A Comparative Pharmacodynamic Study of the Arrhythmogenicity of Antidepressants, Fluvoxamine and Imipramine, in Guinea Pigs

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Among several classes of antidepressants, tricyclic antidepressants are known to prolong QTc intervals (QT interval corrected by heart rate) in electrocardiograms, while selective serotonin uptake inhibitors (SSRI) are considered to be devoid of arrhythmogenicity. In this study, we aimed to compare the arrhythmogenic potencies of imipramine (IMI), a typical tricyclic antidepressant, and fluvoxamine (FLV), an SSRI, at therapeutic and supratherapeutic concentrations using guinea pigs in vivo.

Guinea pigs were anesthetized, and IMI (10 and 20 mg/kg/h) or FLV (20 mg/kg/h) was intravenously administered for 90 minutes to obtain the time-courses of drug concentrations in plasma and the changes in the QTc intervals during and after the drug administration.

IMI induced distinct QTc prolongation in a dose-dependent manner, while FLV prolonged QTc intervals only slightly. A pharmacokinetic-pharmacodynamic analysis revealed that the potency for QTc prolongation of IMI was 1.7-fold higher than that of FLV. Taking the therapeutic concentration into account, the clinical risk of FLV for QTc prolongation was suggested to be 5-fold lower than that of IMI. Therefore, this SSRI agent was suggested to be safer than the tricyclic antidepressant for patients with cardiac risk factors, including arrhythmia, or for those taking other arrhythmogenic drugs concomitantly.

Key words imipramine; fluvoxamine; QT interval; arrhythmia

Tricyclic antidepressants, such as imipramine (IMI), have been widely used for the treatment of depression. However, even under a clinical dosage regimen, they occasionally induce QT prolongation.2) QT prolongation is generally considered to herald fatal ventricular arrhythmia such as torsades de pointes (TdP).3) Indeed, IMI can cause TdP after an overdose.4)

Recently, fluvoxamine (FLV), a selective serotonin reuptake inhibitor (SSRI), has become increasingly prescribed to treat depression. Since FLV potently inhibits the enzymatic activities of several isoforms of cytochrome P450 (CYP), such as CYP1A2, CYP2C19, CYP2D6 and CYP3A4,5,6) it should be used with caution in patients receiving a drug metabolized by these CYP isoforms. When FLV is concomitantly administered with arrhythmogenic drugs, such as terfenadine or cisapride, which are metabolized by these isoforms, QT prolongation and TdP may occur as a result of drug interaction.5) On the other hand, no cases of arrhythmia have been reported for FLV itself. Robinson & Doogan investigated cardiovascular effects of FLV at ordinary dosages (150–300 mg/d) in healthy subjects, and found that the QT interval was slightly prolonged (11–13 ms) by FLV while the QTc interval (QT interval corrected by heart rate) was unaffected because bradycardia was simultaneously induced.6) However, they did not analyze plasma concentration of FLV, so the relationship between plasma FLV concentration and QT prolongation remains unclear. Wouters and Deiman have reported the arrhythmogenic effects of FLV under toxic concentration in comparison with mianserin and amitriptyline in conscious rabbits.7) Although they concluded that FLV was less arrhythmogenic than mianserin and amitriptyline, they did not assess the QT intervals nor the plasma drug concentrations.

We have reported that the arrhythmogenic risk of a drug can be evaluated by the pharmacokinetic-pharmacodynamic analysis of QT prolongation and plasma drug concentration in small animals,9) and investigated the arrhythmogenic risks of various drugs, including non-sedative antihistamines,10,11) an immunosuppressant12) and macrolide antibiotics.13) These investigations could provide quantitatively the arrhythmogenic potency of a drug over a wide range of its plasma concentrations. These results may provide clinically significant information for making a safer choice of drugs, especially for the patients with cardiac or pharmacokinetic risk factors.

In this study, we aimed to compare the arrhythmogenic risks of IMI, a typical tricyclic antidepressant, and FLV, an SSRI, from a pharmacokinetic–pharmacodynamic viewpoint using guinea pigs.

MATERIALS AND METHODS

Chemicals FLV was kindly gifted from Meiji Seika Kaisha, Ltd. (Tokyo, Japan). IMI was purchased from Wako Pure Chemicals Industries (Osaka, Japan). All other chemicals used were of reagent grade and commercially available.

Pharmacodynamic Experiments Male Hartley guinea pigs weighing 300–600 g were purchased from Nihon Ika-gaku Doubutsu Shizai Kenkyusho Co. (Tokyo, Japan) and anesthetized with an intraperitoneal injection of urethane and α-chloralose (1.2 g/kg and 30 mg/kg, respectively). The pre-cordial and limb hair was removed with hair removing cream (Hair remover, Kanebo, Tokyo, Japan). With the animals restrained in a supine position, the trachea, right jugular vein and right carotid artery were cannulated with polyethylene tubings. The body temperature was maintained at 37.5±0.5 °C throughout the experiments by a hot water-circulating heat pad placed beneath the animals. The electrocardiography (ECG) from bipolar limb lead (lead II) was recorded and analyzed by the method of Ohtani et al.9) The QT intervals were derived from the average shape of the ECG recording for 10 s. The QT intervals were corrected with heart rate to derive QTc using Bazett’s formula4) (Eq. 1).

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After stabilization of the ECG and body temperature, a physiological salt solution (PSS; NaCl: 135 mM, NaHCO₃: 11.9 mM, KCl: 5.4 mM, CaCl₂: 1.8 mM, MgCl₂: 1.0 mM) was infused into the jugular vein at different rates of 1.05 ml/h for 90 min by an infusion pump. FLV (20 mg/kg/h) or IMI (40 or 100 mg/kg/h), dissolved into PSS, was then infused for 90 min in the same manner. The QT intervals were measured at −10, 0, 1, 2, 3, 4, 5, 6, 7, 10, 15, 20, 30, 45, 60, 75, 91, 92, 93, 94, 95, 96, 97, 100, 105, 110, 120, 135, 150, 165 and 180 min after the start of the infusion.

Pharmacokinetic Experiments Pharmacokinetic experiments were performed using other animals than those used in the pharmacodynamic experiments to avoid possible effects of blood sampling on pharmacodynamic parameters. All conditions were identical to the pharmacodynamic experiments as mentioned above, with the exception of blood sampling from the carotid artery at 2, 5, 15, 45, 90, 92, 95, 105, 120 and 180 min after the drug administration. Blood samples (150 μl) were centrifuged at 1500×g for 10 min to collect 50 μl of plasma. The concentrations of FLV and IMI in plasma were determined by high-performance liquid chromatography (HPLC) as described below.

Determination of FLV and IMI A plasma sample (50 μl) was transferred into a 10 ml glass tube and spiked with 50 μl of 1 M Na₂CO₃ and 50 μl of 600 ng/ml internal standard (IS) solution. IMI was employed as the IS for the determination of FLV, and vice versa. The sample was extracted with 5 ml of a mixture of n-hexane and isooamyl alcohol (98:2, v/v), using a reciprocal shaker for 10 minutes. The organic phase was separated by centrifugation at 1000×g for 10 minutes and dried under a nitrogen stream. The extract was reconstituted in 50 μl of mobile phase, and 20 μl was applied to the HPLC system. The HPLC system consisted of a pump LC-10AD (Shimadzu, Kyoto, Japan) equipped with a UV detector SPD 10A (Shimadzu, Kyoto, Japan). Detection absorbance was set at 254 nm. The column used for separation was a silica gel column (YMC-Pack ODS-AP, 250 mm×6.0 mm id., particle size: 5 μm) and was kept at 25 °C. The mobile phase consisted of methanol, 0.5% diethylylamino phosphate solution (pH 7.5), acetonitrile and triethanol (78:7:20.1:1:0.2, v/v). The determination limit was 50 ng/ml for both IMI and FLV with 50 μl of plasma.

Model Analysis A conventional 2-compartment open model with a first-order elimination process was employed to analyze the time profiles of plasma concentrations (Cₜₚ) of FLV and IMI. Pharmacokinetic parameters, i.e. distribution volume of the central compartment (V₁), transfer rate constant from the peripheral compartment to the central one (kₑ), and exponential rate constants of the distribution and elimination phase (α and β, respectively), were calculated by simultaneous fitting of the time profiles of Cₜₚ using a non-linear least-squares regression program, MULTI. The effect compartment model introduced by in Shiner et al. was applied for the analysis of QTc prolongation. The pharmacological effect (E), the increase in the QTc intervals in this study, was assumed to be related to the concentration of the effect-compartment (Cₑ) by Eq. 2.

\[
E = K \cdot Cₑ
\]

where K denotes the slope of concentration–response relationship (i.e. potency). Cₑ can be calculated as follows:

\[
t ≤ 90
\]

\[
Cₑ = \frac{1}{V₁ \cdot kₑ} \left[ \frac{1}{\beta β} \left[ \frac{kₑ \beta}{kₑ - \beta} \frac{\beta}{β - \alpha} \exp(\alpha t) \right. \right.
\]

\[
\left. \left. - \exp(-kₑ t) \right] \cdot \frac{kₑ}{kₑ - \beta} \frac{\beta}{β - \alpha} \exp(\alpha t) \right]
\]

\[
t > 90
\]

\[
Cₑ = \frac{1}{V₁ \cdot \alpha - \beta} \frac{\beta}{\alpha \beta} \exp(-kₑ t) \left[ \frac{kₑ}{kₑ - \beta} \frac{\beta}{β - \alpha} \exp(\alpha t) \right. \right.
\]

\[
\left. \left. - \exp(-kₑ t) \right] \cdot \frac{1}{V₁ \cdot \alpha - \beta} \frac{\beta}{\alpha \beta} \exp(-kₑ t) \right]
\]

where kₑ, kₑ, I, and Cₑ₉₀ indicate the elimination rate constant from the central compartment, that from the effect compartment, the infusion rate of the drug and the Cₑ at the end of the infusion (90 min), respectively.

The pharmacodynamic parameters, kₑ and K, were derived by simultaneous fitting of the effect (E, increase in QTc interval) at all infusion rates to Eqs. 2, 3 and 3′ using the nonlinear least-squares regression program, MULTI.

RESULTS

Pharmacokinetics of IMI and FLV Figure 1 presents the time courses of plasma concentrations of IMI (A) and FLV (B) during and after the infusion. The 2-compartment-open model successfully explained the pharmacokinetics of IMI and FLV. The pharmacokinetic parameters of FLV, i.e., α, β, V₁, and kₑ, were 0.740±0.081 [min], 0.0116±0.0048 [min], 593.5±0.26 [ml/kg] and 0.222±0.040 [min] (estimate±S.D.), respectively. Those of IMI were 0.942±0.021 [min], 0.0083±0.0013 [min], 154.9±0.03 [ml/kg] and 0.365±0.025 [min] (estimate±S.D.), respectively. Table 1 summarizes the derived pharmacokinetic parameters of IMI and FLV.

Effects of IMI and FLV on ECG IMI induced QTc prolongation in an infusion rate-dependent manner after the onset of the drug infusion (Fig. 2A). The maximum QTc prolongation induced by a high dose of IMI (20 mg/kg/h) at the end of the infusion was 20 ms¹/₂ and was restored after the stop of the infusion with a lag time. FLV also induced QTc prolongation, although the maximum prolongation was weak and less than 10 ms¹/₂ at 90 min (Fig. 2B). IMI did not affect the heart rate, while FLV induced bradycardia with the maximum decrease of 30 beat/min at 90 min after the onset of the infusion (data not shown).

Pharmacokinetic–pharmacodynamic Analysis of QTc Prolongation Counter-clockwise hystereses were observed between plasma drug concentrations and QTc prolongation in both IMI and FLV (Figs. 3A and B). The effect compartment model with a linear pharmacodynamic relationship (Eq. 2) was applied to explain these hystereses. The esti-
mated pharmacodynamic parameters are shown in Table 2. Figures 3C and D show the relationship between the drug concentrations in the effect compartment and the extents of QTc prolongation.

**DISCUSSION**

In this study, we compared the arrhythmogenic risks of IMI and FLV by means of a pharmacokinetic–pharmacodynamic analysis of QTc intervals and plasma drug concentration in guinea pigs. We have already investigated the arrhythmogenic risks of various agents including antiarrhythmic agents, non-sedative antihistamines, immunosuppressant and macrolide antibiotics, and the obtained results were very consistent with clinical findings. Therefore, our experimental protocol is considered to be useful for evaluating the arrhythmogenic risks of drugs. In this study, we analyzed the arrhythmogenic risks of two typical antidepressants, IMI and FLV, for the first time from a pharmacokinetic–pharmacodynamic viewpoint, and found that both IMI and FLV prolong QTc intervals. IMI has generally been found to prolong QT intervals, while FLV was reported to be scarcely arrhythmogenic. Only Robinson & Doogan reported that FLV slightly prolonged QT intervals but not QTc intervals in humans.

In this study, the QTc-prolonging potency \( K \) of IMI was 1.7-fold higher than that of FLV. However, the therapeutic concentrations of IMI and FLV should be taken into consideration to compare the clinical arrhythmogenic risks of these drugs in clinical settings. In this study, the maximum plasma concentration of each drug was aimed to be 10- to 20-fold of its upper therapeutic level. The maximum plasma FLV concentrations after a single oral dose of 50 mg, and that being after repetitive oral administration of 75 mg/d for 6 d, were reported to be 17.3 ng/ml and 42.3 ng/ml, respectively. As the daily dose of FLV is maximally 150 mg/d in Japan, the maximum therapeutic concentration of FLV is considered to be approximately 100 ng/ml. With regard to IMI, the minimum plasma concentration required to induce antidepressive effects was reported to be 45 ng/ml, while there is a large degree of interpatient variability in the pharmacokinetics and a 20- to 30-fold range is possible for plasma IMI concentrations. Indeed, even under a therapeutic dosage regimen of 225 mg/d, some patients experienced a plasma IMI concentration of 200—250 ng/ml. Therefore, the maximum therapeutic concentration of IMI is considered to be approximately 300 ng/ml. The maximum concentrations of IMI and FLV in this study were 3.94 and 2.02 μg/ml, which correspond to the 13- and 20-folds of the aforementioned concen-
trations considered to be therapeutic in humans. IMI induced more than 20 ms\(^{1/2}\) of QTc prolongation at the 13-fold concentration of the therapeutic dosage, while FLV induced slight (less than 10 ms\(^{1/2}\)) QTc prolongation even at the 20-fold concentration of the therapeutic dosage. In other words, when calculating from the potencies (5.78 vs. 3.45) and their maximum therapeutic concentrations (100 ng/ml vs. 300 ng/ml), the clinical risk of FLV for QTc prolongation was suggested to be 5-fold lower than that of IMI.

There are several significant factors affecting pharmacokinetics, such as pharmacokinetic drug interactions and genetic polymorphisms of metabolic enzymes. FLV is mainly metabolized by CYP2D6; poor metabolizers of CYP2D6 were found in 5—10% of Caucasians and less than 1% of Japanese.\(^{20,21}\) Carrillo et al. studied the relationship between the polymorphic CYP2D6 and the pharmacokinetics of FLV and reported that \(AUC\) in the poor metabolizers was 3.9-fold higher than that in the extensive metabolizers.\(^{22}\) In the case of IMI, it is mainly metabolized by CYP1A2 and CYP3A4,\(^{23}\) and clinically significant poor metabolizers have not been defined for these isoforms. With respect to metabolic inhibition, FLV is well known to inhibit CYP1A2, 2C19, 2D6 and 3A4,\(^{5,6}\) while no reports describe an elevation of plasma FLV concentration by metabolic inhibition. On the contrary, IMI is quite susceptible to metabolic inhibition. For example, FLV was reported to provide a 73% decrease in the clearance of IMI.\(^{24}\) Another report described a 5.7-fold increase in plasma IMI concentration by FLV.\(^{25}\) Therefore, assuming that the concentration of IMI or FLV rises 5-fold by these factors, the concentration of IMI reached such a level to induce obvious QTc prolongation in this study, while FLV is still impotent to induce QTc prolongation. These results are consistent with the clinical fact that IMI can prolong the QTc intervals while there are no reports of FLV-induced QTc prolongation.

With regard to the pharmacokinetics of FLV in rats, the half-life at the elimination phase (\(t_{1/2B}\)) was considerably short. This might be because of the lack of sampling points at the terminal phase. However, the pharmacokinetic parameters were only used to produce the input function for the pharmacodynamic analysis so that this does not provide any errors to the conclusion.

A counterclockwise hysteresis, \textit{i.e.} a lag time, between
QTc prolongation and the plasma concentrations, was clearly shown for both IMI and FLV (Fig. 3). The most plausible explanation of this lag-time is the existence of metabolites. IMI is partly metabolized to desipramine, which also possesses QTc-prolonging activity\(^{26}\) and may take part in the overall QTc prolongation. On the other hand, it has not yet been defined whether metabolites of FLV prolong QTc intervals or not. Another possible explanation is the delayed distribution of these drugs into the ventricle, which is considered to be the “effect site” for QT prolongation.

In conclusion, FLV was found to be less potent than IMI in terms of arrhythmogenicity in guinea pigs. Taking into account the therapeutic plasma concentrations of IMI and FLV, the clinical arrhythmogenic risk of FLV was suggested to be 5-fold lower than that of IMI. Therefore, this SSRI agent was suggested to be safer than the tricyclic antidepressant for patients with cardiovascular risk factors such as arrhythmia or those receiving another arrhythmogenic agent concomitantly.

QTc prolongation was observed with IMI at higher concentrations under certain clinical conditions such as drug interactions or overdose. IMI should be administered with caution in patients with pharmacokinetic and/or cardiac risk factors.

REFERENCES AND NOTES

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