Clinical and ECG Effects of Escitalopram Overdose

Freek van Gorp
Ian M. Whyte, MBBS, FRACP, FRCPE
Geoffrey K. Isbister, MD, BSc, FACEM

From the Department of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands (van Gorp); the Department of Clinical Toxicology and Pharmacology, Calvary Mater Newcastle, Newcastle, Australia (van Gorp, Whyte, Isbister); the Discipline of Clinical Pharmacology, Faculty of Health, University of Newcastle (Whyte, Isbister); and the Menzies School of Health Research, Charles Darwin University, Darwin, Australia (Isbister).

Study objective: We investigate the clinical effects of escitalopram overdose and determine the risk of QT prolongation and serotonin toxicity.

Methods: A review of escitalopram overdoses to a clinical toxicology unit was undertaken. Patient demographics, details of the ingestion, clinical effects, including evidence of serotonin toxicity, complications (arrhythmias and seizures), ICU admission, and length of stay were obtained. QT and QRS intervals were manually measured on ECGs by using a standardized approach. In a subgroup of 34 prospectively recruited patients, escitalopram was detected in blood from 33 patients. Medians and interquartile ranges (IQR) were reported, and QT versus pulse rate was plotted on a QT nomogram to investigate QT prolongation.

Results: Median ingested dose in the 79 presentations was 140 mg (IQR 75 to 260 mg; range 20 to 560 mg), and escitalopram was the only drug ingested or all coingested drugs were nontoxic in 46 cases. Median length of stay for patients receiving clinically important coingestants was 19 hours (IQR 9 to 33 hours) compared with that of patients receiving escitalopram alone (median 12 hours; IQR 7 to 19 hours). Serotonin toxicity occurred in 7 of the 46 escitalopram-alone ingestions (15%) but in only 1 of the 33 patients coingesting other medications. Common features were inducible clonus and hyperreflexia. Central nervous system depression and ICU admission were rare in escitalopram-alone overdoses compared with those in cases with sedative coingestants. Bradycardia (pulse rate <60 beats/min) occurred in 11 cases (14%) and an abnormal QT–HR pair in 11 (14%), which was associated with normal or slow pulse rates. There were no deaths, seizures, or arrhythmias.

Conclusion: Major manifestations of escitalopram overdose were serotonin toxicity, QT prolongation, and bradycardia. The study suggests a potential for cardiac arrhythmias in escitalopram overdose. [Ann Emerg Med. 2009;54:404-408.]

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INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) have been used for more than a decade for the treatment of depression and anxiety disorders. One advantage of this group of antidepressants is they appear to be relatively safe in overdose compared with the older tricyclic antidepressants.[1] The majority of SSRI overdoses cause minor effects characterized by mild to moderate serotonin toxicity and occasionally seizures in large overdoses. However, QT-interval prolongation and arrhythmias have been reported, mainly with citalopram[2] and more recently in case reports of escitalopram toxicity.[3,4]

Escitalopram is the S-enantiomer of citalopram and has been marketed because it is a more potent inhibitor of the serotonin transporter and likely accounts for the majority of the inhibitory effect in racemic citalopram.[5,6] A review of nonclinical and clinical studies of escitalopram versus citalopram shows that on a dose-equivalent basis, escitalopram has greater efficacy and onset of action compared with citalopram. This appears to be due to an inhibitory effect of the R-isomer on escitalopram, possibly because of an allosteric interaction at the serotonin transporter.[7] It is therefore likely that citalopram and escitalopram will cause differing effects in overdose.

During the last 5 years, there has been an increase in the prescription of escitalopram and an associated increase in overdoses. There are few published reports of the effects of escitalopram overdose,[3,4,8-11] and it is unclear whether escitalopram and citalopram are similar in overdose. Serotonin toxicity may be more common with escitalopram than with citalopram or other SSRIs because of its increased serotonergic potency. A single case of prolonged and severe serotonin toxicity has been previously reported with escitalopram overdose,[9] but there is no information on the

Editor's Capsule Summary

What is already known on this topic

Escitalopram, a serotonin reuptake inhibitor (SSRI), is the S-enantiomer of citalopram. Little is known about its toxicity.

What question this study addressed

The toxicity profile of escitalopram was studied in 79 consecutive patients admitted to a clinical toxicology unit in Australia.

What this study adds to our knowledge

Major manifestations of overdose were serotonin toxicity, QT prolongation, and bradycardia. The risk of cardiac arrhythmias according to QT intervals appear similar to that with citalopram. Coingestion of a sedative drug was associated with an increased rate of admission to the ICU and longer length of stay.

How this might change clinical practice

Patients with escitalopram overdose should receive care appropriate for SSRI overdoses, but they should also have monitoring of the QT interval.

frequency and severity of serotonin toxicity in escitalopram overdose.

There is limited information on the risk of QT prolongation and cardiac arrhythmias with escitalopram. We have previously shown that QT prolongation and torsades de pointes are associated with citalopram overdose,[12,13] but it is unclear whether escitalopram has a similar association with QT prolongation. Three cases of QT prolongation with escitalopram overdose have been reported,[3,4,8] and in a retrospective review of escitalopram overdoses from a regional poison center, ECG changes were found, but the specific ECG abnormalities were not reported.[11] No animal studies on the effect of the citalopram enantiomers on the QT interval have been reported, making it difficult to determine whether the QT abnormalities seen with citalopram are due to the S-enantiomer, R-enantiomer or both. It is therefore important to confirm that escitalopram poisoning causes QT prolongation in a larger series of cases and estimate the frequency of abnormal QT intervals.

The aim of the present study was to investigate the effects of escitalopram in overdose and determine the risk of QT prolongation, serotonin toxicity, and any other major clinical complications.

MATERIALS AND METHODS

Study Design and Setting

The study was a review of consecutive presentations of escitalopram overdose to a regional inpatient toxicology unit with a referral population of about 300,000 people. The unit is not a poison center, and all patients are examined and treated by an attending clinical toxicologist in the emergency department (ED) or the inpatient unit. For all toxicology presentations, predefined clinical and laboratory information is recorded in a relational database. The use of this database for research purposes has previously been exempted by the Human Research Ethics Committee as an audit, and separate ethics approval was obtained for prospective collection of clinical data, blood samples, and ECG results from a subgroup of patients.

Selection of Participants

All patients with a diagnosis of escitalopram overdose between October 2003 and September 2008 were identified in the database, and information on clinical effects was extracted. If available, ECGs were obtained from the medical record for each presentation. The history of drug ingestion is always confirmed prospectively on at least 2 occasions for all patients (history from ambulance officers, family, and friends; empty medication containers). For a subgroup of patients who were prospectively recruited to a pharmacokinetic study of drugs in overdose, multiple blood samples were collected and escitalopram was quantified by high-performance liquid chromatography.

Data Collection and Processing

The following data were extracted from the database: patient demographic characteristics (age, sex), details of the ingestion (estimated time of ingestion, dose ingested, coingested drugs), clinical effects (maximum and minimum pulse rate, systolic blood pressure and Glasgow Coma Scale [GCS] score during their hospital stay), evidence of serotonin toxicity (Hunter Serotonin Toxicity Criteria,[14] clonus, myoclonus, hyperreflexia, rigidity, temperature), complications (arrhythmias and seizures), and admission details (ICU admission, length of stay). Coingested drugs were classified as nontoxic (including alcohol alone), sedative, known effect on the QT interval, anticonvulsant, antidepressant, and major toxicity (ie, acetaminophen hepatotoxicity, cytotoxicity).

All 12-lead ECGs were read by using a standardized approach. QT intervals were measured from the beginning of the Q wave up to the point at which the T wave returned to baseline. QT intervals were measured in 6 leads (3 chest and 3 limb leads), and the median interval was calculated. Pulse rate was taken from the automated ECG readout and assumed to be an average measure of the RR for the ECG. QRS intervals were measured manually in all ECGs.

All patients with toxicology presentations at the hospital are treated entirely in the ED (60%), admitted to the toxicology inpatient ward (30%), or admitted to the ICU (10%). Toxicology patients are admitted to the ICU if they have a decreased level of consciousness (GCS score <9), require intubation and ventilation, require hemodynamic monitoring or circulatory support, or have other major organ dysfunction requiring dedicated nursing observation. While in the ED, all

Table 1. Clinical features, outcomes, and treatment of all cases of escitalopram overdose comparing escitalopram alone with patients with coingestants.*

	Escitalopram Alone† (n=46)		Escitalopram and Coingested Drugs (n=33)	
	No.	%	No.	%
Age, y, median (IQR)	28 (18–36)		34 (24–43)	
Sex, female	38	83	25	76
Dose ingested, mg, median (IQR)	140 (78–275)		140 (80–210)	
Tachycardia (pulse rate >100 beats/min)	19	41	14	42
Bradycardia (pulse rate <60 beats/min)	6	13	5	15
Hypotension (systolic BP <90 mm Hg)	2	4	6	18
GCS < 15	2	4	15	45
GCS score <9	0	0	2	6
ICU admission	2	4	5	15
Time to presentation, h, median (IQR)	2.0 (1.4–4.2)		1.8 (1.3–2.8)	
Length of stay, h, median (IQR)	12 (7–19)		21 (11–37)	
QT–HR pair at risk	4	9	7	21
Hunter Serotonin Toxicity Criteria	7	15	1	3

BP, Blood pressure.
*QT–HR pair "at risk" is defined as the absolute QT interval and pulse rate from the same ECG (QT–HR pair) which are above the at-risk line when the QT is plotted against the pulse rate on the QT nomogram, according to Chan et al.[20]
†The 46 escitalopram-alone overdose cases included some patients who ingested escitalopram alone and a nontoxic substance or drug.

toxicology patients have continuous telemetry. If they have prolonged QT on their ECG they are admitted to a telemetry bed for ongoing monitoring.

Primary Data Analysis

For descriptive statistics, medians and interquartile ranges (IQR) are reported. QT–HR pairs were plotted on a previously developed QT nomogram[15] and examined by visual inspection, including with and without coingested drugs that affect the QT interval.

RESULTS

There were 80 presentations for patients with escitalopram overdose during the study period. In one patient reporting a large overdose (750 mg), the blood concentrations were inappropriately low, and this case was excluded. The remaining 79 presentations involved 68 patients. One patient presented 4 times, one patient presented 3 times, and 6 patients presented twice. ECGs were available for 78 of these presentations. There were 46 presentations in which escitalopram was the only drug taken in overdose or all coingestants were classified as nontoxic; these cases comprise the escitalopram-alone overdose group. Blood samples were available for a subgroup of 34 patients, and escitalopram was quantified (median concentration 107.5 μg/L; range 12 to 520 μg/L).

The median age of the 79 patients was 30 years (IQR 22 to 40 years; range 15 to 59 years) and 63 were female patients (80%). Escitalopram-alone overdose presentations are compared with those with ingestion of escitalopram and other drugs (Table 1). The median ingested dose for all cases was 140 mg (IQR 75 to 260 mg; range 20 to 560 mg) and did not differ between escitalopram-alone overdoses and those with coingestants. The median length of stay for patients receiving clinically important coingestants was 19 hours (IQR 9 to 33 hours) and longer than for patients receiving escitalopram-alone overdoses (median 12 hours; IQR 7 to 19 hours). On 7 occasions, patients were admitted to the ICU, but in 5 of those instances, clinically important coingestants were received. There were no deaths, seizures, or arrhythmias documented in any patient.

Table 2. Serotonin toxicity in patients ingesting escitalopram alone and in patients coingesting other drugs.

	Escitalopram Alone* (n=46)		Escitalopram and Coingested Drugs (n=33)	
	No.	%	No.	%
Inducible clonus	12	26	3	9
Spontaneous clonus	2	4	0	
Hyperreflexia	21	46	9	27
Myoclonus	3	7	0	
Ocular clonus	2	4	2	6
Hunter Serotonin Toxicity Criteria	7	15	1	3
Temperature† (°C), median (range)	37.0 (36.6–37.3)		37.6	

*Includes some patients who ingested escitalopram alone and a non-toxic substance or drug.
†For patients fulfilling the Hunter Serotonin Toxicity Criteria.[14]

Serotonin toxicity occurred in 7 escitalopram-alone overdose patients (15%; Table 2) and in 1 patient ingesting escitalopram and coingestants (3%). All serotonergic features were more common in escitalopram-alone overdoses. The commonest serotonergic features were hyperreflexia in 21 (46%) and inducible clonus in 12 cases (26%). Severe serotonin toxicity

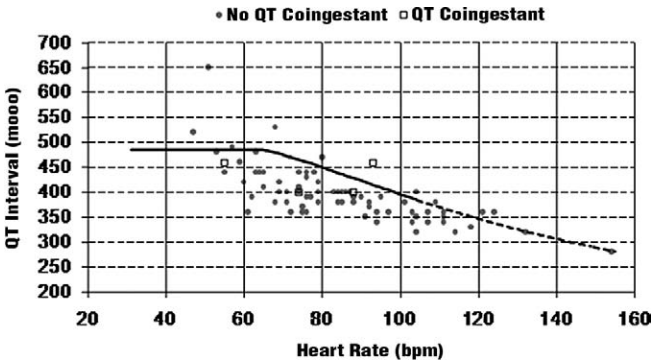

Figure. Plot of QT interval versus pulse rate for all escitalopram overdose presentations with 1 ECG per patient, also indicating patients not coingesting (grey solid circles) and those coingesting a drug known to affect the QT interval (black open squares). Note: QT–HR pairs above the nomogram line are associated with an increased risk of torsades de pointes according to a systematic review of cases of drug-induced torsades de pointes compared with a data set of (control) patients taking noncardiotoxic drugs (acetaminophen, diazepam, oxazepam, temazepam) in overdose.[15] In this study only 4 of 318 (1%) of the control patients had a QT–HR pair above the line.[15] The QT nomogram is available at http://star.ferntree.com as a PDF or Excel file.

characterized by a rapidly increasing temperature greater than 38.5°C (101.3°F) or rigidity resulting in respiratory compromise did not occur. Low GCS score and ICU admission were rare in escitalopram-only overdoses compared with those of patients ingesting coingestants, particularly sedative coingestants. In both patients with a GCS score less than 9, a sedative coingestant was taken (promethazine [250 mg] in one and olanzapine [600 mg] in the other).

Bradycardia (pulse rate <60 beats/min) occurred in 11 escitalopram patients (14%) and tachycardia (pulse rate >100 beats/min) in 33 (42%), which was not different between cases with coingestants or escitalopram alone (Table 1). In the 5 presentations with bradycardia in a patient coingesting other drugs, none of the coingested drugs are known to cause bradycardia. Hypotension (systolic blood pressure <90 mm Hg) occurred in 8 cases (10%), and only 2 of these were escitalopram-alone overdoses (Table 1). QT–HR pairs were plotted on the QT nomogram (Figure), and 11 were considered "at risk" (Table 3). One patient had an abnormal QT result on 2 different hospital presentations, and the remaining 9 were different patients. The median maximum QRS width was 80 ms (IQR 80 to 85 ms; range 70 to 120 ms), and in only 1 case was the QRS 120 ms.

LIMITATIONS

The study was a nonrandomized retrospective analysis of data collected prospectively in a clinical database. Because data are recorded independent of any study hypothesis, detailed information that is relevant to this study may not be recorded. Similarly, in some cases only a single or limited number of ECGs were recorded. However, at least 1 ECG was available in all but 1 case, and in 33 cases in which blood was collected, serial ECGs were prospectively obtained for the entire presentation/admission.

In estimating ingested dose, we relied on patient reports, as well as history from ambulance officers, friends and family, and presence of empty drug containers. This could create a source of inaccuracy because patients may be unable to recall the exact dose ingested. However, previous pharmacokinetic studies[16,17] indicate that patient reports of ingested dose are a reasonable estimate of the true ingested dose. Furthermore, there was only 1 patient who claimed to have taken an overdose but had very low blood concentrations. This may have also occurred in the patients who did not have analytic confirmation of escitalopram. However, according to the fact that 33 of 34 patients who stated they ingested an escitalopram overdose had plasma concentration consistent with an overdose, it is unlikely that this occurred in more than another 1 or 2 patients. An increasing number of studies now support the fact that patient history of an overdose is reliable.[16-19]

Table 3. Comparison of patients with and without QT interval prolongation.

	Patients With QT–HR Pairs at Risk (n=11)	Patients With Normal QT–HR Pairs (n=67)
Age, y, median (IQR)	24 (22–29)	32 (22–41)
Dose ingested, mg, median (IQR)	180 (75–230)	140 (75–260)
Length of stay, h (range)	19 (9–34)	14 (7.5–23)
Coingestants (%)	1 (9)	3 (4)

QT–HR pair "at risk" is defined as the absolute QT interval and pulse rate from the same ECG (QT–HR pair) which are above the at-risk line when the QT is plotted against the pulse rate on the QT nomogram, according to Chan et al.[20]

DISCUSSION

This study describes the clinical effects of escitalopram in overdose, including ECG changes. Serotonin toxicity occurred in 16% of escitalopram-alone overdoses, a similar frequency to other SSRIs and in particular citalopram.[2] There were no cases of life-threatening serotonin toxicity, and serotonin toxicity was less common if coingestants were taken. Other neurologic effects were rare, including central nervous system depression, which occurred exclusively in patients taking sedative coingestants (Table 1). Seizures were not reported and are likely to be rare. The frequency and type of ECG effects were similar to that of citalopram, with 14% of patients having potential risk for torsades de pointes, as indicated by an abnormal QT–HR pair. Bradycardia occurred in 11% of escitalopram overdoses, a frequency similar to that in other SSRI overdoses.[2]

The risk of QT prolongation in patients with citalopram overdose has previously been investigated. In a group of 254 patients with a citalopram overdose, 25 (10%) were considered to have a QT interval at risk.[20] As in our study, patients were considered at risk if their QT–HR pair was out of normal ranges, as defined in the QT nomogram.[15] The number of patients deemed at risk in our study is similar. Another similarity to citalopram overdose is that cases with at-risk QT intervals more often developed bradycardia or had a normal pulse rate, rather than developing tachycardia (Figure),[20] which was a similar pattern to that seen in a separate study in which cases with drug-induced torsades de pointes were plotted on the QT nomogram.[15] This contrasts with drugs such as venlafaxine and quetiapine, in which patients at risk often had tachycardia (pulse rate >105 beats/min).[21] The frequency of at-risk QT–HR pairs in escitalopram overdose with most associated with bradycardia suggests that escitalopram-overdose patients are at risk of torsades de pointes, similar to those taking citalopram overdoses.

Escitalopram causes effects similar to those of other SSRIs in overdose, with the major manifestation being serotonin toxicity.[2] According to this small series, there appears to be an additional risk of torsades de pointes in escitalopram overdose (according to the greater-than-expected number of abnormal QT–HR pairs), which is similar to that with citalopram overdose.

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Address for correspondence: Geoffrey K. Isbister, MD, BSc, FACEM, Department of Clinical Toxicology, Calvary Mater Newcastle, Edith St, Waratah NSW 2298, Australia; 612-4921-1211, fax: 612-4921-1870;E-mail Geoffrey.isbister@menzies.edu.au.

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