ELSEVIER

European Journal of Pharmacology 388 (2000) 171–176

ejp

www.elsevier.nl/locate/ejphar

Effects of zatebradine and propranolol on canine ischemia and reperfusion-induced arrhythmias

Hisaya Naito [a], Yasuyuki Furukawa [b], Daisuke Chino [a], Chikaomi Yamada [a], Keitaro Hashimoto [a,*]

[a] *Department of Pharmacology, Yamanashi Medical University, Tamaho-cho, Nakakoma-gun, Yamanashi, 409-3898, Japan*
[b] *Department of Pharmacology, Shinshu University School of Medicine, Matsumoto, Nagano, 390-8621, Japan*

Received 27 July 1999; received in revised form 22 November 1999; accepted 26 November 1999

Abstract

1,3,4,5-Tetrahydro-7,8-dimethoxy-3 [3-[[2-(3,4-dimethoxyphenyl)-ethyl]methylamino]propyl] -2 *H*-3-benzazepin-2-one-hydrochloride (Zatebradine) is a specific bradycardiac agent, blocking the hyperpolarization-activated pacemaker current (I_f), and thus has no negative inotropic effect. The purpose of this study was to examine whether zatebradine is effective against ischemia and reperfusion-induced arrhythmias in dogs compared to propranolol. Arrhythmia was induced by ligation of the left anterior descending coronary artery followed by reperfusion. Ischemia-induced biphasic arrhythmias were suppressed in both zatebradine and propranolol groups. During ischemia, fatal ventricular fibrillation occurred in four dogs in the control group, 0 in the zatebradine group, and two dogs in the propranolol group. Of the 31 dogs subjected to reperfusion, mortality rates in the zatebradine, propranolol, and control groups were 56%, 75%, and 86%, respectively, and there were no significant differences. In the heart beating 10 beats/min faster than the predrug heart rate by atrial pacing, both zatebradine and propranolol attenuated ischemia-induced arrhythmias but did not affect reperfusion arrhythmias. Our results suggest that I_f and/or β-adrenoceptors rather than the bradycardiac action might be related to the antiarrhythmic effects during ischemia, but that they do not play a role in the generation of the reperfusion-induced ventricular arrhythmias.

Keywords: Zatebradine; Ischemia-induced arrhythmia; Reperfusion arrhythmia; Propranolol; (Dog)

1. Introduction

1,3,4,5-Tetrahydro-7,8-dimethoxy-3[3-[[2-(3,4-dimethoxyphenyl)-ethyl]methylamino]propyl] -2 *H*-3-benzazepin-2-one-hydrochloride (Zatebradine) is a specific bradycardiac agent, blocking the hyperpolarization-activated pacemaker current (I_f) with no effect on β-adrenoceptors, and has no negative inotropic effects leading to myocardial dysfunction, and thus is expected to increase coronary perfusion during increased diastole (Kobinger and Lillie, 1984; O'Brien et al., 1992). By specifically changing the sinus rate, this bradycardiac agent may affect the electrical activity of the heart and also may affect latent pacemaker activity. Effects of zatebradine on arrhythmias have been reported by Furukawa et al. (1996), who used three canine automaticity arrhythmia models (ouabain-, two-stage coronary ligation-, and epinephrine-induced ventricular tachyarrhythmias), and it was speculated that zatebradine may improve automaticity-related ventricular arrhythmias by inhibiting I_f or by other, undetermined, mechanisms. Arrhythmias are generated not only by increased automaticity, but also by re-entry mechanisms. Thus, it is of interest to study zatebradine with different types of canine model arrhythmias, such as coronary occlusion and reperfusion arrhythmias. It is known that many antiarrhythmic agents are ineffective on the canine reperfusion-induced arrhythmias (Naito et al., 1981), but some class III drugs are effective (Hashimoto et al., 1991a, 1995). Also there are reports suggesting that reduction of the heart rate is important for suppressing these arrhythmias (Bolli et al., 1986; Tosaki et al., 1987; Bernier et al., 1989; Wainwright and Parratt, 1993).

The purpose of this study was to examine whether zatebradine is effective against ischemia-induced and reperfusion-induced canine ventricular arrhythmias in vivo,

* Corresponding author. Tel.: +81-552-73-1111 ext. 2260; fax: +81-552-73-6739.

0014-2999/00/$ - see front matter
PII: S0014-2999(99)00845-6

the mechanism of which is considered to be generated both by automaticity and reentry. We compared propranolol to zatebradine in order to examine whether the heart rate reduction itself, regardless of whether the mechanism involves I_f reduction or β-adrenoceptor blockade, alters arrhythmias or whether zatebradine without negative inotropic effects is more effective than propranolol. We chose a canine model of coronary ligation and reperfusion arrhythmia for this study, because the electrophysiological mechanism of this model has been reported to be similar to those observed in humans (Hashimoto et al., 1991b; Xue et al., 1996a), and we have examined other types of antiarrhythmic drugs using the same model.

2. Methods

All experiments in the present study were approved by the Animal Use and Care Committee of Yamanashi Medical University and performed in accordance with Guidelines for Animal Experiments, Yamanashi Medical University.

2.1. Surgical preparation

Forty-nine beagle dogs of either sex, weighing 6.5–13.5 kg, were anesthetized initially with pentobarbital sodium (30 mg/kg, i.v.) and ventilated with room air using a constant-volume ventilator (Shinano, SN-480-4, Tokyo, Japan). The tidal volume and respiratory rate were set at 20 ml/kg and 15 strokes/min, respectively. Anesthesia was maintained by an intravenous infusion of 5 mg/kg/min of pentobarbital sodium. The blood pressure at the right femoral artery and surface lead II electrocardiogram (ECG) were continuously monitored using a polygraph system (NEC medical systems, Monitor Oscilloscope 2G66, Tokyo, Japan). The right femoral vein was cannulated for drug administration. The chest was opened at the 5th intercostal space and the left anterior descending coronary artery was isolated just proximal to the first diagonal branch for ligation. Pacing electrodes were implanted on the left auricular appendix. Bipolar electrodes were sutured onto the epicardial border zone between the ischemic and non-ischemic area of the left ventricle, and the electrograms were continuously monitored. Systemic blood pressure was recorded on a thermal array recorder (Nihon Kohden, RTA 1300M, Tokyo, Japan), while the lead II ECG was recorded continuously on a logger recording system (NEC medical systems, Cardio Logger 322, Tokyo, Japan).

2.2. Experimental protocol

We carried out two series of experiments. In the first series, 37 dogs were randomly divided into three groups; the zatebradine group ($n = 16$), propranolol group ($n = 10$, 9.6 ± 1.9 kg) and control group ($n = 11$, 9.4 ± 1.9 kg). Zatebradine at doses of 1.0 ($n = 6$, 10.2 ± 2.0 kg) and 1.5 mg/kg (3.3 mmol/kg, $n = 10$, 9.6 ± 1.4 kg), propranolol at a dose of 1.0 mg/kg (3.4 mmol/kg) or saline was administered intravenously over 20 s. Zatebradine at a dose of 1.5 mg/kg had fully developed cardiac effects in anesthetized dogs (Furukawa et al., 1996), but since this dose sometimes caused atrial arrhythmias, we used a dose of 1.0 mg/kg zatebradine for the atrial pacing experiments. The dose of propranolol was determined as a dose equimolar to that of zatebradine to induce bradycardia. Arrhythmias were induced by coronary ligation followed by reperfusion, as reported previously (Kaplinsky et al., 1979; Kabeli et al., 1982; Janse and Wit, 1989). Briefly, 10 min after the drug administration, the coronary artery was ligated completely using a nylon thread. After 30 min of coronary occlusion, the nylon thread was released to induce arrhythmias. The number of ventricular premature contractions was counted during the whole experimental period and summarized as the number of beats/min.

In the second series, to determine the effects of heart rate on the ischemia- and reperfusion-induced ventricular arrhythmias, 12 dogs were divided into two groups, zatebradine with pacing group ($n = 6$) and propranolol with pacing group ($n = 6$). Zatebradine at a dose of 1.0 mg/kg or propranolol at a dose of 1.0 mg/kg was administered intravenously over 20 s. On the paced groups, atrial pacing was started 2 min before drug administration, and pacing rates were 10 beats/min faster than the predrug heart rate. Arrhythmias were induced as in the first series of experiments.

2.3. Statistical analysis

Data are shown as the means ± S.E.M. The data were obtained minute by minute from one minute before a drug treatment to the end of the experiment. The statistical significance of the value of each parameter among groups was evaluated with an analysis of variance followed by Dunnett's multiple comparison test. Drug treatment and time were considered to be fixed factors.

2.4. Drugs

The following drugs were used: pentobarbital sodium (Tokyo Kasei, Tokyo), heparin calcium (Mitsui, Tokyo, Japan), zatebradine (kindly supplied by Nippon Boehringer Ingelheim, Hyogo, Japan), and propranolol hydrochloride (Sigma, St. Louis, MO, USA).

3. Results

3.1. Effects of zatebradine and propranolol on the cardiovascular parameters during ischemia

3.1.1. Effects on the heart rate

The time courses of the heart rate of the three groups are shown in Table 1. The average heart rate just before

Table 1
Hemodynamic changes with time
Data are shown as means ± S.E.M. 10 min after drug administration, the coronary artery was ligated.
Significantly different from zero value, Student's *t*-test.

Time after drug administration	Heart rate (beat/min)				
	0 min	5 min	15 min	20 min	30 min
Control	182 ± 7	179 ± 7	197 ± 11	181 ± 11	164 ± 15
Zatebradine 1.0 mg/kg	167 ± 8	93 ± 13[a]	88 ± 13[a]	89 ± 13[a]	88 ± 12[a]
Zatebradine 1.5 mg/kg	171 ± 9	85 ± 7[a]	83 ± 5[a]	84 ± 6[a]	91 ± 7[a]
Propranolol 1.0 mg/kg	185 ± 8	129 ± 6[a]	122 ± 6[a]	120 ± 6[a]	116 ± 7[a]
Zatebradine 1.0 mg/kg with pacing	171 ± 8	171 ± 8	171 ± 8	171 ± 8	171 ± 8
Propranolol 1.0 mg/kg with pacing	181 ± 9	181 ± 9	181 ± 9	181 ± 9	181 ± 9
Time after drug administration	Mean blood pressure (mm Hg)				
	0 min	5 min	15 min	20 min	30 min
Control	117 ± 6	116 ± 6	93 ± 7[a]	104 ± 9	95 ± 11
Zatebradine 1.0 mg/kg	110 ± 6	97 ± 7	82 ± 8	84 ± 9	87 ± 8
Zatebradine 1.5 mg/kg	120 ± 4	106 ± 6	103 ± 5[a]	102 ± 4[a]	105 ± 5[a]
Propranolol 1.0 mg/kg	123 ± 4	116 ± 6	107 ± 7	109 ± 7	110 ± 8
Zatebradine 1.0 mg/kg with pacing	113 ± 5	107 ± 4	101 ± 4	98 ± 3	96 ± 2
Propranolol 1.0 mg/kg with pacing	111 ± 5	102 ± 9	95 ± 10	97 ± 10	96 ± 13

[a] $P < 0.01$.

drug administration was 171 beats/min in the zatebradine group, 185 beats/min in the propranolol group and 182 beats/min in the control group, respectively. After the administration of 1.5 mg/kg of zatebradine, the heart rate decreased significantly and reached a minimum value of 81 beats/min at 4 min, and remained at the decreased rate during the observation period. After the administration of 1.0 mg/kg of zatebradine, the heart rate decreased significantly to 91 beats/min. Propranolol also decreased the heart rate, which reached a minimum value of 115 beats/min at 28 min. The reduction of the heart rate induced by zatebradine was greater ($P < 0.001$) than that induced by propranolol, but the heart rates in the last 3 min during 30-min occlusion were not significantly different.

3.1.2. Effects on the blood pressure

The time courses of the mean blood pressure of the three groups are summarized in Table 1. The mean blood pressure just before drug administration was 110, 120, 123 and 117 mm Hg in the zatebradine at 1.0 and 1.5 mg/kg, propranolol, and control groups, respectively. In the control group, occlusion tended to decrease the mean arterial blood pressure but the reduction was not significant. Zatebradine decreased the arterial blood pressure slightly and coronary occlusion did not affect the blood pressure in zatebradine-treated dogs, either. On the other hand, propranolol decreased arterial blood pressure and occlusion decreased the blood pressure gradually throughout the experiments in propranolol treated dogs.

3.1.3. Effects on the ischemia-induced ventricular arrhythmia

Thirty-minute coronary artery occlusion caused ventricular arrhythmias, ventricular premature contractions and ventricular fibrillation (Fig. 1). During the 30 min complete coronary artery occlusion in the control group, two peaks of the occurrence of ventricular premature contractions were observed at 5 min (immediate ventricular arrhythmias or phase 1a) and 15–17 min (delayed ventricular arrhythmias or phase 1b), as observed previously (Kaplinsky et al., 1979; Kabeli et al., 1982; Janse and Wit, 1989). These phases were not observed in either the zate-

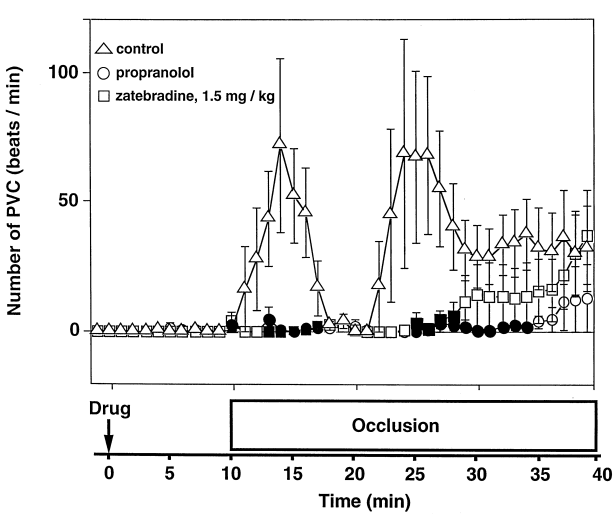

Fig. 1. Effects of zatebradine at a dose of 1.5 mg/kg i.v. and propranolol at a dose of 1 mg/kg i.v. on the number of ventricular premature contractions (VPCs) before and during 30-min coronary artery occlusion in the pentobarbital anesthetized dog. Zatebradine (□, $n = 10$), propranolol (○, $n = 10$), and saline as a control (△, $n = 11$) were given intravenously 10 min before the complete coronary artery occlusion for 30 min. Solid symbols indicate significant ($P < 0.05$) differences from the respective control value. Vertical bars show S.E.M.

bradine or the propranolol groups. Statistical significance was detected for the difference in number of ventricular premature contractions between the zatebradine and control groups ($P < 0.001$), and between the propranolol and control groups ($P < 0.001$). During ischemia, fatal ventricular fibrillation was observed in 4 out of 11 dogs in the control group, in none of 16 dogs in the zatebradine group ($P < 0.01$), and in two of 10 dogs in the propranolol group (not significant).

3.1.4. Effects on the incidence of the reperfusion-induced arrhythmia

Thirty-one of 37 dogs survived coronary ischemia and were subjected to reperfusion. The mortality rate of the zatebradine, propranolol, and control groups was 56%, 75%, and 86%, respectively. There were no significant differences in the incidence of fatal ventricular fibrillation among the three groups. That is, neither zatebradine nor propranolol affected the reperfusion-induced fatal ventricular arrhythmias.

3.2. Effects of atrial pacing

The average heart rate just before drug administration in the pacing groups was 171 beats/min in the zatebradine group, 181 beats/min in the propranolol group, respectively, and the pacing rate was maintained throughout the experiments. The mean blood pressure just before drug administration was 113 and 111 mm Hg in the zatebradine and propranolol groups, respectively, and none of the drugs changed the blood pressure significantly during atrial pacing before the occlusion of the left anterior descending coronary artery. In the paced heart, occlusion tended to decrease the mean arterial blood pressure in each group, but the reductions were not significantly different from the respective blood pressure changes in the non-paced heart.

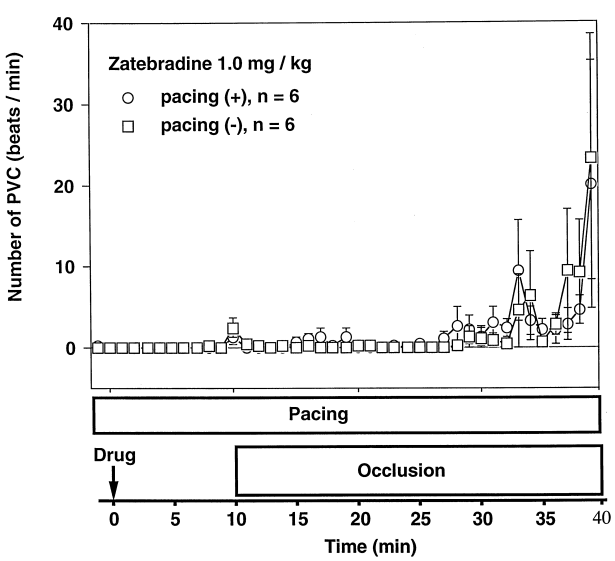

Fig. 2. Effects of zatebradine at a dose of 1.0 mg/kg i.v. with atrial pacing at 10 beats/min faster than predrug heart rate on the number of ventricular premature contractions (VPCs) before and during 30-min coronary artery occlusion in the pentobarbital-anesthetized dog. Zatebradine was given intravenously 10 min before complete coronary artery occlusion for 30 min. Pacing was started 2 min before drug administration. With pacing (○, $n = 6$), without pacing (□, $n = 6$).

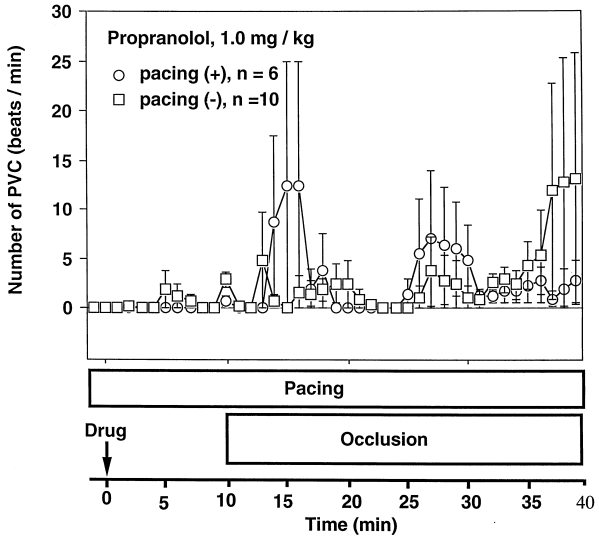

Fig. 3. Effects of propranolol at a dose of 1.0 mg/kg i.v. with atrial pacing at 10 beats/min faster than predrug heart rate on the number of ventricular premature contractions (VPCs) before and during 30-min coronary artery occlusion in the pentobarbital-anesthetized dog. Propranolol was given intravenously 10 min before complete coronary artery occlusion for 30 min. Pacing was started 2 min before drug administration. With pacing (○, $n = 6$), without pacing (□, $n = 10$).

3.2.1. Effects of pacing on the ischemia-induced ventricular arrhythmia

During the 30-min complete coronary artery occlusion in the atrial pacing groups, the two peaks of the occurrence of ventricular premature contractions were not observed in either the zatebradine (1.0 mg/kg) or the propranolol group (Figs. 2 and 3). Statistical significance was not detected for the difference in number of ventricular premature contractions between the zatebradine non-paced and paced groups, and between the propranolol non-paced and paced groups. During ischemia, fatal ventricular fibrillation was observed in one of six dogs in the zatebradine pacing group, and two out of six dogs in the propranolol pacing group. There was no statistically significant difference in incidence of ventricular fibrillation among the drug-treated groups.

3.2.2. Effects of pacing on the incidence of the reperfusion-induced arrhythmia

Nine of 12 dogs in the paced groups survived coronary ischemia and were subjected to reperfusion. The mortality rate in the zatebradine and propranolol groups was 60% and 50%, respectively. There were no significant differences in the incidence of the fatal ventricular fibrillation between the non-paced and paced groups.

4. Discussion

In the present study, we demonstrated that a specific bradycardiac agent, zatebradine, and a β-adrenoceptor antagonist, propranolol, depressed ischemia-induced ventricular arrhythmias, but did not affect reperfusion-induced ventricular arrhythmias in pentobarbital-anesthetized dogs when the heart rate was decreased by both agents or was maintained by atrial pacing.

Complete coronary artery occlusion causes ventricular arrhythmias, i.e., ventricular premature contractions and ventricular fibrillation in mammalian hearts (Kaplinsky et al., 1979; Kabeli et al., 1982; Pogwizd and Corr, 1987; Janse and Wit, 1989). Thirty-minute complete coronary occlusion has been reported to induce ventricular arrhythmias with two distinct phases, immediate ventricular arrhythmias or phase 1a and delayed ventricular arrhythmias or phase 1b. In the present study, we confirmed these bimodal ischemia-induced ventricular arrhythmias during 30-min coronary occlusion in pentobarbital-anesthetized dogs (Fig. 1).

When zatebradine decreased the heart rate from 171 beats/min to 81 beats/min in the pentobarbital-anesthetized dog, it suppressed both phase 1a and 1b ventricular arrhythmias, which were induced by 30-min coronary occlusion (Fig. 1). The reduction of the heart rate induced by zatebradine markedly attenuated the exercise-induced ischemic cardiac dysfunction in dogs (Guth et al., 1987). Wainwright and Parratt (1993) suggested that, in pigs the bradycardia induced by an adenosine A_1 receptor agonist protected from the ischemia-induced ventricular arrhythmias. Bernier et al. (1989) observed that ischemia-induced ventricular arrhythmias depended on the heart rate in the isolated rat heart and the low rate was protective, and concluded that the heart rate influenced susceptibility to ischemia-induced arrhythmias. Also a positive correlation between heart rate and susceptibility to ischemia-induced ventricular arrhythmias was reported for open-chest anesthetized dogs (Bolli et al., 1986). Thus, the reduction of the heart rate by zatebradine might have suppressed the ischemia-induced ventricular arrhythmias through both the improvement of ischemia-induced cardiac dysfunction and the decrease in susceptibility to the ischemia-induced arrhythmias. However, in the present study, even when the heart rate was kept constant at a high level by atrial pacing, zatebradine depressed the ischemia-induced arrhythmias. Therefore, other effects of zatebradine might be responsible for the reduction of the ischemia-induced ventricular arrhythmias in the dog heart.

Phase 1a ischemia-induced ventricular arrhythmias are thought to be induced mainly by a reentry mechanism (Janse and Wit, 1989). As for the phase 1b arrhythmias, they are induced by a reentry mechanism and also non-reentry mechanisms, e.g., abnormal automaticity induced by a release of endogenous catecholamines, have been suggested (Schoemig et al., 1984; Janse and Wit, 1989). In the present study, propranolol prevented phase 1a and 1b ventricular arrhythmias induced by 30-min coronary occlusion (Fig. 1) as reported previously (Penny, 1984). Propranolol also attenuated the ventricular arrhythmias in the electrically paced heart (Fig. 2). Catecholamines activate β-adrenoceptors and increase tissue cyclic AMP, which activates hyperpolarization activated current (I_f) as well as slow inward Ca^{2+} current (I_{Ca}). Zatebradine decreased the heart rate directly and also attenuated the increase in the heart rate evoked by sympathetic nerve stimulation in anesthetized dogs (Furukawa et al., 1995). However, zatebradine did not attenuate the increase in sinus rate in response to a Ca^{2+} channel agonist, methyl-1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoro-methylphenyl)-pyridine-5-carboxylate (BAY k 8644), in isolated dog atria (Sawaki et al., 1995). It is, therefore, suggested that the β-adrenoceptor antagonist, propranolol, in addition to the reduction of the heart rate attenuates the phase 1a and 1b ventricular arrhythmias at least partly. It has been reported that zatebradine did not significantly attenuate the ischemia- and reperfusion-induced ventricular arrhythmias in anesthetized rabbits (Bril et al., 1994). The different effectiveness of zatebradine on ischemia-induced arrhythmias may be related to the dose of zatebradine and the animals used. In rabbits, 20-min coronary occlusion did not induce a clear bimodal occurrence of ventricular arrhythmias (Bril et al., 1994).

Zatebradine's main effect is to suppress I_f. I_f is also known to inhibit rapid type delayed rectifier K^+ currents (I_{Kr}) and I_{Ca} (Van Bogaert and Goethals, 1987; Goethals et al., 1993; Thollon et al., 1994). However, class III antiarrhythmic agents, which inhibit I_{Kr}, did not attenuate the ischemia-induced ventricular arrhythmias in anesthetized dogs (Hashimoto et al., 1991a, 1995; Xue et al., 1996b), but Ca^{2+} channel antagonists inhibit the ischemia-induced ventricular arrhythmias in mammalian hearts (Curtis et al., 1984; Coetzee et al., 1987; Bril et al., 1994). However, zatebradine was shown not to inhibit the positive chronotropic response to a Ca^{2+} channel agonist, BAY k 8644, in isolated dog atria, suggesting that the effect of zatebradine on Ca^{2+} channels are minor in the dog heart (Sawaki et al., 1995). Therefore, it is concluded that the effects of zatebradine on the ischemia-induced ventricular arrhythmias may result from the inhibition of I_f, although other unknown mechanisms may also contribute to the inhibition of the ischemia-induced arrhythmias. It is noteworthy that I_f has been observed not only in SA node pacemaker cells, but in mammalian Purkinje fibers, atrial myocytes, and ventricular myocytes (Irisawa et al., 1993; Yu et al., 1993).

In the present study, neither zatebradine nor propranolol affected the reperfusion-induced ventricular fibrillation after 30-min coronary occlusion in anesthetized dogs. Reperfusion-induced ventricular fibrillation is caused by two different mechanisms (Janse and Wit, 1989). The first is multiple wavelet reentry and the second is increased abnor-

mal automaticity. These reperfusion arrhythmias are speculated to be induced by multiple cellular mechanisms, including the inhibition of Na^+ channels, free-radical formation, activation of ATP-regulated K^+ channels and/or β-adrenoceptor stimulation (Carbonin et al., 1981; Corr et al., 1981; Janse and Wit, 1989). I_{Kr} blockers reduced the incidence of ventricular fibrillation after reperfusion following 30-min complete coronary occlusion in anesthetized dogs (Hashimoto et al., 1991a, 1995; Xue et al., 1996b). Zatebradine inhibits I_{Kr} (Goethals et al., 1993; Thollon et al., 1994) but it did not affect the reperfusion-induced arrhythmias. Thus, it is unlikely that the I_{Kr} inhibitory property of zatebradine is enough to prevent the reperfusion-induced ventricular fibrillation in dog hearts. In conclusion, a low heart rate or β-adrenoceptor blockade is not enough to inhibit the reperfusion-induced ventricular fibrillation, although a low heart rate prevents reperfusion-induced arrhythmias as well as ischemia-induced arrhythmias in rats (Bernier et al., 1989).

References

Bernier, M., Curtis, M., Hearse, D., 1989. Ischemia-induced and reperfusion-induced arrhythmias: importance of heart rate. Am. J. Physiol. 256, H21–H31.

Bolli, R., Fisher, D., Entman, M., 1986. Factors that determine the occurrence of arrhythmias during acute myocardial ischemia. Am. Heart J. 111, 261–270.

Bril, A., Forest, M., Cheval, B., Landais, L., Gout, B., 1994. Effect of zatebradine, a specific bradycardic agent, on ischemia-induced arrhythmias in anesthetized rabbits. Pharmacology 48, 308–319.

Carbonin, P., DiGennaro, M., Valle, R., Weisz, A., 1981. Inhibitory effect of anoxia on reperfusion-and digitalis-induced ventricular tachyarrhythmias. Am. J. Physiol. 240, H730–H737.

Coetzee, W.A., Dennis, S.C., Opie, L.H., Muller, C.A., 1987. Calcium channel blockers and early ischemic ventricular arrhythmias: Electrophysiological versus anti-ischemic effects. J. Mol. Cell. Cardiol. 19 (Suppl), 77–97.

Corr, P., Shayman, J., Kramer, J., Kipnis, R., 1981. Increased alpha-adrenergic receptors in ischemic cat myocardium. A potential mediator of electrophysiological derangements. J. Clin. Invest. 67, 1232–1236.

Curtis, M.J., MacLeod, B.A., Walker, M.J.A., 1984. Antiarrhythmic actions of verapamil against ischemia arrhythmias in the rat. Br. J. Pharmacol. 83, 373–385.

Furukawa, Y., Nakano, T., Oguchi, T., Kasama, M., Hoyano, Y., Chiba, S., 1995. Selective inhibition by zatebradine and discrete parasympathetic stimulation of the positive chronotropic response to sympathetic stimulation in anesthetized dogs. J. Pharmacol. Exp. Ther. 272, 744–749.

Furukawa, Y., Xue, Y.X., Chiba, S., Hashimoto, K., 1996. Effects of zatebradine on ouabain-, two-stage coronary ligation- and epinephrine-induced ventricular tachyarrhythmias. Eur. J. Pharmacol. 300, 203–210.

Goethals, M., Raes, A., Van Bogaert, P.P., 1993. Use-dependent block of the pacemaker current I_f in rabbit sinoatrial node cells by zatebradine. Circulation 88, 2389–2401.

Guth, B., Heusch, G., Seitelberger, R., Ross, J. Jr., 1987. Elimination of exercise-induced regional myocardial dysfunction by a bradycardiac agent in dogs with chronic coronary stenosis. Circulation 75, 661–669.

Hashimoto, K., Haruno, A., Matsuzaki, T., Hirasawa, A., Awaji, T., Uemura, Y., 1991a. Effects of a new class III antiarrhythmic drug (E-4031)on canine ventricular arrhythmia models. Asia. Pacific. J. Pharmacol. 6, 127–137.

Hashimoto, K., Haruno, A., Hirasawa, A., Awaji, T., Xue, Y.X., Wu, Z.J., 1995. Effects of the new class III antiarrhythmic drug MS-551 and *d*-sotalol on canine coronary ligation-reperfusion ventricular arrhythmias. Jpn. J. Pharmacol. 68, 1–9.

Hashimoto, K., Haruno, A., Matsuzaki, T., Sugiyama, A., Akiyama, K., 1991b. Effects of antiarrhythmic drugs on canine ventricular arrhythmia models: which electrophysiological characteristics of drugs are related to their effectiveness?. Cardiovasc. Drug. Ther. 5, 805–818.

Irisawa, H., Brown, H.F., Giles, W., 1993. Cardiac pacemaking in the sinoatrial node. Physiol. Rev. 73, 197–227.

Janse, M.J., Wit, A.L., 1989. Electrophysiological mechanisms of ventricular arrhythmias resulting from myocardial ischemia and infarction. Physiol. Rev. 69, 1049–1169.

Kabeli, G., Scherlag, B.J., Hope, R.R., Lazzara, R., 1982. Regional myocardial blood flow and ventricular arrhythmias following one-stage and two-stage coronary artery occlusion in anesthetized dogs. Am. Heart J. 104, 537–545.

Kaplinsky, E., Ogawa, S., Balke, W., Breifus, L.S., 1979. Two periods of early ventricular arrhythmia in the canine acute myocardial infarction model. Circulation 60, 397–403.

Kobinger, W., Lillie, C., 1984. Cardiovascular characterization of UL-FS 49,1,3,4,5-tetrahydro-7,8-dimethoxy-3-[3-[[2-(3,4-dimethoxyphenyl) ethyl]methylimino]propyl]-2*H*-3-benzazepin-2-on hydrochloride, a new ''specific bradycardic agent''. Eur. J. Pharmacol. 104, 9–18.

Naito, M., Michelson, E., Kmetzo, J.J., Kaplinsky, E., Dreifus, L.S., 1981. Failure of antiarrhythmic drug to prevent experimental reperfusion ventricular fibrillation. Circulation 63, 70–79.

O'Brien, P., Drage, D., Saeian, K., Brooks, H., Warltier, D., 1992. Regional redistribution of myocardial perfusion by UL-FS 49, a selective bradycardic agent. Am. Heart. J. 123, 566–574.

Penny, W.J., 1984. The deleterious effects of myocardial catecholamines on cellular electrophysiology and arrhythmias during ischaemia and reperfusion. Eur. Heart. J. 5, 960–973.

Pogwizd, S., Corr, B., 1987. Reentrant and nonreentrant mechanisms contribute to arrhythmogenesis during early myocardial ischemia: Results using three-dimensional mapping. Circ. Res. 61, 352–371.

Sawaki, S., Furukawa, Y., Inoue, Y., Oguchi, T., Chiba, S., 1995. Zatebradine attenuates cyclic AMP-related positive chronotropic but not inotropic responses in isolated, perfused right atria of the dog. Clin. Exp. Pharmacol. Physiol. 22, 29–34.

Schoemig, A., Dart, A.M., Dietz, R., Mayer, E., Kuebler, W., 1984. Release of endogenous catecholamines in the ischemic myocardium of the cat. Part A: locally mediated release. Circ. Res. 55, 689–701.

Thollon, C., Cambarrat, C., Vian, J., Prost, J.F., Peglion, J.L., Vilaine, J.P., 1994. Electrophysiological effects of S 16257, a novel sinoatrial node modulator, on rabbit and guinea-pig cardiac preparations: comparison with UL-FS 49. Br. J. Pharmacol. 112, 37–42.

Tosaki, A., Szekeres, L., Hearse, D., 1987. Metoprolol reduces reperfusion-induced fibrillation in the isolated rat heart: protection is secondary to bradycardia. J. Cardiovasc. Pharmacol. 10, 489–497.

Van Bogaert, P.P., Goethals, M., 1987. Pharmacological influence of specific bradycardic agents on the pacemaker current of sheep Purkinje fibers. A comparison between three different molecules. Eur. Heart. J. Suppl. 8, 35–42.

Wainwright, C.L., Parratt, J.R., 1993. Effects of R-PIA, aselective A1 adenosine agonist, on haemodynamics and ischemic arrhythmias in pigs. Cardiovasc. Res. 27, 84–89.

Xue, Y.X., Aye, N.N., Hashimoto, K., 1996a. Antiarrhythmic effects of HOE642, a novel Na^+–H^+ exchange inhibitor, on ventricular arrhythmias in animal hearts. Eur. J. Pharmacol. 317, 309–316.

Xue, Y.X., Eto, K., Akie, Y., Hashimoto, K., 1996b. Antiarrhythmic and Proarrhythmic effects of sematilide in canine ventricular arrhythmia models. Jpn. J. Pharmacol. 70, 129–138.

Yu, H., Chang, F., Cohen, I.S., 1993. Pacemaker current exists in ventricular myocyte. Circ. Res. 72, 232–236.