Clinical Case Report

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Vortioxetine overdose in a suicidal attempt

A case report

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Abstract

Rationale: Vortioxetine is a new multimodal antidepressant approved by the Food and Drug Administration for the treatment of Major Depressive Disorder and recently introduced in Europe. While antidepressant properties of vortioxetine and its tolerability have been demonstrated by preclinical and clinical studies data on the safety of vortioxetine after overdose are still lacking.

Patient concerns: A 50-year-old Caucasian man presenting a severe depressive episode that in a suicide attempt he took vortioxetine at 250 mg.

Diagnoses: Suicide attempt by vortioxetine in a patient affected by Major Depressive Disorder.

Interventions: General evaluations and gastric lavage with 2 L of water plus 50 g of activated charcoal was performed. After 12 hours of clinical stability, the patient was discharged from the emergency department and considering the suicidal ideation he was admitted to the inpatients psychiatric department.

Outcomes: After vortioxetine overdose the patient displayed no clinical signs or symptoms resulting from the exposure suggesting a good safety in overdose.

Lesson: Overdose safety of different antidepressant drugs is a matter of great considering that overdose in individuals affected by Major Depressive Disorder frequently involves prescribed antidepressants. Previous studies showed wide variation in the relative toxicity of different antidepressant drugs with higher toxicity for tricyclic antidepressants, followed by venlafaxine bupropion and mirtazapine and lower for selective serotonin reuptake inhibitors. By now there is limited clinical trial experience regarding human overdose with vortioxetine and the maximum single dose tested was 75 mg in men associated with increased rates of nausea, dizziness, diarrhea, abdominal discomfort, generalized pruritus, somnolence, and flushing. Even if there is still limited available evidence and further investigation is needed to better understand the potential risk of vortioxetine overdose; from our case, it seems that vortioxetine overdose at 250 mg (12 times the common daily dose) showed no signs or symptoms resulting from the exposure suggesting a good safety in overdose.

Abbreviations: 5-HT = serotonin, DSM-5 = Statistical Manual of Mental Disorders-5, ECG = electrocardiogram, GGT = gamma-glutamyl transpeptidase, MDD = major depressive disorder, SNRI = serotonin–norepinephrine reuptake inhibitor.

Keywords: antidepressant, case report, major depressive disorder, overdose, suicide attempt, vortioxetine

1. Introduction

Vortioxetine is a new multimodal antidepressant approved by the Food and Drug Administration for the treatment of Major Depressive Disorder (MDD) and recently introduced in Europe.

In addition to blocking the traditional serotonin (5-HT) transporter, vortioxetine is also an antagonist at 5-HT3A, 5-HT7, and 5-HT1D receptors; is a partial agonist at 5-HT1B receptors and a full agonist at 5-HT1A receptors.[1–3] Vortioxetine has a bioavailability of 75% with a mean T-max of 7 hours and mean T1/2 of 66 hours meaning a low risk of discontinuation syndrome. The rate of binding of vortioxetine to plasma protein is 96%; vortioxetine is metabolized by P450 enzymes (especially CYP2D6) with no significant induction or inhibition of P450 and no pharmacologically inactive metabolites.[2,3] Antidepressant properties of vortioxetine have been demonstrated by preclinical and clinical studies. Vortioxetine is more effective than placebo in terms of response, remission, and depressive symptoms; when compared with serotonin–norepinephrine reuptake inhibitor (SNRI), there is no advantage or disadvantage for vortioxetine.[4,5] A series of short-and long-term studies confirmed the efficacy and safety of vortioxetine in patients with MDD, especially it was found that treatment-emergent sexual dysfunction was not significantly different between vortioxetine and placebo and sleep-related symptoms were low and not dose-related. The main adverse effect of vortioxetine is nausea and vomiting.[6–10] Data on the safety of vortioxetine after overdose are still lacking. Here, we report the case of a suicide attempt by vortioxetine overdose committed by a patient affected by MDD.

2. Case presentation

A 50-year-old white man outpatient diagnosed as MDD according to Statistical Manual of Mental Disorders-5 criteria (DSM-5). From October 2013, the patient has treated with

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amisulpride 50 mg ½ tablet per day and trazodone 150 mg 1 tablet per day. Starting from August 2016, because of a partial efficacy of pharmacological therapy, trazodone was suspended and was introduced vortioxetine 10 mg 1 tablet per day and clonazepam 2 mg per die. This therapy was well tolerated without any adverse reactions. The patient had a previous history of substance use disorder (heroin dependence from 14 to 24 years; cocaine dependence from 31 to 33 years) and a previous history of alcohol use disorder (from 14 to 31 years). He was also diagnosed with hepatitis C when he was 31-year-old and immediately treated with a rapid virological response, in general, good physical health (body height of 180 cm; body weight of 70 kg; body mass index of 22).

At 6:00 AM of June 13, 2017 the patient took about 250 mg of vortioxetine (50 tablets of 5 mg) and approximately 10 mg of clonazepam in a suicide attempt.

At 10:50 AM he presented himself at the emergency department, he was conscious and able to walk. Glasgow Coma Scale score was 15. There was no neck stiffness. Cranial nerves were intact. Muscle power and tendon reflexes were normal. Sensations were intact. He denied any incontinence or biting his tongue. No signs or symptoms of serotonin syndromes were observed. Hearts, lungs, and abdomen showed no abnormalities at physical examination. No abuse of alcohol or other drugs was reported by the patient and it was confirmed by urine drug test. The vital signs were within the normal ranges (Table 1).

Table 1

Vital signs, ECG, and laboratory findings during the observation period after vortioxetine overdose.

Type of analysis	At emergency department (5 h after ingestion)	At psychiatric ward admission (24 h after ingestion)	At psychiatric ward discharge (7 d after ingestion)
Vital signs			
Blood pressure, mm Hg	110/65	105/65	110/70
Pulse rate (beats per minute)	70	72	65
Saturation of peripheral oxygen, %	98	98	99%
Respiratory rate (breaths per minute)	12	13	12
Temperature, °C	36.5	36.6	36.8
Electrocardiogram	Normal (QTc 413)		Normal (QTc 420)
Laboratory findings			
Red blood cell count, M/mmc	4.61	4.75	4.85
Hemoglobin, g/dL	15.7	16.5	16.8
White blood cell count, K/mmc	6.0	7.3	6.8
Platlets cell count, K/mmc	245	278	323
Lymphocyte count, %		27	
Neutrophyle count, %		59	
Eosinophyle count, %		4	
Basophyle, %		0	
Monocytes, %		10	
Prothrombin time, s	12.6		
Prothrombin time (INR)	1.09		
Activated clotting time, s	37.5		
Activated clotting time (ratio)	1.17		
Creatinine, mg/dL	0.77	0.76	0.84
Creatine-kinase, U/L	102		
Lactate dehydrogenase, U/L	342		
Blood sugar level, mg/dL	95	82	60
Glomerular Filtration Rate (mL/min/1.73 m^2)	>90	>90	>90
Sodium, mMol/L	142	141	140
Potassium, mMol/L	4.5	4.8*	4.5
Chloride, mMol/L	104		
Calcium, mMol/L		2.49	2.44
Aspartate aminotransferase, U/L	21	19	23
Alanine aminotransferase, U/L	34	37	38
Gamma-glutamyl transpeptidase, U/L		71*	82*
Total cholesterol, mg/dL		143	131
HDL cholesterol, mg/dL		55	55
LDL cholesterol, mg/dL		75.5	58
Triglycerides, mg/dL		75	108
Urine drug testing			
Ethanol	0		
Barbiturates	0		
Benzodiazepines	40 ng/mL*		
Opiates	0		
Cocaine	0		
Methadone	0		
Marijuana	0		

ECG = electrocardiogram.
* Point out abnormal values.

Mental state examination performed by a psychiatrist in the emergency department suggested the diagnosis of severe depressive episode according to DSM-5 criteria. The patient showed depressed mood and congruent affect, diminished interest and pleasure almost all activities most of the day, fatigue and loss of energy, feelings of worthlessness and insomnia for some months now. Investigating the suicidal ideation, the patient acknowledged the suicidal intent of vortioxetine overdose.

The laboratory tests and the electrocardiogram (ECG) made in the emergency department were normal (Table 1). Only urine value of benzodiazepines was positive (40 ng/mL). After general evaluations at 11:20 AM gastric lavage with 2 L of water plus 50 g of activated charcoal was performed. After 12 hours of clinical stability, the patient was discharged from the emergency department and considering the suicidal ideation he was admitted to the inpatients psychiatric department. When admitted to psychiatry ward vital signs were normal such as ECG and laboratory tests apart from a slight hyperkaliemia and increased gamma-glutamyl transpeptidase (GGT) (Table 1).

The patient's condition improved after 1 week of recovery. The psychopharmacology therapy was modified since the lack of efficacy of the previous therapy: vortioxetine was suspended while sertraline 100 mg 1 tablet per day, amisulpride 50 mg 1 tablet per day, flurazepam 30 mg 1 tablet per day, and delorazepam 0.5 mg per day was introduced. The vital parameters were always normal, the patient never showed any organic signs or symptoms resulting from the overdose and he denied of having suicidal ideation any longer. Patient's mood improved such as interest and feelings of worthlessness, he recovered energy and a regular sleep. After 7 days of hospitalization, the patient has discharged from the psychiatry ward in generally good physical health with normal ECG and normal laboratory tests apart from slight increased GGT (Table 1).

After, we contacted our institutional review board; there was no need for ethical approval for this case report article. Informed patient consent was obtained for the publishing of this case report, all in accordance with Declaration of Helsinki.

3. Discussion

Overdose safety of different antidepressant drugs is a matter of great interest given that in patients affected by MDD overdose of prescribed drugs is a frequent method used for suicidal act.[11–14] Antidepressants are involved in around 20% of all overdose suicides and in 20% to 30% of nonfatal overdoses.[15] Considering that the way used for suicidal attempt is often determined by availability, overdose in individuals affected by MDD frequently involves prescribed antidepressants.[16]

In spite of the high risk of antidepressant overdose in patients affected by MDD practitioners have to consider prescribing patterns headed for less toxic antidepressant drugs that are equally efficacious in order to reduce fatality.

Previous studies show wide variation in the relative toxicity of different antidepressants drugs.[13–17]. It is known that the toxicity is higher for tricyclic antidepressants, followed by venlafaxine bupropion and mirtazapine and is lower for selective serotonin reuptake inhibitors. Among the selective serotonin reuptake inhibitors, citalopram and fluvoxamine appeared to be associated with the higher case fatality rates in overdose.[12,13] An antidepressant is considered safe when a dose 14 times the daily therapeutic dose does not lead to a life-threatening situation. For selective serotonin reuptake inhibitors moderate overdoses (up to 30 times the common daily dose) are associated with minor or no symptoms and very high doses (>75 times the common daily dose) result in more serious adverse events, including seizures, ECG changes, and decreased consciousness may occur. Contrary tricyclic antidepressants can be fatal if ingested in quantities exceeding 10 times the daily dose.[18]

To our knowledge, there is limited clinical trial experience regarding human overdose with vortioxetine. In premarketing clinical studies, cases of overdose were limited to patients who accidentally or intentionally consumed up to a maximum dose of 40 mg of vortioxetine and the maximum single dose tested was 75 mg in men (3–4 times the common daily dose). Ingestion of vortioxetine in the dose range of 40 to 75 mg was associated with increased rates of nausea, dizziness, diarrhea, abdominal discomfort, generalized pruritus, somnolence, and flushing.[19]

Thus in order to improve knowledge about safety in the overdose of this novel antidepressant drug we decided to report this case of vortioxetine overdose. From our case, it seems that vortioxetine overdose at 250 mg (12 times the common daily dose) showed no signs or symptoms resulting from the exposure suggesting a good safety in overdose.

At clinical, laboratory, and ECG assessment, we only find abnormal values of urine benzodiazepines at emergency department evaluation, potassium at psychiatric ward admission evaluation and GGT at psychiatric ward admission and discharge evaluation. A positive value of urine benzodiazepines is explained by the clonazepam use since August 2016 and by its overdose in the suicide attempt.[20]

Considering the raised GGT, to exclude the possible effect of the overdose on the liver, we investigated previous evaluation of GGT and found GGT were raised yet before the overdose. Likely previous history of hepatitis C and alcohol use disorder could explain the increased GGT value.[21]

Regarding the hyperkaliemia at psychiatric ward admission evaluation, we excluded the most common cause of hyperkalemia such as acute kidney failure, chronic kidney disease, Addison disease (adrenal failure), type 1 diabetes, and use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. Even if it is to underline that it was only a slight and temporary increase, it was not possible to identify a cause and we cannot exclude that hyperkaliemia was induced by vortioxetine overdose.

A great limitation of our case report is that we were not able to test the patient for vortioxetine levels in his blood or urine; thus we cannot be fully accurate about the number of drugs the patient took. The motivation, the setting, and other details of the overdose were investigated by 2 independent psychiatrists during the daily psychiatric interview and the overdose seemed to be really sustained by a suicidal intention. In addiction, the patient carried at emergency department the empty blisters of drugs he took in the overdose to demonstrate his attempt.

Due to the limited available evidence, further investigation is needed to better understand the potential risk of vortioxetine overdose.

Author contributions

Conceptualization: Mario Gennaro Mazza.
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Investigation: Mario Gennaro Mazza.
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