

Venlafaxine poisoning-induced severe hypoglycemia in a non-diabetic patient: a case report

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Abstract

Introduction: Venlafaxine is a serotonin and norepinephrine reuptake inhibitor (SNRI) used to treat major depressive episodes and anxiety. The risk of hypoglycemia is mentioned in the Summary of Product Characteristics (SmPC) of venlafaxine in the “warnings and precautions” section in diabetic patients. This effect appears neither in the “adverse reactions” nor in the “overdose” section. We herein report a case of severe hypoglycemia with coma in relation to venlafaxine poisoning.

Case Report: A 35-year-old non-diabetic obese woman (BMI, 29 kg/m²) was found unconscious a few hours after ingesting venlafaxine and bromazepam in a suicide attempt. Vital signs on day 1 were as follows: Glasgow Coma score of 7, blood pressure of 99/66 mmHg and heart rate of 100/min. Electrocardiogram showed no abnormality. She was admitted to the intensive care unit. Due to sustained hypoglycemia [0.5 g/L (day1); 0.41 g/L (day2); 0.8 to 1.20 (day3)], she received continuous intravenous 10% glucose infusion for 3 days to normalize blood glucose. Plasma venlafaxine concentration was 11.7 times the upper the limit of therapeutic dose range (UTDR) on day 2 and reached the therapeutic dose range (TDR) on day 6. Plasma bromazepam concentration was 6.7 times UTDR on day 3 and reached TDR on day 8. Alternative etiologies of hypoglycemia were excluded, i.e. hypoglycemic sulfonamide, insulin poisoning, insulinoma, and disease of the adrenal gland, liver and thyroid. She was transferred to a psychiatric unit after one week.

Discussion: Impairment of blood glucose homeostasis is rarely described with venlafaxine. In our patient, hypoglycemia appeared to be correlated with plasma venlafaxine concentrations and may be explained by increased insulin sensitivity, considering her obesity.

Conclusion: Healthcare professionals should be aware of hypoglycemia induced by venlafaxine or other SNRIs in non-diabetic patients.

Keywords: Venlafaxine; poisoning; hypoglycemia; antidepressant; serotonin

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INTRODUCTION

Diabetes is highly linked with the development of depression and the risk is 15% to 20% higher in insulin-dependent and non-insulin-dependent diabetic patients than in the general population (1,2). Every antidepressant treatment must be adapted in diabetic patients, given the hyperglycemic or hypoglycemic effects of these drugs. Literature mentions some case reports of hypoglycemia induced by selective serotonin reuptake inhibitors (SSRIs) but hypoglycemia induced by SNRIs such as venlafaxine or duloxetine is little described.

Hypoglycemia is very suggestive of psychostimulant poisoning (3). Actually, hypoglycemia induced by SSRIs, particularly fluoxetine, is very well described and may lead to serious consequences (4-7). There are others SSRIs associated with hypoglycemia. A case-report mentions a significant increase in glycaemia level five days after escitalopram administration to a patient and the return to normality as soon as treatment is stopped (8). Some authors

report that severe hypoglycemia is logically a common side effect of SSRIs overdose such as citalopram overdose (9).

Regarding SNRI-induced glucose metabolism alteration, there are a small number of reports of hypoglycemia related to venlafaxine (11-13). Furthermore, the risk of hypoglycemia is mentioned in the SmPC of venlafaxine in the “warnings and precautions” section in diabetic patients but does not appear in the “adverse reactions” or in the “overdose” section.

We herein describe an overdose case with venlafaxine, a SNRI, in a 35-year-old non diabetic woman which resulted in severe hypoglycemia. In the case reported here, hypoglycemia was not improved despite infusion of 10% glucose over 3 days. Furthermore, no other cause of hypoglycemia was found after a complete differential diagnosis in our patient. This case highlights the severity of hypoglycemia which may occur with venlafaxine overdose, even in the absence of risk factors.

CASE REPORT

The patient is a 35-year-old woman with depression

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antecedents. She does not take any medication for her disease nor and does not have any other medical background. She was found to be drowsy by firemen, who transferred her to the intensive care unit. Upon admission, she had a low Glasgow Coma score (GCS) of 7, a blood pressure (BP) of 99/66 mmHg, a heart rate (HR) of 100/min and hypoglycemia (blood glucose level 4.2 mmol/l). The patient did not resent symptoms suggesting hypoglycemia, such as sweating or seizures. The patient was intubated and received glucose infusion over three days but plasma glucose did not significantly improve [0.5 g/L (day1); 0.41 g/L (day2); 0.8 to 1.20 (day3)]. Then, the patient was transferred to the toxicological intensive care service. VS and GCS were once again measured: GCS 12-13, temperature 39.7°C, BP 118/79 mmHg, HR 77/min and blood glucose 5.1 mmol/l. No decontamination was performed. Toxicological screening showed a venlafaxine plasma level ten times higher than standard and a bromazepam plasma level four times higher than standard. Furthermore, the differential diagnosis allowed to us to exclude several other etiologies: hypoglycemic sulfonamide intoxication, exogenous insulin, insulinoma, adrenal gland injury, liver injury and thyroid injury. Then, we noticed an improvement of glucose levels linked to the venlafaxine level decrease (Figure 1). At this point, the patient was transferred to the psychiatric unit.

DISCUSSION

Although fluoxetine is well-known to induce hypoglycemia, there is a lack of evidence to show that dual-mechanism antidepressants such as duloxetine and venlafaxine perturb glucose homeostatic dynamics (10). To

our knowledge, this is the fourth case report from the literature of hypoglycemia induced by venlafaxine overdose (11-13). We highlight the large amount of information which allowed us to describe this case the best: chronology, semiotics, and differential diagnosis. All the documentation we share allows us to relate the hypoglycemia to the venlafaxine overdose.

Some case reports have already shown hypoglycemia properties with antidepressants. Most of these act on serotonin uptake, meaning this neurotransmitter may be the culprit in antidepressant induced hypoglycemia. In mice models, direct serotonin administration induced apparent hypoglycemia by increasing serum insulin level. Both hypoglycemia and serum insulin level were strongly antagonized by methysergide (14). A recent study on “in vitro” mice has shown the capacity of fluoxetine, a SSRI antidepressant, to increase glucose uptake by palmitoylation of glucose receptors GLUT1 and GLUT3, two insulin non-dependent receptors (fluoxetine had no effect in insulin concentration in this study) (15).

Concerning SNRI antidepressants, we may put forward a hypothesis to explain the mechanism of venlafaxine induced hypoglycemia. First, there are similarities between the chemical structures of venlafaxine and tramadol, the latter having shown some hypoglycemia properties (16,17). It is possible that venlafaxine-induced hypoglycemia involves the same hypothetical mechanisms as tramadol, in which serotonin directly acts on glucose plasmatic levels and there is stimulation of β -endorphin secretion which alters the glucose utilization by muscles(18) or an enhancement of peripheral glucose utilization via the glutamate receptor 4

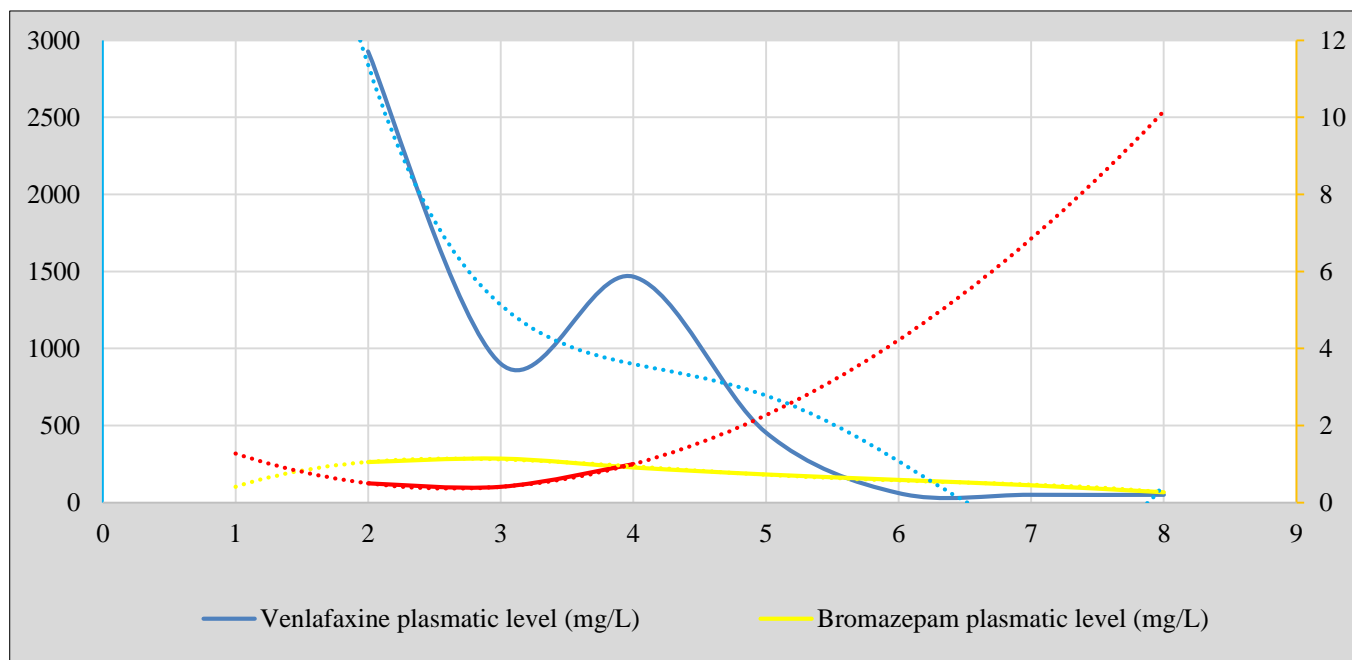


Figure 1. Toxicological screening of venlafaxine and bromazepam in connection with plasmatic glycaemia level (D0 referring to the intoxication day)

(19). Other mechanisms involved in SSRI-induced hypoglycemia have been suggested such as decreasing of carbohydrate intake linked to increase in serotonin levels, increased insulin sensitivity, interference with the metabolism of sulphonylureas (only in diabetic patients), decreasing triglycerides and free fatty acids, glucose oxidation perturbation, alteration of the insulin binding to the insulin receptor, and decrease of neoglucogenesis (4,20,21). All the mechanisms mentioned are linked with serotonin reuptake inhibition so as there is a possible class effect of SSRIs and SNRIs. This may explain the absence of duloxetine induced hypoglycemia in literature. In fact, duloxetine blocks serotonin and norepinephrine reuptake with a 10-fold selectivity for serotonin while venlafaxine has a 30-fold selectivity for serotonin (22).

Then, the action of antidepressants on glucose metabolism may have clinical repercussion, more particularly in diabetes mellitus patient. The drug-drug interaction between antidepressant and antidiabetic agents, such as metformin or sulphonylureas, involves inhibition or induction of cytochrome enzymes and transporters. We have to consider two pharmacokinetic interactions: 1) SSRIs or SNRIs are able to significantly alter renal function, which may lead to metformin accumulation, increased risk of hypoglycemia (independently of the risk of antidepressant induced hypoglycemia), and risk of lactic acidosis (23) and 2) antidepressants can provoke the increase of sulphonylurea plasma level by disturbing their plasma protein bounding (24).

CONCLUSION

Management of drug poisoning is very dependent on clinician knowledge (25). Healthcare professionals should be aware of hypoglycemia induced by venlafaxine or other SNRIs in both diabetic and non-diabetic patients, particularly in patients with high risk, such as diabetic patients, patients with lots of medications, patients with autonomy loss... We think that hypoglycemia is an adverse effect which needs to appear either in the "adverse reactions" or in the "overdose" section of the SmPC of venlafaxine.

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LIMITATIONS

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