QTc prolongation and torsades de pointes due to a coadministration of fluoxetine and amiodarone in a patient with implantable cardioverter–defibrillator

Case report and review of the literature

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Abstract

Rationale: Drug-induced prolongation of the corrected QT interval (QTc) may lead to serious and potentially life-threatening ventricular tachyarrhythmia, such as torsades de pointes (Tdp), which is worthy of clinical attention. Here, we report 1 case of Tdp after a coadministration of fluoxetine and amiodarone.

Patient concerns: A 62-year-old Chinese male who placed with the implanted cardioverter-defibrillator (ICD) appeared the QTc prolongation and Tdp after the concurrent administration of fluoxetine and amiodarone.

Diagnoses: Torsades de pointes (Tdp).

Interventions: The patient was treated with magnesium and potassium immediately. Her ICD–brady pacing mode was reprogrammed to 90bpm. Meanwhile, both of fluoxetine and amiodarone were discontinued.

Outcomes: The further episodes of Tdp were prevented. After a few days, the QTc gradually decreased without clinically significant arrhythmias.

Lessons: The present case demonstrates that a potential drug–drug interaction (DDI) may lead to a life-threatening drug adverse reaction (ADR) especially in special subjects. Therefore, clinicians should closely monitor the electrocardiogram (ECG) when QTc-prolonging agents are given to patients with cardiac abnormalities, and avoid combining 2 QTc-prolonging drugs.

Abbreviations: ADR = adverse drug reaction, CYPs = cytochrome P-450 isoenzymes, DDI = drug–drug interaction, ECG = electrocardiogram, hERG = human ether-a-go-go–related gene, ICD = implanted cardioverter defibrillator, QTc = corrected QT interval, SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants, Tdp = torsades de pointes.

Keywords: adverse drug reaction, amiodarone, drug–drug interaction, fluoxetine, torsades de pointes

1. Introduction

Many antiarrhythmic drugs including amiodarone show the proarrhythmic properties, which has been obtained with clinical concerns. However, it is easy to ignore the potential arrhythmogenic effects of noncardiovascular drugs. So far, a variety of commonly prescribed noncardiovascular drugs, including antifungal agents and psychotropic drugs, have been reported the cardiac toxicity with bradycardia, the corrected QT interval (QTc) prolongation, and even torsades de pointes (Tdp), which is worthy of clinical attention.\textsuperscript{1,2} As depression is an independent risk factor for mortality and morbidity in cardiovascular disease patients, antidepressant drugs were frequently given to these patients for the treatment of depressive and anxious state.\textsuperscript{2} Pharmacovigilance studies confirmed that a variety of antidepressant drugs may cause a varying degree prolongation of QTc.\textsuperscript{3} Compared with traditional tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) have shown a significant antidepressant activity and good tolerability recommended by guideline.\textsuperscript{4} Jacqueline et al\textsuperscript{5} showed that fluoxetine could be safely used to treat patients with major depression after myocardial infarction. However, the real-world data exposed that the cardiac adverse effects of SSRIs should be cautious in certain high-risk patients. The presence of pharmacokinetics and pharmacodynamics drug–drug...
interaction (DDI) may increase the risk of QTc prolongation and even Tdp. Here, we report 1 case of Tdp induced by concurrent administration of fluoxetine and amiodarone in a patient with implantable cardioverter–defibrillator, in which amiodarone may increase the plasma concentration of fluoxetine by hepatic cytochrome P-450 isoenzymes (CYPs).

2. Case report

Approval for the study by the local institutional review board was not required because it was a case report. The present patient provided a written informed consent. A 62-year-old Chinese male with a past medical history of asthma presented to the cardiovascular department with shortness of breath, chest tightness, fever, orthopnea, cough, and expectoration for the past a week. Vital signs were normal: blood pressure 137/88 mm Hg and heart rate 98 bpm. Serum potassium, magnesium, liver function, and renal function tests were within normal limits except for serum BNP (1320 pg/mL). Echocardiography showed depressed left ventricular function with left ventricular ejection fraction of 32%. Hence, the diagnosis of dilated cardiomyopathy...

Figure 1. (A) ECG on admission (QTc = 386 ms); (B) ECG showing QT prolongation (QTc = 501 ms); (C) The continuous ECG monitoring an episode of Tdp; (D) The continuous ECG monitoring the lapse of Tdp. (E) ECG showing pacing rhythm reprogrammed to 90 bpm (QTc = 493 ms). (F) ECG showing pacing rhythm reprogrammed to 60 bpm on discharge (QTc = 446 ms).
was confirmed and the implanted cardioverter-defibrillator (ICD) (MAXIMO II VR D284VRC; Medtronic) was placed. The initial value of pacing rhythm was programmed to 60 bpm. The electrocardiogram (ECG) on admission demonstrated a QTc interval of 386 ms (Fig. 1A). Fluoxetine at 20 mg daily was given to this patient for the comorbidity of depression. During the next 3 days, the QTc interval gradually increased to 501 ms and the ventricular rate was 91 bpm (Fig. 1B). On the third day, the patient frequently experienced episodes of ventricular premature beat. Intravenous amiodarone was given as a 450 mg bolus followed by 600 mg orally daily to stabilize the electrical activity of the heart. After 13 hours, the continuous ECG monitoring showed a prolonged QTc interval, an R on T phenomenon, and twisting of the QRS axis around the isoelectric line, which was refined as an episode of Tdp (Fig. 1C). After 16 seconds, conversion to sinus rhythm was achieved automatically, and the relapse of Tdp was recorded again after 12 hours (Fig. 1D). The patient was treated with continuously intravenous injection of magnesium (total 25 g) and potassium (total 15 g) immediately. The ICD–brady pacing mode was reprogrammed to 90 bpm for overdriving (Fig. 1E). Meanwhile, pharmacist considered that the patient’s Tdp was probably caused by a DDI between fluoxetine and amiodarone. The Naranjo Adverse Drug Reaction Probability Scale was applied to determine the possibility of drug-related adverse reaction, in which terms such as definiteness (10 points) and doubtfulness (0 points) are calculated (Table 1). The patient’s score being 7 resulted in the discontinuation of fluoxetine and amiodarone. These maneuvers prevented further episodes of Tdp. ECG taken next day showed pacing rhythm of 89 bpm with QTc interval of 493 ms. During the next 2 days, the QTc interval gradually decreased without clinically significant arrhythmias. Thus, VVI pacing was programmed to the initial value of 60 bpm. After a few days, ECG showed the QTc interval of 446 ms and the patient was discharged home without any complications (Fig. 1F). At 3 months follow-up, the patient has been doing well with normal QTc of 430 ms and without recurrent Tdp.

3. Discussion

In this case, the patient’s Tdp was probably caused by the combination therapy of fluoxetine and amiodarone according to the high score of Naranjo Adverse Drug Reaction Probability Scale. To be our best knowledge, this is the first report on QTc prolongation and Tdp due to a potential DDI with fluoxetine and amiodarone.

It is generally known that the QTc prolongation significantly increases a patient’s risk of Tdp development, which about 2 to 3 folds’ increase is associated with a QTc of over 500 ms.[1] Many other risk factors, including female sex, age over 65 years, bradycardia, hypokalemia, hypomagnesaemia, underlying heart disease, renal and hepatic dysfunction, DDI, higher concentrations of one more QTc-prolonging drugs, and genetic predisposition, may further increase the risk of Tdp.[7] In our case, we found a clear temporal relationship between Tdp and the combination therapy of fluoxetine and amiodarone. Fluoxetine is a member of the drug family known as SSRIs. Compared with TCAs, SSRIs have shown significant antidepressant activity and good tolerability.[4] When taken alone, fluoxetine was associated with a low risk of cardiac adverse effects. However, overdose or interaction with other medications could increase the likelihood of cardiac toxicity with bradycardia, QTc prolongation, and Tdp.[8] We searched the PubMed database for studies containing the keywords “fluoxetine,” “torsades de pointes” and “QTc” and obtained 4 case reports[6–10] (Table 2). In these cases, combining with other QTc interval prolonging medications was considered as the major cause of Tdp. Meanwhile, the electrolyte disturbances, substance abuse, and cardiac history were likely additional risk factors. Rajamani et al.[12] reported that the possible mechanisms of QTc prolongation were the concentration-dependent and selective blockade of the human ether-a-go-go related gene (hERG) via direct channel blocking and indirectly disrupting channel protein trafficking.

Amiodarone is known to be a class III antiarrhythmic drug with the QTc prolongation potential. The mechanism is also blockade of hERG encoded Ikr.[11] Drugs that block the Ikr channel increase the QTc interval and allow inward current, particularly calcium, to reactivate, leading to early afterdepolarization in cardiac tissue.[13] In terms of pharmacokinetics, amiodarone has a large individual variation in systemic bioavailability. The highest concentrations of amiodarone were found in fat, liver, bone marrow, and lung tissue, which remained that concentrations of amiodarone were present in these tissues at several-fold higher than those in plasma.[14] Kinetic analysis of plasma levels of i.v. amiodarone (5 mg/kg in 5 minutes) in 4 patients during the electrophysiological study did not support a direct association between plasma concentration and its effect.[15] The current studies also demonstrated that acute amiodarone therapy results in a use-dependent inhibition of inward sodium and inward calcium currents, as well as a noncompetitive alpha- and beta-blockade effect. In patients with impaired ventricular function, intravenous

### Table 1: Adverse drug reaction probability scale of the present case.

| Question                                                                 | Yes | No | Do not know | Score |
|--------------------------------------------------------------------------|-----|----|-------------|-------|
| Were the adverse event confirmed by any objective evidence?              | +1  | 0  | 0           | +1    |
| Did the reaction more severe when the dose was increased, or less severe when the dose was decreased? | 10  | 0  | 0           | 0     |
| Were there alternative causes (other than the drug) that could on their own have caused the reaction? | -1  | 2  | 0           | +2    |
| Did the patient have a similar reaction to the same or similar drugs in any previous exposure? | +1  | 0  | 0           | 0     |
| Did the adverse reaction reappear when the drug was readministered?     | +2  | -1 | 0           | 0     |
| Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered? | +1  | 0  | 0           | +1    |
| Were there conclusive reports on this reaction?                          | 10  | 0  | 0           | 0     |
| Did the adverse event appear after the suspected drug was administered? | 10  | 0  | 0           | 0     |
| Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered? | 10  | 0  | 0           | 0     |
| Are there alternative causes (other than the drug) that could on their own have caused the reaction? | -1  | 2  | 0           | +2    |

Total score = 7
amiodarone increased the right ventricular effective refractory period and showed rate-dependent prolongation of the QTc interval. Hence, the QTc interval is the more favorable indicator than the plasma concentration for predicting the cardiac toxicity. However, although amiodarone is known to prolong QTc interval, it rarely causes Tdp. A meta-analysis reported an incidence of Tdp <1.0% with amiodarone. One explanation is that amiodarone also blocks the slow inward calcium current mediated through the L-calcium channels, and does not increase the QT dispersion. The risk for amiodarone-induced Tdp greatly increases when other predisposing conditions are present, such as electrolyte imbalance and concomitant medications delaying ventricular repolarization.

In addition, amiodarone is a moderate inhibitor of CYP2C9 and CYP2D6, and fluoxetine is mainly metabolized by the 2C9 and 2D6 isoenzyme. CYPs are a large class of enzymes and play an important role in the metabolism of both endogenous and xenobiotic compounds. CYPs also catalyze the conversion of some prodrugs into active drugs and of procarcinogens and promutagens into highly toxic compounds. CYP2C9 is one of the important superfamily. So far, about 16% of the clinical drug, the CYP2C9 is responsible for the metabolism. CYP2D6 only accounts for 2% to 9% of the total liver enzymes, but was involved in 20% to 30% drug metabolism, including anti-depressants, anti-arrhythmic drugs, antipsychotics, analgesics, and so on. Concomitant use of these agents may cause an increase in plasma concentration of fluoxetine, which may in turn increase the risk of QTc interval prolongation. Fayssoil et al reported a case of Tdp induced by citalopram, one of SSRIs, given in combination with amiodarone. Thus, we concluded that the combined use of fluoxetine and amiodarone was the probable cause of the development of recurrent Tdp. Older age and deterioration of congestive heart failure were likely additional risk factors.

4. Conclusion

Coadministration of fluoxetine and amiodarone that is known to prolong QTc increased exposure to fluoxetine mediated by the CYP2C9 and 2D6 isoenzyme, leading an enhanced risk of Tdp in these fragile patients with cardiac abnormalities. Therefore, potential DDI is worthy of clinical attention and optimal treatment strategy should be considered to ensure the safety of drugs.

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Table 2

Case reports of QTc prolongation and Tdp related to fluoxetine.

| Source          | Age | Sex  | Dosage          | Tdp risk factors | Concomitant QT-prolonging medication       | Change of QTc, ms |
|-----------------|-----|------|-----------------|-----------------|-------------------------------------------|------------------|
| Nykamp et al    | 40  | Female | 10 mg daily     | Potassium = 2.8 mEq/L | Levofloxacin and imipramine | Before: 509 Tdp: 403 |
| Varriale       | 52  | Male  | 20 mg daily for 2 wks followed by 40 mg daily for 2.5 mo | None | None | 380 560 380 |
| Wilting et al   | 83  | Female | 20 mg daily     | Left bundle branch block | Abusing history (IV cocaine and cannabinoids); potassium = 4.5 mEq/L, magnesium = 1.5 mEq/L | None 478 / 421 |
| Deamer et al   | 41  | Female | 20 mg daily     | None | None | 710 / 610 |