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CASE REPORT

# Citalopram-Induced Long QT Syndrome and the Mammalian Dive Reflex

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**Abstract** While SCUBA diving, a 44-year-old Caucasian patient had an abnormal cardiac rhythm, presumably Torsade de Pointes (TdP), during the initial descent to depth. Upon surfacing, she developed ventricular fibrillation and died. The patient had been treated for mild depression for nearly a year with citalopram 60 mg per day, a drug known to cause prolonged QT interval. She had also been treated with two potentially hepatotoxic drugs. Liver impairment causes selective loss of cytochrome P450 (CYP) 2C19 activity, the major pathway for metabolism of citalopram. The post mortem blood level of citalopram was 1300 ng/mL. The patient was found to be an intermediate metabolizer via CYP2D6, the major pathway for metabolism of desmethylcitalopram; the level of which was also abnormally high. It is suggested that drug-induced long QT syndrome (DILQTS), caused by citalopram, combined with the mammalian dive reflex triggered malignant ventricular rhythms resulting in the patient's death. It is further suggested that, in general, the dive reflex increases the risk of fatal cardiac rhythms when the QT interval is prolonged by drugs.

**Key Points**

Long-term high dosage and impaired metabolism apparently accounted for accumulation of high, but presumably non-lethal levels, of citalopram and desmethylcitalopram in a 44-year-old woman who died while SCUBA diving.

Prolongation of the QT interval, a well-known effect of citalopram, increases the risk of fatal cardiac rhythms; a risk that is further increased by bradyarrhythmias.

It is suggested that citalopram-induced long QT coupled with the mammalian dive reflex resulted in a fatal cardiac rhythm in this case.

## Introduction

In August 2011, the US FDA issued a Drug Alert concerning citalopram (Celexa®). The alert indicated that citalopram should not be used at doses greater than 40 mg per day because it causes dose-dependent QT interval prolongation. The maximum recommended dose was 20 mg per day for patients with hepatic impairment, age greater than 60 years, cytochrome P450 (CYP) 2C19 poor metabolizers, or patients taking concomitant CYP2C19 inhibitors, such as cimetidine. It was further noted that citalopram should not be used in patients with congenital long QT syndrome (LQTS). Electrocardiographic monitoring was recommended if citalopram is used in patients with congestive heart failure, bradyarrhythmias, predisposition to hypokalemia or hypomagnesemia, or in combination with other QT-prolonging drugs.

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## Citalopram

The 44-year-old patient, who was a non-smoker and rarely consumed small amounts of alcohol, had taken citalopram 40 mg per day for mild depression since before July 2009. At that time, she was also taking bupropion (Wellbutrin®) 200 mg per day. Likewise, since before July 2009 she had taken nadolol 40 mg/day for mild hypertension that was well controlled. In July 2009 she was prescribed divalproex (Depakote® extended release [ER]) 250 mg/day, the dosage of which was increased to 500 mg per day in 2010 and increased again to 1000 mg per day in January 2011. At that time, she was also taking meloxicam (Mobic®) 15 mg per day. The latter two medications were given for frequent migraine headaches. In January 2011, bupropion was discontinued when the dosage of citalopram was increased from 40 to 60 mg per day.

On 5 May 2011, aspartate aminotransferase (AST) was 146 (range 6–35 U/L) and alkaline phosphatase (ALK PHOS) was 118 (range 30–125 U/L). Repeat testing on 8 May 2011 found AST at 75, ALK PHOS at 210, and alanine transaminase (ALT) at 172 (range 8–40 U/L). At that time, the meloxicam dosage was discontinued. However, divalproex was continued at 1000 mg per day and citalopram at 60 mg per day. No further liver function tests were performed, and no electrocardiogram testing or therapeutic drug monitoring was performed in 2011.

The patient was a certified SCUBA diver, although she had not been diving for over a year when, in December 2011, she arranged to dive in a tropical location while on a family vacation. While diving with a small group of SCUBA divers led by a qualified guide, the patient "developed problems" during the initial descent to a depth of about 40 feet. The guide immediately took her to the surface and she was placed on the deck of the nearest dive boat—a boat equipped with an automatic defibrillator. Although no permanent recording exists, the patient's rhythm changed from apparent Torsade de Pointes (TdP) to ventricular fibrillation, and defibrillation was not successful.

Autopsy performed the next day by the local medical examiner revealed an obese (body mass index [BMI] ~36) Caucasian body with pulmonary congestion and edema, hepatic congestion, splenic congestion, and cardiomegaly. The heart was mildly hypertrophic (420 g) and dilated. Microscopic examination revealed interstitial myocardial fibrosis and cardiomyocyte hypertrophy as well as an isolated liver granuloma. The post mortem blood concentration of citalopram was reported at 1300 ng/mL, well above the therapeutic level [1]. In addition, analysis of post mortem blood resulted in the following findings: ethanol 35 mg/dL, ibuprofen 10 mcg/mL, and caffeine positive but not quantified. While a high level of caffeine might have contributed to the fatal outcome, it seems unlikely since caffeine is routinely 'positive' in the blood of those who consume beverages containing caffeine. In view of the "slightly enlarged heart" and level of citalopram, and in the absence of other relevant findings, the medical examiner concluded that the cause of death was a fatal cardiac arrhythmia. For ease of comparison, the blood levels of citalopram reported by various authors are expressed as ng/mL or ng/mg.

The ratio of plasma to whole blood concentration of citalopram is $0.74 \pm 0.04$ [2]. Thus, the blood concentration of 1300 ng/mL is equivalent to a plasma level of approximately 962 ng/mL. Citalopram therapeutic and comatose-fatal plasma concentrations are reported to be 5–110 and 5000–6000 ng/mL, respectively [1]. Thus, although the level of citalopram in the patient's post mortem blood was substantially above the therapeutic range, it was not an obvious cause of death, per se.

A number of questions arose in this case. Why was the post mortem level of citalopram so high? It was much higher than would be predicted if the patient had normal metabolism of citalopram, even at the dosage of 60 mg per day. Furthermore, why did the patient die only after approximately 11 months of such high dosage?

One possible explanation for a high level of citalopram and death might be an acute overdose; possibly suicidal. However, there is no evidence that the patient was suicidal, and family members were confident that she was happily enjoying a vacation. Also inconsistent with acute overdose is the fact that additional toxicology analysis in a different laboratory resulted in a blood level of citalopram of 1426 ng/mL and a level of desmethylcitalopram of 846 ng/mL. In patients chronically taking citalopram, the levels are typically three to four times higher than the metabolite, desmethylcitalopram [3]. In acute overdose, the ratio of the parent drug to metabolite would be higher. In this patient, the ratio of parent drug to metabolite was lower than expected and is inconsistent with acute overdose. Compared with citalopram, the relatively high level of the metabolite that is normally eliminated mainly by CYP2D6 supported the speculation that the deceased might have been a poor metabolizer via 2D6. Subsequent testing of post mortem blood indicated that, genotypically, she was an intermediate metabolizer via 2D6. In any event, acute overdose, suicidal or accidental, was not the cause of the high level of citalopram and its metabolite in this patient at the time of her death.

Metabolism of citalopram to desmethylcitalopram is carried out mainly by CYP2C19. In turn, the metabolism of desmethylcitalopram to didesmethylcitalopram is carried out mainly by CYP2D6 [3]. While about 7 % of

Caucasians are poor metabolizers via 2D6, only about 3 % are poor metabolizers via 2C19 [4]. The probability that a person would be a poor metabolizer via both pathways is very low, although such cases have been reported [4–6]. The patient in this case was found to be a genotypically normal metabolizer via CYP2C19 and an intermediate metabolizer via CYP2D6. The question thus arose regarding the post mortem blood level of citalopram of approximately 1300–1400 ng/mL. How did the level get so high, and was citalopram the cause of the patient's death?

Post mortem redistribution did not account for the high level of citalopram in the patient's blood. Because the autopsy was performed the morning after death, there was little time for redistribution. While some antidepressants show substantial post mortem increases in blood concentration, citalopram increased by only 25 %, even after 6.4 days post mortem [7]. Many drugs are inhibitors of one or more CYP isoforms, but such classical drug interactions were not apparent in this case. On the other hand, low activity of CYP2C19 and/or CYP2D6 (especially and) as caused by a poorly functioning liver, would promote the accumulation of citalopram and desmethylcitalopram to higher than expected levels [8, 9].

Irrespective of her genetic background, it is apparent that the patient in this case became a poor metabolizer phenotypically via both 2C19 and 2D6. The latter was genetically determined in part and possibly worsened by liver damage. The former was a consequence of liver damage. Drug-induced damage to the liver by meloxicam and by divalproex is likely. Both drugs have warnings regarding liver dysfunction; the latter with a prominent black box warning. Meloxicam was discontinued when the patient's liver enzymes were found to be elevated in May of 2011. Divalproex, the dose of which had been increased from 500 mg per day to 1000 mg per day in January of 2011, was continued to the time of her death. At autopsy, her liver did not show gross anatomical defects, but impaired function of CYP enzymes would not be apparent. Mild to moderate liver disease is associated with a 77 % decrease in the clearance of mephenytoin (CYP2C19) [8, 10]. Essentially, all CYP enzymes are inhibited in later stages of liver disease [9], with a 28 % decrease in the clearance of dapsone (CYP3A4) and a 4 % decrease in clearance of debrisoquine (CYP2D6) [8]. The fact that mild to moderate liver disease selectively and profoundly inhibits CYP2C19, but barely inhibits CYP2D6, is nevertheless consistent with the relatively high level of desmethylcitalopram found in post mortem blood because the patient inherited intermediate metabolism via CYP2D6. As noted above, no liver function or tests were carried out after May 2011, and no determination of citalopram levels was ever performed. Although we cannot rule out other explanations, based on the scant but abnormal liver function tests in May 2011, as well the continued application of divalproex, we suggest that impaired metabolism caused accumulation of citalopram in this patient. No electrocardiogram was performed during 2011; thus, we are also uncertain of the extent of QT prolongation caused by the high level of citalopram.

Even in the absence of measured levels of the drug, it is evident that impaired metabolism of citalopram and its metabolite were present in this patient. Most likely, accumulation of citalopram to such a high level occurred slowly during 2011. The post mortem blood level of 1300 ng/mL (equivalent to a plasma level of 962 ng/mL [2] was thus about nine times the upper limit of the therapeutic plasma level range (5–110 ng/mL) but less than that usually associated with death (5000–6000 ng/mL) [1].

In cases in which citalopram was judged to be the cause of death, concentrations ranged from 2000 to 6200 ng/mg whole blood [11]. The specific density of blood is approximately 1.04 at 25 °C; thus, concentrations expressed as ng/mg are comparable to mg/L [12]. Toxic concentrations of citalopram in autopsy cases (most were accidental death) ranged from 400 to 900 ng/mg whole blood. In living individuals (mostly traffic violations) citalopram concentrations ranged from 0.0 to 300 ng/mg [11]. The blood alcohol in these samples ranged from 0.0 to 3.1 mg/g (~310 mg/dL). Some individuals were alive with supratherapeutic concentrations of citalopram and, in many cases, very high levels of alcohol [11]. Therefore, alcohol does not necessarily increase citalopram mortality and moderately supratherapeutic concentrations of citalopram do not increase alcohol mortality. However, the authors speculated that "lower concentrations [of citalopram] may cause death if combined with the intake of high concentrations of alcohol." The low level of alcohol (35 mg/dL) in the post mortem blood of the patient in this case may or may not have contributed to the outcome.

In 13 cases examined forensically, citalopram was not judged to be the underlying cause of death, but only an "incidental" finding. The authors concluded, "there is a large apparent therapeutic index with postmortem concentrations in blood possibly ranging as least as high as 1300 ng/mL compared to its therapeutic concentration of approximately 200 ng/mL" [13]. Some other individuals survived levels of citalopram ranging from 90 to 1640 ng/mL in post mortem blood only to die of what were judged to be other causes [14]. These observations may help explain how, in the case reported here, the patient survived for nearly a year as citalopram accumulated in her body to a concentration that was between therapeutic and a more patently fatal concentration. They also raise the questions of the effect of citalopram on the QT interval and why she died while SCUBA diving.

## Drug-Induced Long QT Syndrome

Citalopram, like a number of drugs listed on CredibleMeds (http://www.crediblemeds.org), is known to cause prolonged QT. The official labeling for Celexa® (citalopram) includes the following:

> "Citalopram causes dose-dependent QTc prolongation, an ECG abnormality that has been associated with Torsade de Pointes (TdP), ventricular tachycardia, and sudden death, all of which have been observed in postmarketing reports for citalopram."

The risk of a fatal outcome as a consequence of drug-induced long QT syndrome (DILQTS) and TdP is substantial [15, 16]. QTc is linearly dependent on the predicted citalopram plasma concentration, with a slope of 40 ms per mg per liter of citalopram—with a between-subject coefficient of variation of 70 % [17]. If that average value were applied in this case, then the predicted increase in QTc would be 38 ms. Wide inter-individual variability precludes precise prediction and the RR interval has a large effect on QT that would be additive to the effects of citalopram in this case. It is unlikely that the low concentration of alcohol in this patient contributed to QT prolongation that is observed with moderate and high levels of alcohol [18, 19].

Unterecker et al. [20] found a close relationship between the QTc and serum level as citalopram was eliminated from the body following an acute overdosage [20]. At the initial serum level of 1200 ng/mL, equivalent to 1620 ng/L blood level [2], the QTc was approximately 540 ms. When the drug was finally eliminated, the QTc was 430 ms [20]. At a blood level of 1300 ng/mL, as in the case described here, the best fit curve predicts a QTc (Bazett) of about 497 ms [20].

Individuals with genetically determined LQTS are particularly at risk for further increases in the QT interval when the dive reflex is initiated. Facial immersion in water causes greater increases in QT interval in children with non-familial LQTS [21], and nearly 30 % of swimming-related drowning cases that were referred to Tester et al. [22] for genetic analysis carried a cardiac channel mutation. Many such drownings occur in LQTS children because their risk of a fatal cardiac arrhythmia is significantly increased when the dive reflex is elicited. Catecholaminergic polymorphic ventricular tachycardia (CPVT), a condition that mimics LQTS in some ways, is also associated with drowning or near drowning [23].

## The Mammalian Dive Reflex

The mammalian dive reflex involves concurrent sympathetic and parasympathetic activation [24] and parasympathetically mediated bradycardia [25]. In addition, the 'cold shock response' involves sympathetically mediated tachycardia [25]. Various conduction abnormalities, with individual differences, are observed when a subject's face is immersed in water [26]. Whether this is due to one or both of these reflexes may be uncertain. What seems patently clear is that 'autonomic conflict' and abnormal cardiac rhythms may arise when parasympathetic and sympathetic divisions of the nervous system innervating the heart are simultaneously activated. The FDA warning concerning citalopram and prolonged QT specifically mentions bradyarrhythmias. The bradycardia and autonomic conflict associated with SCUBA diving is a potential trigger for sudden death in a person with a prolonged QT interval. Other contributing factors may have included hypoxia caused by breath holding while equilibrating to depth. In the case described here, DILQTS caused by a high level of citalopram, which in turn was related to excessive dosage and poor metabolism, may have set the patient up for a fatal cardiac arrhythmia while diving.

## Drug-Induced Long QT Syndrome and Drowning

In light of the occurrence of sudden death (i.e., fatal cardiac rhythm) in water of individuals with inherited LQTS [22], it seems reasonable to suggest that, in general, DILQTS is an independent risk factor for apparent drowning. It is well known that alcohol is the drug most commonly associated with drowning [27, 28]. What is not commonly appreciated is that moderate levels of alcohol induce prolonged QT and increased QT dispersion [18, 19]. These changes increase the risk of malignant ventricular rhythms. The question arises whether alcohol-associated drowning in any particular case is due to psychomotor impairment and/or to a fatal cardiac arrhythmia. Increased risk of drowning as caused by DILQTS needs further investigation. Preliminary data, to be published separately, suggest an association of citalopram with drowning. The case reported here is an example of a fatal outcome when prolonged QT interval was combined with the autonomic conflict of the mammalian dive reflex.

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