Original Article

Fluvoxamine by itself has potential to directly induce long QT syndrome at supra-therapeutic concentrations

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ABSTRACT — Fluvoxamine is one of the typical selective serotonin-reuptake inhibitors. While its combined use with QT-prolonging drugs has been contraindicated because of the increase in plasma concentrations of such drugs, information is still limited whether fluvoxamine by itself may directly prolong the QT interval. We examined electropharmacological effects of fluvoxamine together with its pharmacokinetic profile by using the halothane-anesthetized dogs (n = 4). Fluvoxamine was intravenously administered in three escalating doses of 0.1, 1 and 10 mg/kg over 10 min with a pause of 20 min between the doses. The low dose provided therapeutic plasma drug concentration, whereas the middle and high doses attained approximately 10 and 100 times of the therapeutic ones, respectively. Supra-therapeutic concentration of fluvoxamine exerted the negative chronotropic, inotropic and hypotensive effects; and suppressed the atrioventricular nodal and intraventricular conductions, indicating inhibitory actions on Ca^{2+} and Na^+ channels, whereas it delayed the repolarization in a reverse use-dependent manner, reflecting characteristics of rapidly activating delayed rectifier K^+ current channel-blocking property. Fluvoxamine prolonged the terminal repolarization phase at 100 times higher concentration than the therapeutic, indicating its proarrhythmic potential. Thus, fluvoxamine by itself has potential to directly induce long QT syndrome at supra-therapeutic concentrations.

Key words: Fluvoxamine, Long QT syndrome, Arrhythmia, I_{Kr}, SSRI

INTRODUCTION

Fluvoxamine is a typical selective serotonin-reuptake inhibitor, and has been widely used for the treatment of major depression over 30 years (Omori *et al*., 2009). On the other hand, combined use of fluvoxamine with other drugs having risks of QT-interval prolongation has been contraindicated, since it may increase the plasma concentration of such drugs via prolongation of their half-lives (Granfors *et al*., 2004). Moreover, fluvoxamine by itself was reported to inhibit human ether-a-go-go-related gene (hERG) channels (Milnes *et al*., 2003). Indeed, in some previous clinical studies (Klok *et al*., 1981; Nia *et al*., 2012), the QT interval was prolonged by clinical dos-

es of fluvoxamine; however, such prolongation was not observed in the other clinical reports (Beach *et al*., 2014; Okayasu *et al*., 2012). Furthermore, specific data are very limited regarding the proarrhythmic effects of fluvoxamine (Claassen, 1983; Manet *et al*., 1993; Wouters and Deiman, 1983).

In order to bridge the gap between *in vitro* information of fluvoxamine and its clinically reported cardiovascular consequences, in the present study we precisely assessed *in vivo* electropharmacological effects of fluvoxamine together with its pharmacokinetic profile. For this purpose, we used the halothane-anesthetized *in vivo* canine model (Sugiyama, 2008). To better analyze the electrophysiological effects of the drugs on the depolarization

and repolarization phases, we recorded the His bundle electrograms and monophasic action potentials (MAPs), respectively, in addition to analyzing the standard lead II ECG. Moreover, a MAP recording/pacing combination catheter was used to simultaneously measure both MAP and effective refractory period at the same site and directly compare the drug effects on the repolarization and refractoriness (Kise *et al.*, 2010; Mitsumori *et al.*, 2010; Sugiyama, 2008; Sugiyama *et al.*, 2004).

MATERIALS AND METHODS

Experiments were performed with male beagle dogs weighing approximately 10 kg (n = 4). Animals were obtained through Kitayama Labes (Nagano, Japan). All experiments were approved by the Animal Research Committee for Animal Experimentation of Toho University (No. 12-52-151) and performed in accordance with the Guidelines for the Care and Use of Laboratory Animals of Toho University.

Cardiohemodynamic parameters

The dogs were anesthetized initially with thiopental sodium (30 mg/kg, i.v.). After intubation with a cuffed endotracheal tube, 1% halothane vaporized with 100% oxygen was inhaled with a volume-limited ventilator (SN-480-3; Shinano, Tokyo, Japan). 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 clinically available catheter-sheath set (FAST-CATH® 406108, St. Jude Medical Daig Division, Inc., Minnetonka, MN, USA) was placed at the aorta through the right femoral artery to measure the aortic blood pressure. A pig-tail catheter was placed at the left ventricle through the catheter-sheath to measure the left ventricular pressure. The maximum upstroke velocity of the left ventricular pressure ($LVdP/dt_{max}$) and the left ventricular end-diastolic pressure (LVEDP) were obtained during sinus rhythm to estimate the contractility and the preload to the left ventricle, respectively. A thermodilution catheter (TC504-NH; Nihon Kohden, Tokyo, Japan) was positioned at the right side of the heart through the right femoral vein. The cardiac output was measured with a standard thermodilution method by using a cardiac output computer (MFC-1100, Nihon Kohden). The total peripheral resistance was calculated with the basic equation: total peripheral resistance=mean blood pressure/cardiac output.

Electrophysiological parameters

The surface lead II ECG was obtained from the limb electrodes. Corrected QT interval (QTc) was calculated with Van de Water's formula (Van de Water *et al.*, 1989). A quad-polar electrodes catheter was positioned at the non-coronary cusp of the aortic valve through the left femoral artery to obtain the His bundle electrogram. A bi-directional steerable monophasic action potential (MAP) recording/pacing combination catheter (1675P; EP Technologies, Inc., Sunnyvale, CA, USA) was positioned at the endocardium of the right ventricle through the left femoral vein to obtain MAP signals. The signals were amplified with a DC preamplifier (model 300; EP Technologies, Inc.). The duration of the MAP signals was measured as an interval, along a line horizontal to the diastolic baseline, from the MAP upstroke to the desired repolarization level. The interval (ms) at 90% repolarization level was defined as MAP_{90}. The heart was electrically driven by using a cardiac stimulator (SEC-3102, Nihon Kohden) with the pacing electrodes of the combination catheter placed in the right ventricle. The stimulation pulses were rectangular in shape, 1-2 V (about twice the threshold voltage) and of 1-ms duration. The MAP_{90} was measured during 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 of the right ventricle was assessed by the programmed electrical stimulation. The pacing protocol consisted of 5 beats of basal stimuli in a cycle length of 400 ms followed by an extra stimulus of various coupling intervals. Starting in late diastole, the coupling interval was shortened in 5 ms decrements until refractoriness occurred. The duration of the terminal repolarization period of the ventricle was calculated by the difference between the $MAP_{90(CL400)}$ and effective refractory period at the same site, which reflects the extent of electrical vulnerability of the ventricular muscle (Sugiyama, 2008; Sugiyama and Hashimoto, 2002).

Experimental protocol

The aortic blood pressure, left ventricular pressure, ECG, His bundle electrogram and MAP signals were monitored with a polygraph system (RM-6000, Nihon Kohden) and analyzed by using a real time full automatic data analysis system (Win VAS3 ver 1.1R24; Physio-Tech, Tokyo, Japan). Each measurement of ECG and MAP as well as atrio-His (AH) and His-ventricular (HV) intervals was the mean of three recordings of consecutive complexes. The cardiac output was measured three times. The ECG, His bundle electrogram, aortic and left ventricular pressure and MAP signals were recorded under the sinus rhythm. In addition, MAP signals were recorded during the ventricular pacing at a cycle length of 400 and 300 ms. Then, effective refractory period was

measured. All parameters described above were usually obtained within 1 min at each time point.

After the basal control assessment, fluvoxamine in a low dose of 0.1 mg/kg, which corresponds to a clinically recommended daily p.o. dose, was intravenously administered over 10 min and each parameter was assessed 5, 10, 15, 20 and 30 min after the start of the infusion. Then, fluvoxamine in a middle dose of 1 mg/kg, was intravenously administered over 10 min, and each parameter was observed in the same manner. Finally, fluvoxamine in a high dose of 10 mg/kg was intravenously administered over 10 min, and each parameter was observed 5, 10, 15, 20, 30, 45 and 60 min after the start of the infusion.

Plasma drug concentration

A volume of 3 mL of blood was withdrawn from the left femoral artery just before the assessment of cardiovascular parameters. The blood samples were centrifuged at $1,500 \times g$ for 30 min at 4°C. The plasma was stored at −80°C until the drug concentration was measured. The plasma concentration was determined as follows. The samples in a volume of 100 μL were added into 100 μL of methanol. After vortex mixing, the tubes were centrifuged at $900 \times g$ for 20 min. An aliquot of the sample solution (40 μL) was injected onto an analytical C_{18} reversed-phase column (150 mm × 4.6 mm, 5 μm, Capcell pak; Shiseido Co., Ltd., Tokyo, Japan) maintained at 40°C. The mobile phase in the high performance liquid chromatography (HPLC) system was an aqueous solution containing 50 mM potassium phosphate buffer (pH 4.7) and 28% acetonitrile (v/v) at a flow rate of 0.5 mL/min. The elution profiles of fluvoxamine were monitored with a UV detector at wavelength of 214 nm.

Drugs

Fluvoxamine maleate 5-Methoxy-1-[4-(trifluoromethyl) pheny1]pentan-1-one-(*E*)-*O*-(2-aminoethyl) oxime monomaleate was extracted from a commercially available tablet (Luvox®, Abbott Japan Co., Ltd., Tokyo, Japan) with distilled water in a concentration of 10 mg/mL, which was diluted with saline in concentrations of 0.1 and 1 mg/mL. Other drugs used were thiopental sodium (Ravonal® 0.5 g for Injection, Mitsubishi Tanabe Pharma Corporation, Osaka, Japan), halothane (Fluothane®, Takeda Pharmaceutical Co., Ltd., Osaka, Japan) and heparin calcium (Caprocin®, Sawai Pharmaceutical Co., Ltd., Osaka, Japan).

Statistical analysis

Data are presented as the mean ± S.E. The statistical significances within a parameter were evaluated by one-way repeated-measures analysis of variance (ANOVA) followed by post-hoc test; Contrasts, for mean values comparison, whereas those of paired data within a parameter were evaluated by paired *t*-test. A *p* value < 0.05 was considered significant.

RESULTS

No animals exhibited lethal ventricular arrhythmias or cardiohemodynamic collapse, leading to the animal's death during the experimental period.
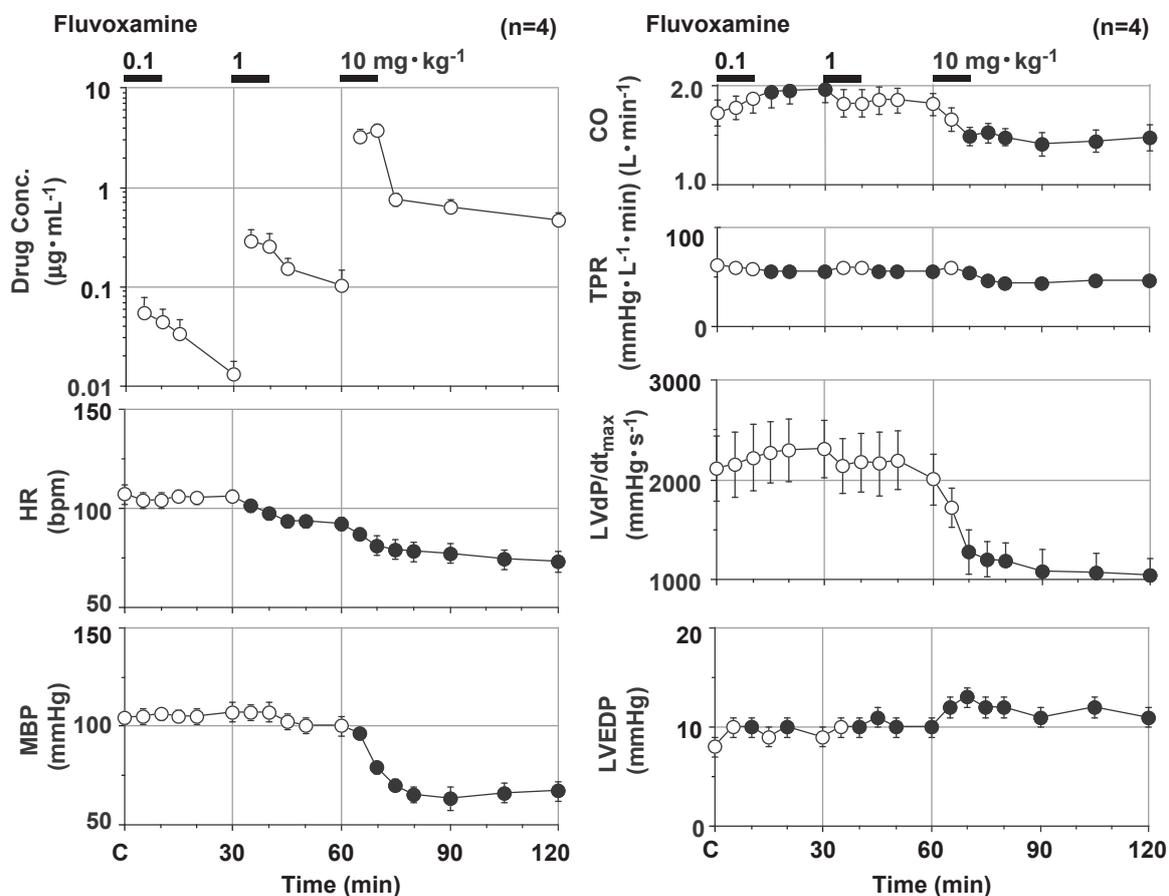
Plasma drug concentration

The time course of the plasma drug concentration of fluvoxamine is summarized in Fig. 1. The peak plasma concentrations of fluvoxamine after the start of 0.1, 1 and 10 mg/kg infusion were 55 ± 22 ng/mL (0.17 μM), 289 ± 86 ng/mL (0.91 μM) and 3,720 ± 590 ng/mL (11.69 μM), respectively. The plasma concentrations apparently decreased in distribution and elimination phases.

Effects on the heart rate and blood pressure

The time courses of changes in the heart rate and mean blood pressure are summarized in Fig. 1 (n = 4) and typical tracings of the blood pressure are depicted in Fig. 2. The heart rate and mean blood pressure at pre-drug control (C) were 107 ± 5 beats/min and 104 ± 3 mmHg, respectively. After the start of the low dose of 0.1 mg/kg of fluvoxamine infusion, no significant change was detected in these variables. After the start of the middle dose of 1 mg/kg infusion, the heart rate decreased for 5-30 min, whereas no significant change was detected in the mean blood pressure. After the start of the high dose of 10 mg/kg infusion, the heart rate and mean blood pressure decreased for 5-60 min.

Effects on the cardiac output and total peripheral resistance

The time courses of changes in the cardiac output and total peripheral resistance are summarized in Fig. 1 (n = 4). The cardiac output and total peripheral resistance at pre-drug control (C) were 1.72 ± 0.13 L/min and 62 ± 5 mmHg·min/L respectively. After the low dose, the cardiac output transiently increased for 15-30 min, but the total peripheral resistance decreased for 15-30 min. After the middle dose, the total peripheral resistance decreased for 15-30 min, whereas no significant change was detected in the cardiac output compared with pre-drug control (C). After the high dose, the cardiac output and total peripheral resistance decreased for 10-60 min.

Fig. 1. Cardiohemodynamic effects of fluvoxamine. Time courses of the plasma drug concentration (Drug Conc.), heart rate (HR), mean blood pressure (MBP), cardiac output (CO), total peripheral resistance (TPR), maximum upstroke velocity of the left ventricular pressure (LVdP/dt$_{max}$) and left ventricular end-diastolic pressure (LVEDP). Date are presented as mean ± S.E. (n = 4). Closed symbols represent significant differences from each control value (C) by $p < 0.05$.

Effects on the LV/dP$_{max}$ and LVEDP

The time courses of changes in the LVdP/dt$_{max}$ and LVEDP are summarized in Fig. 1 (n = 4) and typical tracings of the left ventricular pressure are depicted in Fig. 2. The LVdP/dt$_{max}$ and LVEDP at pre-drug control (C) were 2,112 ± 323 mmHg/s and 8 ± 1 mmHg, respectively. After the low dose, the LVEDP increased at 10 and 20 min, whereas no significant change was detected in the LVdP/dt$_{max}$. After the middle dose, the LVEDP increased for 10-30 min, whereas no significant change was detected in the LVdP/dt$_{max}$. After the high dose, the LVdP/dt$_{max}$ decreased for 10-60 min, but the LVEDP increased for 5-60 min.

Effects on the ECG

Typical tracings of the ECG are depicted in Fig. 2, and

the time courses of changes in the ECG variables are summarized in Fig. 3 (n = 4). The PR interval, QRS width, QT interval and QTc at pre-drug control (C) were 96 ± 5 ms, 68 ± 2 ms, 293 ± 12 ms and 331 ± 11, respectively. After the low dose, no significant change was detected in any of these variables. After the middle dose, the QT interval and QTc were prolonged for 10-30 min, whereas no significant change was detected in the PR interval or QRS width. After the high dose, the PR interval, QRS width, QT interval and QTc were prolonged at 15 min and for 30-60 min, for 5-45 min, for 5-60 min, and for 5-60 min, respectively. J wave, which was defined as an elevation of the QRS-ST junction of at least 0.1 mV from baseline, manifested as QRS slurring or notching (Haïssaguerre *et al.*, 2008), was observed in 2 animals out of 4 before the administration of the drug. In 1 animal out of the 2 with J
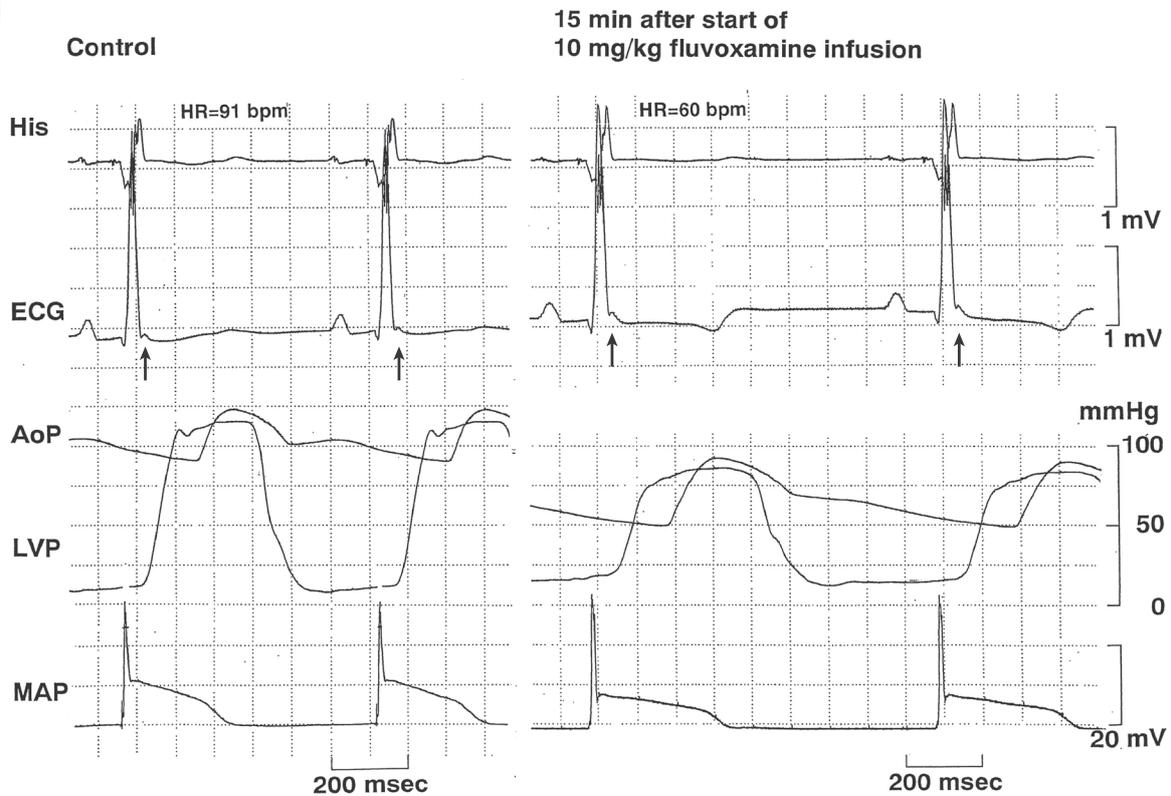
Fig. 2. Typical tracings of the His Bundle electrogram (His), surface lead II electrocardiogram (ECG), aortic blood pressure (AoP), left ventricular pressure (LVP) and monophasic action potential (MAP) recorded from the right ventricle during the sinus rhythm at pre-drug control (Control) and 15 min after the start of 10 mg/kg of fluvoxamine infusion. Note that J-wave was observed before and after the drug administration (arrow).

wave, elevation of J wave was induced by fluvoxamine as depicted in Fig. 2.

Effects on the AH and HV intervals and MAP duration during sinus rhythm

Typical tracings of the His bundle electrogram and MAP are depicted in Fig. 2, and the time courses of changes in the AH and HV intervals and $MAP_{90(sinus)}$ during sinus rhythm are summarized in Fig. 3 (n = 4). The AH and HV intervals and $MAP_{90(sinus)}$ at pre-drug control (C) were 64 ± 8, 26 ± 2, and 252 ± 3 ms, respectively. After the low dose, no significant change was detected in any of these variables. After the middle dose, the HV interval and $MAP_{90(sinus)}$ were prolonged for 10-20 and 15-30 min, respectively, whereas no significant change was detected in the AH interval. After the high dose, AH and HV intervals and $MAP_{90(sinus)}$ were prolonged for 5-60 min.

Effects on the MAP₉₀ during the ventricular pacing

The time courses of changes in the MAP_{90} during the ventricular pacing at a cycle length of 400 and 300 ms are summarized in Fig. 3 (n = 4). The $MAP_{90(CL400)}$ and $MAP_{90(CL300)}$ at pre-dose control (C) were 240 ± 10 and 223 ± 10 ms, respectively. After the low and middle doses, no significant change was detected in these variables. After the high dose, the $MAP_{90(CL400)}$ and $MAP_{90(CL300)}$ were prolonged for 5-60 min. The time courses of the increments from the pre-drug control (C) in the $MAP_{90(CL400)}$ and $MAP_{90(CL300)}$ were calculated (not shown in the figure). The extent of the increment in the $MAP_{90(CL400)}$ from pre-drug control was greater than that of the $MAP_{90(CL300)}$ for 10-20 and 60 min after the high dose, indicating the reverse use-dependent prolongation of repolarization.
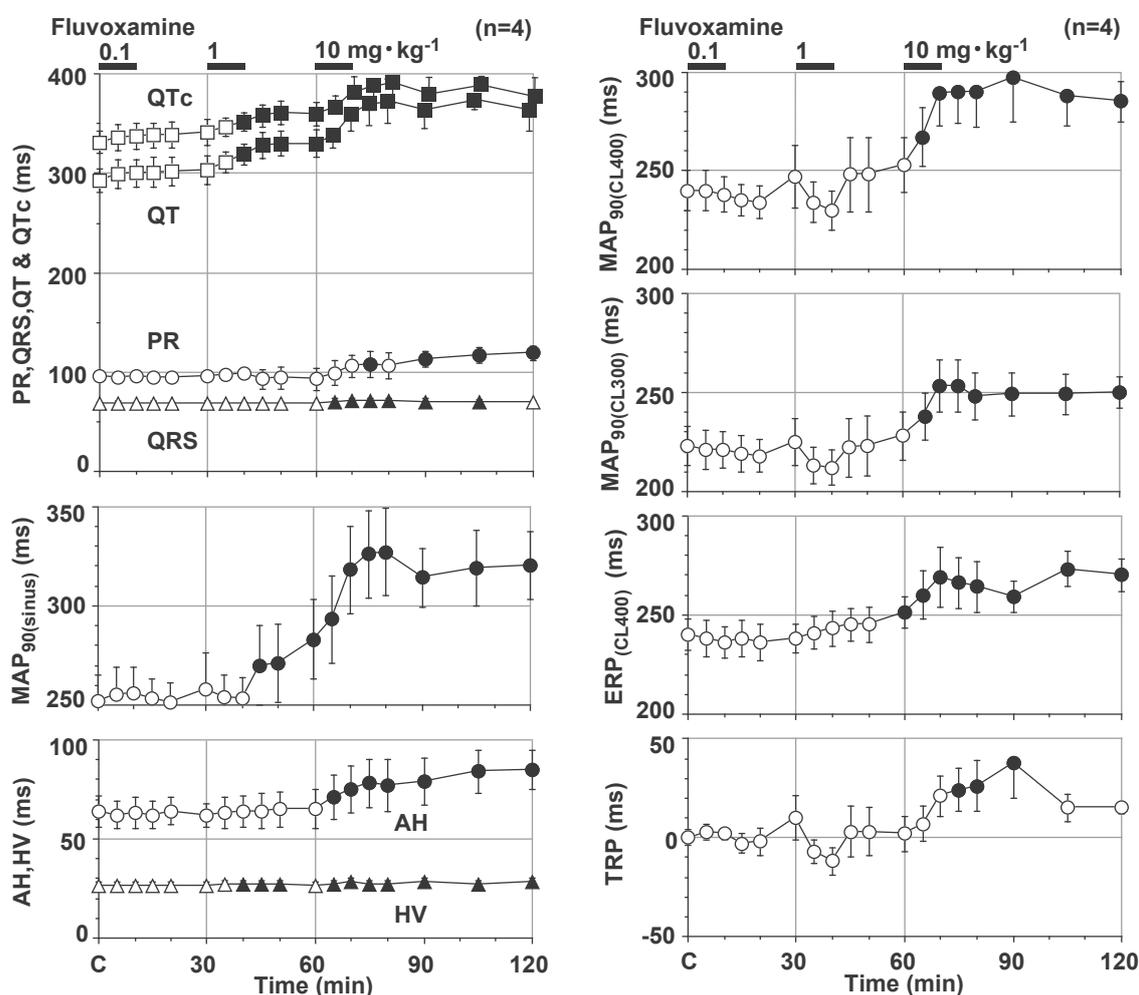
Fig. 3. Electrophysiological effects of fluvoxamine. Time courses of the PR interval (PR: circles), QRS width (QRS: triangles), QT interval (QT: squares) and QTc corrected by Van de Water's formula (QTc: squares) (left upper panel); those of the atrio-His interval (AH, circles), His-ventricular interval (HV, triangles) and MAP_{90} during the sinus rhythm ($MAP_{90(sinus)}$) (left lower panels); those of the MAP_{90} at a pacing cycle length of 400 ms ($MAP_{90(CL400)}$) and 300 ms ($MAP_{90(CL300)}$) (right upper panels); and the effective refractory period (ERP) and terminal repolarization period (TRP = $MAP_{90(CL400)}$-ERP) (right lower panels). MAP_{90} represents the duration of monophasic action potential at 90% repolarization level. Date are presented as mean ± S.E. (n = 4). Closed symbols represent significant differences from each control value (C) by $p < 0.05$.

Effects on the effective refractory period and terminal repolarization period

The time courses of changes in the effective refractory period and terminal repolarization period are summarized in Fig. 3 (n = 4). The effective refractory period and terminal repolarization period at pre-drug control (C) were 240 ± 8 and 0 ± 4 ms. After the low dose, no significant change was detected in these variables. After the middle dose, the effective refractory period was prolonged at 30 min, whereas no significant change was detected in the terminal repolarization period. After the high dose,

the effective refractory period and terminal repolarization period were prolonged for 5-60 and 15-30 min, respectively.

DISCUSSION

While only one clinical case of fluvoxamine-induced torsade de pointes has been reported (Manet *et al.*, 1993), bradycardic action (de Wilde *et al.*, 1983; Granfors *et al.*, 2004; Pacher and Kecskemeti, 2004; Saletu *et al.*, 1977), QT-interval prolongation (Klok *et al.*, 1981; Nia *et al.*,

2012) and hypotensive effect (de Wilde *et al*., 1983; de Wilde and Doogon, 1982; Granfors *et al*., 2004; Guelfi *et al*., 1983; Rodriguez de la Torre *et al*., 2001) have been observed in patients during fluvoxamine treatment. In the present study, we simultaneously assessed the electropharmacological effects of fluvoxamine together with its plasma concentrations using the halothane-anesthetized *in vivo* canine model under physiologically maintained electrical and mechanical conditions. Administration of fluvoxamine suppressed the atrioventricular nodal and intraventricular conductions, and prolonged the repolarization period together with exerting negative chronotropic, inotropic and hypotensive effects.

Drug doses in this study

Since the clinically recommended maximum p.o. dose of fluvoxamine has been 150 mg/body in Japan (interview form from the manufacturer), in this study we assessed its cardiovascular effects in intravenous doses of 0.1, 1 and 10 mg/kg. In phase I study, the C_{max} values after a single oral administration of 100 and 200 mg of fluvoxamine were reported to be 44 and 92 ng/mL, respectively (Ishigooka *et al*., 1993). Protein binding ratio of fluvoxamine was described to be 81% in human in the interview form of fluvoxamine from the manufacturer and 82% in rats in a previous study (Sato *et al*., 1995). On the other hand, values of the plasma unbound fraction (fu,p) and the octanol-water partition coefficient (logP) of fluvoxamine were obtained by in silico estimation using SimCYP and ChemDrawBioUltra software (Emoto *et al*., 2009), which were 0.322 and 3.025, respectively; and the liver to plasma concentration ratio (Kp,h) and the blood to plasma concentration ratio (Rb) were estimated from fu,p and logP (Tsukada *et al*., 2013; Yamashita *et al*., 2014), which were 3.202 and 0.920, respectively. Lack of difference in the protein binding ratio of fluvoxamine between humans and rats together with the information from the in silico estimation suggests that the ratio in dogs may be close to humans. Thus, the doses of the drug assessed in this study can be considered to provide therapeutic to supra-therapeutic levels of plasma drug concentrations. The time course of the plasma concentration of fluvoxamine after the high dose followed a pattern that could be predicted by the two-compartment theory of pharmacokinetics, whereas it did not necessarily reflect the extent of the changes in the cardiohemodynamic or electrophysiological variables.

Cardiohemodynamic effects

The low dose of fluvoxamine decreased the total peripheral resistance, but increased the cardiac output and left ventricular end-diastolic pressure, whereas it hardly affected the heart rate, left ventricular contraction or mean blood pressure. The middle dose decreased the total peripheral resistance and heart rate, but increased the left ventricular end-diastolic pressure, whereas the left ventricular contraction, cardiac output and mean blood pressure were hardly affected. Lack of decrease in the mean blood pressure, cardiac output or left ventricular contraction after the low or middle doses may suggest the presence of reflex-mediated increase of sympathetic tone derived from the vasodilator action. The high dose decreased the total peripheral resistance, heart rate, ventricular contraction, cardiac output and mean blood pressure, but increased the left ventricular end-diastolic pressure. The decrease of the left ventricular contraction, cardiac output and mean blood pressure may suggest that direct suppressive effects of the drug on the cardiovascular system were greater than compensatory action by the increased sympathetic tone.

In this study, fluvoxamine decreased the heart rate and ventricular contraction. Although *in vitro* chronotropic or inotropic effect of fluvoxamine has not been reported, *in vivo* negative chronotropic effect of fluvoxamine has been observed in dogs (Roos, 1983) and patients (de Wilde *et al*., 1983; Granfors *et al*., 2004; Pacher and Kecskemeti, 2004; Saletu *et al*., 1977), and *in vivo* negative inotropic effect has been shown in rabbits (Claassen, 1983; Wouters and Deiman, 1983). Meanwhile, fluvoxamine decreased the total peripheral resistance, leading to the hypotensive action. Although *in vitro* vasodilator effect of fluvoxamine has not been reported, the hypotensive action has been observed in patients (de Wilde *et al*., 1983; de Wilde and Doogon, 1982; Granfors *et al*., 2004; Guelfi *et al*., 1983; Rodriguez de la Torre *et al*., 2001), which was not detected in dogs, cats (Roos, 1983) or healthy human volunteers (Robinson and Doogan, 1982). Importantly, fluvoxamine increased the LVEDP in a dose-related manner; however, the maximum value was 13 ± 1 mmHg at 10 min after the high dose, which still remained within a physiological range.

Electrophysiological effects

Supra-therapeutic doses of fluvoxamine prolonged the atrioventricular nodal as well as intraventricular conductions, which is in accordance with previous studies in rabbits (Claassen, 1983; Wouters and Deiman, 1983), indicating that fluvoxamine may inhibit Ca^{2+} and Na^+ channels *in vivo*, whereas no significant change was detected in them at therapeutic concentration. These results may reflect a previous clinical report (Roos, 1983) that no significant change was detected in the PR interval or QRS width by

clinical doses of fluvoxamine.

Fluvoxamine delayed the repolarization in a reverse use-dependent manner, reflecting characteristics of rapidly activating delayed rectifier K^+ current (I_{Kr}) channel-blocking property (Sugiyama, 2008). These results were in good accordance with previous *in vitro* experimental study with human embryonic kidney 293 cells expressing hERG channels (Milnes *et al.*, 2003), in which fluvoxamine inhibited hERG K^+ current with IC_{50} value of 3.8 μM. Also, in previous *in vivo* experiments, the QT interval was prolonged by 10 mg/kg, i.v. in dogs (Roos, 1983) and by 20 mg/kg/h, i.v. in guinea pigs (Ohtani *et al.*, 2001). It should be noted that in some previous clinical studies (Klok *et al.*, 1981; Nia *et al.*, 2012), the QT interval was prolonged by clinical doses of fluvoxamine; however, such prolongation was not observed in the other clinical reports (Beach *et al.*, 2014; Okayasu *et al.*, 2012). Since fluvoxamine prolonged the QT interval in a dose-related manner in this study, one can speculate that the discrepancy among the previous reports might in part depend on the difference of the plasma free drug concentration and/or concomitant use of other drugs.

Most of the selective serotonin-reuptake inhibitors have been reported to prolong the QT interval, occasionally resulting in the onset of torsade de pointes (de Boer *et al.*, 2005; Kanjanauthai *et al.*, 2008; Kogut *et al.*, 2013; Singh and Maldonado-Duran, 2014; Wenzel-Seifert *et al.*, 2011; Wilting *et al.*, 2006), suggesting that the potential of induction of long QT syndrome by fluvoxamine may be class effects of selective serotonin-reuptake inhibitor. Meanwhile, common chemical structures responsible for inhibiting I_{Kr} channel have been reported (Carlsson *et al.*, 1997; Sugiyama and Hashimoto, 1998), in which a substituted phenyl ring is connected to a basic amine via a highly variable linking group, the distance between the phenyl ring and the basic amine seems to be of critical importance for a high I_{Kr} blocking potency; and 3 to 4 atoms are considered to be optimum. The selective serotonin-reuptake inhibitors often contain such common chemical structures, also supporting our hypothesis that fluvoxamine-induced long QT syndrome may be class effects of selective serotonin-reuptake inhibitor.

Proarrhythmic effects

Specific data for proarrhythmic adverse effects of fluvoxamine are very limited, which has been reported in rabbits and a patient (Claassen, 1983; Manet *et al.*, 1993; Wouters and Deiman, 1983). Generally, impulses that reach the ventricles during the middle and terminal portions of the T wave can initiate the ventricular tachycardia and fibrillation, as the repolarization is most heterogene-ous and channels are in different phases of recovery during this phase, which can be estimated by using the terminal repolarization period (Sugiyama, 2008; Sugiyama and Hashimoto, 2002). The drug-induced prolongation of terminal repolarization period has been shown to be a reliable marker that can predict the onset of slow conduction and re-entry, leading to perpetuation of torsade de pointes (Sugiyama, 2008; Sugiyama and Hashimoto, 2002). In this study, the terminal repolarization period was prolonged after the high dose, indicating that fluvoxamine may provide such proarrhythmic potentials.

In conclusion, supra-therapeutic concentration of fluvoxamine exerted the negative chronotropic, inotropic and hypotensive actions; and suppressed the atrioventricular nodal and intraventricular conductions, indicating its inhibitory actions on Ca^{2+} and Na^+ channels *in vivo*, whereas it delayed the repolarization in a reverse use-dependent manner, reflecting characteristics of I_{Kr} channel blocking property. Furthermore, fluvoxamine by itself prolonged the terminal repolarization period at 100 times higher than the therapeutic concentration, indicating its proarrhythmic potential. Fluvoxamine should be used with caution on patients having been treated with drugs that can inhibit hepatic metabolizing enzymes of fluvoxamine and/or those with hepatic dysfunction, since its higher plasma concentration will increase the risk of lethal arrhythmias.

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Conflict of interest---- The authors declare that there is no conflict of interest.

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