RESEARCH ARTICLE

Drug monitoring of a case of citalopram overdosage

Jérôme Liotier¹,² and François Coudoré³,⁴

¹CHU Clermont-Ferrand, Hospital G. Montpied, Nephrology and Intensive Care Unit, Clermont- Ferrand, France, ²University Clermont 1, UFR Médecine, Clermont-Ferrand, France, ³Assistance Publique Hôpitaux de Paris, European Georges Pompidou Hospital, Pharmacology and Toxicology Department, Paris, France, and ⁴Paris 11University, Faculty of Pharmacy, Paris, France

Abstract
Selective serotonin reuptake inhibitors are widely prescribed drugs without recognized cardiovascular risk. We report the case of a 54-year-old patient who developed QTc interval prolongation, followed by ventricular fibrillation episodes, 10 hours after admission to the ICU, in the setting of a citalopram overdose. Citalopram plasma values dropped from 5.88 to 0.34 mg/L at 9 days postadmission. The patient was treated by oral activated charcoal, and final outcome was favorable.

Keywords: SSRI, TdP, overdosage, kinetics

Introduction
After overdose, selective serotonin reuptake inhibitors (SSRIs) are thought to be less toxic than imipraminic antidepressants, but citalopram has shown higher toxicity than the other SSRIs. Serotonin syndrome can occur, but is not considered a serious complication. However, QTc prolongation and arrhythmia are reported to be more frequent after treatment with citalopram than with fluoxetine, fluvoxamine, paroxetine, and sertraline, particularly if large amounts are ingested and if patients have associated cardiac diseases (Aström-Lilja et al., 2008). The clinical and electrophysiological data are never put in parallel with blood levels of citalopram, which, in terms of interindividual variations in the metabolism of citalopram, may seem surprising. We report here a case of a rare, nonfatal citalopram overdose with pharmacokinetic data obtained during treatment of heart-rhythm disturbances.

Case report
A 54-year-old woman presented to the emergency unit of the university hospital with altered consciousness and under the influence of alcohol. She had a medical history of psychotic depression treated with citalopram (20 mg/day) and zopiclone (7.5 mg/day). She had intentionally ingested citalopram with alcohol. Time of ingestion was unknown. On presentation, patient temperature was 36.8°C, blood pressure was 65/25 mmHg, heart rate was 77 bpm, and arterial oxygen saturation was 86% in ambient air.

Physical examination highlighted jugular venous distension and a Glasgow Coma Scale (GCS) of 8 with bilateral Babinski without sensory motor deficit. Blood ethanol level was 0.2 g/L, with metabolic acidosis (pH 7.15), hypokalemia (2.9 mmoles/L), and hyperlactatemia (10 mmoles/L). Rapid urine toxicology screen was negative for tricyclic antidepressants, benzodiazepines, cocaine, or opiates. Serum acetaminophen and salicylate levels were undetectable. Calculated using a high-performance liquid chromatography/ultraviolet method, the first serum citalopram level was 5.88 mg/L. Activated charcoal was administered (50 g), and monitoring on citalopram plasma levels was started.

At admission to the ICU, the patient convulsed twice and had a ventricular dysfunction with two
episodes of ventricular fibrillation (VF) treated by midazolam and multiple external electric shocks (EESs). Electrocardiogram (ECG) and cardiac enzymes did not show myocardial infarction, but did reveal a long QT interval (0.44 seconds; QTc: 0.62 seconds) and a left-bundle branch-block pattern. Ten hours after admission to the ICU, she had a sustained ventricular tachycardia with VF episodes resolved by EES and sternum strike. The arrhythmia persisted for 48 hours, but no cardiac arrest was noted. The patient completely recovered without recurrence and was discharged 16 days after admission. The time-course evolution of citalopram plasma values is given in Figure 1.

Discussion
Citalopram overdose primarily causes QTc prolongation, seizures, cardiac arrhythmia, acute respiratory distress syndrome, and renal failure (Flanagan, 2008). However, no literature reporting citalopram kinetics after intoxication was reported, whereasTdPs are classically reported (Friberg et al., 2005; Aström-Lilja et al., 2008; Kanjanauthai et al., 2008).

The first citalopram concentration was 5.88 mg/L, which was very high and was responsible for the unstable clinical situation. Coma occurred at above the 5-mg/L threshold (Jimmink et al., 2008), and six suicidal overdoses with postmortem blood concentrations were reported at levels between 5.2 and 49 mg/L (Ostrom et al., 1996). Therapeutic citalopram concentrations range from 0.01 to 0.2 mg/L, and toxicity starts at approximately 0.3 mg/L, which is far below the concentrations recorded in our clinical case.

Plasma levels generally peak 2–4 hours after therapeutic dose or overdose, as citalopram is well absorbed (Friberg et al., 2005). A simulation of the kinetics of citalopram concentrations over time showed a two-compartment open model with Bayesian fitting (Jimmink et al., 2008). Although toxicokinetic parameters are always difficult to assess without early samples, we extrapolated, from the patient history, that our first concentration corresponded to the elimination phase of this two-compartmental open model, as it was obtained at least 24 hours after admission. Calculated in Figure 1, the elimination half-life time was 47.1 hours. This slightly longer half-life time may reflect the patient’s individual physiology and the elimination half-life time may reflect the poor clinical conditions of this particular patient. However, this value was slightly higher than those previously reported (30–36 hours) (Jimmink et al., 2008). The prolonged lag times from citalopram exposure to emergency department arrival could be associated with this delayed onset of QT prolongation, as didemethylated metabolite didemethylcitalopram (DDCT), which has a roughly 3-fold longer half-life than citalopram, is also involved in cardiac toxicity (Friberg et al., 2005). Effectively, if the parent compound is metabolized into active metabolites, no relation exists between drug concentrations and symptoms. So, the dose-dependent QT-interval prolongation occurs with DDCT alone or combined with citalopram. Because DDCT seems to be only a minor metabolite (<10%) in humans, it appears that cardiotoxicity is due only to the amount of DDCT present in overdose and not the percentage (Jimmink et al., 2008). DDCT amount may be high, given the high citalopram values observed in our case, but, unfortunately, DDCT was not assayed here.

The long heart-rate–corrected QT intervals were related to the high citalopram concentrations (Friberg et al., 2005) (Table 1; Figure 2). The probability of having a QT interval higher than 447 milliseconds at RR of 760 milliseconds has been shown to be maximal at 10 hours after overdose (Friberg et al., 2005). Our results are far from these last researchers, but in line with Tarabar et al. (2008), who presented more delayed deleterious clinical signs at over 33 hours after ingestion, although their plasma citalopram concentration was 0.477 mg/L (i.e., far below our values). A QTc prolongation without TdR is, nevertheless, presented in 26 citalopram overdoses (200–4,960 mg ingested) (Jimmink et al., 2008). However, it always lacks one element, which, alone, could quantify the lengthening of the QT interval that could be attributed to citalopram, is a measure of the QT interval before starting treatment.

Concerning the precise relationship between QT prolongation and increased risk of TdP, there is no well-established ECG value for assessing the risk of TdP (Isbister et al., 2006). These researchers propose the use of a nomogram to determine the at-risk QT interval. Accordingly, the two QT heart-rate–corrected values of our patient are both above the at-risk threshold, suggesting a higher risk for TdP. In addition, it must be emphasized that the association with alcohol and zopiclone may worsen toxicity, justifying the need to include all clinical and biological data to obtain reliable indicators.

The long half-life elimination time of citalopram prompted us to place the patient under monitoring with seizure precautions. The uncertainties on time of ingestion and ingested amount would require a Bayesian approach to estimate the exposure-effect relationships to improve
therpay. Thereby, the amount ingested would be better estimated by extrapolating plasma concentrations and fitting the population model to the patient’s data. Using this approach, the researchers suggest using a single dose of activated charcoal to treat citalopram overdose (Friberg et al., 2005). Ideally, activated charcoal should be administered 4 hours after citalopram overdose (Isbister et al., 2006). However, it has been shown that there is always a benefit in treating the patient with activated charcoal, even later than 4 hours (Cuenca et al., 2004).

Some researchers reported that the cardiac toxicities noted in citalopram overdose were similar to tricyclic antidepressants, and suggest that citalopram may have anti- as well as proarrhythmic properties due to impairment of atrio- or intraventricular conduction and shortening of repolarization (Pacher et al., 1999). Thus, the sodium-bicarbonate administration that was initially made in our case to treat the acidosis may also have normalized QRS, QTc, and left-bundle branch and avoided a fatal issue (Bruculleri et al., 2005).

<table>
<thead>
<tr>
<th>Citalopram concentrations (mg/L)</th>
<th>22/12 11 hours</th>
<th>22/12 18 hours</th>
<th>23/12 8 hours</th>
<th>24/12 8 hours</th>
<th>24/12 20 hours</th>
<th>25/12 8 hours</th>
<th>27/12 8 hours</th>
<th>30/12 8 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>N.A.</td>
<td>5.88</td>
<td>2.42</td>
<td>2.40</td>
<td>2.52</td>
<td>2.10</td>
<td>0.94</td>
<td>0.34</td>
<td></td>
</tr>
</tbody>
</table>

| Heart rate (bpm)                  | 100            | 113            | 75            | 140           | N.A.          | N.A.          | N.A.          |

| QTm (seconds)                     | 0.52           | 0.44           | 0.60          | 0.42          | N.A.          | N.A.          | N.A.          |

| QTc (seconds)                     | 0.67           | 0.62           | 0.67          | 0.64          | N.A.          | N.A.          | N.A.          |

N.A., not assessed.

Figure 2. Electrocardiogram of the patient one day after ICU admission (December 23, 8 hours) (25 mm/sec), showing increase of QT interval (0.67 seconds).
This observation is particularly interesting, due to the association of citalopram plasma levels monitoring with major cardiac events. Accordingly, clinicians prescribing SSRIs need to be aware that it is important to screen patients with an ECG, especially if they suffer from acquired or congenital long QT intervals (Pacher et al., 1999), and it may be recommend the collection of serial plasma samples to have a pharmacokinetic-pharmacodynamic approach and improve the management of such overdoses (Megarbane et al., 2008). Because of the citalopram high half-life elimination time, longer monitoring may be warranted, if patients present any other concomitant comorbidity.

Declaration of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the article.

References


