Predictive factors for generalized seizures after deliberate citalopram overdose

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Citalopram is a common means of self-poisoning in young adults.
- Generalized seizures are a recognised complication after selective serotonin reuptake inhibitor overdose (including citalopram overdose).

WHAT THIS STUDY ADDS

- The minimum stated citalopram dose associated with seizures in the absence of co-ingested drugs was 400 mg.
- Co-ingestion of a tricyclic antidepressant or venlafaxine confers a 15-fold increased risk of seizures.

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AIMS

Seizures are a recognized complication of citalopram overdose. The present study sought to establish risk factors for seizures in this high-risk patient group, including stated dose ingested, co-ingested drugs or ethanol, and electrolyte disturbances.

METHODS

A retrospective casenote review was carried out of patients who attended the Emergency Department due to citalopram overdose between January 2000 and July 2007 inclusive. Stepwise logistic regression analysis considered age, gender, stated citalopram dose, acute ethanol consumption, co-ingested drugs, administration of activated charcoal, and hyponatraemia.

RESULTS

There were 241 patients (177 women), and the median (interquartile range) stated citalopram dose was 300 mg (200 to 600 mg). Generalized seizures occurred in 18 patients (7.5%). Logistic regression analysis found co-ingested tricyclic antidepressants or venlafaxine predicted seizures with odds ratio = 15 (95% confidence interval 3, 75). In the absence of co-ingested drugs, the minimum citalopram dose associated with seizures was 400 mg. Odds ratio for seizures = 1.1 (95% confidence interval 1.0, 1.2) for every 100 mg increment in citalopram dose. Seizures were associated with a greater need for invasive ventilatory support, higher creatine kinase activity, and prolonged hospital stay.

CONCLUSIONS

Generalized seizures are an important manifestation of citalopram toxicity, and cannot be explained solely by electrolyte disturbances or co-ingestion of other drugs or ethanol. The strongest predictors of seizures in this patient series were ingestion of high citalopram dosages and co-ingestion of drugs capable of lowering seizure threshold.

Introduction

Citalopram is a selective serotonin re-uptake inhibitor (SSRI) that possesses similar efficacy to other SSRI and tricyclic antidepressants [1]. Its principal metabolites, demethylcitalopram and didemethylcitalopram, have negligible effects on serotonin reuptake [2, 3]. The typical therapeutic citalopram dose is 20 mg daily, and recognized adverse effects include headache, dry mouth, sweating, nausea, dizziness, somnolence, and fatigue [4]. Existing data have not shown an increased risk of seizures. However, this is a recognized adverse effect of other antidepressants, particularly in patients with a lowered seizure threshold [5]. Generalized seizures are recognized in 2 to 6% of patients who present to hospital after deliberate citalopram overdose [6, 7]. Onset of seizures may be within 1 h of ingestion or delayed for up to 13 h [8, 9]. They tend to be short-lived, and may be terminated promptly by benzodiazepine administration [10]. Recurrent seizures have been described in a child despite administration of midazolam and fosphenytoin [8].

The mechanisms underlying generalized seizures after citalopram overdose are unclear, but massive increases in brain serotonin concentrations might be directly responsible [11, 12]. Seizures are a recognized complication of other drugs capable of blocking serotonin reuptake. For example, venlafaxine promotes the risk of seizures during therapeutic use or after deliberate ingestion [6, 13]. Despite the strong association between citalopram overdose and seizures, it is possible that co-ingested drugs or ethanol might contribute to seizure risk. Electrolyte disturbances might also be important, for example hyponatraemia due to inappropriate antidiuretic hormone sensitivity [14–16].

The present study was designed to establish whether clinical characteristics might allow prediction of seizures in patients who present to hospital after deliberate ingestion, namely pre-existing epilepsy, age, hyponatraemia, stated citalopram dose, acute ethanol co-ingestion, chronic ethanol excess, and concomitant ingestion of drugs known to alter seizure threshold. The study also addressed the impact of seizures on clinical outcome, including the need for invasive ventilatory support, occurrence of rhabdomyolysis, and duration of hospital stay.

Methods

The design was a retrospective casenote review of patients who attended the Emergency Department due to citalopram overdose between 1st January 2000 and 30th June 2007 inclusive. The standard practice is that suspected poisoned patients may be admitted to the Toxicology Unit, or the High Dependency Unit if non-invasive ventilatory support is likely to be required, or the Intensive Treatment Unit if invasive ventilation is required. Patients in all of

these clinical areas were included. The study met the local research ethics committee criteria for a clinical audit, so formal ethical approval was not sought.

Data collection

A standardized data collection sheet was used to record age, gender, date and time of overdose, quantity ingested, type and quantity of any co-ingested drugs and ethanol, and any documented clinical history of epilepsy or antiepileptic use. Variables considered as possible risk factors were age, gender, stated citalopram dose, acute ethanol consumption, chronic excess ethanol (consumption of more than 28 units (224 g) per week in men or 21 units (168 g) per week in women for more than 1 month), co-ingested drugs, administration of activated charcoal, hyponatraemia, and QTc (QT interval corrected by Bazett's formula). Citalopram dose relied on patient self-reporting supported, where available, by drug packaging and bystander accounts. Co-ingestion of tricyclic antidepressants and venlafaxine are known to increase seizure risk, whereas benzodiazepines lower it and, therefore, these drugs were considered separately from other co-ingested drugs [6, 13]. Primary outcome variables were the occurrence of seizures, maximum serum creatine kinase, referral to the High Dependency Unit or Intensive Treatment Unit, invasive ventilation, and duration of hospital stay. Creatine kinase values $>1000 \text{ U l}^{-1}$ were accepted as indicative of significant drug-related myopathy [17].

Data analyses

Data are presented as median and interquartile ranges. Between-group comparisons were made using Mann-Whitney tests and two-tailed Yates' corrected Chi-square tests. Predictive variables were entered into a stepwise logistic regression analysis that examined the effect of age interval 10 years and citalopram dose interval 100 mg; variables were retained if the *P* value was <0.05 and rejected if the *P* value was >0.1 . Analyses were performed using MedCalc software v. 9.1.0.1 (MedCalc, Mariakerke, Belgium), and *P* values <0.05 were accepted as statistically significant in all cases.

Results

There were 241 patients with a median age 33 years (23 to 41 years), including 177 women (73.4%). The reason for presentation was deliberate self-poisoning in 239 (99.2%) and inadvertent ingestion in two (0.8%). The stated median dose of citalopram ingested was 300 mg (200 to 600 mg). Ethanol was co-ingested in 151 cases (62.7%), and other drugs in 159 (66.0%); the most commonly co-ingested drugs were paracetamol (69), benzodiazepines (48), opiates (35), non-steroidal anti-inflammatory drugs (30), other antidepressants (24), and antipsychotic drugs (19). Generalized seizures occurred in 18 patients; eight of these

Table 1

Characteristics of patients who presented to hospital after citalopram overdose, shown as median and interquartile range. Comparisons between the subgroups with and without seizures are by Mann-Whitney tests and Chi-square proportional tests. QTc = QT interval corrected by Bazett's formula

	No seizures <i>n</i> = 223	Seizures <i>n</i> = 18	<i>P</i> value
Men	61 (27.4%)	3 (16.7%)	0.4771
Age (years)	33 (24 to 41)	24 (20 to 37)	0.0515
Citalopram dose (mg)	280 (180 to 560)	600 (400 to 1260)	0.0025
Ethanol co-ingested	143 (64.1%)	8 (44.4%)	0.1590
Chronic ethanol excess	14 (6.3%)	1 (5.6%)	0.6979
Number of co-ingested drugs	2 (1 to 3)	1 (1 to 2.5)	0.5208
Co-ingested tricyclic antidepressant or venlafaxine	8 (3.6%)	5 (27.8%)	0.0001
Co-ingested benzodiazepine	45 (20.2%)	3 (16.7%)	0.9594
Co-ingested other drugs	151 (67.7%)	8 (44.4%)	0.0804
Serum sodium (mmol l ⁻¹)	140 (137 to 141)	140 (138 to 143)	0.1893
Hyponatraemia	11 (4.9%)	0 (0.0%)	0.7097
QTc (ms)	426 (412 to 442)	440 (423 to 466)	0.0551
Critical care required	2 (0.9%)	5 (27.8%)	<0.0001
Invasive ventilation required	1 (0.4%)	3 (16.7%)	<0.0001
Maximum creatine kinase (U l ⁻¹)	76 (55 to 118)	585 (110 to 1011)	<0.0001
Creatine kinase >1000 U l ⁻¹	1 (0.5%)	5 (27.8%)	<0.0001
Duration of hospital stay (h)	20 (15 to 29)	33 (23 to 43)	0.0004
Transfer to psychiatric unit	17 (7.6%)	3 (16.7%)	0.3689

patients had co-ingested other drugs whereas 10 had not (5.0% vs 12.2% respectively, $P = 0.0788$). In patients who did not co-ingest other drugs, the median stated citalopram dose associated with seizures was 800 mg (590 to 3100 mg) compared with 335 mg (240 to 560 mg) without seizures ($P = 0.0010$); the minimum citalopram dose associated with seizures was 400 mg. A higher proportion of the patients that developed seizures required transfer to a critical care area, needed invasive ventilatory support, developed significant creatine kinase elevation, and had longer duration of hospital stay compared with those without seizures (Table 1).

Stated citalopram dose was similar between patients who did and did not co-ingest a tricyclic antidepressant or venlafaxine, and between patients who did and did not co-ingest a benzodiazepine. None of the patients with seizures reported co-ingestion of other pro-convulsant drugs, for example ecstasy, certain antipsychotics, and mefenamic acid. Stated citalopram dose was lower in patients who co-ingested other drugs than in those who did not: 280 mg (140 to 560 mg) vs 400 mg (255 to 640 mg), $P = 0.0011$. Stepwise logistic regression analysis gave a model that included citalopram dose, age, co-ingested tricyclic antidepressant or venlafaxine, and co-ingested other drugs (excluding benzodiazepines). Other factors were not retained because they did not achieve statistical significance, namely activated charcoal administered, co-ingested benzodiazepine, co-ingested other, chronic ethanol excess, ethanol co-ingested, male, hyponatraemia, and QTc (Table 2). The number of patients who co-ingested other drugs and or developed seizures is presented in Table 3.

Table 2

Stepwise logistic regression analysis of variables associated with seizures after citalopram overdose. Variables not retained in the model were male, acute ethanol co-ingestion, chronic ethanol consumption, co-ingestion of benzodiazepines, co-ingestion of other drugs, activated charcoal administration, hyponatraemia and QTc

Variables included	Coefficient	Odds ratio (95% CI)	<i>P</i> value
Constant	-1.02		
Age (10 years increment)	-0.54	0.6 (0.3 to 1.0)	0.042
Citalopram dose (100 mg increment)	0.09	1.1 (1.0 to 1.2)	0.036
Co-ingested tricyclic antidepressant or venlafaxine	2.44	15.1 (3.0 to 75.3)	0.001
Co-ingested other drugs*	-1.87	0.1 (0.0 to 0.7)	0.013

*Excluding benzodiazepines.

Table 3

Two-by-two contingency table indicating the occurrence of seizures and drug co-ingestion across the whole study population. $P = 0.0675$ by Fisher's exact test

		Co-ingested drugs		Total
		No	Yes	
Seizures	No	72	151	223 (92.5%)
	Yes	10	8	18 (7.5%)
	Total	82 (34.0%)	159 (66.0%)	241

At the end of the acute episode, all patients were discharged home or to a psychiatric facility for further assessment, and no deaths occurred.

Discussion

Generalized seizures occurred in 7.5% of patients. This is higher than reported elsewhere, which might reflect higher ascertainment due to the patients being managed in a specialist Toxicology unit. In keeping with earlier reports, seizures were short-lived and terminated spontaneously or soon after systemic benzodiazepine administration [6, 7]. None of the patients had pre-existing epilepsy, and the most important predictor was co-ingestion of a tricyclic antidepressant or venlafaxine. Concomitant use of drugs capable of lowering seizure threshold has previously been identified as a major risk factor for seizures during SSRI treatment [18]. A positive association was found between increasing citalopram dose and seizure risk, although the statistical significance was weak. In the absence of co-ingested drugs, the minimum stated citalopram dose associated with seizures was 400 mg, which is in keeping with an earlier series that found seizures occurred only after ingestion of >600 mg, and occurred in all patients that ingested >1900 mg [19]. A high prevalence of seizures has been reported after ingestion of massive citalopram quantities, at 20 to 260 times the defined daily dose [20]. The occurrence of seizures was higher in this series than reported in other series, and might reflect differences in the ingested dose and patterns of co-ingested drugs.

Therapeutic citalopram doses do not influence seizure risk, even in patients who have co-existent epilepsy [5, 21]. Conventional citalopram dosages might even increase seizure threshold in selected patient groups [12]. In contrast, administration of very high doses is capable of provoking seizures in mice and dogs [22, 23]. Generalized seizures occurred in a significant proportion of patients who ingested citalopram in the absence of other drugs or ethanol. The study design does not allow discrimination between the possibilities of a threshold dose effect or continuous risk across a wide range of citalopram doses. Hyponatraemia was not encountered in any patient who suffered seizures and, therefore, this mechanism does not appear to be relevant. The lack of discernible effect of charcoal administration is likely to be due to comparatively small patient numbers. Although not addressed directly in the present study, other existing data support the early administration of oral activated charcoal after citalopram overdose [24].

As expected, the occurrence of seizures was associated with a significantly greater need for invasive ventilatory support, a higher likelihood of skeletal muscle injury (determined by elevated creatine kinase activity), and longer duration of hospital stay. The proportion of patients

requiring transfer to a psychiatric unit at the end of the acute episode was similar irrespective of whether or not seizures occurred.

Limitations of the regression model are that only a small number of patients developed seizures. Therefore, the relationships between seizures and age, citalopram dose, and co-ingested other drugs need to be interpreted with some caution, in view of the weak statistical significance. The stated citalopram dose relied on patient self-reporting without confirmatory laboratory measurements. Nonetheless this appears to be a valid approach and a positive correlation exists between the stated dose and drug concentrations in the setting of acute overdose [25, 26]. The prevailing limits for safe ethanol consumption may be too conservative in this setting, and regular consumption of higher ethanol quantities might influence seizure risk. A high proportion of the study population consisted of young adults, as reported elsewhere among patients presenting to hospital after SSRI ingestion, and this might limit the generalizability of the data [6, 27]. A further limitation is that the study design cannot address the underlying biological mechanisms of seizures after citalopram overdose, and cannot discriminate the contribution of citalopram vs co-ingested drugs.

In conclusion, seizures are an important complication of citalopram overdose, particularly if co-ingested with drugs known to lower seizure threshold. In the absence of co-ingested drugs, seizures are associated with ingestion of high stated citalopram doses (>400 mg). The risk of seizures should be considered in all patients who attend the Emergency Department after suspected citalopram overdose, even in the absence of pre-existing epilepsy.

Competing interests

None declared.

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