Psychopharmacology for the Clinician

The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column is a composite with characteristics of several real patients.

Clozapine, elevated heart rate and QTc prolongation

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A 45-year-old man with treatment-resistant schizophrenia was treated with 400 mg/d of clozapine. A routine electrocardiographic (ECG) assessment upon admission to our facility revealed a measured QT interval of 440 ms, a resting heart rate of 80 beats/min, and a corrected QT (QTc) interval of 508 ms, as calculated using Bazett's formula (normal range for QTc interval: < 440 ms for men and < 460 ms for women). It is widely accepted that a QTc interval greater than 500 ms is the threshold considered to markedly increase the risk of torsades de pointes (TdP), a malignant ventricular arrhythmia, which may contribute to unexplained sudden deaths in patients with schizophrenia.[1,2] The treating psychiatrist weighs the risk versus the benefit and considers discontinuing clozapine treatment.

The QT interval is a measure of the ECG that reflects the onset of ventricular depolarization to the end of ventricular repolarization. The QT interval is inversely proportional to heart rate and therefore must be corrected for the patient's heart rate.[3–6] To date, various formulae have been developed to derive the QTc, including the Bazett, Fridericia, Framingham and Hodges formulae,[3–6] of which Bazett's formula is most widely used in clinical settings. Bazett's formula divides the measured QT interval by the square root of the RR interval to derive the heart rate–adjusted value:

$$QTc = \frac{QT}{\sqrt{RR}}$$

Unfortunately, it is not widely recognized that using this formula in patients with elevated heart rate will overcorrect the QT interval because of its exponential term.[2,7,8] For this reason, the American Heart Association guidelines for ECG interpretation do not recommend Bazett's formula,[8] "particularly when the heart rate is high," as the "adjusted QT values may be substantially in error." Furthermore, in a recent study, the use of Bazett's formula detected QTc prolongation in 40% of 6723 individuals with sinus tachycardia, yet failed to predict an increased risk of death, suggesting a high false-positive rate.[2]

Clozapine has been shown to prolong the QTc interval in a dose-dependent fashion; however, clinically significant prolongation is rare.[7,9] Clozapine commonly increases heart rate either as a compensatory mechanism to orthostatic hypotension via α1-adrenergic antagonism or as persistent sinus tachycardia resulting from antagonism of presynaptic α2-adrenergic receptors as well as antagonism of muscarinic M2 receptors located on the sinoatrial node.[10] The prevalence of tachycardia associated with clozapine treatment ranges from 25% to 33%.[11,12] Thus, in a typical case of clozapine-induced tachycardia, Bazett's formula will overcorrect the QT interval.[7] Consequently, clinicians may unknowingly make less than optimal clinical decisions based on QTc values computed using Bazett's formula in patients with elevated heart rate.[7] In our patient's case, Bazett's formula computed a QTc interval of 508 ms, whereas other formulae that do not overcorrect the QT interval resulted in much lower values (i.e., Fridericia = 484 ms, Framingham = 479 ms, and Hodges = 475 ms).

Prolongation of the QTc interval is the most extensively used surrogate marker for the risk of TdP, even though it is considered imprecise and is associated with measurement error. In our patient's case, the overestimation of the QT interval using Bazett's formula could have resulted in the unnecessary discontinuation of clozapine treatment. Clinicians should therefore apply other QT interval correction methods that are more appropriate for patients susceptible to tachycardia, no matter what the cause. Furthermore, it merits mention that the risk of TdP depends not only on medication, but also on the patient's risk factors, including older age, female sex, congenital long QT syndrome, heart conditions (e.g., myocardial infarction, bradycardia, left ventricular dysfunction, cardiac conduction or structural abnormalities, or heart failure), electrolyte abnormalities (e.g., hypokalemia, hypocalcemia, and hypomagnesemia) and concomitant use of medications that prolong the QT interval or inhibit the metabolism of a drug known to prolong the QT interval.[1,13] To minimize the risk of drug-induced QT prolongation, clinicians should consider the risk of QT prolongation when starting a new medication, assess other risk factors for QT prolongation, avoid QT-prolonging drugs in patients with congenital long QT syndrome and correct any modifiable risk factors, such as electrolyte disturbances.

References

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