of these drugs.

Though many unsolved problems still exist such as to what extent the QT interval may be prolonged to induce arrhythmia or suppress the occurrence of reperfusion VF or as to what was the reason for the different results by the use of different anesthetics, class III drugs are quite different from other antiarrhythmic drugs in their effectiveness on canine ventricular arrhythmia models. It is interesting to know whether such data will be obtained in clinical situations and whether these drugs will be effective especially to suppress postinfarction VF or to prevent sudden death.

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