Clozapine-Induced Corrected QT-Interval Prolongation and Relationship With Serum Clozapine Concentration

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Clozapine is well known as an efficacious atypical antipsychotic for treatment-resistant schizophrenia.[1] Despite its effectiveness, clozapine may cause serious adverse drug reactions, including corrected QT (QTc) interval prolongation.[2] A normal QTc interval is generally defined as 360–450 ms for males and 370–460 ms for females.[3] Prolongation of the QTc interval is an important clinical finding because it increases the risk of torsades de pointes, which can cause sudden cardiac death.[4] Treatment guidelines for clozapine reported that the therapeutic range of the plasma clozapine concentration is 350–600 ng/mL.[1] A study revealed that serum clozapine levels were associated with a high risk of QTc prolongation[5]; however, another study showed no such association.[6] Thus, the relationship between serum clozapine concentration and QTc prolongation remains controversial. Here, a case of clozapine-induced QTc prolongation is presented, and its relationship with serum clozapine concentration is discussed.

Case Report

Ms A, a 50-year-old Japanese woman with schizophrenia, was treated with clozapine 600 mg/d. The patient also received lithium 800 mg/d, valproic acid 900 mg/d, and flunitrazepam 0.5 mg/d. Electrocardiography (ECG) revealed a prolonged QTc interval of 490 ms. Laboratory tests, including complete blood count; sodium, potassium, creatinine, urea, calcium, and magnesium levels; liver function; and thyroid function, showed normal results. The serum clozapine concentration and N-desmethylclozapine concentration were 1,320 ng/mL and 266 ng/mL, respectively. The clozapine/N-desmethylclozapine [C/N] ratio was 4.96. The serum concentrations of lithium and valproic acid were within the therapeutic range: 0.63 mEq/L and 75.3 µg/mL, respectively. It was suspected that QTc prolongation was an adverse effect of clozapine, and the dose was reduced to 450 mg/d. Four weeks after clozapine reduction, the serum concentrations of clozapine and N-desmethylclozapine decreased to 711 ng/mL and 175 ng/mL, respectively, and the C/N ratio was 4.06. The QTc interval returned to the normal range at 447 ms.

Discussion

In this case of clozapine-induced QTc prolongation, the serum clozapine concentration was higher than the therapeutic range. In a previous retrospective study, Grande et al[6] found no significant correlation between clozapine concentrations above 400 ng/mL and QTc prolongation. However, in that study,[6] the mean serum clozapine concentration was 305.56 ng/mL, which was within the reference range. In contrast, Kim et al[5] reported that a serum clozapine concentration above 600 ng/mL was associated with a high risk of QTc prolongation. In addition, the QTc prolongation group (>470 ms) was older than the non-QTc prolongation group, with a mean age of 48.3 years and 40.3 years, respectively.[5] Clozapine demonstrates variable pharmacokinetics affected by numerous parameters of inter- and intraindividual differences, such as age, sex, genetic, dietary, clinical, and pharmacologic factors, as well as drug interactions.[7] In particular, women have fewer ion channels in the cardiac cell membrane than men, and this could contribute to the increased sensitivity of QT-prolonging agents observed among women.[8] In the present case, the patient was female and aged 50 years, increasing her risk of QTc prolongation during clozapine treatment. In addition, her QTc interval returned to the normal range, although serum clozapine concentrations were higher than the therapeutic range (711 ng/mL in this case). The therapeutic reference range of clozapine (350–600 ng/mL) is useful; however, some patients have been reported to show symptomatic improvement at 600–1,000 ng/mL,[9] suggesting that levels exceeding the guideline-recommended range may be necessary for certain patients. Therefore, the serum clozapine concentration should be measured, and ECG should be performed regularly to assess the risk-benefit of treatment for each patient. Further clinical studies are needed to determine the association between clozapine-induced QTc prolongation and serum clozapine concentration.

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