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Zatebradine inhibits tachycardia induced by bronchodilators without affecting respiratory resistance in dogs

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Abstract

Bronchodilators used for bronchial asthma reduce respiratory resistance but also increase heart rate to some extent. It is often difficult to use such bronchodilators with elderly patients and patients with heart disease. The object of our study was to investigate whether a specific bradycardic agent, zatebradine, inhibited the heart rate increased by bronchodilators without affecting respiratory resistance. We evaluated the effects of zatebradine on the increases in heart rate and inhibition of the respiratory resistance in response to the bronchodilators, isoproterenol, procaterol (a β_2-adrenoceptor agonist), 6-(3-dimethylaminopropionyl)-forskolin, NKH 477 (an adenylyl cyclase activator) and aminophylline in the anesthetized and artificially ventilated dog. When zatebradine in doses of 0.05–1.5 mg/kg i.v. decreased heart rate without affecting arterial blood pressure, it dose dependently attenuated the increase in heart rate in response to isoproterenol, procaterol, NKH 477 and aminophylline but did not affect the inhibition by these substances of the increase in respiratory resistance induced by histamine. Propranolol (0.01–0.3 mg/kg i.v.) dose dependently inhibited not only the increase in heart rate but also the inhibition of the respiratory resistance induced by isoproterenol and procaterol. The present results indicate that zatebradine selectively inhibits the increase in heart rate in response to cyclic AMP-dependent bronchodilators without affecting their bronchodilator effects in anesthetized dogs and suggest that zatebradine may be a useful drug for prevention of the tachycardia induced by bronchodilators used for patients with bronchial asthma.

Keywords: Zatebradine; Tachycardia; Respiratory resistance; cAMP

1. Introduction

β-Adrenoceptor agonists and other bronchodilators are used for patients with bronchial asthma and other pulmonary diseases. However, patients often suffer from tachycardia, one of the side effects of bronchodilators. It is very dangerous to administer such drugs to asthma patients with coronary heart disease. Nebulized β_2-adrenoceptor agonists frequently aggravate angina, provoke myocardial infarction and cause cardiac arrhythmias (Neville et al., 1982; Higgins et al., 1987; Shovlin and Tam, 1990).

Zatebradine has been reported as a specific bradycardic agent that inhibits hyperpolarization-activated inward currents (I_f) (Kobinger and Lillie, 1987; Van Bogaert and Goethals, 1987; Goethals et al., 1993; DiFrancesco, 1994), although at a high concentration it inhibits delayed rectifier K^+ currents and slow inward Ca^{2+} currents (Doerr and Trautwein, 1990; Thollon et al., 1994). Zatebradine selectively decreased tachycardia provoked by isoproterenol, aminophylline and 6-(3-dimethylaminopropionyl)-forskolin, NKH 477 in isolated mammalian hearts (Lillie and Kobinger, 1986; Sawaki et al., 1995), and during exercise in conscious dogs (Guth et al., 1987; Raberger et al., 1987). Zatebradine also attenuated the positive chronotropic response to sympathetic nerve stimulation without affecting other cardiac functions, inotropic and dromotropic responses, in anesthetized dogs (Furukawa et al., 1995).

Therefore, we hypothesized that zatebradine could attenuate the heart rate increased by bronchodilators without affecting respiratory resistance. To verify this hypothesis, we studied the effects of zatebradine on the increase in heart rate and the decrease in respiratory resistance in response to the bronchodilators, isoproterenol (a non-selective β-adrenoceptor agonist), procaterol (a β_2-adrenoceptor agonist), NKH 477 (an adenylyl cyclase activator) (Hosono et al., 1992) and aminophylline in anesthetized and artificially ventilated dogs. We also compared these effects of zatebradine with the effects of a non-selective β-adrenoc-

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eptor antagonist, propranolol, on the increase in heart rate and the decrease in respiratory resistance elicited by isoproterenol and procaterol.

2. Materials and methods

2.1. Preparations

Forty-two mongrel dogs of either sex, weighing 8–18 kg, were used in this study. Each dog was anesthetized with sodium pentobarbital (30 mg/kg, i.v.) and supplemented hourly with 10 mg/kg doses. They were ventilated at a rate of 18 breaths/min with room air at a volume of 20 ml/kg through a cuffed tracheal tube, using a Harvard respirator (Millis, MA, USA, model 607). Respiratory overflow and the pressure between intratracheal lumen and atmosphere were measured by differential pressure transducers (Nihon Kohden, Tokyo, Japan, TP-602T and TP-603T) in the respiratory circuit. Arterial blood pressure was measured via the left femoral artery. Heart rate was derived from a body surface electrogram with a cardiotachometer (Nihon Kohden, AT600G). Respiratory overflow volume, its derivative, intratracheal pressure, electrocardiogram (ECG), heart rate and blood pressure were recorded and displayed on a thermo-writing rectigraph (Nihon Kohden, RTA 1200). Respiratory resistance (cmH_2O/l per s) was measured by the use of the modified method (Yabuuchi et al., 1977) of Konzett and Rössler (1940), and calculated according to principles of Amdur and Mead (1958).

2.2. Protocols

We investigated the effects of zatebradine in doses of 0.05–1.5 mg/kg i.v. on the increase in heart rate and decrease in the respiratory resistance in response to isoproterenol and procaterol, a β_2-adrenoceptor agonist, and compared them with the effects of propranolol in doses of 0.01–0.3 mg/kg i.v. on the responses to isoproterenol and procaterol in 5 anesthetized dogs in each experimental group. We also investigated the effects of zatebradine on the increase in heart rate and decrease in the respiratory resistance in response to NKH 477 ($n = 5$), an adenylyl cyclase activator, and aminophylline ($n = 5$).

The bronchodilator effects of drugs were assessed by their antagonism of the increase in respiratory resistance elicited by histamine in the following way. First, 10 or 30 μg/kg i.v. of histamine, a dose causing a submaximal increase in respiratory resistance, was given to a dog as a challenge dose. Then, isoproterenol (1 or 3 μg/kg i.v.), procaterol (1 or 3 μg/kg i.v.), NKH 477 (0.05 mg/kg) or aminophylline (5 mg/kg i.v.) was injected and the challenge dose of histamine was given 1 min or more after the bronchodilator injection (Fig. 1). We used one dose of each bronchodilator, except for aminophylline, which almost abolished the increase in respiratory resistance induced by histamine. Thirty minutes after determination of the bronchodilator effect of each agonist, zatebradine (0.05–1.5 mg/kg), propranolol (0.01–0.3 mg/kg) or vehicle (saline) was given i.v. at 30-min intervals cumulatively and then we determined the cardiac and respiratory responses to each agonist repeatedly (Fig. 1).

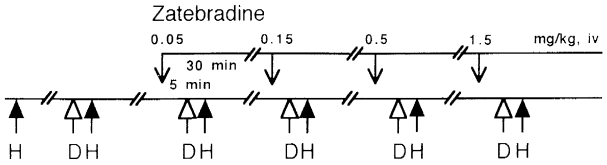

Fig. 1. Protocol for the experiment. After determination of the challenge dose of histamine (H, black arrow), the inhibition by a bronchodilator (D, white arrow) of the increase in respiratory resistance induced by histamine and the increase elicited by the bronchodilator in heart rate were evaluated. Then, zatebradine (0.05–1.5 mg/kg) was given i.v. at 30-min intervals cumulatively and the cardiac and respiratory responses to the bronchodilator were determined repeatedly.

The increase in heart rate and inhibition of the histamine-induced respiratory resistance in response to isoproterenol were complete within 10 min, but the responses to procaterol, NKH 477 and aminophylline continued for more than 30 min. Thus, the effects of zatebradine or propranolol on the cardiac and respiratory responses to procaterol, NKH 477 or aminophylline were compared with the effects of vehicle on those responses.

2.3. Drugs

The drugs used in the present experiments were 1,3,4,5-tetra-hydro-7,8-dimethoxy-3[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-2*H*-3-benzazepin-2-one-hydrochloride (zatebradine, generously donated by Boehringer Ingelheim, Kobe, Japan), propranolol hydrochloride (Sumitomo, Osaka, Japan), *l*-isoproterenol hydrochloride (Nikken Kagaku, Tokyo, Japan), procaterol hydrochloride (Otsuka Pharmaceutical Corp., Tokushima, Japan), 6-(3-dimethylaminopropionyl)-forskolin hydrochloride (NKH 477, generously donated by Nippon Kayaku Co., Tokyo, Japan), aminophylline (Eisai, Tokyo, Japan) and histamine (Wako Pure Chemical, Osaka, Japan). All drugs were dissolved in physiological saline before the start of the experiment.

2.4. Statistical analysis

All data are expressed as means ± S.E.M. Fifty percent inhibition doses (ID_{50}) were determined for each dose-inhibition curve. The data were analyzed with an analysis of variance and Bonferroni's method for multiple comparisons of data. P values of less than 0.05 were considered statistically significant.

3. Results

3.1. Effects of isoproterenol, procaterol, NKH 477 and aminophylline on heart rate and increases in respiratory resistance induced by histamine

When histamine (10 or 30 μg/kg i.v.) increased the respiratory resistance in anesthetized dogs, isoproterenol (1 or 3 μg/kg i.v.), procaterol (1 or 3 μg/kg i.v.) and NKH 477 (0.05 mg/kg i.v.) suppressed this increase in respiratory resistance (Figs. 2–5) and these substances also increased heart rate, as shown in Table 1. The basal heart rate and basal respiratory resistance did not differ significantly in all experimental groups. Isoproterenolol, procaterol, NKH 477 and aminophylline significantly increased heart rate from the basal heart rate ($P < 0.05$). The increase in heart rate in response to isoproterenol or procaterol was not significantly different between the zatebradine and propranolol treatment groups. Histamine increased respiratory resistance significantly ($P < 0.01$) in all experimental groups (Table 1). The inhibition of the respiratory resistance induced by histamine and increases in heart rate induced by isoproterenol, procaterol and NKH 477 were maintained throughout the experimental period when vehicle was given. We investigated the effects of zatebradine on the responses to 5 mg/kg i.v. of aminophylline, because aminophylline at a dose of 10 mg/kg i.v. or more did not inhibit the respiratory resistance increased by histamine. The positive chronotropic response to aminophylline at 5 mg/kg i.v. was also maintained when vehicle was given.

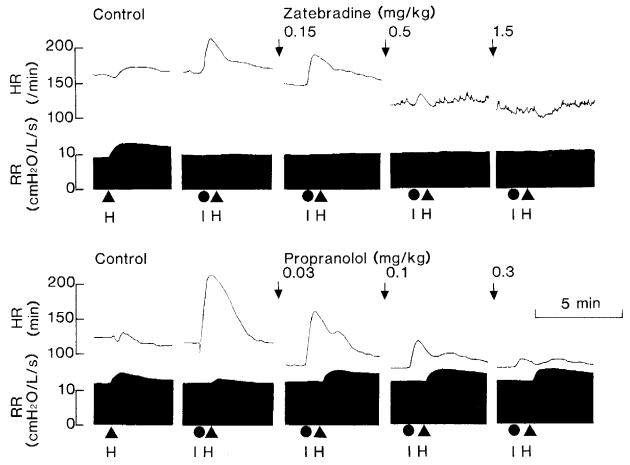

Fig. 2. The effects of zatebradine in doses of 0.15, 0.5 and 1.5 mg/kg i.v. on the increases in heart rate and the inhibition of the histamine (30 μg/kg i.v.)-induced increase in respiratory resistance by isoproterenol at 1 μg/kg i.v. in an anesthetized dog (upper panel) and the effects of propranolol in doses of 0.03, 0.1 and 0.3 mg/kg i.v. on the increase in heart rate and the inhibition of the histamine (30 μg/kg i.v.)-induced increase in respiratory resistance by isoproterenol at 1 μg/kg i.v. in another anesthetized dog (lower panel). HR, heart rate; RR, respiratory resistance; H, histamine; I, isoproterenol.

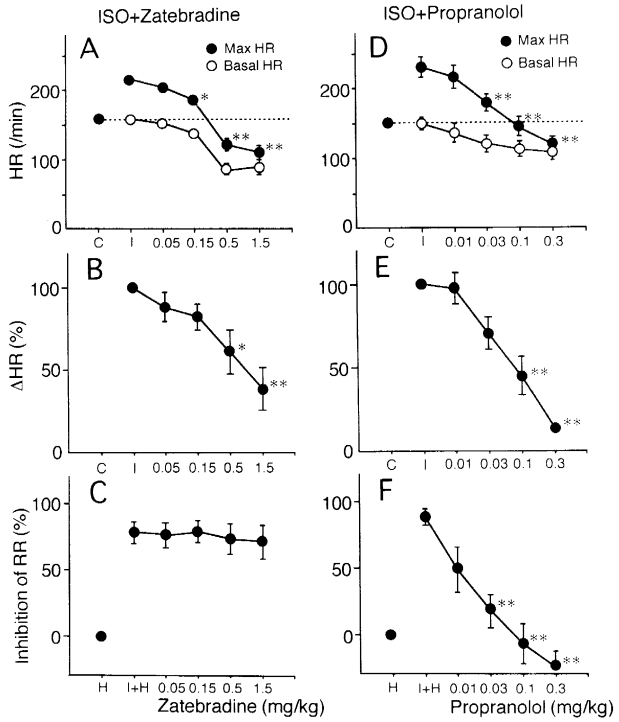

Fig. 3. The effects of zatebradine and propranolol on the basal heart rate and the increase in heart rate in response to isoproternol, and on the percentage inhibition of the histamine-induced increase in respiratory resistance by isoproterenol in 5 anesthetized dogs in each experimental group. The dotted line represents the control heart rate before zatebradine or propranolol (see Table 1). Vertical bars show S.E.M. HR, heart rate; ΔHR, percentage changes in the increase in heart rate in response to isoproterenol; RR, respiratory resistance; Max HR, maximal heart rate increased by isoproterenol; ISO, isoproterenol; C, control; I, isoproterenol; H, challenge dose of histamine; I+H, histamine after isoproterenol. * $P < 0.05$, ** $P < 0.01$ vs. I (upper and middle panel) or I+H (lower panel).

3.2. Effects of zatebradine and propranolol on the increase in heart rate and decrease in respiratory resistance increased by histamine in response to isoproterenol or procaterol

When histamine (30 μg/kg i.v.) increased respiratory resistance in an anesthetized dog, isoproterenol (1 μg/kg i.v.) suppressed this increase and increased heart rate (Fig. 2). Zatebradine in doses of 0.15, 0.5 and 1.5 mg/kg i.v. decreased basal heart rate and the increase in heart rate in response to isoproterenol dose dependently, but did not affect the inhibition by isoproterenol of the respiratory resistance increased by histamine (Fig. 2, upper panel). Propranolol in doses of 0.03, 0.1 and 0.3 mg/kg i.v. inhibited basal heart rate, the increase in heart rate in response to isoproterenol and the inhibition by isoproterenol of the histamine-induced respiratory resistance in another anesthetized dog (Fig. 2, lower panel). Fig. 3 summarizes the data of the effects of zatebradine and propranolol on the increase in heart rate and inhibition of

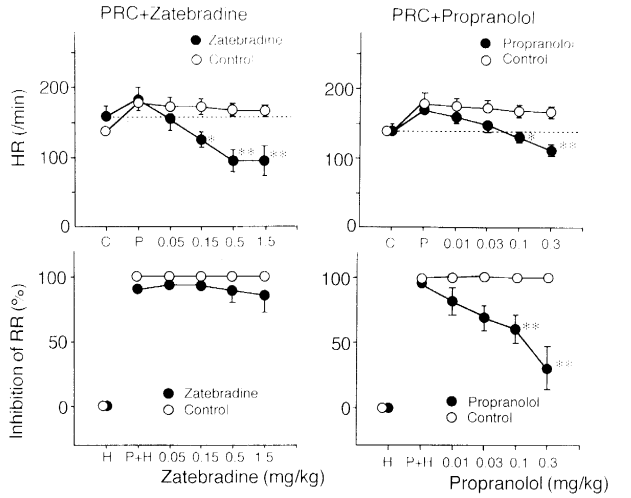

Fig. 4. Effects of zatebradine and propranolol on the heart rate increase elicited by procaterol and on the percentage inhibition of the histamine-induced increase in respiratory resistance by procaterol in 5 anesthetized dogs in each experimental group. The dotted line represents the control heart rate before zatebradine or propranolol (see Table 1). Vertical bars show S.E.M. Open circle shows data of the control group without zatebradine or propranolol. HR, heart rate; RR, respiratory resistance; PRC, procaterol; C, control; P, procaterol; H, challenge dose of histamine; P+H, histamine after procaterol. * $P < 0.05$, ** $P < 0.01$ vs. control group (open circle).

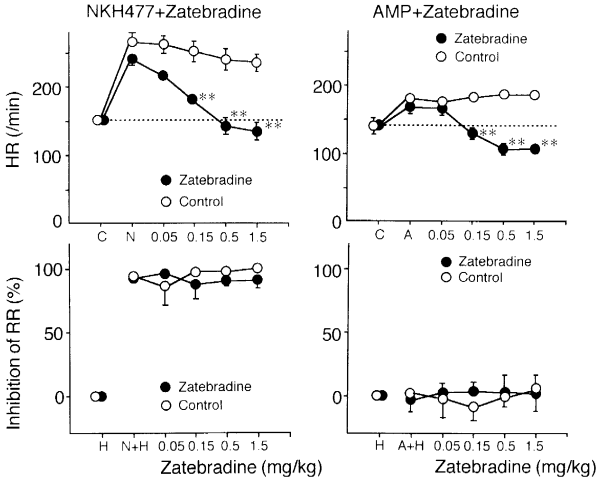

Fig. 5. Effects of zatebradine on the increase in heart rate elicited by NKH 477 and aminophylline, and on the percentage inhibition of the histamine-induced increase in respiratory resistance by NKH 477 and aminophylline in 5 anesthetized dogs in each experimental group. The dotted line represents the control heart rate before zatebradine (see Table 1). Vertical bars show S.E.M. Open circle shows data of the control group without zatebardine. HR, heart rate; RR, respiratory resistance; AMP, aminophylline; C, control; N, NKH 477; A, aminophylline; H, challenge dose of histamine; N+H, histamine after NKH 477; A+H, histamine after aminophylline. ** $P < 0.01$ vs. control group (open circle).

the histamine-induced respiratory resistance in response to isoproterenol in the anesthetized dog.

When isoproterenol at 1 or 3 μg/kg i.v. was given to the dogs in the zatebradine and propranolol treatment groups, it increased heart rate by 39 ± 5.2% and 49 ± 7.3%, and inhibited the increase in respiratory resistance induced by histamine by 89 ± 6.2% and 78 ± 8.7%, respectively. Zatebradine in doses of 0.05–1.5 mg/kg i.v. dose dependently ($P < 0.001$) decreased the increase in heart rate in response to isoproterenol (Fig. 3A and 3B) as well as the basal heart rate (Fig. 3A), but did not change the inhibitory effects of isoproterenol on the histamine-induced respiratory resistance (Fig. 3C) in 5 anesthetized dogs. Zatebradine did not affect arterial blood pressure throughout the experiments. Propranolol in doses of 0.01–0.3 mg/kg i.v. blocked the increase in heart rate (Fig. 3D and 3E) and the inhibition of the histamine-induced respiratory resistance in response to isoproterenol (Fig. 3F) in 5 anesthetized dogs ($P < 0.001$). Propranolol also decreased the basal heart rate significantly ($P < 0.001$, Fig. 3D). Fifty percent inhibition doses of zatebradine and propranolol for the positive chronotropic response to isoproterenol were 0.98 ± 0.41 mg/kg and 0.08 ± 0.03 mg/kg, respectively.

Table 1
Basal heart rate and increases in heart rate induced by bronchodilators, and basal respiratory resistance and increases in respiratory resistance induced by histamine of five anesthetized dogs in each experimental group

Experimental group	HR (bpm)	ΔHR (bpm)	Respiratory resistance (cmH_2O/l per s)	ΔRR (cmH_2O/l per s)
ISP+Zat.	155± 7.5	59± 4.6	9.2± 1.2	2.5±0.4
ISP+Prop.	146±10.6	70± 9.1	10.2± 0.9	2.3±0.3
PRC+Zat.	158±16.4	22± 7.0	9.7± 0.8	3.5±0.8
PRC+Prop.	141± 8.6	32±11.6	9.6±41.5	3.4±1.0
NKH+Zat.	154± 6.7	89±15.0	9.7± 0.3	2.6±0.4
AMP+Zat.	141±11.6	29± 3.9	9.6± 1.0	2.9±0.5

Data are shown as means±S.E.M. HR, heart rate; ΔHR, increase in heart rate induced by bronchodilators; ΔRR, increase in respiratory resistance induced by histamine; ISP, isoproterenol; Zat., zatebradine; Prop., propranolol; PRC, procaterol; NKH, NKH 477; AMP, aminophylline. Isoproterenol at a dose of 1 or 3 μg/kg, procaterol at a dose of 1 or 3 μg/kg, NKH 477 at a dose of 0.05 mg/kg and aminophylline at a dose of 5 mg/kg were administrated i.v.

Procaterol at doses of 1 or 3 μg/kg i.v. inhibited the increase in respiratory resistance in response to histamine but increased heart rate much less ($P < 0.05$) than did isoproterenol (Table 1). Zatebradine (0.05–1.5 μg/kg i.v.) attenuated the positive chronotropic response to procaterol ($P < 0.001$) but did not affect the inhibition by procaterol of the respiratory resistance increase elicited by histamine (Fig. 4, left panel). Propranolol blocked both the positive chronotropic and bronchodilatory responses to procaterol dose dependently ($P < 0.001$) (Fig. 4, right panel).

3.3. Effects of zatebradine on the changes in heart rate and respiratory resistance in response to NKH 477 and aminophylline

When NKH 477, an adenylyl cyclase activator, increased heart rate and attenuated the increase in respiratory resistance induced by histamine, zatebradine selectively

($P < 0.001$) attenuated this heart rate increase but did not affect the inhibition of the histamine-induced increase in respiratory resistance in 5 anesthetized animals (Fig. 5, left panel).

Zatebradine also blocked the heart rate increase elicited by aminophylline in a dose-dependent manner ($P < 0.001$) but did not change the respiratory resistance after aminophylline treatment (Fig. 5, right panel).

4. Discussion

In the present study, we demonstrated that zatebradine, a specific bradycardic agent, selectively inhibited the increase in heart rate in response to isoproterenol, procaterol, NKH 477 (an adenylyl cyclase activator) and aminophylline when these substances (except aminophylline) inhibited the increase in respiratory resistance induced by histamine in the anesthetized dog. These results suggest that zatebradine may be a useful drug for preventing the tachycardia induced by bronchodilators used to treat patients with asthma.

Zatebradine in the doses tested (0.05–1.5 mg/kg i.v.) did not affect the basal respiratory resistance and the inhibition by isoproterenol of the increase in respiratory resistance elicited by histamine in anesthetized dogs (Figs. 2 and 3), whereas it inhibited the positive chronotropic response to isoproterenol in anesthetized dogs (Figs. 2 and 3) as previously reported (Breall et al., 1993). Furthermore, we demonstrated that zatebradine did not affect the inhibition of the increased respiratory resistance elicited by a β_2-adrenoceptor agonist, procaterol, and an adenylyl cyclase activator, NKH 477, whereas it inhibited the increase in heart rate elicited by these substances (Figs. 4 and 5). A non-selective β-adrenoceptor antagonist, propranolol, inhibited β_1- and β_2-adrenoceptor-mediated positive chronotropic responses as well as β_2-adrenoceptor-mediated inhibition of the respiratory resistance increase elicited by histamine (Figs. 2–4). These results, therefore, suggest that inhibition by zatebradine of the hyperpolarization activated inward current (I_f) is not involved in respiratory resistance in anesthetized dogs. I_f exists in smooth muscle cells of the portal vein but not in those in coronary artery and mesenteric artery of the rabbit (Kamouchi et al., 1991). However, the role of I_f on bronchial smooth muscle cells has not been determined in electrophysiological studies yet. Zatebradine inhibits I_f of the mammalian sinoatrial nodal cells although a high concentration of zatebradine also inhibits delayed rectifier K^+ currents (I_K) and slow inward Ca^{2+} currents (I_{Ca}) (Doerr and Trautwein, 1990; Goethals et al., 1993; Thollon et al., 1994). We recently reported that zatebradine selectively inhibited the sinus rate and the increase in sinus rate induced by sympathetic nerve stimulation without affecting other cardiac responses. Verapamil, an inhibitor of I_{Ca}, attenuated both positive chronotropic and inotropic responses to sympathetic stimulation and E-4031, an inhibitor of a rapid type of I_K (I_{Kr}), affected neither the positive chronotropic nor inotropic responses in anesthetized dogs (Furukawa et al., 1995; Furukawa and Chiba, 1996). Thus, it is likely that at the low doses used in the present study zatebradine mainly works as an I_f inhibitor in the anesthetized dog.

Even at relatively low doses of 0.15 and 0.5 mg/kg i.v. zatebradine decreased the basal heart rate as well as the increase in heart rate in response to isoproterenol, procaterol, NKH 477 and aminophylline without affecting the respiratory resistance. That is, zatebradine at the doses used could decrease the increased heart rate to less than the pre-drug control heart rate (Figs. 2–5). A β-adrenoceptor agonist, isoproterenol, a β_2-adrenoceptor agonist, procaterol (Saitou et al., 1979), an adenylyl cyclase activator, NKH 477 (Hosono et al., 1992), and aminophylline increased heart rate and decreased respiratory resistance following bronchial smooth muscle relaxation due to an increase in tissue cyclic AMP, at least in part. I_f is activated by cyclic AMP in sinoatrial nodal cells directly and indirectly (DiFrancesco, 1991; DiFrancesco and Tortora, 1991). Therefore, we suggest that zatebradine at relatively low doses selectively preserves the pre-drug control heart rate even after administration of cyclic AMP-related bronchodilators that decrease respiratory resistance adequately. Our suggestion is also supported by the selective inhibition by zatebradine of the increases in sinus rate in response to the cyclic AMP-dependent cardiotonics, isoproterenol, norepinephrine, 3-isobutyl-1-methylxanthine as a phosphodiesterase inhibitor, and NKH 477 in isolated mammalian heart preparations (Lillie and Kobinger, 1986; Sawaki et al., 1995).

Heart rate in the pentobarbital-anesthetized dog varied from 141 (mean) bpm to 158 bpm among the experimental groups (Table 1). The heart rate in the conscious dog is less than 90 bpm and the heart rate of the denervated heart is between 90 and 120 bpm (Donald and Samueloff, 1966; Vatner and Boettcher, 1978). Thus, in the pentobarbital-anesthetized dog used in the present study, sympathetic nerve activity would predominate. In the autonomic denervated heart of the pentobarbital-anesthetized dog, the heart rate was between 98 and 121 bpm and zatebradine at approximately 1.5 mg/kg i.v. decreased the heart rate to 70% of the pre-drug level (Furukawa et al., 1995). In the present study, zatebradine decreased the basal heart rate to 56% of the pre-drug level, suggesting that zatebradine attenuates the increase in heart rate induced by sympathetic activation under pentobarbital anesthesia in autonomic intact dog hearts. A non-selective β-adrenoceptor antagonist, propranolol, also decreased the basal heart rate to 70% of the pre-drug level, suggesting that the sympathetic nervous system of the dogs used in the present study was active, although propranolol at a high dose has a direct depressant action. Zatebradine suppressed the positive chronotropic responses to sympathetic nerve stimulation in the autonomically denervated heart of the anesthetized dog (Furukawa et al., 1995, 1996) and to norepinephrine, iso-

proterenol, NKH 477 and 3-isobutyl-1-methylxanthine in the isolated perfused dog atrium (Sawaki et al., 1995). It is, therefore, suggested that the inhibition by zatebradine of the positive chronotropic responses to isoproterenol, procaterol, NKH 477 and aminophylline is due to its direct inhibition of the basal heart rate and to its inhibition of the positive chronotropic responses to those substances in the pentobarbital-anesthetized dog.

Mortality associated with bronchial asthma is higher in elderly patients than in younger patients, but mortality among younger patients is also increasing (Higenbottam and Hay, 1990). Inhalation of β-adrenoceptor agonists is thought to be one of the causes of this increasing mortality (Sears et al., 1990; Robin and McCauley, 1992; Spitzer et al., 1992). β-Adrenoceptor agonists cause a fall in serum K^+ concentrations with increasing heart rate and prolong the QTc interval (Wong et al., 1990). Prolongation of QTc causes sudden cardiac death by provocation of torsade de pointes. Additionally, some old patients have complications such as coronary artery disease. It is, therefore, expected that zatebradine may be beneficial in preventing the tachycardia induced by cyclic AMP-related bronchodilators and in decreasing mortality among bronchial asthma patients by inhibiting the increased heart rate. However, we have to study the adverse effects of zatebradine because I_f exists in many tissues including central nervous system (Maccaferri et al., 1993; Solomon and Nerbonne, 1993; Travagli and Gillis, 1994). One of the adverse effects of zatebradine is visual disturbance, as indicated in a clinical trial of zatebradine (Frishman et al., 1995), although it does not have arrhythmogenic properties in anesthetized dogs (Furukawa et al., 1996).

Zatebradine is also expected to enhance the positive inotropic effects of dobutamine in ischemic myocardium (Wynsen et al., 1994) and to decrease mortality due to acute myocardial infarction with thrombolytic therapy (Van de Werf et al., 1993), although zatebradine dose not increase exercise tolerance benefit in patients with angina taking extended-release nifedipine (Frishman et al., 1995). Thus, zatebradine may be a useful drug for prophylactic treatment of tachycardia with a minor adverse effect on other functions.

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