Citalopram-induced QTc prolongation: A brief review of the data

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ABSTRACT

Recently, Forest Laboratories warned about QTc prolongation associated with the use of citalopram. After these reports, the FDA warned that citalopram should no longer be used at doses greater than 40 mg/day for patients ≤ 60 years of age or greater than 20 mg/day in patients over 60 years of age. As a result, providers and formulary managers were advised to reevaluate the use of citalopram to conform to current FDA guidelines. Clinicians have the option to: (1) maintain the patient on the current dose (no change), document that the current EKG (with QTc) is within a normal range and inform the patient of the current recommendations or (2) change the therapy, which consists of either a dose reduction or change to an alternate agent. It may be appropriate to keep a patient on current therapy above the FDA recommended maximum if proper documentation is maintained (e.g., past history of severe depression, normal EKG). Citalopram should be discontinued in patients who have persistent QTc measurements greater than 500 ms.

KEYWORDS

Citalopram, QTc prolongation, dosing

Until last year, the selective serotonin reuptake inhibitor (SSRI), citalopram, a first-line agent used in the treatment of depressive disorders, was considered safe and well-tolerated in the therapeutic dose range of 20-60 mg/day.[1,2] Distinct from some of the other agents in its class, citalopram exhibits linear pharmacokinetics and minimal drug interaction potential, making it a preferred agent for use in the elderly or in patients taking concomitant medications.[2]

In August 2011, Forest Laboratories, Inc, the manufacturer of citalopram, issued a ***Dear Healthcare Professional*** letter that warned about QTc prolongation associated with the use of citalopram. Prior to this, the FDA evaluated the results of a "thorough QT/QTc study" (unpublished) assessing the effects of 20 mg and 60 mg doses of citalopram on the QTc interval in adults. In this randomized, multi-center, double-blind, placebo-controlled, crossover study, 119 subjects received citalopram 20 mg/day on day 9 and 60 mg/day on day 22. The results showed that the maximum mean prolongations in the individually corrected QTc intervals were increased by 8.5 and 18.5 milliseconds (ms) for citalopram doses of 20 mg/day and 60 mg/day, respectively, when compared to placebo. For citalopram doses of 40 mg/day, prolongation of the corrected QTc interval was estimated to be 12.6 ms.[5] For reference, increases in QTc to ≥ 500 ms or a drug-induced increase from baseline of ≥ 60 ms would represent significant changes in clinical trials.[6] In a "thorough QT/QTc study," the threshold level of concern is around 5 ms, supported by an upper bound of the 95% confidence interval around the mean effect on QTc of 10 ms. There are several factors that may influence the risk of drug-induced QTc prolongation, including: female gender (i.e., documented to have baseline QTc intervals that are usually 20 ms greater than males), cardiac conditions (e.g., bradycardia, heart failure), electrolyte abnormalities (e.g., hypokalemia, hypocalcemia, hypomagnesaemia) and genetic mutations within the cardiac sodium channels.[7,8] There are also diurnal variations in QTc interval. Both QT and QTc intervals are longer during sleep and reach a peak shortly after awakening. This time peak corresponds to the period of reported increased vulnerability to ventricular tachycardia and sudden cardiac death.[9]

On August 24, 2011, the FDA warned that citalopram should no longer be used at doses greater than 40 mg/day for patients ≤ 60 years of age. The manufacturers reported that doses above 40 mg/day caused substantial QTc interval prolongation without conferring any additional benefits; prior studies have not shown a benefit in the treatment of depression at doses higher than 40 mg/day.[10,11] Additionally, the FDA's warning stated that citalopram should no longer be used at doses greater than 20 mg/day in patients over 60 years of age, those with

hepatic impairment, and/or those considered to be CYP 2C19 poor metabolizers.

A literature search was conducted to examine evidence of citalopram-induced QTc prolongation. Camm et al (2004), authors of the book titled ***Acquired Long QT Syndrome***, discussed the mechanisms behind QTc prolongation and Torsades de Pointes. They focused primarily on the risk of individual cardiac and non-cardiac drugs in provoking long QT syndrome. In regards to psychotropic medication-induced QTc interval prolongation and Torsade de Pointes, they mentioned that QTc interval prolongation associated with citalopram doses up to 60 mg/day is extremely rare. The risk may be increased in patients with underlying cardiac risk factors or in those who overdose.[12] One group of authors were concerned that providers may apply the newly established FDA warnings and possibly destabilize patients who may be responding well to citalopram 60 mg/day or higher.[13] They compiled nine-case reports of citalopram and QTc prolongation/Torsades and found no occurrences of citalopram-associated QTc interval prolongation in patients who neither overdosed on citalopram nor had well-known risk factors for QTc interval prolongation. Five cases of QTc prolongation were associated with citalopram overdose (up to 400 mg), two cases were associated with polypharmacy, and two cases were associated with risk factors (e.g., advancing age, hypokalemia, hypomagnesaemia, hypertension, diabetes). The authors commented that there were no documented cases of citalopram-related QTc interval prolongation associated with doses in the "therapeutic range" of 20 - 60 mg/day. Additionally, they noted that citalopram 60 mg/day appeared no more likely to induce QTc prolongation than drugs such as ziprasidone at 160 mg/day or quetiapine at 750 mg/day. At the doses indicated, ziprasidone monotherapy increased QTc by 20.3 ms and quetiapine, in the presence of the CYP3A$ inhibitor ketoconazole, increased QTc by 19.7 ms.[14] However, there are varying reports on the degree of QTc prolongation certain atypical antipsychotics can induce. Glassman et al (2001) and Harrigan et al (2004) reported that the mean QTc interval change was 20.2 ms and 15.9 ms for ziprasidone and 14.5 ms and 5.7 ms for quetiapine, respectively.[15,16]

Following the FDA update, providers and formulary managers were advised to reevaluate the use of citalopram to conform to current FDA guidelines. Clinicians have the option to: (1) maintain the patient on the current dose (no change), document that the current EKG (with QTc) is within a normal range and inform the patient of the current recommendations or (2) change the therapy, which consists of either a dose reduction or change to an alternate agent. It may be appropriate to keep a patient on current therapy above the FDA recommended maximum if proper documentation is maintained (e.g., past history of severe depression, normal EKG). However, it remains unclear which is the preferred option, as future risk/benefit studies are necessary. Overall, clinicians should abide by the newly established FDA-recommended guidelines on citalopram and not titrate patients to doses above 40 mg/day (or above 20 mg/day for patients greater than 60 years of age) to prevent liability issues. In situations where the patient has exceeded the dosing limitations, is currently stable, has none of the aforementioned risk factors for QT prolongation and has a normal QTc interval, it may be wise to carefully discuss with the patient the risks/benefits with the higher dose and obtain written consent to document the patient's understanding. Providers should investigate the family history for any known cardiac conditions, obtain a baseline EKG prior to prescribing citalopram and monitor regularly (e.g. signs/symptoms of arrhythmias [irregular heartbeat, shortness of breath, dizziness or fainting], EKG, and electrolytes [magnesium and potassium]) during treatment. Citalopram should be discontinued in patients who have persistent QTc measurements greater than 500 ms.[17]

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