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Effects of Aripiprazole on the QTc:

A Case Report

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The use of neuroleptics in the elderly has been a topic of debate since 2005 when the US Food and Drug Administration issued a black-box warning of increased risk of mortality in elderly patients with dementia-related psychosis.¹ Antipsychotic alternatives such as divalproex are sometimes favored on an “off-label” basis to manage agitation in the demented elderly, and antipsychotic use is often clinically necessary to treat psychosis in older adults, with or without dementia. Concurrently, risk for iatrogenic corrected QT (QTc) prolongation on electrocardiogram (ECG) remains a concern with the use of many antipsychotic agents because of its associated potential for fatal arrhythmias.² Many elderly patients require antipsychotic pharmacotherapy yet incur risks from inherent cardiac disease, begging the question: How does one treat a psychotic or delirious patient with a prolonged QTc? The following case illustrates experience at our institution with safe reinitiation of aripiprazole after myocardial infarction-related QTc prolongation in an older adult with chronic psychosis.

Case report. Ms A is an 80-year-old retired, divorced white woman with a past psychiatric history of *DSM-IV-TR*-defined schizoaffective disorder, bipolar type, and a past medical history of hypertension. The patient had been maintained for many years on aripiprazole 10 mg/d and fluoxetine 20 mg/d. The patient additionally took lisinopril 5 mg/d, simvastatin 10 mg/d, and aspirin 81 mg/d.

In May 2014, on follow-up after a deep venous thrombosis, new ECG changes were found, indicating a new myocardial infarction. The patient had T wave inversions in leads V1–V6 as well as leads 1 and aVL, with myocardial perfusion imaging revealing apical dyskinesia. She was hospitalized, and aripiprazole treatment was stopped while fluoxetine treatment was continued. Her prior (pre-MI) baseline QTc of around 475 ms rose to 568 ms (post MI) and remained there on repeat ECGs, with the change believed to be the result of the myocardial infarction. The only other known risk factors for QTc prolongation were being elderly and

female and, potentially, receiving fluoxetine, which had not shown that effect in this patient previously.² Ms A's serum potassium and magnesium levels were both within normal limits. Manual QTc measurements were done with lead V5 using the tangential method with heart rate correction using the Bazett formula.

Two weeks later, off aripiprazole treatment, the patient became paranoid and required psychiatric hospitalization. Her ECG continued to show a prolonged QTc, ranging from 552 ms to 561 ms, while she was receiving no antipsychotics, antiarrhythmics, or other medications associated with QTc prolongation other than fluoxetine (which has rarely been shown to prolong QTc,³ although not previously in this patient). After deliberation, aripiprazole was restarted and titrated to 15 mg/d, a dose higher than the previous dose, to control her psychotic symptoms. Daily ECGs demonstrated lowering of the QTc from 561 ms to 444 ms over the following 30-day period. At an aripiprazole dose of 15 mg/d, Ms A's aripiprazole level was > 400 ng/mL, and her level of the active metabolite, dehydroaripiprazole, was 131 ng/mL, suggesting supratherapeutic plasma concentrations.⁴

Our case suggests that aripiprazole may be a relatively safe treatment for psychosis in older adults who incur post-MI QTc prolongation. Of note, a 2013 case study⁵ identified aripiprazole as a possible offending agent in causing torsades de pointes in a nonelderly (42-year-old) man with type 2 diabetes who was taking famotidine and was without extensive preexisting cardiac disease. Notably, concomitant use of famotidine in that patient confounds the etiology of observed QTc prolongation.⁶

While all neuroleptics carry a risk for serious adverse events, cumulative risk factors for QTc prolongation must be considered when gauging safety. Torsades de pointes with neuroleptic use has been reported to occur at a rate of only 10–15 events per 10,000 person-years of observation.⁷ Because QTc prolongation may be a dose-related phenomenon with some antipsychotics,⁸ appropriate management should involve the minimum dose needed to achieve adequate response, along with consideration of pharmacokinetic interactions that may increase plasma antipsychotic levels (in this case, concomitant fluoxetine, an inhibitor of cytochrome P450 (CYP)3A4 and CYP2D6, was the only other medication with this effect).

Aripiprazole has been reported to have the least effect on QTc of the atypical neuroleptics and may even be

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associated with lowering of the QTc.^{9–11} It is likely that our patient's decreasing QTc was associated with normalization of ventricular function after myocardial infarction, unimpeded by any arrhythmogenic effects of aripiprazole. The apparent neutral effect of aripiprazole on cardiac conduction merits its consideration as a preferred second-generation antipsychotic for the treatment of psychosis in elderly patients.

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