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Effects of mexiletine on the canine model of sparfloxacin-induced long QT syndrome

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Abstract

Potential utility of mexiletine for the treatment of sparfloxacin-induced long QT syndrome was assessed using the in vivo halothane-anesthetized canine model. At 30 min after the administration of a supratherapeutic dose of sparfloxacin (30 mg/kg, i.v.), the mean blood pressure and heart rate decreased, whereas repolarization process and effective refractory period of the ventricular muscle were significantly prolonged. Additional administration of a clinically recommended dose of mexiletine (3 mg/kg, i.v.) at this time point increased the mean blood pressure, suppressed ventricular contraction, delayed atrioventricular as well as intraventricular conduction, and shortened repolarization process and effective refractory period. The extent of abbreviation of the repolarization was more prominent than that of the refractoriness, indicating that mexiletine could decrease the electrical vulnerability of the heart during sparfloxacin overdose. Thus, mexiletine may become a promising pharmacological strategy against the drug-induced long QT syndrome.

Keywords: Mexiletine; Sparfloxacin; Long QT syndrome; Monophasic action potential; Effective refractory period

1. Introduction

Acquired type of long QT syndrome is occasionally observed during pharmacotherapies with antiarrhythmics, antihistamines, prokinetic drugs, antibiotics and psychotropics (Roden, 1996; Tamargo, 2000). It has been clarified that the mechanism for QT prolongation by such drugs is closely associated with blockade of rapid component of the delayed rectifier K^+ current (I_{Kr}), which ultimately results in the onset of polymorphic ventricular tachyarrhythmias called torsades de pointes (Roden, 1996; Tamargo, 2000). Intravenous administration of magnesium, isoproterenol and propranolol as well as the temporal cardiac pacing have been used for managing such lethal arrhythmia besides withdrawal of the QT prolonging drug (Roden, 1996; Tamargo, 2000). While exploring alternative pharmacological strategy, recently, we found a class Ib antiarrhythmic drug mexiletine that can effectively abbreviate the prolonged repolarization process by a prokinetic drug cisapride in the in vivo canine heart (Satoh et al., 2000a). However, information regarding utility of mexiletine against the drug-induced long QT syndrome is still limited (Shimizu and Antzelevitch, 1997; Fazekas et al., 1998).

The present study was designed to examine the electropharmacological effects of mexiletine on the halothane-anesthetized dogs complicating a nonspecific I_{Kr} channel blocker, fluoroquinolone antibiotic sparfloxacin-induced long QT syndrome (Dupont et al., 1996; Chiba et al., 2000). To precisely analyze the electrophysiological effects of the drugs on the depolarization and repolarization processes, we recorded His bundle electrograms and monophasic action potentials (MAPs), respectively, in addition to the standard lead II electrocardiograms (ECGs). Moreover, a monophasic action potential recording/pacing combination catheter was used to simultaneously estimate the drug effects on the repolarization and refractoriness, which will provide essential information of proarrhythmic and/or antiarrhythmic potentials of drugs (Franz, 1994; Sugiyama and Hashimoto, 1998, 2002; Sugiyama et al., 2001, 2002, 2003).

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2. Materials and methods

All experiments were performed according to Guidelines for Animal Experiments, University of Yamanashi.

2.1. Cardiohemodynamic parameters

Six female beagle dogs were initially anesthetized with thiopental sodium (30 mg/kg, i.v.). After intubation with a cuffed endotracheal tube, 1.0% halothane vaporized with 100% oxygen was inhaled with a volume-limited ventilator (SN-408-3; Shinano, Tokyo, Japan). The tidal volume and respiratory rate were set at 20 ml/kg and 15 strokes/min, respectively. To prevent blood clotting, heparin calcium (100 IU/kg) was intravenously administered. A heparinized catheter was inserted through the right femoral artery for continuous monitoring of the systemic blood pressure. A thermodilution catheter (TC-704; Nihon-Kohden, Tokyo, Japan) was positioned at the right side of the heart via the right femoral vein, and the cardiac output was measured by a standard thermodilution method by using a cardiac output computer (MFC-1100; Nihon-Kohden). Total peripheral vascular resistance was calculated using the basic equation: mean blood pressure/cardiac output. A pigtail catheter was positioned at the left ventricle through the right femoral artery to measure ventricular pressure. The maximal upstroke velocity of the left ventricular pressure ($LVdP/dt_{max}$) and left ventricular end-diastolic pressure (LVEDP) were obtained to estimate the contractility and preload to the left ventricle, respectively.

2.2. Electrophysiological parameters

The surface lead II ECG was obtained from the limb electrodes. Corrected QT interval (QTc) was calculated using Bazett's (1920) and Van de Water's et al., (1989) formulas. A quad-polar electrodes catheter was positioned at the non-coronary cusp of the aortic valves via the left femoral artery to record His bundle electrogram. A bi-directional steerable monophasic action potential recording/pacing combination catheter (1675P; EP Technologies, Sunnyvale, CA, USA) was positioned at the endocardium of the interventricular septum in the right ventricle via the left femoral vein to obtain the monophasic action potential signals. The signals were amplified with a direct-current preamplifier (300; EP Technologies). The duration of the monophasic action potential signal was measured as an interval, along a line horizontal to the diastolic baseline, from the upstroke to the desired repolarization level, and the interval (ms) at 90% repolarization was defined as MAP_{90}.

The heart was electrically driven using a cardiac stimulator (SEC-3102; Nihon-Kohden) with the pacing electrodes of the monophasic action potential recording/pacing combination catheter in the right ventricle. Stimulation pulses were rectangular in shape, 1–2 V (about twice the threshold voltage) and of 1-ms duration. MAP_{90} was measured during the sinus rhythm ($MAP_{90(sinus)}$) and at a pacing cycle length of 400 ms ($MAP_{90(CL400)}$) and 300 ms ($MAP_{90(CL300)}$). The effective refractory period was assessed by a programmed electrical stimulation to the right ventricle. The pacing protocol consisted of five beats of basal stimuli in a cycle length of 400 ms followed by an extra stimulus of various coupling intervals. Starting in the late diastole, the coupling interval was shortened in 5- to 10-ms decrements until refractoriness occurred. The duration of the terminal repolarization phase of the ventricle, namely phase 3 repolarization of the action potential, was calculated by the difference between the $MAP_{90(CL400)}$ and the effective refractory period at the same site, which can quantitatively reflect the extent of electrical vulnerability of the ventricular muscle (Franz, 1994; Sugiyama and Hashimoto, 1998, 2002; Sugiyama et al., 2001, 2002, 2003).

2.3. Experimental protocol

The cardiohemodynamic and electrophysiological parameters were continuously monitored using a polygraph system (RM-6000; Nihon-Kohden), and analyzed with a real time full automatic data analysis system (MP/VAS 3 for Macintosh, ver 1.0, Physio-Tech, Tokyo, Japan). Each measurement of ECG, the monophasic action potential, atrio-His and His-ventricular interval was the mean of three consecutive recordings. The cardiovascular variables were assessed in the following order. The cardiac output was measured twice. Next, the ECG, His bundle electrogram, systemic and left ventricular pressure and the monophasic action potential signals were recorded under a sinus rhythm. Then, the monophasic action potential signals were recorded during the ventricular pacing at a cycle length of 400 and 300 ms. Finally, the effective refractory period was assessed by the programmed electrical stimulation, as described above.

In our previous study, we assessed the cardiovascular effects of sparfloxacin alone using the same animal model as used in this study and found that cardiohemodynamic as well as electrophysiological responses became relatively stable for 30–60 min after the administration of 30 mg/kg of sparfloxacin (Satoh et al., 2000b). Based on this previous knowledge, we performed the current experiment. After the basal assessment, sparfloxacin in a dose of 30 mg/kg was intravenously administered over 10 min. The effects of sparfloxacin on each cardiovascular variable were assessed at 30 min after the start of the drug administration. Then, 3 mg/kg of mexiletine was intravenously administered over 1 min, and each parameter was assessed 1, 3, 5, 7, 10, 15, 20 and 30 min after the administration of mexiletine.

2.4. Plasma drug concentration

A volume of 3 ml of blood was drawn from the left femoral artery at each time point to measure the plasma drug concentration. The blood samples were centrifuged at

1500 × *g* for 20 min at 4 °C, and the plasma was stored at − 80 °C until the drug concentration was measured. Determinations of the concentration of mexiletine and sparfloxacin were performed using a high-performance liquid chromatographic method.

2.5. Drugs

Sparfloxacin was extracted from a commercial source (Spara; Dainippon Pharmaceuticals, Osaka, Japan) and dissolved in 10 mg/ml lactate solution. We have confirmed that intravenous administration of the solvent does not affect any of the cardiovascular parameters for >3 h (Sugiyama and Hashimoto, 1998). The following drugs were purchased: mexiletine (Mexitil Inj.; Boehringer, Hyogo, Japan), thiopental sodium (Tanabe, Osaka, Japan), halothane (Takeda, Osaka, Japan) and heparin calcium (Mitsui, Tokyo, Japan).

2.6. Statistics

Data are expressed as the mean ± S.E.M. The statistical comparisons within a parameter were evaluated by one-way, repeated-measures analysis of variance (ANOVA) followed by Contrasts for mean values comparison. A P value <0.05 was considered statistically significant.

3. Results

3.1. Plasma drug concentration

The time courses of the plasma concentration of mexiletine and sparfloxacin are summarized in Fig. 1. The plasma concentration of sparfloxacin was in a range of 13.1 ± 0.4 to 21.9 ± 2.2 μg/ml (33.4 ± 1.0 to 55.8 ± 5.6 μM) during the assessment of the effects of mexiletine. The peak plasma concentration of mexiletine was 7.4 ± 0.4 μg/ml (34.3 ± 1.8 μM), and the decrease of the plasma concentration of mexiletine followed a pattern that could be predicted by the two-compartment theory of pharmacokinetics.

3.2. Effects on the heart rate and mean blood pressure

The time courses of changes in the heart rate and mean blood pressure are summarized in Fig. 1, of which pre-drug control values were 137 ± 9 beats/min and 123 ± 6 mm Hg, respectively. Sparfloxacin significantly decreased the heart rate and blood pressure at 30 min compared with respective control values. Additional administration of mexiletine increased the mean blood pressure, while it hardly affected the heart rate.

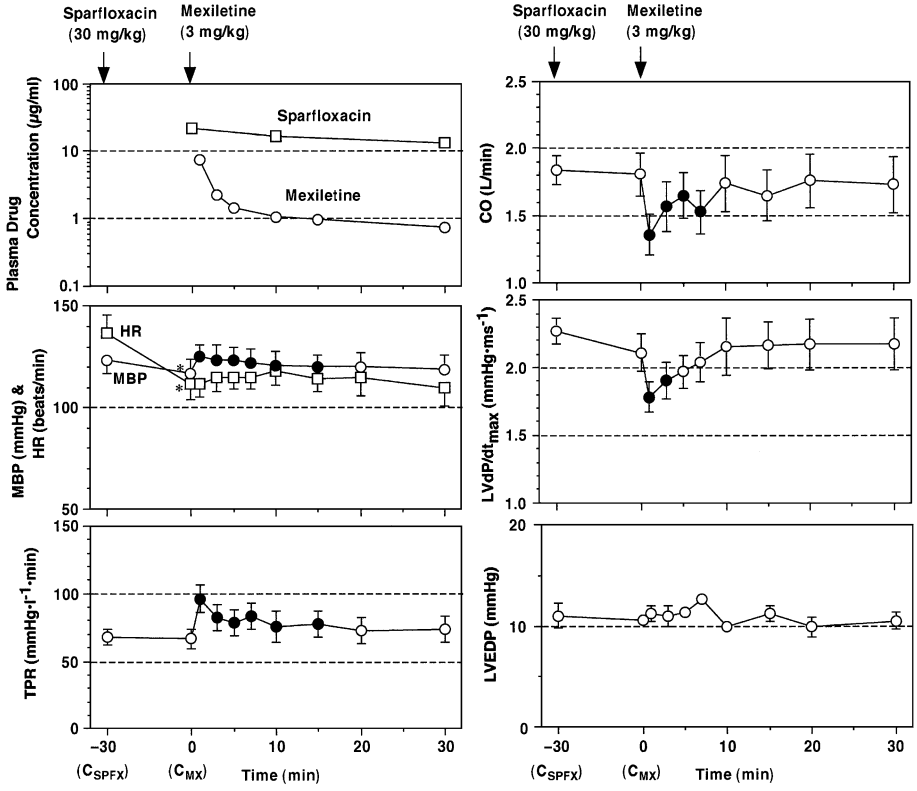

Fig. 1. Time courses of the plasma drug concentration (left upper panel); heart rate (HR, squares) and mean blood pressure (MBP, circles) (left middle panel); total peripheral vascular resistance (TPR, left lower panel); cardiac output (CO, right upper panel); maximum upstroke velocity of left ventricular pressure ($LVdP/dt_{max}$, right middle panel); and left ventricular end-diastolic pressure (LVEDP, right lower panel). Data are presented as mean ± S.E.M. ($n=6$). The asterisks represent significant differences between sparfloxacin control (C_{SPFX}) and a value at 30 min after the administration of sparfloxacin by $P<0.05$. Closed symbols represent significant differences from mexiletine control (C_{MX}) by $P<0.05$.

3.3. Effects on the cardiac output and total peripheral vascular resistance

The time courses of changes in the cardiac output and total peripheral vascular resistance are summarized in Fig. 1, of which pre-drug control values were 1.84 ± 0.11 l/min and 68 ± 6 mm Hg·min/l, respectively. Sparfloxacin did not affect the cardiac output or total peripheral vascular resistance at 30 min compared with respective control values. Additional administration of mexiletine decreased the cardiac output, while it increased the total peripheral vascular resistance.

3.4. Effects on the LVdP/dt$_{max}$ and LVEDP

The time courses of changes in the LVdP/dt_{max} and LVEDP are summarized in Fig. 1, of which pre-drug control values were 2.27 ± 0.10 mm Hg/ms and 11.0 ± 1.2 mm Hg, respectively. Sparfloxacin did not affect the LVdP/dt_{max} or LVEDP at 30 min compared with respective control values. Additional administration of mexiletine decreased the LVdP/dt_{max}, while it hardly affected LVEDP.

3.5. Effects on the ECG

Typical tracings of the effects of the drugs on the ECG are depicted in Fig. 2. The time courses of changes in the ECG parameters are summarized in Fig. 3. The pre-drug control values of the PR interval, QRS width, QT interval and QTc corrected by Bazett and Van de Water were 103 ± 4, 62 ± 1, 215 ± 9 ms, 322 ± 8 and 263 ± 7, respectively. Sparfloxacin did not affect the PR interval or QRS width at 30 min compared with respective control values, while it prolonged the QT interval and QTc. Additional administration of mexiletine prolonged the PR interval and QRS width, while it shortened the QT interval and QTc. Maximum changes in the QT interval and QTc from the effects of sparfloxacin are shown in Table 1.

3.6. Effects on the His bundle electrogram and monophasic action potential during sinus rhythm

Typical tracings of the effects of the drugs on the His bundle electrogram and monophasic action potential are depicted in Fig. 2. The time courses of changes in the atrio-His and His-ventricular intervals and MAP$_{90(sinus)}$ during sinus rhythm are summarized in Fig. 3, of which pre-drug control values were 76 ± 4, 27 ± 1 and 216 ± 9 ms, respectively. Sparfloxacin did not affect the atrio-His or His-ventricular intervals at 30 min compared with respective control values, while it prolonged the MAP$_{90(sinus)}$. Additional administration of mexiletine prolonged the atrio-His and His-ventricular intervals, while it shortened the MAP$_{90(sinus)}$. Maximum change in the MAP$_{90(sinus)}$ from the effect of sparfloxacin is shown in Table 1.

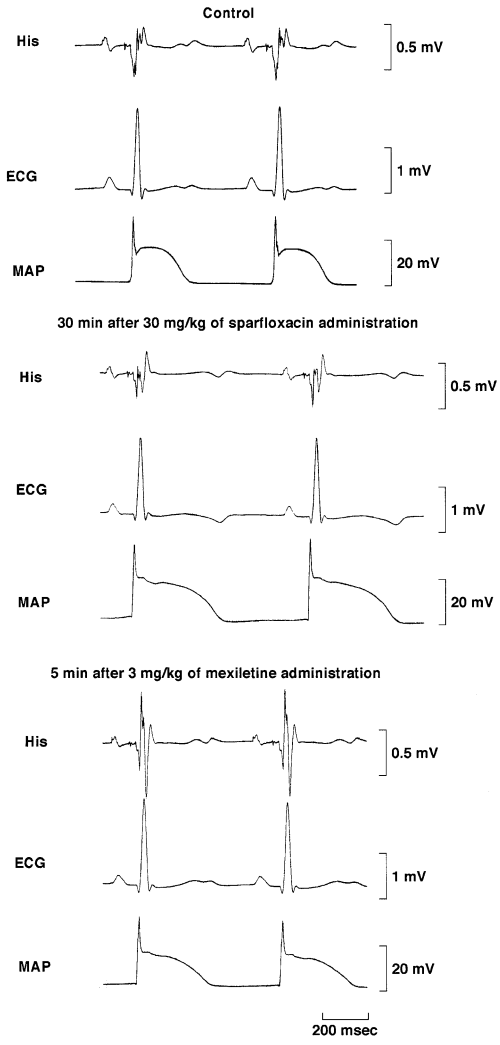

Fig. 2. Typical tracings of the His bundle electrogram (His), surface lead II electrocardiogram (ECG) and monophasic action potentials (MAP) recorded from the right ventricle during sinus rhythm before the administration of sparfloxacin (Control), 30 min after the start of sparfloxacin infusion and 5 min after the mexiletine administration.

3.7. Effects on the monophasic action potential, effective refractory period and terminal repolarization period during ventricular pacing

The time courses of changes in the MAP$_{90(CL400)}$, MAP$_{90(CL300)}$, effective refractory period and terminal repolarization period are summarized in Fig. 3, of which pre-drug control values were 223 ± 8, 206 ± 7, 186 ± 7 and 37 ± 5 ms, respectively. Sparfloxacin prolonged the MAP$_{90(CL400)}$, MAP$_{90(CL300)}$ and effective refractory period at 30 min compared with respective control values, while it did not affect the terminal repolarization period. Additional administration of mexiletine shortened the MAP$_{90(CL400)}$, effective refractory period and terminal repolarization period, while it did not affect the MAP$_{90(CL300)}$. Maximum changes in the MAP$_{90(CL400)}$, MAP$_{90(CL300)}$

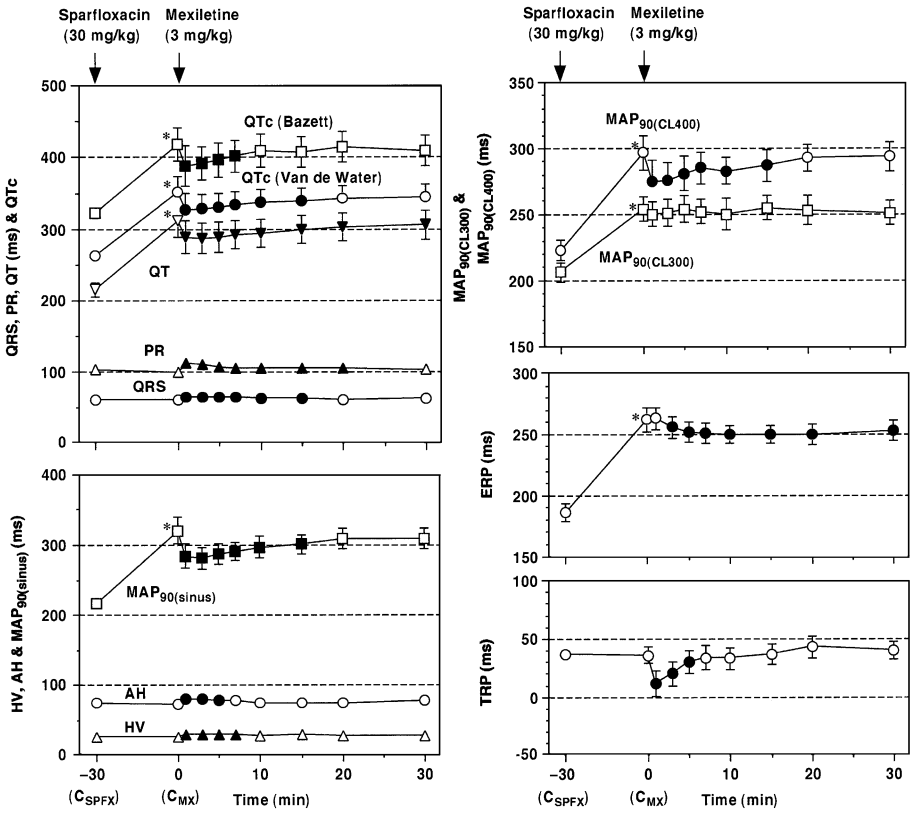

Fig. 3. Time courses of the PR interval (triangles), QRS width (circles), QT interval (triangles) and QTc (squares: Bazett; circles: Van de Water) (left upper panel); atrio-His interval (AH, circles) and His-ventricular interval (HV, triangles) and duration of monophasic action potential at a level of 90% repolarization (MAP_{90}) during sinus rhythm recorded from the right ventricle ($MAP_{90(sinus)}$, squares) (left lower panel); MAP_{90} during the ventricular pacing at a cycle length of 400 ms ($MAP_{90(CL400)}$, circles) and 300 ms ($MAP_{90(CL300)}$, squares) (right upper panel); effective refractory period of the right ventricle (ERP, right middle panel) and terminal repolarization period (TRP, lower right panel). Data are presented as mean ± S.E.M. ($n=6$). The asterisks represent significant differences between sparfloxacin control (C_{SPFX}) and a value at 30 min after the administration of sparfloxacin by $P<0.05$. Closed symbols represent significant differences from mexiletine control (C_{MX}) by $P<0.05$.

effective refractory period and terminal repolarization period from the effects of sparfloxacin are shown in Table 1.

Table 1
Maximum changes by mexiletine in the repolarization process from the effects of sparfloxacin

	Delta changes (ms)	% Changes
QT	− 25 ± 8	− 7.8 ± 2.2
QTc (Bazett)	− 31 ± 10	− 7.7 ± 2.5
QTc (Van de Water)	− 24 ± 8	− 6.9 ± 2.1
$MAP_{90(sinus)}$	− 35 ± 4	− 11.0 ± 1.2
$MAP_{90(CL400)}$	− 27 ± 5	− 9.0 ± 1.5
$MAP_{90(CL300)}$	− 4 ± 3	− 1.4 ± 1.4
ERP	− 12 ± 4	− 4.3 ± 1.5
TRP	− 29 ± 6	− 92.0 ± 26.1

$MAP_{90(sinus)}$, duration of monophasic action potential at a level of 90% repolarization (MAP_{90}) during sinus rhythm recorded from the right ventricle; $MAP_{90(CL400)}$, MAP_{90} during the ventricular pacing at a cycle length of 400 ms; $MAP_{90(CL300)}$, MAP_{90} during the ventricular pacing at a cycle length of 300 ms; ERP, effective refractory period of the right ventricle; and TRP, terminal repolarization period.

4. Discussion

We assessed the electropharmacological effects of mexiletine on the halothane-anesthetized canine model complicating sparfloxacin overdose to clarify the potential utility of mexiletine for the treatment of a drug-induced long QT syndrome.

4.1. Plasma concentrations of sparfloxacin and mexiletine

Plasma concentration of sparfloxacin was 13–22 μg/ml during the assessment of the effects of mexiletine, which is about 10 times higher than clinically known antibiotic concentration of 1–2 μg/ml (Montay, 1996; Goa et al., 1997). A similar time course of plasma drug concentration has been shown by the administration of sparfloxacin alone (Satoh et al., 2000b), indicating that mexiletine does not significantly modify the pharmacokinetics of sparfloxacin. On the other hand, after the administration of a clinically recommended dose of mexiletine, the plasma concentration of mexiletine was 0.8–7.4 μg/ml, which is quite similar to that obtained after the admin-

istration of mexiletine alone (Yoshida et al., 2002). In our previous studies using digitalis-, epinephrine- and coronary-ligation-induced canine ventricular arrhythmia models, minimum effective plasma concentration of mexiletine was reported to be 1.8–3.7 μg/ml (Hashimoto et al., 1991). Meanwhile, a clinical study indicated that therapeutic concentration of mexiletine was 0.7–1.6 μg/ml (Podrid, 1996). Thus, experimentally as well as clinically antiarrhythmic concentrations can be obtained by 3 mg/kg, i.v. of mexiletine in the presence of sparfloxacin overdose.

4.2. Cardiohemodynamic and electrophysiological effects of sparfloxacin

A supratherapeutic dose of sparfloxacin decreased the mean blood pressure and heart rate, while it significantly prolonged the ventricular repolarization process and effective refractory period without affecting other cardiovascular variables in this study. This observation is in good accordance with our previous studies (Chiba et al., 2000; Satoh et al., 2000b). Also, such in vivo cardiohemodynamic and electrophysiological effects of sparfloxacin were quite similar to those induced by other nonspecific I_{Kr} channel blockers which have induced torsades de pointes in clinical practice (Anderson et al., 2001; Kang et al., 2001; Satoh et al., 2000a; Sugiyama and Hashimoto, 1998, 2002; Usui et al., 1998). Thus, the use of sparfloxacin may be an appropriate drug to study the potential utility of mexiletine for the treatment of a drug-induced long QT syndrome.

4.3. Cardiohemodynamic effects of mexiletine during sparfloxacin overdose

Additional administration of mexiletine decreased the cardiac output but increased the total peripheral resistance resulting in a slight increase of the mean blood pressure, which would be most likely due to nonspecific actions. Meanwhile, the drug decreased the ventricular contraction possibly through Na^+ channel blockade, but it did not affect the heart rate or LVEDP. These cardiohemodynamic effects were essentially in accordance with those observed by mexiletine alone in the previous reports, except that 3 mg/kg of mexiletine hardly affected or slightly decreased the mean blood pressure (Podrid, 1996; Satoh et al., 2000a; Yoshida et al., 2002). Thus, one can speculate that hypotension induced by sparfloxacin may have modulated the cardiohemodynamic effects of mexiletine. In addition, since some QT prolonging drugs have been shown to suppress the ventricular contraction via nonspecific mechanisms (Sugiyama and Hashimoto, 1998; Sugiyama et al., 2001; Usui et al., 1998), caution has to be paid on the negative inotropic effect of mexiletine for patients with impaired left ventricular contraction.

4.4. Electrophysiological effects of mexiletine during sparfloxacin overdose

Additional administration of mexiletine delayed the atrioventricular as well as intraventricular conduction, whereas it enhanced the repolarization process. It should also be noted that the extent of shortening of the MAP_{90} by mexiletine was greater at slower heart rate, indicating the reverse use-dependent abbreviation of repolarization process. This property of mexiletine could be ideal for the treatment of the drug-induced long QT syndrome, since most of the QT prolonging drugs delay repolarization process more significantly at slower heart rate (Sugiyama and Hashimoto, 1998, 2002; Sugiyama et al., 2002; Usui et al., 1998; Satoh et al., 2000b). Previous knowledge from the in vitro studies can largely explain these multifarious in vivo electrophysiological effects of mexiletine. The intraventricular conduction delay may reflect the Na^+ channel inhibition by mexiletine (Sugiyama et al., 1994), whereas the prolongation of the atrioventricular conduction time could be explained by the Ca^{2+} current reduction (Sato et al., 1995). Also, several mechanisms have been proposed for the repolarization abbreviation action by mexiletine, including reduction of Na^+ window current and/or Ca^{2+} current in addition to activation of the ATP-sensitive K^+ channels (Kiyosue and Arita, 1989; Sato et al., 1995). Even more important is that these in vivo electrophysiological effects were essentially the same as those observed by mexiletine alone in the previous reports (Satoh et al., 2000a; Yoshida et al., 2002). Thus, the present observation may at least in part indicate that mexiletine can exert these electrophysiological effects in the in vivo heart in the presence as well as absence of sparfloxacin overdose.

4.5. Effects on the effective refractory period

Additional administration of mexiletine shortened the effective refractory period like the repolarization phase, which is in sharp contrast with our previous studies, in which effective refractory period was prolonged by 3 mg/kg of mexiletine with or without a prokinetic drug cisapride overdose (Satoh et al., 2000a; Yoshida et al., 2002). It should also be noted that there was no difference in the time courses of plasma concentration of mexiletine between the present and the previous studies. Similar intriguing observation regarding the effective refractory period has been reported in the in vitro study with the Purkinje fibers from canine false tendon (Burke et al., 1986). In their report, mexiletine shortened the effective refractory period at low concentration of 25 μM, but the effect leveled off and then reversed at higher concentration of 100 μM. They ascribed the basis of this observation to the function of the kinetics of recovery from phasic Na^+ current block. Thus, current observation is in accordance with their in vitro result by lower concentration of mexiletine, whereas our previous findings may have reflected that by higher concentration.

Further analysis should be performed to clarify the precise mechanisms of the effects of mexiletine in vivo on the effective refractory period.

4.6. Effects on the terminal repolarization phase

In a previous study, we have demonstrated that backward shift of the phase 3 repolarization; namely terminal repolarization period, may be the mechanism for the torsadogenic action of sparfloxacin, which increases the chance of "R on T" phenomenon leading to torsades de pointes (Chiba et al., 2000). In this study, we confirmed the same effect of sparfloxacin on the terminal repolarization period. In the presence of sparfloxacin overdose, additional mexiletine shortened both effective refractory period and repolarization phase. More importantly, the extent of shortening was more prominent in the repolarization than in the refractoriness at the same site, resulting in the prominent abbreviation of the terminal repolarization period as shown in Table 1, which would reduce the chance of "R on T" phenomenon and prevent the onset of lethal arrhythmias (Satoh et al., 2000a; Yoshida et al., 2002). Thus, mexiletine can decrease the extent of the electrical vulnerability of the heart complicating the sparfloxacin overdose.

4.7. Conclusions

Use of mexiletine may become a promising pharmacological strategy against the drug-induced long QT syndrome. However, caution has to be paid on the negative inotropic effect of mexiletine for patients with impaired left ventricular contraction.

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