

## CASE REPORT

# Paroxetine-induced QTc prolongation

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Email: otsuka@hospital.asahi.chiba.jp**Abstract**

There have been only two previous reports of paroxetine-induced corrected QT (QTc) prolongation on electrocardiogram (ECG). Here, we report a 43-year-old woman with QTc prolongation (476 ms). She had taken 50 mg of paroxetine for 17 days. Three days after discontinuation of paroxetine, QTc returned to within the normal limits (396 ms). Paroxetine blocks the human ether-a-go-go-related gene (HERG) channels. Genetic polymorphisms of channels related to cardiac function are involved in drug-induced QTc prolongation. Moreover, autonomic nervous system instability due to unstable psychotic symptoms may also affect QTc. These factors are related to this rare event induced by paroxetine.

**KEYWORDS**

ECG, HERG, paroxetine, QTc prolongation, SSRI

## 1 | INTRODUCTION

QTc prolongation can result in Torsades de Pointes (TdP), one of the most critical types of arrhythmia. There have been several case reports of QTc prolongation by selective serotonin reuptake inhibitors (SSRIs).<sup>1</sup> There have been only two reports regarding paroxetine-induced QTc prolongation.<sup>2,3</sup> Here, we report QTc prolongation resulting from the therapeutic dose of paroxetine.

## 2 | CASE

A 43-year-old woman was admitted to hospital due to an attempted suicide involving burning of coal briquettes in her car. She had been found unconscious by her family, but the degree of carbon monoxide poisoning was mild. Her history included major depression and low blood pressure. However, she had not taken any drugs for several years because she had no symptoms. Routine physical and laboratory examinations revealed no abnormalities other than low blood pressure, 91/57 mm Hg. The QTc interval in ECG on admission was 392 ms. The end of the T wave was the intersection of a tangent to the steepest slope of the descending limb of the T wave and

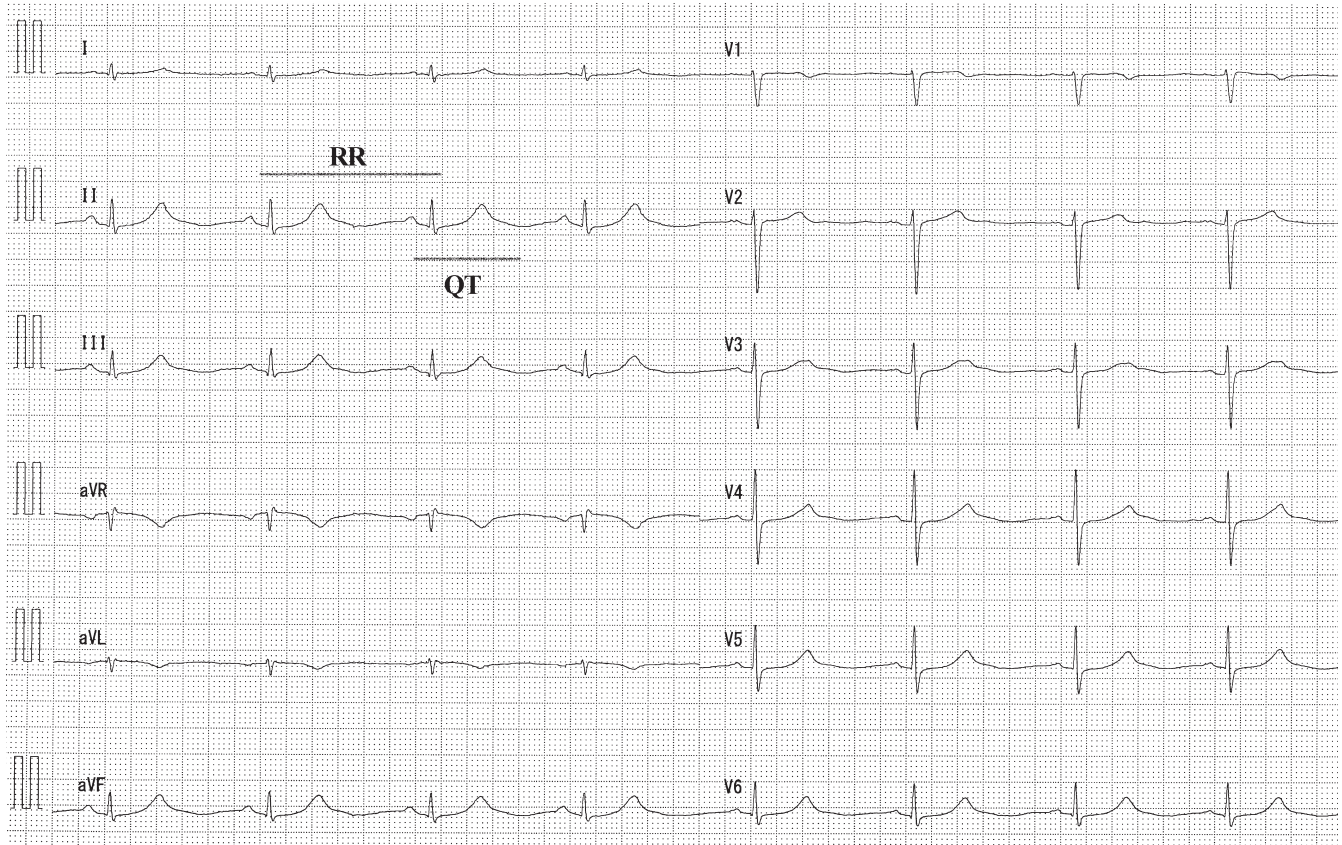
the baseline in lead II.<sup>4</sup> QTc was determined by Bazett's formula:  $QT/\sqrt{RR}$ . She was diagnosed with major depression and posttraumatic stress disorder (PTSD). She was first administered olanzapine, then quetiapine. After hospital discharge, paroxetine was prescribed for her symptoms.

Paroxetine was started at 12.5 mg with addition of 12.5 mg every week up to 50 mg. She had also taken 10 mg of nitrazepam, 1 mg of ethyl loflazepate, and 660 mg of magnesium oxide regularly, with 0.25 mg of brotizolam and 0.5 mg of lorazepam as needed. She collapsed immediately after standing and was taken to hospital after 17 days of taking 50 mg of paroxetine. On arrival at the hospital, she had blood pressure of 82/53 mm Hg, pulse rate of 75 per minute, and body temperature of 36.1°C. She was prescribed amezinium for low blood pressure. She took 10 mg of amezinium twice but experienced syncope immediately after standing the following day and was readmitted to hospital.

On admission, routine physical and laboratory examinations revealed no abnormalities other than low blood pressure. The patient had blood pressure of 77/46 mm Hg, pulse rate of 58 per minute, and body temperature of 36.9°C. Serum levels of potassium, calcium, sodium, and magnesium were within the respective normal limits. Thyroid function and echocardiography findings were normal. QTc

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**FIGURE 1** ECG of the patient on the first hospital day. RR was measured between the second and third components. QT was measured on the third element. Both were determined in lead II. RR was 1251 ms, QT was 533 ms, and QTc was 476 ms

interval was 476 ms. (Figure 1) A diagnosis of drug-induced QTc prolongation was made, and she stopped taking paroxetine, nitrazepam, ethyl loflazepate, and magnesium oxide on the first day of admission. She continued to take brotizolam and lorazepam as needed.

QTc was 449 ms on the second hospital day, 444 ms on the third day, and 396 ms on the fourth day when she was discharged (Figure 2). After leaving the hospital, SSRI was changed to 50 mg of fluvoxamine. Nitrazepam, ethyl loflazepate, magnesium oxide, brotizolam, and lorazepam were prescribed again. ECGs were taken 11 times after discharge over a period of 2 years 9 months. The QTc remained between 374 and 426 ms, with chronological ordered QTc of 395, 421, 388, 375, 419, 426, 416, 374, 380, 421, and 375 ms, respectively. She has not experienced syncope again over the follow-up period.

### 3 | DISCUSSION

None of the drugs administered concurrently with paroxetine had been reported to cause QTc prolongation. These drugs are not included in the QTdrugs lists in CredibleMeds®.<sup>5</sup> QTc had been shortened when taking brotizolam and lorazepam. The drugs other than amezinium were prescribed with fluvoxamine again. Although fluvoxamine can cause QTc prolongation,<sup>1</sup> QTc remained within normal

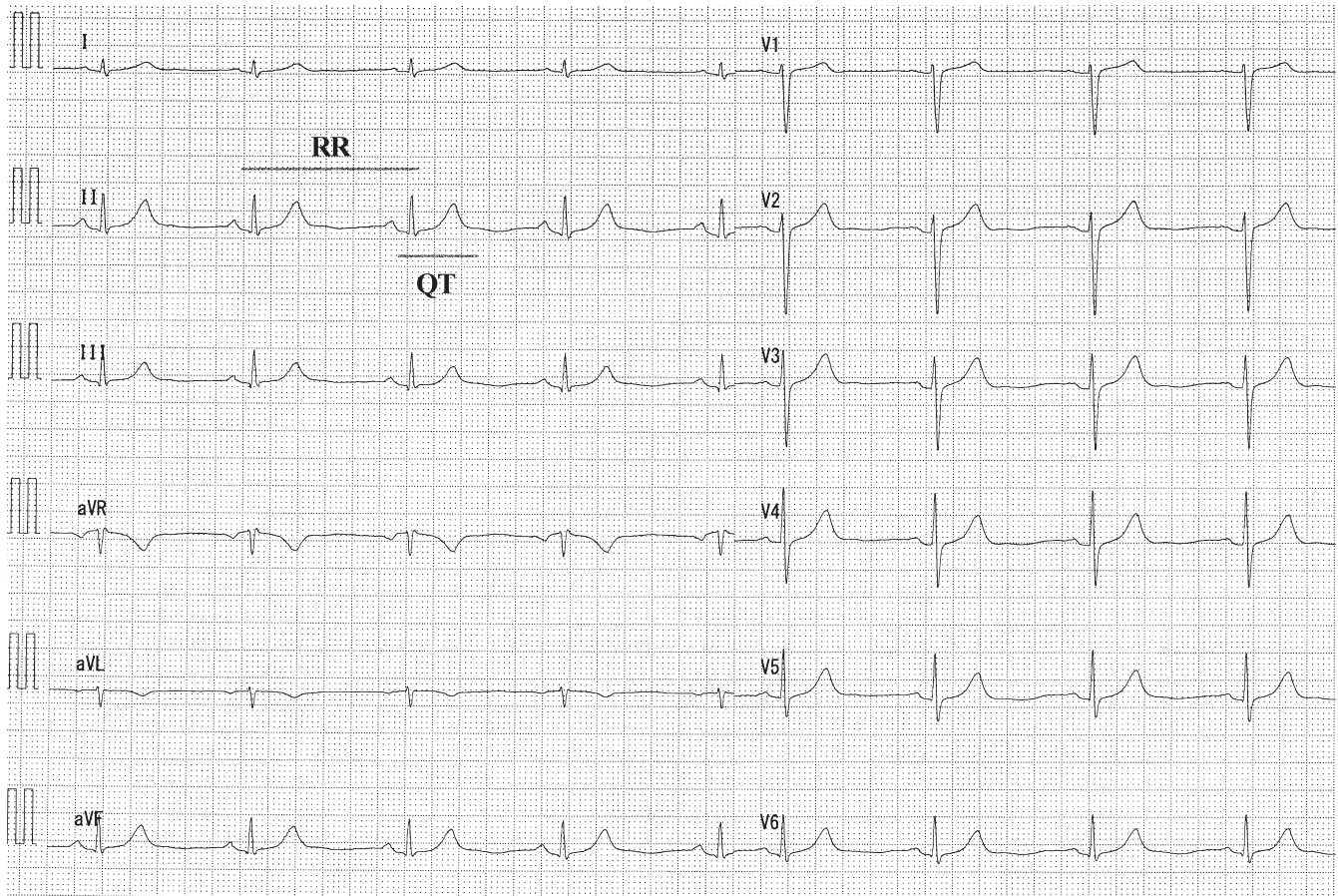
limits. The patient took 10 mg of amezinium twice 1 day before admission. However, vital signs and ECG on the day of admission showed no adrenergic activation. Therefore, amezinium did not have an effect in this patient. Furthermore, QTc before administration of paroxetine was within the normal limits. These results indicated that paroxetine induced QTc prolongation.

Paroxetine had been thought to have less risk of causing QTc prolongation than other antidepressants, including SSRIs.<sup>1</sup> CredibleMeds® lists paroxetine as having QTc/TdP risks under certain conditions.<sup>5</sup>

There have been only two previous reports regarding QTc prolongation caused by paroxetine. GlaxoSmithKline advised that paroxetine increases plasma pimozide levels when coadministered.<sup>2</sup> Cytochrome P450 (CYP) 2D6 is involved in pimozide metabolism,<sup>6</sup> and as paroxetine is a strong CYP2D6 inhibitor it leads to QTc prolongation by increasing plasma pimozide levels.

The other report described a 41-year-old woman that showed TdP and QTc prolongation after overdosing on 5740 mg of paroxetine. The serum paroxetine level 7 days after the overdose was 5645 ng/mL. QTc remained > 496 ms at 14 days after the overdose. They proposed that this was due to self-induction of CYP2D6.<sup>3</sup>

We postulated that three factors could cause QTc prolongation: that is, a direct effect on HERG channels, some genetic changes in ion channels, and disturbance of the autonomic nervous system.



**FIGURE 2** ECG of the patient on the fourth hospital day. RR and QT were determined in the same way as described in Figure 1. RR was 1157 ms, QT was 426 ms, and QTc was 396 ms

SSRIs can induce QTc prolongation via blockade of the delayed potassium rectifier current (IKr).<sup>7</sup> Paroxetine blocks HERG channels that encode IKr in vitro.<sup>8</sup>

Niemeijer et al.<sup>9</sup> reviewed categories of genetic factors related to drug-induced QTc prolongation. The genes related to pharmacodynamics include potassium, sodium, and calcium channels, and mutations of these genes can cause drug-induced QTc prolongation. We postulated that if some genetic factors are involved, pharmacodynamics may affect QTc.

The duration of syncope was short in this case, and the prognosis was good. We did not record TdP. Psychiatric symptoms induce disturbance of the autonomic nervous system. Therefore, vasovagal reflex was assumed to be the cause of syncope in our case. The autonomic nervous system can influence QTc directly or by altering the heart rate.<sup>10</sup> Autonomic nervous system disturbance may also participate in this rare adverse event.

## 4 | CONCLUSIONS

This is the first case report indicating that the therapeutic dose of paroxetine, administered along with non-QT-prolonging drugs, could induce QTc prolongation. Although the reasons for this rare

adverse event are not clear, we postulated that HERG channel blockade by paroxetine, some genetic changes, or autonomic nervous factors may have been involved in this rare event induced by paroxetine.

## CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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