PSYCHOPHARMACOLOGY:

QTc Prolongation Associated With Atypical Antipsychotic Use in the Treatment of Adolescent-Onset Anorexia Nervosa

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Introduction

Anorexia nervosa (AN) is a chronic illness that is associated with significant morbidity and mortality. Large scale prospective placebo-controlled studies supporting the use of psychotropic medications, including atypical antipsychotics, for the treatment of AN are currently limited. A recent double-blind placebo-controlled trial in an adult population provided evidence for efficacy in olanzapine-treated patients as indicated by greater rates of weight gain, earlier achievement of target body mass index (BMI), and a greater rate of decrease in obsessive symptoms (Bissada et al., 2008). To date, prospective controlled studies examining the use of atypical antipsychotics in paediatric AN populations are non-existent. As a result, little has been published on the side effects of these medications in this population (Fairburn et al., 2003).

Herein, we describe a case of corrected QT (QTc) prolongation associated with atypical antipsychotic use in an adolescent patient with AN and discuss safety and medical monitoring issues as it pertains to antipsychotic use in this population.

The QT interval is the time taken for the ventricle to depolarize and repolarize and is measured from the beginning of the Q wave to the end of the T wave on an electrocardiogram (ECG). The QT interval can vary with heart rate, and as such can be corrected (QTc) using various methods, including the Fridericia, Hodges, and Framingham formulas. The Bazett formula ($QTc=RR/QT^{1/2}$) is most often cited in Canadian clinical practice and is used by cardiologists within our pediatric center. Risk factors for QT prolongation include female sex, bradycardia, hypokalemia, and cardiac disease (Roden, 2004). A number of medications, including various antiarrhythmic drugs (class IA and III), antibiotics, antihistamines, methadone, and psychotropic medication have also been associated with QTc prolongation (Harrigan et al, 2004). Given the prevalence of these risk factors in patients with AN, care should be taken in the cardiac monitoring of low weight medically compromised patients, as baseline QTc have been shown to be longer than those of healthy controls (Cooke et al., 1994). Acute risk associated with prolongation of the QTc includes torsade de pointes, a potentially fatal type of arrhythmia (Al-Khatib, 2003).

There are few studies that comment on the safety of atypical antipsychotics in the child and adolescent population. In one non-eating disorder (ED) paediatric study involving 20 subjects, use of ziprasidone was associated with an average QTc prolongation of 28 msec ($p = 0.07$) (Blair et al., 2005). McConville's 2000 open-label study of quetiapine in adolescents with psychotic disorders also commented specifically on tolerability relating to medical effects of the drug. No significant changes in QTc were observed. QTc prolongation has been reported in adolescents who have overdosed on quetiapine and on ziprasidone in combination with bupropion (Biswas et al., 2003; Kurth & Maguire, 2004).

Case

A 15 year old female with a known diagnosis of AN, restricting type was admitted in transfer from another tertiary care center to the in-

patient eating disorders program at our institution. She had been hospitalized multiple times previously at another regional center for ongoing management of AN. Her body mass index (BMI) at transfer was 18 and her weight was 48 Kg. Her medications included fluoxetine 20 mg daily and olanzapine 5 mg nightly. Her past medical history was unremarkable. She had been previously diagnosed with a co-morbid mood and anxiety disorder. There was no history of substance abuse. Apart from her low weight, physical examination and laboratory investigations were normal. An ECG at the time of transfer revealed a prolonged QTc of 457 msec (<450 msec generally regarded as normal).

The patient's olanzapine was held in the early days because of the prolonged QTc and her fluoxetine was increased to 40mg to target her increased anxiety. Also, 0.5 mg of clonazepam was added twice daily. On the 15th day of her hospital stay, olanzapine was re-started at 2.5 mg nightly for overwhelming anxiety. Objective and subjective improvements were noted with her anxiety, although her QTc (which had normalized prior to the re-initiation of olanzapine) increased to 483 msec, resulting in discontinuation of the drug on day 22. Her QTc normalized again over the next week but her psychiatric symptoms intensified. Her fluoxetine was subsequently increased to 60 mg daily on day 30. Given the perceived response to olanzapine, the patient and her family were counseled about and agreed to a trial of risperidone. A dose of 0.25 mg of risperidone was started on day 30 and the total daily dose was increased to 0.5 mg on day 37 and then to a total daily dose of 0.75 mg on day 42. Despite a normal QTc at initiation, her QTc was again prolonged (473 msec) on an ECG performed on day 55, resulting in risperidone discontinuation. The QTc normalized within a week but her anxiety and eating disorder (ED) preoccupation intensified, resulting in a further trial of low dose quetiapine starting on day 71. The patient tolerated 25 mg of quetiapine and the dose was increased to 50 mg nightly without any noted QTc changes. Clinically, the patient's anxiety improved with this low dose of quetiapine resulting in dose stabilization. Weekly ECGs completed thereafter demonstrated no further abnormality with her QTc interval. Overall, our patient showed marked improvement over her hospital stay as evidenced by continued weight restoration, re-establishment of a healthy weight, and greater stability regarding mood and anxiety. Medication, psychotherapy and group programming were each felt to contribute to this success.

Discussion

Given the inherent cardiac risks associated with the treatment of low weight patients with AN, care should be taken when atypical antipsychotic use is being considered. Special attention to pre-existing cardiac history, clinical symptoms, and ongoing monitoring are advisable in patients receiving such therapy.

There is some controversy associated with the best available method for calculation of QTc intervals. Guidelines advocate for interval measurement using tracings obtained directly from a limb lead on the ECG and averaging multiple measurements (Al-Khatib et al., 2003). Consensus regarding choice of formula used to correct the QT interval for heart rate has not been reached, although the Bazett formula is routinely used in clinical practice. Each correction method has been noted to have specific strengths and weaknesses. Both the Bazett and Fridericia formula have been shown to be problematic for evaluation of drug effects (Indik, 2006). Other research studies have shown that linear formulae may be preferred for investigating the effect of drugs on the QT interval, however these are not implemented in commercially available recording equipment and therefore are hard to utilize for immediate clinical decision making (Luo, 2004). For this reason we have presented the data in the usual manner using the Bazett formula, being aware, however, of the debate that currently exists.

Other points to consider regarding QTc measurement includes timing of drug delivery and potential drug interactions. Ideally, ECGs should be recorded at peak serum concentrations of the suspect drug. From a clinical sense however, timing predicted pharmacokinetic effects based upon drug administration to ECG completion is not realistic and in itself is prone to other confounding variables. In our patient's case, all ECGs were completed between 9AM and 2 PM. Potential drug interactions resulting in subsequent QTc prolongation should also be considered as possible in this case. Fluoxetine

inhibits cytochrome P450 1A2 and 2D6. Olanzapine and risperidone are substrates for these enzymes respectively (Robinson & Owen, 2005). It is possible (although less likely given the frequency by which this drug combination is used in clinical practice and the absence of other reported cases) that the concomitant use of fluoxetine with olanzapine and risperidone may have resulted in elevated serum levels of the two antipsychotic drugs.

Large clinical studies have not found a link between fluoxetine and QTc prolongation (Varriale, 2001). Isolated case reports of people over 50 years of age indicate that fluoxetine may rarely be implicated in QTc prolongation (Appleby, 1995; Ravina, 1998; Varriale, 2001; Wilting 2006). While antipsychotic medications were being used in our patient for acute relief from anxiety, fluoxetine was introduced as a longer term treatment for co-morbid anxiety and depression. It is common practice at our center to start fluoxetine for co morbid anxiety and depression once a patient's BMI reaches 18 or higher. In our patient, changes in QTc were temporally related to changes in antipsychotic medication, not to the dose of fluoxetine. Our patient's QTc returned to baseline on several occasions independent of fluoxetine dosing and as such, did not correlate at any point with her observed QTc prolongation.

At our center, baseline ECGs are completed on all patients at the initiation of eating disorder treatment. Testing is repeated whenever medications are introduced that are known to affect QTc intervals. The interval is monitored over the course of drug therapy and after incremental dose adjustments are made. ECGs should also be repeated whenever a patient experiences any other risk factor known to alter QTc while on antipsychotic medication. In our population, this situation most commonly occurs when patients develop concomitant electrolyte disturbances. Patients that purge (as a means of attempting to facilitate weight loss) are especially at risk for electrolyte abnormalities and should be monitored very closely. In cases where patients experience prolongation of QTc greater than 450 msec, suspect medications should be held and ECGs are repeated serially until normalization occurs. In our center, patients with documented prolonged QTc intervals are also prohibited from any physical activity until QTc correction has occurred. In cases where baseline values increase significantly during drug treatment (more than 60 msec) it is advisable to either hold or taper medication with continued close observation of QTc intervals (weekly ECGs are generally suggested).

Keeping each of these clinical pearls in mind, the importance of intensive medical monitoring in low weight patients with AN cannot be overstated. Anticipating and treating such sequelae alleviates added risk in a disease already marked with significant medical co morbidity. As the number of prospective controlled trials using this class of medication increases, it will be important for investigators to incorporate parameters of medical tolerability into study design. Given the inherent challenges associated with the treatment of adolescent AN, it is critical that our understanding of the potential merits of adjunctive pharmacotherapy incorporate both medical and psychological aspects of treatment as a means of ensuring informed consent in clinically applicable patient populations.

Acknowledgments/Conflict of Interest

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Commentary to QTc Prolongation Associated With Atypical Antipsychotic Use in the Treatment of Adolescent-Onset Anorexia Nervosa

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In this paper, Ritchie & Norris remind us of the need to remain vigilant for drug-induced adverse reactions while treating patients with anorexia nervosa (AN). The authors are to be commended for their submission, as some recent studies show adverse reactions may be underreported by 80-95%, even for serious events (Hazell & Shakir, 2006). In other words, for every adverse event reported, it is reasonable to think that from 4-19 similar incidents have occurred elsewhere, but have not been formally reported.

Drug-induced QTc interval prolongation has become a prominent issue as clinicians struggle with decision making around drug therapy in an era which has seen multiple drugs either restricted in their use or removed from the market due to QTc prolongation (Roden, 2004). A recent publication in a prominent journal demonstrated an increased rate of sudden cardiac death in an adult cohort for patients receiving atypical antipsychotics (Ray et al., 2009). A meta-analysis of AN patients showed that QTc interval was within normal range, though significantly longer than in controls. Electrocardiogram (ECG) data appears to have been collected at baseline prior to starting any drug therapy (Lesinskiene et al., 2008).

Diurnal variation in QTc interval, controversy over choice of QT interval correction method and a relative lack of information in the literature about QTc effects of psychotropic drugs, especially in specific patient subgroups which may be at greater risk for sudden cardiac death further muddy the waters. There is hope, however, as the currently underway Canadian trial investigating the efficacy and safety of adjunctive olanzapine in patients with AN will obtain ECG data at baseline and on treatment (Spettigue et al., 2008). Hopefully the trial (one of the trial investigators is a co-author of this case report) and others like it will shed more light on this complex issue.

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