



## **Citalopram Drug Interaction: Prolonged QT and Risk of Arrhythmia**

### **KEY POINTS**

- **The interaction between citalopram and omeprazole or esomeprazole has the potential to significantly increase citalopram serum levels, prolong the QT interval and increase risk of TdP. Avoid this combination if possible.**
- **Concurrent use of citalopram and oral contraceptives is unlikely to have an adverse effect in healthy women.**
- **Avoid use of citalopram and escitalopram in combination with other drugs which prolong the QT interval.**

### **INTRODUCTION**

A number of new drug interactions involving citalopram have appeared recently on electronic interaction programs. These stem from post-marketing reports of dose dependent prolongation of the QT interval with citalopram and escitalopram therapy ECGs.<sup>1,2,3</sup> QT prolongation can precipitate Torsade de pointes (TdP), a rare but potentially fatal ventricular arrhythmia.<sup>1,2</sup> Based on these reports, the American Food and Drug Administration has issued an alert advising the dose of citalopram not exceed 40 mg daily (the previous limit was 60 mg daily).<sup>1</sup> Health Canada is currently reviewing the cardiac safety of citalopram.<sup>4</sup>

The FDA further recommends limiting the dose of citalopram to 20 mg per day for patients who have hepatic impairment, are greater than 60 years of age, are CYP 2C19 poor metabolizers, or are taking concomitant cimetidine.<sup>1</sup> Cimetidine interacts with citalopram via inhibition of the enzymes CYP 2C19 and CYP 3A4, the major metabolic pathways of citalopram.<sup>5</sup> This results in increased citalopram serum levels<sup>5</sup> which could put patients at risk of TdP<sup>1</sup>. The potential for this type of interaction has been extrapolated to include proton pump inhibitors, oral contraceptives and other CYP 2C19 inhibitors.

## REVIEW OF QT INTERVAL PROLONGATION AND TDP

The QT interval on an ECG is the time for ventricular depolarization and subsequent repolarization.<sup>6</sup> In healthy cardiac tissue, the QT interval corrected for heart rate is 440 msec or less.<sup>6</sup> Prolongation of QT may, in certain people, progress to TdP.<sup>6</sup> Factors which can increase the risk of TdP are listed in Table 1. Patients with two or more predisposing factors are at high risk of TdP.<sup>6,7</sup> There is essentially no cardiac output while TdP lasts.<sup>7</sup> Symptoms experienced by the patient depend on the duration of the arrhythmia<sup>7</sup>. (See Table 2.)

**Table 1: Risk factors for Torsades de Pointes<sup>6-9</sup>**

Non-Modifiable	Possibly Modifiable	Drug-induced *
<ul style="list-style-type: none"> <li>• Congenital long QT syndromes</li> <li>• Elderly (&gt; 65 years old)</li> <li>• Family history of sudden cardiac death (&lt; 50 years)</li> <li>• Female sex</li> <li>• History of arrhythmias</li> <li>• Myocardial infarction</li> </ul>	<ul style="list-style-type: none"> <li>• Bradycardia (pulse &lt; 50 b/m)</li> <li>• Electrolyte disorders (hypokalemia, hypomagnesimia, hypocalcemia)</li> <li>• Eating disorders</li> <li>• Heart failure</li> <li>• Hypoglycemia</li> <li>• Hypertension</li> <li>• Hypothyroidism</li> <li>• Myocardial ischemia</li> </ul>	<ul style="list-style-type: none"> <li>• Drugs which can increase QT interval (Examples)               <ul style="list-style-type: none"> <li>○ Anti-arrhythmics e.g. amiodarone, quinidine, sotalol</li> <li>○ Antibiotics e.g. erythromycin, moxifloxacin</li> <li>○ Antidepressants e.g. TCAs**, venlafaxine, SSRIs***</li> <li>○ Antipsychotics e.g. haloperidol, quetiapine</li> <li>○ Methadone</li> </ul> </li> </ul>

\* Comprehensive lists of drugs which can prolong the QT interval are available at Rxfiles: [www.rxfiles.ca/rxfiles/uploads/documents/members/cht-QA%20TORSADESdePoint.pdf](http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-QA%20TORSADESdePoint.pdf) and Arizona Cert: [www.qtcdrugs.org](http://www.qtcdrugs.org)

\*\* TCAs – tricyclic antidepressants

\*\*\* SSRIs – selective serotonin reuptake inhibitor antidepressants (case reports)

**Table 2: Symptoms of TdP<sup>7</sup>**

TdP < 10 seconds	TdP > 10 seconds
<ul style="list-style-type: none"> <li>• Lightheaded, dizzy</li> <li>• Palpitations</li> <li>• Shortness of breath</li> </ul>	<ul style="list-style-type: none"> <li>• Unconsciousness</li> <li>• Tonic-clonic seizure may occur</li> <li>• Death if TdP persists for more than 1 – 2 minutes</li> </ul>

## **CITALOPRAM + PROTON PUMP INHIBITORS**

*Pharmacokinetic Interaction:* The proton pump inhibitors (PPIs) are all substrates of CYP2C19 and in theory could interfere with the metabolism of citalopram by competing for the enzyme.<sup>10</sup> Competitive inhibition is dose-dependent, reversible and tends to have only modest effects.<sup>11</sup> Recent evidence suggests that omeprazole, specifically the *s*-enantiomer of omeprazole, is a mechanism-based inhibitor of 2C19.<sup>11</sup> Mechanism-based inhibition irreversibly inactivates enzyme and is more likely to have a significant clinical effect than competitive inhibition.<sup>11</sup> Lansoprazole, pantoprazole and rabeprazole do not appear to have this effect.<sup>11</sup>

*Pharmacodynamic Interaction:* Use of PPIs for more than one year may deplete magnesium, potassium and calcium.<sup>12</sup> These electrolyte deficiencies are risk factors for TdP.<sup>6</sup> Adding citalopram to long-term PPI therapy could, in theory, increase this risk.

### **Management of Interaction:**

- Consider patient risk factors for TdP. If risk is high, recommend an alternate SSRI, mirtazapine, bupropion or non-pharmacological therapy.
- Ensure there is a valid indication for PPI therapy and/or reassess need for ongoing therapy.
- If the patient is currently on a PPI, recommend measurement of electrolytes before initiating citalopram. If potassium and magnesium levels are in the normal range and there is no history of cardiovascular disease, then addition of citalopram to therapy is not likely a concern.
- If PPI use is indicated, recommend lansoprazole, pantoprazole or rabeprazole rather than omeprazole or esomeprazole.
- If omeprazole or esomeprazole is prescribed, limit dose of citalopram to 20 mg daily. Advise patient to report any symptoms that might indicate a rhythm disorder : dizziness, palpitations (sensation of rapid, pounding, or irregular heart beat), fainting, or seizures.<sup>7</sup>

## **CITALOPRAM + ORAL CONTRACEPTIVES**

*Pharmacokinetic Interaction:* In vitro studies report that ethinyl estradiol is mechanism-based inhibitor of 3A4 but a relatively weak competitive inhibitor of 2C19.<sup>13</sup> Progestins are substrates of 2C19 so in theory could compete with citalopram for 2C19 metabolism.<sup>13</sup> However, competitive inhibition is dose dependent and the small dose of ethinyl estradiol and progestin in oral contraceptive would not be likely to have a significant effect on citalopram concentration.

*Pharmacodynamic Interaction:* Estrogens and progestins have opposing effects on QT interval: estrogens prolong and progestins shorten the interval.<sup>14</sup> Based on this, oral contraceptives containing both estrogen and progestin would not be expected to affect QT.<sup>14</sup> However, the impact of oral contraceptives on QT interval has not been studied *in vivo*.<sup>12</sup>

### **Management of Interaction:**

- Evaluate patient risk factors for TdP.
- For women with no risk factors (other than female sex), no intervention is necessary.
- If the patient has additional risk factors, recommend alternate SSRI, mirtazapine, bupropion or non-pharmacological therapy.

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### **References:**

1. FDA Drug Safety Communication: Abnormal heart rhythms associated with high doses of Celexa (citalopram hydrobromide). Available at <http://www.fda.gov/Drugs/DrugSafety/ucm269086.htm> . Accessed December 2011.
2. Astrom-Lilja C, Odeberg J, Ekman E, Hagg S. Drug-induced torsades de pointes: a review of the Swedish pharmacovigilance database. *Pharmacoepidemiology and drug safety* 2008; 17: 587–592.
3. Drug Safety Update Dec 2001 vol 5, issue 5: A1.
4. Citalopram: Health Canada reviewing dose-related heart risk. Available at [http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2011/2011\\_134-eng.php](http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2011/2011_134-eng.php). Accessed December 2011.
5. Malling D, Poulsen M, Søgaard B. The effect of cimetidine or omeprazole on the pharmacokinetics of escitalopram in healthy subjects. *Br J Clin Pharmacol* 2005 60 287-90.
6. Crouch M, Limon L, Cassano A. Clinical relevance and management of drug-related QT interval prolongation. Available at <http://www.medscape.com/viewarticle/458868>. Accessed December 2012.
7. [Arizona CERT. Professional education: overview of long QT syndrome and Torsades.](#) Available at <http://www.qtdrugs.org/>. Accessed December 2012.
8. [Health Canada. QT/QTc Interval Prolongation: Guidance for Product Monograph Content.](#) Available at [http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/qtqtc/qt\\_pm\\_mp-eng.php#qt](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/qtqtc/qt_pm_mp-eng.php#qt). Accessed December 2012.
9. [Downey S, Jensen B, Regier L. Rxfiles Q&A: QT prolongation and Torsades de Pointes: drugs and sudden death.](#) Available at [www.RxFiles.ca](http://www.RxFiles.ca). Accessed December 2012.

10. Rocha A, Coelho EB, Sampaio SA, Lanchote VL. Omeprazole preferentially inhibits the metabolism of (+)-(S)-citalopram in healthy volunteers. *Br J Clin Pharmacol.* 2010 Jul;70(1):43-51.
11. Ogilvie B, Yerino P, Kazmi F et al. The Proton Pump Inhibitor, Omeprazole, but Not Lansoprazole or Pantoprazole, Is a Metabolism-Dependent Inhibitor of CYP2C19: Implications for Coadministration with Clopidogrel. *Drug metabolism and disposition.* 2011;39:2020-2033.
12. Mouchantaf R. Proton pump inhibitors: hypomagnesemia accompanied by hypocalcemia and hypokalemia. *Can Adverse Reaction Newsletter* 2011;21(3). Available at [http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei\\_v21n3-eng.php# Proton\\_pump\\_inhibitors](http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v21n3-eng.php# Proton_pump_inhibitors): Accessed December 2011.
13. Zhang H, Cui D, Wang B et al. Pharmacokinetic Drug Interactions Involving 17[alpha]-Ethinylestradiol: A New Look at an Old Drug. *Clinical Pharmacokinetics* 2007; 46: 133-157.
14. Laine K, Yasar O, Widén J, Tybring G. A Screening Study on the Liability of Eight Different Female Sex Steroids to Inhibit CYP2C9, 2C19 and 3A4 Activities in Human Liver Microsomes. *BCPT* 2003;93:77-81. Available at: [http://onlinelibrary.wiley.com/doi/10.1034/j.1600-0773.2003.t01-1-930202\\_93\\_2.x/full](http://onlinelibrary.wiley.com/doi/10.1034/j.1600-0773.2003.t01-1-930202_93_2.x/full). Accessed December 2011.