Corrected QT interval prolongation after an overdose of escitalopram, morphine, oxycodone, zopiclone and benzodiazepines

Adrian Baranchuk MD¹, Christopher S Simpson MD FRCPC¹, Michelle Methot R Ph BScPharm², Kara Gibson MD³, David Strum MD⁴

A Baranchuk, CS Simpson, M Methot, K Gibson, D Strum. Corrected QT interval prolongation after an overdose of escitalopram, morphine, oxycodone, zopiclone and benzodiazepines. *Can J Cardiol* 2008;24(7):e38-e40.

Escitalopram is the recently marketed S-enantiomer of the widely used antidepressant citalopram. Data from intentional overexposure to this medication are limited. Twelve-lead electrocardiogram (ECG) effects from racemic citalopram have been described; however, the present report is the first, to the best of the authors' knowledge, that describes all the reported abnormalities in a single patient receiving escitalopram. A 52-year-old man with a history of depression treated with escitalopram 10 mg/day, extended-release morphine 30 mg/day and zopiclone 15 mg/day was found unconscious at his home. He was known to have attempted suicide three weeks previously. Partially emptied bottles of escitalopram, morphine, oxycodone, zopiclone, lorazepam and diazepam were found close to the patient. He was transferred to the emergency department, where airway management and other supportive care were initiated. The patient was transferred to the intensive care unit. The initial 12-lead ECG demonstrated junctional rhythm at 48 beats/min, a wide complex escape (145 ms) with right bundle branch morphology and a prolonged corrected QT interval at 650 ms. Cardiac monitoring was undertaken. No ventricular arrhythmias or torsade de pointes were detected. No specific treatment for shortening the QT was implemented. Another 12-lead ECG performed 48 h later demonstrated sinus tachycardia with a normal corrected QT, normal PR interval and normal QRS duration. The effects of the overdose of escitalopram on the ECG and its interactions with other drugs are reviewed.

Key Words: Escitalopram; Cardiac arrhythmia; Overdose

A 52-year-old man with a history of depression treated with escitalopram 10 mg/day, extended-release morphine 30 mg/day and zopiclone 15 mg/day was found unconscious at home. His medical history was significant for severe depression, with a suicide attempt three weeks before this admission.

His medical history also included a recent anterior cervical decompression for spinal stenosis (three months previously), hypertension (treated with ramipril 5 mg/day), asthma, reflux disease and possible sleep apnea.

Partially emptied bottles of escitalopram, morphine, oxycodone, zopiclone, lorazepam and diazepam were found close to the patient. A list of drugs he was prescribed is summarized in Table 1.

The patient was transferred to the emergency department (ED), where airway management and other supportive measures were initiated. The patient was then transferred to the intensive care unit. A physical examination revealed an afebrile man with Glasgow Coma

Correction d'un allongement de l'intervalle QT consécutif à une surdose d'escitalopram, de morphine, d'oxycodone, de zopiclone et de benzodiazépines

L'escitalopram est l'énantiomère-S, récemment mis sur le marché, du citalopram, antidépresseur souvent utilisé. Il existe peu de données sur la prise excessive et volontaire du médicament. Certes, l'on a déjà décrit les effets du citalopram racémique sur le tracé électrocardiographique à 12 dériviations mais, à la connaissance de l'auteur, c'est la première fois que l'on fait état de toutes les anomalies relevées chez un même patient prenant de l'escitalopram. Un homme âgé de 52 ans, ayant des antécédents de dépression traitée par l'escitalopram, 10 mg/jour; la morphine à libération prolongée, 30 mg/jour; et la zopiclone, 15 mg/jour, a été trouvé inconscient chez lui. Il avait commis une tentative de suicide trois semaines auparavant. Des fioles à moitié vides d'escitalopram, de morphine, d'oxycodone, de zopiclone, de lorazépam et de diazépam ont été trouvées près de lui. Le patient a été transporté au service d'urgence où l'on a entrepris des mesures de rétablissement de la perméabilité des voies aériennes et d'autres soins de soutien. Le patient a été muté au service des soins intensifs. Le premier électrocardiogramme (ECG) à 12 dériviations a montré un rythme jonctionnel avec une fréquence de 48 battements/minute, un échappement à complexe large (145 ms) présentant une morphologie de la branche droite du faisceau de His et un allongement corrigé de l'intervalle QT de 650 ms. La surveillance du rythme cardiaque n'a pas révélé d'arythmie ventriculaire ou de torsades de pointe. Aucun traitement particulier visant le raccourcissement de l'intervalle QT n'a été entrepris. Un autre ECG à 12 dériviations, effectué 48 h plus tard, a montré de la tachycardie sinusale; un intervalle QT normal, corrigé; un intervalle PR normal et un complexe QRS d'une durée normale. Il sera donc question, dans le présent article, des effets d'une surdose d'escitalopram sur l'ECG et de ses interactions avec d'autres médicaments.

Scale score of 3, requiring mechanical ventilation, and a blood pressure of 80/60 mmHg, heart rate 57 beats/min and oxygen saturation 89% (before intubation at the ED). Initial laboratory investigations revealed a hemoglobin level of 153 g/L, a white blood cell count of $9.2 \times 10^9/L$, platelets of $270 \times 10^9/L$, potassium level of 7.0 mmol/L, carbon dioxide 15 mmol/L, creatinine level of 311 $\mu\text{mol/L}$, urea level of 8.6 mmol/L, magnesium level of 0.83 mmol/L and a calcium level of 1.94 mmol/L. Arterial blood gases revealed the following: pH of 7.18, oxygen concentration of 293 mmHg, carbon dioxide partial pressure of 32 mmHg and a bicarbonate partial pressure of 11.5 mmol/L.

The international normalized ratio was 1.5 and the partial thromboplastin time was 42 s. The troponin T level was 0.328 $\mu\text{g/L}$ and the creatine kinase level was 2534 U/L.

A urine toxicology screen using the Triage 8 system (Biosite, USA) was positive for opioids and benzodiazepines. Confirmatory urinalysis using the REMEDI HS Drug Profiling System (Bio-Rad, USA)

¹Arrhythmia Service; ²Cardiac Care Program; ³Department of Anaesthesiology; ⁴Intensive Care Unit, Kingston General Hospital, Queen's University, Kingston, Ontario

Correspondence: Dr Adrian Baranchuk, Cardiac Electrophysiology and Pacing, Kingston General Hospital, Queen's University, Kingston, Ontario

K7L 2V7. Telephone 613-549-6666 ext 3801, fax 613-548-1387, e-mail barancha@kgk.kari.net

Received for publication August 25, 2006. Accepted October 16, 2006

TABLE 1
Drugs found close to the patient

Drugs found with patient	Maximum possible ingestion
Escitalopram 10 mg tablets	140 mg
Diazepam 10 mg tablets	1800 mg
Zopiclone 7.5 mg tablets	187.5 mg
Lorazepam 1 mg tablets	30 mg
Morphine, extended-release 100 mg	9500 mg
Morphine, extended-release 30 mg	2640 mg
Morphine, extended-release 15 mg	420 mg
Acetaminophen 325 mg and oxycodone 5 mg	150 tablets missing; however, serum acetaminophen level was not elevated, so unlikely that this was ingested
Citalopram 40 mg	Not found with patient; dispensed 90 tablets year before event – possible that patient ingested
Oxycodone, extended-release 10 mg	Not found with patient; dispensed 60 tablets year before event – possible explanation for oxycodone in urine and no elevated acetaminophen in blood
Oxycodone, extended-release 20 mg	Not found with patient; dispensed 60 tablets year before event – possible explanation for oxycodone in urine and no elevated acetaminophen in blood

Figure 1) Electrocardiogram on admission. QTc Corrected QT interval

identified the presence of racemic citalopram and metabolites, oxycodone and metabolites, and morphine. A quantitative analysis of urine and serum concentrations of each drug was not performed. It was estimated that the ingestion occurred more than 12 h before arrival and, thus, activated charcoal was not used.

The chest x-ray was unremarkable and a two-dimensional echocardiogram showed normal left ventricular function.

The initial 12-lead electrocardiogram (ECG) obtained in the intensive cardiac care unit (Figure 1) showed junctional rhythm at 48 beats/min, a wide complex escape (145 ms) with right bundle branch morphology and a prolonged corrected QT interval (QTc) of 650 ms.

No specific treatment was used for the QTc prolongation. Neither torsade de pointes nor other ventricular arrhythmias were detected during continuous ECG monitoring. Hyperkalemia was treated in the usual way with calcium gluconate, insulin and sodium polystyrene sulphate.

A second laboratory investigation was performed 4 h later, showing normalization of arterial blood gases and a reduction of serum potassium to 4.9 mmol/L. After 48 h, the patient remained intubated with the same Glasgow Coma Scale score.

The next 12-lead ECG (performed 48 h later) showed sinus tachycardia at 102 beats/min, a PR interval of 140 ms, a QRS complex of 80 ms and a QTc of 416 ms (Figure 2).

A resting ECG was performed daily for the next week until the patient was extubated. No further changes were found.

DISCUSSION

The present case describes ECG changes seen as the result of an overdose of several different central nervous system depressors, including a

Figure 2) Electrocardiogram 48 h after admission. QTc Corrected QT interval

selective serotonin reuptake inhibitor commonly used for depression treatment.

Escitalopram is the S-enantiomer of citalopram. Citalopram is a racemic mixture of R- and S-enantiomers. The S-enantiomer is thought to be responsible for the antidepressant activity of citalopram and the R-enantiomer may possibly decrease its activity. Both drugs are selective serotonin reuptake inhibitors. Escitalopram is considered to be twice as potent as racemic citalopram. Escitalopram has a half-life of approximately 27 h to 32 h (1).

To our knowledge, there are only two published reports on overdose of escitalopram. In one report (2), a young woman ingested 190 mg and arrived to the ED with a confusion syndrome. Minor QTc prolongation was observed. After gastric lavage, symptoms disappeared and QTc normalized. The second report (3) was a chart review of isolated escitalopram ingestions at a poison control centre. Twenty-eight overdoses of escitalopram (mean doses 5 mg to 300 mg) in patients ranging from two to 75 years of age were described. No ECG abnormalities were found, and all patients recovered without sequelae.

Because there are few data on escitalopram overdose, it is of interest to note the consequences of racemic citalopram overdose, because they may be similar. The safety of racemic citalopram in overdose remains controversial. Reports of intoxication with racemic citalopram (4-7) have suggested that overdoses above 600 mg may be fatal due to the consequences of severe QTc prolongation (usually ventricular arrhythmias); however, lower doses may produce nausea, dry mouth, tremors, dizziness, tachycardia, somnolence and minor ECG changes.

Reports (6,7) also indicate that high doses of racemic citalopram may produce significant ECG alterations, including QTc prolongation (very rarely with torsade de pointes), widening of the QRS complex and junctional rhythm with sinus arrest and/or atrioventricular dissociation.

Guidelines for the management of QT prolongation after racemic citalopram overdose have been developed using a pharmacokinetic-pharmacodynamic model that predicts the timecourse of QT prolongation (8). The recommendations include decontamination with single-dose-activated charcoal for doses of 600 mg or higher, and cardiac monitoring at least for the first 13 h postingestion is recommended for doses greater than 1000 mg.

The molecular mechanism for QTc prolongation is inhibition of the human ether-a-go-go-related gene channel current that may reduce repolarizing currents. This can result in ventricular action potential prolongation and, consequently, QTc prolongation (9). An attenuation of this effect is related to a simultaneous inhibition of cardiac L-type calcium current $I_{Ca,L}$, which creates an equilibrium between both effects over the action potential.

The subject of the present case report had the additional complexity of having ingested multiple drugs. There are no reports of cardiac conduction abnormalities and QTc interval changes with morphine, zopiclone, oxycodone or benzodiazepines on their own (10). There may be an additive effect at the central nervous system level; however, no pharmacokinetic drug interactions were found among escitalopram, morphine, oxycodone, zopiclone and benzodiazepines.

The present patient developed all the ECG alterations that were previously described for racemic citalopram overdose. We calculated that our patient could have ingested as much as 140 mg of escitalopram from his current prescription and possibly some racemic citalopram from an old prescription. The urine screen identified citalopram and citalopram metabolites but was unable to differentiate between the presence of citalopram and escitalopram.

REFERENCES

1. Murdoch D, Keam SJ. Escitalopram: A review of its use in the management of major depressive disorder. *Drugs* 2005;65:2379-404.
2. Yuksel FV, Tuzer V, Goka E. Escitalopram intoxication. *European Psychiatry* 2005;20:82.
3. LoVecchio F, Watts D, Winchell J, Knight J, McDowell T. Outcomes after supratherapeutic escitalopram ingestions. *J Emerg Med* 2006;30:17-9.
4. Odar-Cederlöf I, Hjelmström P, Jersenius I, Andersson M, Rasmanis G, Bergman U. [Citalopram is not safe from the cardiac point of view – SSRI preparations can cause prolonged QTc time.] *Läkartidningen* 2006;103:1112-4.
5. Meuleman C, Jourdain P, Bellowini M, et al. [Citalopram and torsades de pointes. A case report.] *Arch Mal Coeur Vaiss* 2001;94:1021-4.
6. Catalano G, Catalano MC, Epstein MA, Tsambiras PE. QTc interval prolongation associated with citalopram overdose: A case report and literature review. *Clin Neuropharmacol* 2001;24:158-62.
7. Oström M, Eriksson A, Thorson J, Spigset O. Fatal overdose with citalopram. *Lancet* 1996;348:339-40.
8. Isbister GK, Friberg LE, Duffull SB. Application of pharmacokinetic-pharmacodynamic modelling in management of QT abnormalities after citalopram overdose. *Intensive Care Med* 2006;32:1060-5.
9. Witchel HJ, Pabbathi VK, Hofmann G, Paul AA, Hancox JC. Inhibitory actions of the selective serotonin re-uptake inhibitor citalopram on HERG and ventricular L-type calcium currents. *FEBS Lett* 2002;512:59-66.
10. Goodnick PJ, Jerry J, Parra F. Psychotropic drugs and the ECG: Focus on the QTc interval. *Expert Opin Pharmacother* 2002;3:479-98.
11. Surawicz B. The interrelationship of electrolyte abnormalities and arrhythmias. In: Mandel WJ, ed. *Cardiac Arrhythmias: Their Mechanisms, Diagnosis, and Management*. Philadelphia: JB Lippincott Company, 1980:83-106.
12. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239-45.

Finally, hyperkalemia might also have played a role in the ECG manifestations seen in the present case. Usually, when plasma potassium concentrations become markedly elevated, widening of the QRS occurs. However, a left bundle branch block-like pattern, rather than right bundle branch block, would be expected (11). In addition, with this ECG, the morphology of the T wave was not characteristic of the changes ordinarily seen with hyperkalemia. Sinoatrial block may be explained by hyperkalemia, but in the absence of other typical manifestations (steep, narrow and tall T wave), it is more likely that the QT prolongation is due to escitalopram intoxication. Scoring according to the Naranjo probability scale (12) revealed a possible relationship between escitalopram and QT prolongation.

There are some limitations that must be acknowledged. First, we did not obtain urine or serum concentrations of the ingested drugs; thus, levels were unknown. Second, it was not known whether the patient ingested escitalopram or a combination of escitalopram and racemic citalopram.

CONCLUSION

Escitalopram, a selective serotonin reuptake inhibitor commonly used for depression, may affect cardiac repolarization when ingested in supratherapeutic quantities. Alterations seen on the ECG with racemic citalopram overdose include sinus arrest, widening of the QRS interval, QTc interval prolongation and, less frequently, malignant ventricular arrhythmias. Those findings may also be present with escitalopram intoxication. Cardiac monitoring is recommended for high dose ingestion or for unknown dose ingestion along with ECG manifestations of potential intoxication.