

Correlation of QTc Interval Prolongation and Serum Level of Citalopram after Intoxication – A Case Report

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Abstract

Citalopram (CIT) is a widely used antidepressant which acts by a selective serotonin reuptake inhibition. It is considered to be safer than tricyclic antidepressants at therapeutic levels, but also with respect to intoxications. We report the case of a 46-year-old woman, who ingested in suicidal intention 1400 mg CIT. During the following inpatient treatment repeatedly ECGs and determinations of the serum level of CIT were performed. Initially the patient's serum level of CIT was 1231 ng/mL and QTc interval was 541.60 ms. It took 12 days until the serum level of CIT fell below the upper threshold of the recommended therapeutic range (130 ng/mL). The QTc interval on the sixth day after the intoxication for the first time was below 500 ms. The QTc interval correlated significantly with the serum level of CIT after intoxication ($r=0.943$; $p<0.005$). Although CIT is estimated as a safe antidepressant regarding serious adverse effects, toxic doses can lead to potentially hazardous ECG changes which according to our findings correlate strongly with the serum level of the drug.

Key words

citalopram · QTc · intoxication · serum level · therapeutic drug monitoring

Introduction

Citalopram (CIT) belongs to the group of selective serotonin reuptake inhibitors (SSRI), which are widely used antidepressant drugs. Until the development of Escitalopram it was the most selective serotonin reuptake inhibitor. CIT has an elimination half-life of approximately 33 h and is metabolized in the liver by CYP2C19, CYP3A4 and CYP2D6 to desmethylcitalopram and didesmethylcitalopram, which have negligible clinical effects [1]. Although SSRIs generally are considered to be safer than other antidepressant drugs like tricyclics or monoamine oxidase (MAO) inhibitors with respect to intoxications [2–6], CIT together with its S-enantiomer escitalopram represents one of five compounds which cover approximately 80% of all antidepressants found in suicides [2].

Electrocardiographic changes like QRS changes and QT interval prolongation in patients with CIT overdose are well known [7–11] and cases of fatal overdose with CIT have already been described [12]. It is suggested however, that an overdose of CIT is not associated with serious complications in the majority of cases [6,13], and the most frequent severe symptom in cases of CIT overdose are seizures [14,15]. While a prolongation of QT interval dependent on the ingested daily dose has been reported in the literature [7,9] and a modelling of QT interval prolongation with a

linear dependence of heart rate corrected QT interval on the predicted CIT level has been proposed [16], a direct correlation between serum level of CIT and prolongation of the QT interval has not yet been observed. The present case report of a CIT intoxication with repeated serum level determinations of CIT and multiple ECG recordings over the course of 23 days after ingestion of the drug is the first report of such a direct correlation.

Methods

We report the case of a 46-year-old woman suffering from major depression without a history of suicide attempts, who had ingested 70 tablets of CIT 20 mg and 10 tablets of opipramol 50 mg in suicidal intention. About 16 h after ingestion the patient was admitted to the University Hospital of Würzburg. She was moderately agitated, but alert and fully orientated. Comprehension, memory and mental focusing were slightly reduced. There were no neurological symptoms observable except for an ataxia. Vital signs were stable with a blood pressure of 145/90 mmHg and a heart rate of 83/min. Further medical examination revealed no clinical pathological findings with the exception of isolated pathological laboratory tests. Magnesium was initially 0.6 mmol/L (normal range 0.7–1.05 mmol/L) and normalized after substitution with values in the lower normal range. Especially serum potassium was always within normal range as was the case with sodium, calcium, phosphate and chloride. Creatinine, glomerular filtration rate, urea, uric acid, choline esterase, bilirubin, alanine aminotransferase, glutamate dehydrogenase, alkaline phosphatase, lactate dehydrogenase, amylase and lipase also were within normal ranges. γ -Glutamyl transferase was until day 14 slightly above the upper threshold (>40 U/L) with values up to 61 U/L at day 2. Aspartate aminotransferase also was above the upper threshold (>35 U/L) with values up to 42 U/L and normalized at day 2. Creatinine kinase at the beginning was elevated with 386 U/L (>170 U/L) and normalized at day 12. Moreover, the patient in the beginning had a slight anaemia with a haemoglobin value of 11.1 g/dL and erythrocyte count of 3.51 million per μ L.

The body weight was 55 kg. The patient was monitored on an intensive care unit over 9 days. Over a time period of 23 days ECG recordings and determinations of the serum level of CIT were performed repeatedly in the course of clinical routine with the patient's informed consent.

The serum level of CIT was determined by an isocratic reversed phase high-performance liquid chromatography (HPLC) method with fluorescence detection in the TDM laboratory of the Psychiatric University Hospital of Würzburg. Unfortunately, the determination of desmethylcitalopram was not possible, as there is no established method in our laboratory. The laboratory participates in an external quality control program (Cardiff Bioanalytical Services, The Cardiff Medic Center, Cardiff, UK) with control samples analyzed monthly. The quality control program was operated without reject.

Results

The serum level of CIT measured for the first time about 29 h after ingestion of 1400 mg of the drug was 1231 ng/mL. This represents a 10-fold increase with respect to the recommended therapeutic range of 50–130 ng/mL [17]. The serum level of CIT

decreased only slowly and was at day 23 after ingestion of the drug no longer detectable (● Fig. 1). The calculated elimination half-life of CIT after this overdose was about 80 h. Because of the rather slow decrease of CIT serum level a determination of the CYP2D6-genotype was performed, in which CYP2D6*3, -*4, -*5, -*6, -*9, -*10 and -*41 were negative and therefore no indications of a genetically determined poor metabolism could be found.

Immediately after admission to the hospital about 16 h after ingestion of CIT the first ECG was performed, in which the QT interval in lead II was 440 ms. This QT interval was frequency-corrected applying Bazett's formula resulting in a QTc interval of 541.6 ms. Since a QTc interval of 500 ms is usually considered to represent a critical limit above which there is an increased risk of serious complications like malignant tachyarrhythmia, this finding indicates a potentially hazardous ECG change. In the following 3 weeks repeated ECG recordings showed a slow but continuous decrease of QTc interval down to 430.3 ms at day 23 (● Fig. 2).

Within the total observation period of 23 days ECG was performed 8 times and the serum level of CIT was measured 11 times including a determination of both serum level and QTc interval within 24 h at 6 measuring times. In 5 cases the date for serum level determination and ECG was the same, in one case ECG

at the afternoon and determination of the serum level at the following morning were used to build a pair of values (● Table 1). Thus, altogether 6 pairs of values were considered for the calculation of a Spearman's rho correlation (● Fig. 3). The correlation between CIT serum level and QTc interval was statistically significant ($p < 0.005$) with a very high correlation coefficient of $r = 0.943$.

Discussion

▼ An association of ECG changes under CIT treatment with serum level of CIT was up to now investigated only by Friberg et al. [16]. In this study ECG was monitored after overdose events over up to 100 h and CIT level was predicted in a hypothetical effect compartment. It was shown that ECG changes after intoxication with CIT persist over several days and normalize parallel to the decrease of the serum level of CIT, however no direct correlation was determined. In our case report CIT serum levels and QTc interval were monitored over 3 weeks until complete elimination of the drug, in 6 cases with parallel determination within 24 h. Comparably to the findings of Pedersen et al. [18] who found a highly significant correlation between amitriptyline and nortriptyline levels and QTc intervals in 14 amitriptyline-intoxicated patients, our results for the first time could demonstrate a

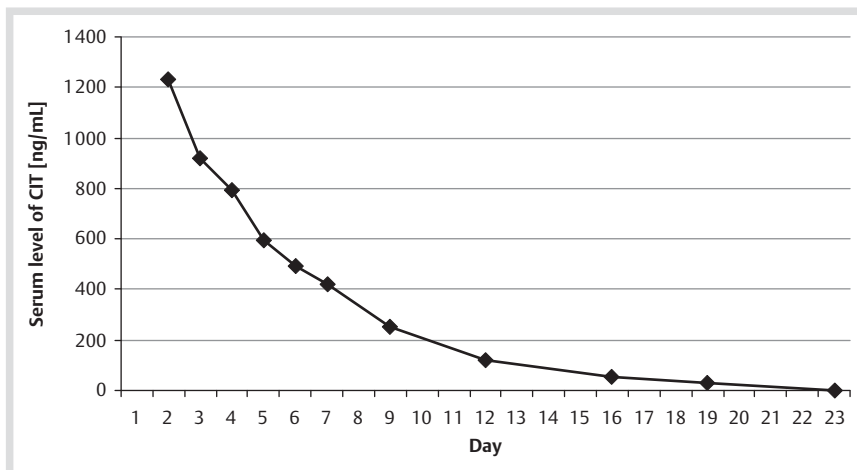


Fig. 1 Serum levels of citalopram from day 1 to day 23.

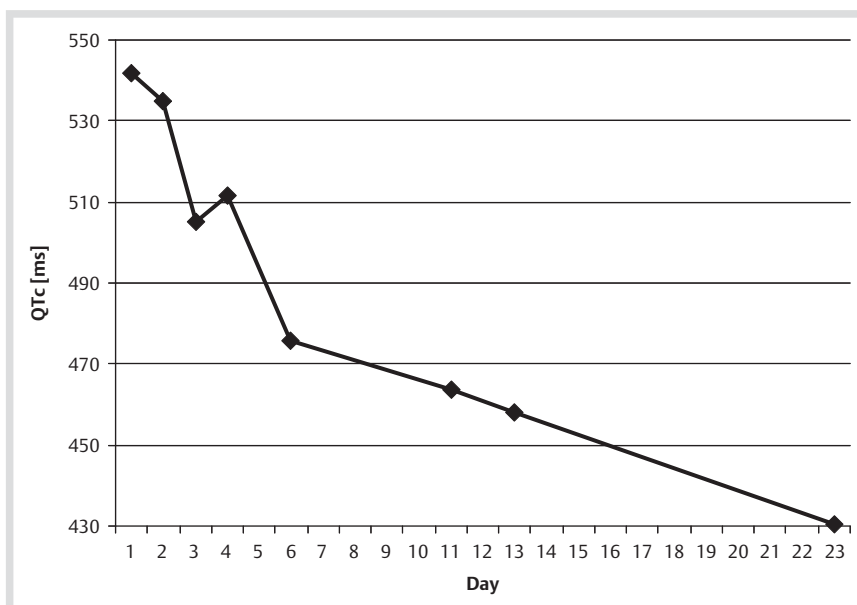


Fig. 2 QTc intervals from day 1 to day 23.

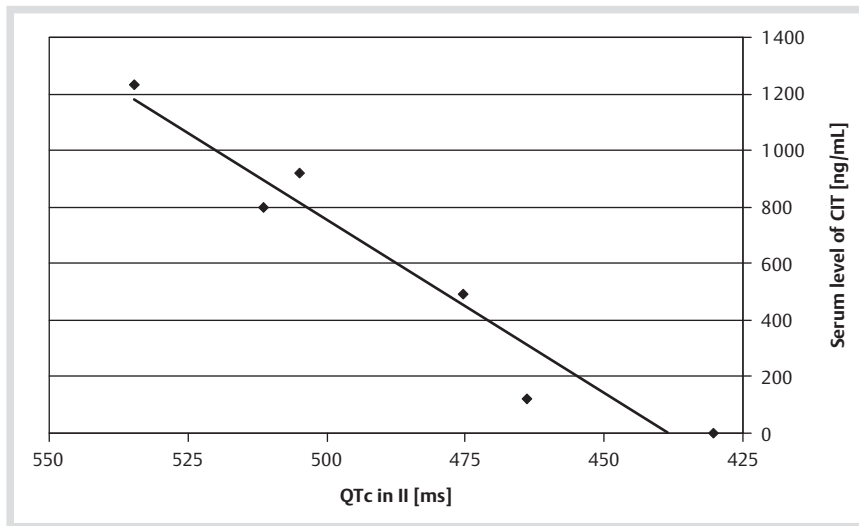


Fig. 3 Serum levels of citalopram and corresponding QTc intervals (n=6, Spearman rho $r=0.943$, $p<0.005$).

Table 1 Serum levels of CIT and QT intervals.

Day	Blood level	QT in II	RR dist in sec	QTc
1		440	0.66	541.60
2	1 231	460	0.74	534.74
3	922	460	0.83	504.92
4	796	440	0.74	511.49
5	592			
6	491	420	0.78	475.56
7	418			
9	252			
11		440	0.90	463.80
12	122			
13		420	0.84	458.26
16	55			
19	29			
23	0	380	0.78	430.27

strong correlation between the level of CIT and the duration of the QTc interval. The prolonged elimination half-life of CIT which we observed in our case is in congruence with results of Jimmink et al. [19], who reported that high levels of CIT lead to saturated metabolic pathways with the consequence of a reduced CIT metabolism.

Interpreting our findings, the parallel overdosing of the tricyclic antidepressant opipramol has to be considered. Its serum level could not be determined because a validated determination method was not available in our laboratory. Even if opipramol was overdosed to a far lesser degree than CIT (2.5-fold vs. 35-fold), it could not be ruled out that it might have contributed to the QTc interval prolongation, as it can also lead to QTc interval prolongation [20]. This possibility however, does not invalidate the observed direct correlation between CIT serum level and QTc interval prolongation.

The present case report confirms literature data [19,21], that despite a high safety of SSRIs in comparison to tricyclic antidepressants or irreversible MAO-inhibitors, CIT may cause serious ECG abnormalities when applied in overdose. In particular, CIT overdose is associated with significant QT prolongation, making a close monitoring of ECG necessary [10]. After intake of highly supratherapeutic quantities greater than 1000mg it is recommended to perform cardiac monitoring at least for the first 13h and additionally to administer single-dose activated charcoal if doses of more than 600mg were ingested [22]. Whereas it is

assumed by Personne et al. [9] that ECG abnormalities are caused only if more than 600mg of CIT are ingested, according to a case report of Catalano et al. [7] an overdose of 400mg already led to a QTc prolongation (457ms) in a young woman without a history of cardiac pathology. The QTc prolongation was detected 13h after ingestion and occurred despite treatment with activated charcoal and gastric lavage. Normalization (353ms) was reached 21h later. In contrast, a long-term CIT treatment with doses above the recommended upper level of 60mg/day, but lower than the very high doses reported in cases of an acute intoxication, had no impact on the QTc interval, and the only effect of CIT on the ECG was a small reduction of heart rate without clinical relevance [23]. The pathophysiological mediators of QTc prolongation by CIT can be derived from a blockade of HERG channel [24] and a small quinidine-like effect of CIT, which causes a level-dependent inhibition of sodium current and an inhibition of L-type calcium channel [25–27].

In summary, the present case report suggests a close relationship between the serum level of the antidepressant CIT and QTc interval prolongation as a highly relevant serious adverse reaction after intoxication. Therefore, it is recommendable to treat patients intoxicated with CIT on an intensive care unit and to monitor not only ECG recordings but to control also the serum level of the drug in the course of the intoxication.

Conflict of Interest



The authors declare no conflict of interests.

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